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ACCESS TO THERAPIES, INCLUDING ADVANCED AND INNOVATIVE ONES

OUTCOMES OF THE UNIAMO - STAKEHOLDER WORK TABLES

THE EFFEMERIDS OF UNIAMO 6/2022

ÜNIAMO
Federazione Italiana Malattie Rare

UNIAMO THE ITALIAN FEDERATION OF RARE DISEASES

Access to therapies, including advanced and innovative ones Multi-stakeholder discussion table (05/12/2019, 12/01/2021, 19/01/2021, 15/09/2021, 09/28/2021, 07/06/2022, 09/29/2022).

Version dated November 30, 2022

This notebook finalized on November 30, 2022, illustrates the results of the discussions, promoted by UNIAMO Italian Federation of Rare Diseases, within multi-stakeholder working tables regarding the problems of access to drugs, with a special focus on advanced and innovative therapies, experienced by patients during their treatment journey.

The opinions expressed by the participants are to be understood as personal and not representative of the official positions of the respective public or private bodies they belong to.

The document is a summary of what was discussed and aims to be a tool to support Italian policies, also with respect to Europe, highlighting points of convergence and also what does not yet have a unanimous opinion among the subjects involved, but on which we can work to find a concordance.

The Federation will continue to stimulate debate on these issues, involving all the actors involved and illustrating the positions of the community of people with rare diseases, collected through comparison processes internal and external to the Federation and in collaboration with Eurordis.

Cite this document as follows:
UNIAMO F.I.M.R. Access to therapies - Multi-stakeholder discussion table, 2022.

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This document has been translated using IA: please forgive any mistake!

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Premises

30 million Europeans live with a rare disease, 72% of these pathologies are of genetic origin.

Advanced Therapies (Advanced Therapy Medicinal Product or ATMP), in increasing numbers in recent years, are highly innovative therapies that mark a new and important turning point opportunity and hope in the treatment of many rare pathologies. However, they have high costs that undermine the sustainability of the NHS due to the elaborate production and infrastructure process of the delivery network and the generally very low number of patients.

They represent a great medical innovation and include a multiplicity of medicinal products defined by Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on medicinal products for advanced therapies amending Directive 2001/83/EC and the Regulation (EC) n. 726/2004.

In general, the issue of access to therapies, from the first regulatory approvals to actual use by the patient, represents a highly topical issue of fundamental importance for the entire community of people with rare diseases.

Furthermore, the dispensing of some therapies under the extra-LEA regime creates further elements of inequality between citizens of the same country. It is therefore necessary to find an agreement on the lowest common denominator of therapies that can be provided by the NHS, which can be included in the LEAs in order to bridge, at least partially, these differences.

ATMP definitions

ATMP: a single name for various categories

Advanced therapy medicines are biotechnological products that are classified into the following four categories:

- Gene Therapy Products: consisting of a recombinant nucleic acid capable of inducing a therapeutic, prophylactic or diagnostic effect. These drugs allow you to regulate, repair, replace, add or delete a genetic sequence. In the case of genetic diseases in which a gene is defective or absent, gene therapy allows the transfer of the working copy of the gene in question.

- Somatic Cell Therapy Products: consisting of cells or tissues that have undergone a significant manipulation process with the aim of modifying their biological characteristics, physiological functions or structural properties or which are not intended to be used for the same original functions as body. The purpose of these medicines is to treat, prevent or diagnose diseases. The starting cells or tissues for the production of these therapies can be:
  1. of autologous origin (derived from the patient himself),
  2. of allogeneic origin (obtained from a donor),
  3. of xenogeneic origin (derived from a donor of an animal species other than humans).

- Tissue Engineering Products: contain cells or tissues that have been significantly manipulated or are not intended to be used for the same original functions as the organism, for the purpose of repairing, regenerating or replacing human tissue.

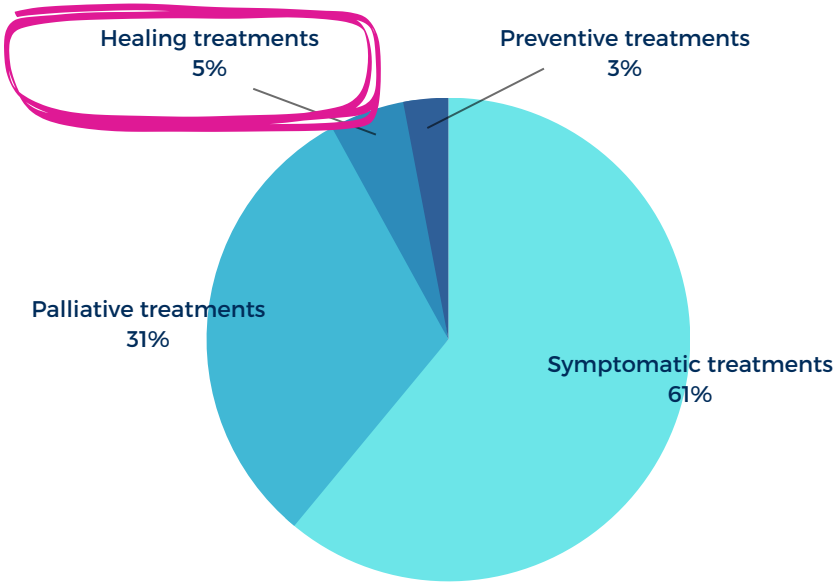
- Medicinal Products for Advanced Combined Therapy: contain one or more medical devices as an integral part of the medicinal product containing cells or tissues

The treatment situation for the community of people with rare diseases*

69% have experienced treatment for their condition

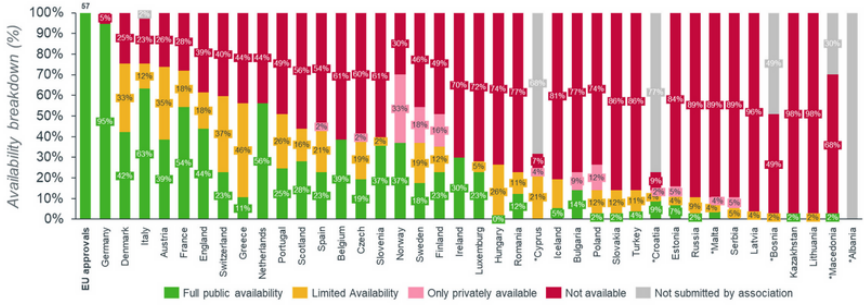
31% have NEVER had treatment for their pathology

Only 5% have a cure



*Eurord, 2019

Inequities in access to therapies



*IQVIA, 2022

In 2019

Patients with RD

Patients in general

+6%

They were unable to access treatments because they had no money to pay for them

12% — 6%

+5%

They were unable to access treatments because they were not available in their country

22% — 7%

+5%

They were unable to access treatments because the waiting list was too long

14% — 6%

*Eurord, 2019

Context analysis

MonitoRare's evidence on the accessibility of drugs for rare diseases*

- the total number of orphan drugs available in Italy at the end of 2020 was 75 (there were 71 at the end of 2019);
- in 2020, 8 million doses of orphan drugs were dispensed in Italy (9.7 million in 2019), i.e. 0.03% of total pharmaceutical consumption;
- spending on orphan drugs in Italy in 2020 amounted to €1,393 million with an incidence of 6.0% on total pharmaceutical spending (in 2019 it was €1,547 million with an incidence of 6.6%;
- the number of drugs for rare diseases included in the list of Law no. 648/1996 grew from 27 in 2012 to 38 in 2021;
- the number of people with rare diseases who have benefited from the AIFA fund (as per Law 326/2003, Art. 48) increased exponentially, going from 20 people in 2016 to 1,361 in 2020 (the number of beneficiaries rises to 2,298 also including rare tumors) fell to 1010 in 2021.
- as many as 8 of the 14 Advanced Therapy Medicinal Products (ATMPs) with European approval (end of 2021) are currently reimbursed in Italy, while 3 ATMPs are being evaluated - one has concluded the evaluation phase of the Prices and Reimbursement Committee and is pending of publication in the Official Journal, two under evaluation by the Prices and Reimbursement Committee (in Europe we are second only to Germany and England who reimburse 10).

*MonitoRare, VIII Report on the condition of people with rare diseases, UNIAMO 2022

MonitoRare's evidence on ATMPs - Europe*

Within the European Union all Advanced Therapies are authorized by the EMA through a centralized procedure which involves an evaluation by the Committee for Advanced Therapies (CAT). This committee has the aim of evaluating the quality, effectiveness and safety of advanced therapies for which marketing authorization is requested. Once its assessment has been carried out, the CAT sends a draft opinion to the (Committee for Medicinal Products for Human Use) (CHMP), which adopts it on a definitive basis. This is followed by the decision phase of the European Commission and the national negotiation process between the competent authority and the pharmaceutical companies for reimbursement and price. Currently, in Italy, these drugs are considered the same as all other medicines, and therefore follow the same procedural process.
In October 2020, the EMA had approved a total of 15 ATMPs (of which more than half in the last 5 years: 1 in 2020, 1 in 2019, 4 in 2018, 1 in 2017 and 2 in 2016): of these 5 were withdrawn for reasons commercial (note that 4 of these 5 were authorized by the EMA before 2014), thus bringing the number of advanced therapies present on the European market to 10 (data updated at the end of October 2020).
Italy, from the beginning, has played a key role in the research and development of ATMPs, so much so that among the first 5 approved by EMA, 3 are the result of Italian research.

However, although the authorization is centralized, the drug must subsequently follow national procedures to obtain reimbursement and price in each member country: each EU country, in fact, has its own regulation, consequently, access to drugs and the cost of these is not uniform at European level.

*MonitoRare, VIII Report on the condition of people with rare diseases, UNIAMO 2021

The evidence from Eurordis

At European level:

- approximately 70% of patients with rare diseases have experienced treatments that were curative in only 5/6% of cases; in other cases, however, the treatments are mainly symptomatic and non-curative. A third of patients have never received any type of treatment;

- the majority of authorizations for orphan drugs concern pathologies for which treatments are already available, in particular for "less rare" pathologies, with a strong inequity between pediatric and adult treatments. Furthermore, most of the authorizations concern drugs for the treatment of metabolic diseases and rare tumors.

Eurordis search:

- 95% patients have no treatment options
- 98% of patients are affected by 11% of pathologies

MonitoRare's evidence on ATMPs - Italy*

In Italy, according to the latest data available (October 2020), 4 ATMPs are reimbursed (as in France while there are 9 in Germany and 7 in England), 4 are in the evaluation phase and 2 are not reimbursed (for both it has not been price and reimbursement request has been submitted).

Furthermore, the uncertainty regarding the long-term benefits of these drugs has pushed many countries, including Italy, to stipulate reimbursement agreements based on patient response, the so-called. "payment at results"*. Currently, the path for the reimbursement of ATMPs follows the process of traditional drugs, therefore in a first step the Technical Scientific Commission (CTS) expresses its opinion on the value of the drug, on any limitations regarding reimbursement (in relation to the population segment indicated) and on the type of buyer, in order to determine the refundable price. In a second step, the Prices and Reimbursements Committee (CPR) examines the proposals and defines the price, taking into consideration the opinion of the CTS, thus explaining the costs of the therapy and the expected number of patients.

*This is one of the forms of deferred payment: if the drug does not have the expected effects, the company reimburses the buyer via credit note.

- We would like to point out that among the various types of payment there is also **payment by result**, currently used for CAR-Ts. Another formula used is that of the **budget cap** based on two indicators: number of patients and negotiated price (the objective of the budget is prescriptive appropriateness and management of pharmaceutical spending) at the contractual expiry of 12/24 months, AIFA verifies compliance with the negotiation condition and in case of excess spending the pharmaceutical company will have to pay a payback to the NHS

*MonitoRare, VIII Report on the condition of people with rare diseases, UNIAMO 2022

Italian Report - ATMP Forum*

The "First Italian report on Advanced Therapy Medicinal Products" prepared by the ATMP Forum in 2018, provided an interesting insight into the state of interventional clinical studies in the most advanced phase (II/III and III) in which ATMP represents the experimental therapy.

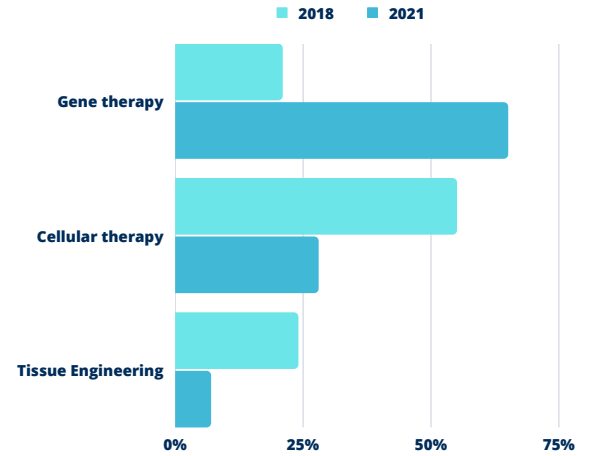
Of the 158 phase III and II/III interventional clinical trials, active or completed in the period June 2016-November 2018, specific to ATMPs, the majority are financed by pharmaceutical companies (54%), while the remaining 46% are financed by public bodies or non-profit research institutions.

In the Italian panorama, the role of pharmaceutical companies is even greater (75% of the studies considered).

More than half of the studies (55%) are aimed at cell therapy while 24% concern tissue engineering and 21% gene therapy.

As regards the areas in which the studies focus, only 31% specifically concern rare diseases.

In the V Report, published in 2022, 950 trials on therapies classified as ATMP were identified (6.83% of the total - equal to 13,903 studies). The distribution of studies has shifted significantly towards gene therapy research.



*ATMP Forum, Report Italiano sulle Advanced Therapy Medicinal Product

Of the 250 studies completed, 50% focus on rare diseases.
The most representative areas are onco-hematology (41 therapies), oncology (26 therapies) and ophthalmology (17 therapies).

The spending forecasts for the five-year period 2023-2027, based on two different models (one with 100% price consideration, one at 50% in anticipation of discounts and other variability) are those shown in the table.

2023	2024	2025	2026	2027
263.713.859	754.756.229	1.681.445.305	1.591.182.299	1.810.038.683
131.856.929	377.378.115	840.722.653	795.591.149	905.019.342

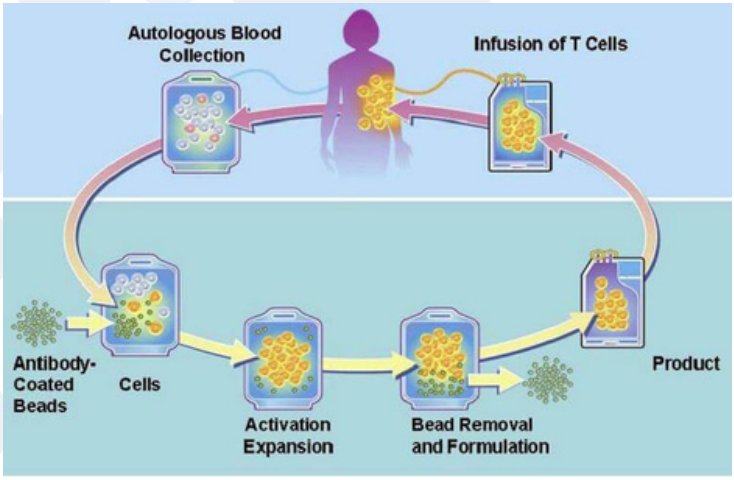
There are also focal points to pay attention to for the authors of the ATMP* Report

- the early availability of therapies through the implementation of early access programs to avoid the risk of losing eligibility of patients who in fact already constitute part of the target population
- the financial sustainability of therapies, to ensure that spending is not the limiting factor for patients' access to care.
- the organizational evolution of the centres, networks and patient care pathways to accommodate and make operational and efficient the new availability of care that science has made available.

*ATMP Forum, V Report Italiano sulle Advanced Therapy Medicinal Product

The specificity of CAR-Ts

In this context, it is appropriate to delve deeper into CAR-T therapies, i.e. the latest generation immunotherapy drugs, which, unlike other advanced therapies, have a different access model, in which payment at results is introduced for the first time, i.e. payment is conditional on obtaining the expected patient outcome. In other words, the NHS is required to pay for the drug only if the expected therapeutic result is observed. With this mechanism, the National Health System is protected, offering the possibility of deferring payment, remunerating only patients who actually benefit from the therapy. Once the price and payment method have been determined, the next step is implemented by the Regions, which, following the parameters set by AIFA, indicate the centers suitable for prescribing CAR-T therapies. According to the latest data collected, the prescribing centers identified by the regions for CAR-Ts reimbursed in Italy are 43 in total: in 5 Regions, however, the prescribing centers have not yet been identified. The regional strategy for identifying prescribing centers has also been diversified: some Regions have in fact chosen to define multiple prescribing centers (13 in Lombardy alone and 6 in Campania), while others, however, have preferred to indicate a single regional centre. Furthermore, not all the prescribing centers identified by the Regions have already been qualified by the companies holding marketing authorizations, through the verification of parameters established by the companies themselves, with consequent uneven opportunities for access to therapy for people with rare diseases.



*ATMP Forum, Report Italiano sulle Advanced Therapy Medicinal Product

The participants in the work of the Tables

The participants at the tables were chosen for their expertise on the topics covered, trying to give a global representation of the main system stakeholders, from European to Italian institutions to the pharmaceutical industry.

Simona Aliprandi - Pipeline Partner, Roche Anna Ambrosini - AriSLA Delegate Giacomo Baruchello - Vice President and General Manager Region Europe South · Blueprint Medicines Simona Bellagambi - EURORDIS Delegate, UNIAMO Foreign Representative Barbara Bonamassa - Committee for Advanced Therapies (CAT) alternate member Italian Medicines Agency (AIFA) - Innovation and Pharmaceutical Strategy Division (Former European Assessment Unit) Simone Boselli - Public Affairs Director - EURORDIS Rare Diseases Europe Loris Brunetta - President of the Thalassemici Liguri Association Agnese Cangini - Health economist - Member of the Executive Board at EunetHTA - AIFA Francesca Caprari - Market Access Alexion, AstraZeneca Rare Disease Rita Cataldo - Delegate ASSOBIOTEC FEDERCHIMICA Americo Cicchetti - Director of the High School of Economics and Management of Health Systems Maria Elena Congiu - MinSal - DG Health Planning Chiara Cordova - Conference of Regional Councils Filippo Cristoferi - Chief of Staff & External Affair AIP Erica Daina - Coordination of Rare Diseases Lombardy Region Francesco De Lorenzo - President F.A.V.O.
Giulia Di Blasio - Public Affairs Specialist - Rare diseases · Sanofi Paola Facchin - Coordinator of the interregional technical table on Rare Diseases Michela Gabaldo - Head Alliance Management & Regulatory Affairs - Telethon Foundation Nicola Gianfelice - General Manager Italy & Greece · Amryt Pharma Vincenzo Giustozzi - Market Access Lead - Medac Farma

Angela Ianaro - Member of the XII Social Affairs Commission Tommasina Iorno - Delegate of the Giambrone Foundation Roberta Joppi - Regional Technical Commission on Medicines, Pharmaceutical-Prosthetics-Medical Devices Directorate, Veneto Region Yllka Kodra - Medical Director - Office 5 - Essential levels of assistance, territorial assistance and socio-health - DG Health Planning - Ministry of Health Elena Paola Lanati - Director ATMP Forum Beppe Lanzillotta - Director Government Affairs Italy & International Government Affairs and Policy at Alexion Pharmaceuticals Giovanni Leonardi - General Director Innovation and Research in Health - Ministry of Health Armando Magrelli - Vice Chair Committee for Orphan Drugs (COMP). European Medicines Agency, London Cristiana Marchese - ASS Delegate. RETINA Marco Marchetti - Director of the Health Technology Assessment Operational Unit, National Agency for Health Services Sarah Marktel - Hematologist at San Raffaele Hospital Massimo Marra - President of CIDP Italy Antonio Medica - Director of the Military Chemical Pharmaceutical Plant Francesco Saverio Mennini - President of the Italian Society of Health Technology Assessment Cristiano Niccolini - Support Secretariat - Pre-Authorisation Area - AIFA Immacolata Pagano - Manager of healthcare professionals - Pre-Authorisation Area - AIFA Anita Pallara - President of SMA FAMILIES Riccardo Palmisano - President of Assobiotec Federchimica Francesca Pasinelli - General Director - Telethon Foundation Sandra Petraglia - Manager Pre-Authorization Area - AIFA Paolo Pietrangelo - Conference of Regional Councils Lara Pippo - Head of Market Access & Government Affairs - CSL Behring Cesare Pisacane - Regional Access Manager - CSL Behring Michela Policella - Member of the Board - ASAMSI Elena Pompeo - Patient Partnership Manager, Medical Affairs and Clinical Operations Department · Roche Italia Concetta Quintarelli European Medicines Agency (EMA). Scientific Committee members and experts Angelo Ricci - FIAGOP President Zeno Righetti - Product Manager - Roche

Antonella Ronchi - Associate Professor - University of Milan-Bicocca, Dept. of Biotechnology and Biosciences Anna Chiara Rossi - VP& General Manager Italy · Alexion, AstraZeneca Rare Disease, delegate Assobiotec Federchimica Massimo Scaccabarozzi - President Farmindustria Annalisa Scopinaro - President UNIAMO Giovanna Scroccaro - President of the Prices and Reimbursement Committee, AIFA Rossana Sovani - Head of Legal Public Affairs · LS CUBE Law Firm, VYTA delegate Luisa Strani - Patient Advocacy Lead Alexion, AstraZeneca Rare Disease

Points for reflection

Equal accessibility of ATMPs

- EMA has a centralized authorization that refers to the individual States for the definition of Price & Refund. This leads to differences in approval times and therefore actual availability for patients in various countries.

- To accelerate these processes, some avenues could be explored and evaluated:

1. joint negotiation and joint procurement for ATMPs with respect to which a possible critical element could be determined by the heterogeneity of the different national healthcare systems of the EU countries.
2. the possibility of directly accessing a European Fund for ATMPs at least in the case of treatments for very small numbers of the patient population (ultra-rare diseases).

- At an Italian level, the subsequent passage in the Regional handbooks must also be considered and resolved, which involves further waiting times.

Recognition of the economic value of advanced therapies - system analysis

Value analysis - Joint assessment.

The role played by national regulatory agencies in evaluating efficacy and safety will be carried out at European level.
At a national level we will have to evaluate

- organizational impacts
- the economic implications
- the social implications,
- the ethical aspects
- equity issues on drugs and medical devices

Investments in building these skills are needed now.

the European HTA Regulation will come into force in 2030 and the skills of citizens/patients will also have to grow.

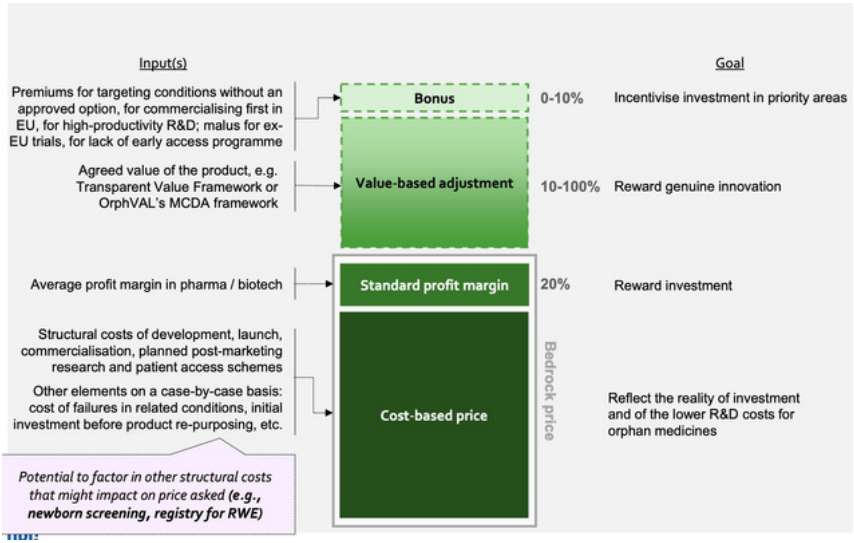
Recognition of the economic value of advanced therapies - possible improvements

It would be appropriate **to implement evaluation systems, including evidence of cost-effectiveness, which reflect the real benefits and also the costs avoided in the long term**, also through the valorisation of the various information sources available.
Identify possible modifications to facilitate the recognition of an innovative drug for ATMPs.

New contracting models are necessary (e.g. **payment at results**, **by result** or other "dynamic" remuneration systems based on the number of patients treated and the actual clinical results obtained over time) which, through adequate forms of risk-sharing, allow the therapy to arrive to people with rare diseases while ensuring the overall stability of the system in terms of sustainability. Also in this case, a possible differentiation based on the type of therapy (gene, cellular, tissue, combined) must be evaluated.

A further effort is necessary in terms of verifying and improving the efficiency of pharmaceutical spending both with respect to prescriptive appropriateness and the possibilities of using generic and biosimilar drugs also in rare diseases to address the high costs of ATMPs, **which are not limited to the cost development but also to home support therapies which must be taken into account.** In this regard, it is also useful to remember that **the cost of ATMP does not only lie in the cost of the therapy, but also in the definition of the infrastructure and organizational processes necessary for its correct administration, as well as in the hospitalization costs.**

At a European level, the model that patient representatives are developing includes two fundamental elements: the cost of developing therapies and the recognition of added value under certain conditions.
However, the starting point must be a transparent explanation of the cost incurred, an essential basis for calculating everything else.
Furthermore, we expect the strengthening of the European network on RWE with the birth of a single model that could help mitigate evidentiary uncertainty at the time of the launch of a new drug, allowing timely access to the patient while new data are collected (currently also for surrogate endpoints, each Agency of each Member State evaluates endpoints differently during the HTA).



Recognition of the economic value of advanced therapies - critical issues and possible improvements - further ideas

The Scientific Technical Commission sometimes receives small and poor quality studies. An interlocutory judgment is possible, but not with certain data. The caseload is low but often the study designs are also poor.
Furthermore:

- orphan drugs: we often see new formulations of an old product; with a high price increase request
- very high cost in general

Compared to the price request:

- there are no cost/effectiveness or pharmaco-economic studies
- there are no research cost statements

If an agreement on the price is not reached, the drug is placed in band C, the regions can buy them but with extra-Lea funds.

Suggestions:

1. The level of quality of the evidence (clinical study) must be improved to demonstrate the added value. The dossiers should be more complete (the HTA regulation already approved at European level provides support on this point)
2. Cost/effectiveness studies must also be submitted in the dossier
3. Furthermore, in subsequent times they must be implemented with observational studies and real world evidence.
4. Generation: the competitiveness that leads to discounts. Once the patent expires, costs should hopefully drop.

Evidence generation

There is a need to have certain data to understand the real impact of the therapy, today there is a problem generated by incomplete data due to the few cases treated (and for the ultrarare it cannot be otherwise). In the coming years, the clinical evaluation of HTA will involve the patient or his representatives.

- It would be appropriate to identify useful recommendations to align standards for generating evidence on ATMP.
- Improve transparency and interoperability to optimize data in small registries
- The European Commission has given funding to ERNs for disease registries but these do not have legal entities. We should think about how the data collected serves to make decisions at EU level.
- Identify specifically what you intend to measure. The data sources are of two types: the real world and clinical cases. Both should be used in the overall design.
- Structure the role of the PCMR representative and the Associations as co-creators of solutions and as data providers.
- Empowerment of the patient and representative of the PCMR is necessary in the generation and evaluation of evidence therefore from the early stages of the development of the therapy in the PROMs (Patient reported outcomes measures) but also RWE (Real World Evidence) collected with the new wearable devices

Identification of reference centers for ATMPs

The ATMP centers have been identified; it is necessary to monitor the maintenance of the necessary requirements (e.g. infrastructure) and implement the number if necessary.

- It would be appropriate to identify new reference models such as the creation of a homogeneous network dedicated to advanced therapies (e.g. on the model of the National Transplant Network) for large areas of the population (the number is to be defined according to the request - number of patients - and of complexity). The network should not be structured by pathology or groups of pathologies (like ERNs) but would potentially serve multiple ERNs.

- It would be appropriate to provide solutions to support travel, food and accommodation costs for families in the event of access to advanced therapies in regions other than their own of residence.

- Given the high concentration of ATMP centers in the north, it would be appropriate to support the growth of other centers in order to make their spread more homogeneous across the national territory

Some points discussed during the meetings for the European Orphan Drug Regulation, relating to access to therapies*

- Use and access to the AIFA 5% fund: it was highlighted that there are some critical issues related to the transparency of its use and management of nominal requests, aspects which AIFA is already monitoring with a view to greater clarity and simplification.

- Need for better harmonization and in some cases revision, at Italian level, of early access methods: 5% fund, Law 648/96, compassionate use and open label extension studies. It is underlined that some obstacles are of a bureaucratic nature.

- It would be important to strengthen the monitoring conducted by AIFA with horizon scanning, thus anticipating the structural needs that will become essential once the therapy is approved or to identify the most promising drugs that can gain early access. We need data collection systems, specialized personnel and equitable distribution across the territory. Adequate planning is required.

- In order to guarantee the homogeneous accessibility of the drug to all people with rare diseases on the national territory, it is necessary to monitor so that the times of inclusion in the regional handbooks after AIFA approval are as homogeneous as possible.

- During the discussion, the topic of infrastructures serving the trials and administration of therapies was also raised. The issue of infrastructural needs, despite being more of a domestic concern than a community one, is nevertheless an important issue, in light of the constant budget limitations on the current expenditure front. In fact, there are important items in the state budget intended for healthcare construction and technological updating which should be allocated with respect to the needs of transformation of the patient's diagnostic-therapeutic and healthcare path, especially if as a consequence of "paradigm changes" deriving from advancement of therapies and diagnostic techniques.

*(see Ephemeris n. 1 for the participants at the table)

- With respect to ultra-rare pathologies and the need for equal access in all countries, the proposal from a few years ago by Nordic countries* was explored regarding the possibility of activating European funds which, once the registration procedure is closed, immediately make available for all European patients receive new drugs at an established and fixed price, then leaving individual national HTAs with a year or two to close the price/reimbursement process to guarantee fair access to the therapy. This proposal has received various consensus, despite the difficulty in actually putting it into practice.

- Again with respect to ultra-rare diseases and closely linked to the above, a further hypothesis was to leverage the application of cross-border law, to therefore move patients to the center or few centers of excellence truly capable of administering the therapy. If there are no doctors capable of providing the treatment, a contract for all 27 states could be redundant.

- At the same time, however, some points must be kept in mind that need to be evaluated: the patient's condition, which does not always allow for movement; costs associated with travel, especially if there are no refunds in the country of origin; the travel commitment, often borne by the caregivers.

- The COVID experience has shown that some procedures can be optimized and accelerated, in emergency conditions (which could be true for many rare diseases). Using tools such as rolling review, rapid scientific advice as well as the creation of objective task forces could guarantee a faster registration and access process.

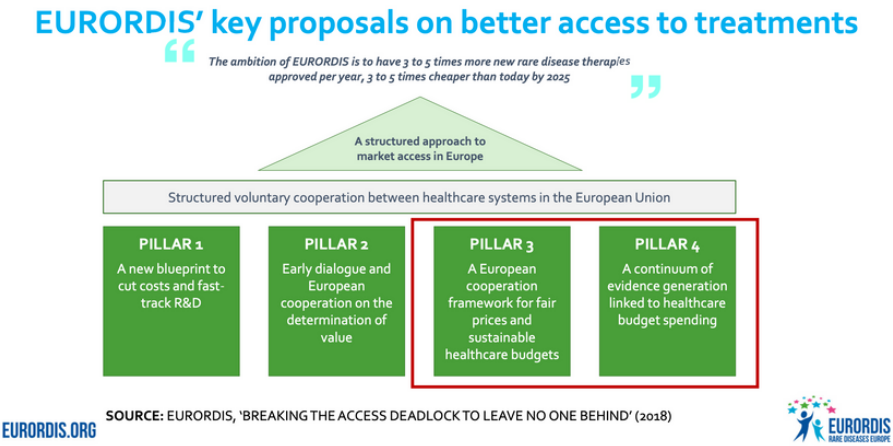
*(see http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/12/WC500218602.pdf)

- Compassionate use, currently limited to some states with very different legislation, could be managed at the EMA advice level, promoting early access to the drug before actual centralized registration.

- It is necessary to outline precise areas of collaboration between countries, aiming at the simplification and de-bureaucratization of existing processes and the benefit of which is the prerogative of all European countries. The proposal of adaptive licensing is brought to the table, a new, already tested approach to drug approval, in order to speed up times and adapt current rules to make effective drugs more quickly available to patients who can benefit from them. Adaptive licensing consists of the early authorization of a medicine in a limited patient population and continues with a series of phases of gathering real-world evidence and adapting the marketing authorization to broaden access to the medicine to larger patient populations.

- The example of the Joint Procurement Agreement experimented during the Covid-19 pandemic for vaccines and monoclonal antibodies was given. Some have highlighted that it could easily be applied to drugs for rare and ultra-rare diseases. On the other hand, it was observed that if the idea of structuring a centralized HTA were to come to fruition, it would be superfluous.

Eurordis' key proposals on access to treatments



Eurordis' proposals, developed during a series of working groups in 2018, aim at fairer access to treatments that will lead to more and more people being able to access them.

The perspective is clearly the European one, correlated to the table based on IQVIA data on page 4.
Based on 100 approved treatments, no country ensures full availability of all. Germany, which is the country with the highest number of available therapies, still has a residual 5% of unavailability.

The Blubird Bio and Orchard "cases".

In the summer of 2021, **the Bluebird Bio company** decided to withdraw its gene therapies for beta thalassemia and adrenoleukodystrophy from the European market, despite both having been approved by the European Medicines Agency (EMA): the basis of the company's decision company, the lack of agreement with the paying bodies of various European countries on the price and reimbursement methods of these therapies.
Subsequently, on March 30, 2022, the **Orchard Therapeutics (OTL)** company announced its intention **to disinvest** from the field of gene therapy of **primitive immunodeficiencies**, rare genetic diseases that compromise the development of the immune system from birth: paying the price , among other programs, also **Strimvelis**, gene therapy for the treatment of **Ada-Scid**, a disease which otherwise can lead to death already in childhood. Born in the laboratories of the San Raffaele-Telethon Institute for Gene Therapy in Milan, this gene therapy was made available on the market in 2016 by GlaxoSmithKline (which sold the license to OTL in 2018): **it is the first drug approved in the world of ex vivo gene therapy** (which involves gene correction outside the organism), and to date **has made it possible to treat over 40 children from all over the world** who are unable to access the only other possible treatment, stem cell transplant, due to lack of a compatible donor.

These two cases are emblematic of a more general situation, which will require a joint commitment from all stakeholders so that advanced therapies can truly continue to represent a possibility of cure even for people with very rare diseases.

In the meantime, Telethon got involved on Strimvelis. This is the statement from Francesca Pasinelli, General Director of the Telethon Foundation: «We have therefore decided to take over the marketing of gene therapy for Ada-Scid from Orchard Therapeutics, taking on all the management and maintenance costs on the market. These costs are the same as those required to keep much more profitable drugs on the market, including over-the-counter ones: but when it comes to therapies for ultra-rare diseases, which perhaps are only administered to one patient per year, even just the impact of tariffs imposed by regulatory bodies is very high. We are therefore asking from now on for support from Italian and European institutions to help us keep available a drug which is not only the result of excellent Italian research supported by donors, but which represents the only possibility of a future for children with a very serious illness. The fact that it is a very rare disease does not justify that such an effective drug is not made available."

UNIAMO Italian Federation of Rare Diseases

UNIAMO Italian Federation of Rare Diseases is the body representing the community of people with rare diseases.

It has been operating since 1999 for the protection and defense of the rights of people with rare diseases and their families, and has over 160 affiliated associations which are constantly growing.

Develop a constant dialogue with representatives of the institutions (Ministries, AIFA, Istituto Superiore di Sanità, Agenas, Regions, clinical reference centres, ERN network, GPs and PLS, scientific societies, etc.), researchers, private players representing the requests of people with rare disease and possible solutions.

It gives a voice to all the people who find themselves affected by a rare or ultra-rare disease, as well as those who are still looking for a diagnosis.

The sense of disorientation, uncertainty, loneliness, the pain felt when receiving a diagnosis of a rare disease are alleviated by the awareness that the Federation, together with all the Associations, makes every possible effort to improve the quality of life of the person and their his family members and caregivers.

Concrete support is given with the SAIO service (listening, information and orientation service) - aimed at individuals and associations -, with other support projects and with awareness-raising, promotion and protection of rights, advocacy in all the sectors, from research to bioethics, from health approaches to social supports.

You can support our action in many ways:

- making your professionalism available
- offering us pro-bono services
- with your 5x1000 (tax code 92067090495)
- with a deductible/deductible contribution in the tax return:
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The Ephemèrides of UNIAMO

The idea of a Uniamo editorial series is not new. However, a series of conditions had to be met for it to become reality.
In the search for a name that would characterize our publications we came across "effemèride".
The Treccani dictionary reports the following definition:

effemèride (or efemèride) s. f. [from lat. ephemĕris -ĭdis, gr. ἐφημερίς -ίδος «diary», comp. of ἐπί «above» and ἡμέρα «day»]. –
1. a. Anticam., the books in which the king's actions were recorded were called ephemerides, first day by day (hence the name), then according to a broader chronological scheme. b. In full, diary, daily chronicle of events: but what more do I spend in giving you an e. of my life? (D. Bartoli).
2. In more recent times, the term has been used as the title of periodical publications, especially of a literary or scientific nature (never of political newspapers); for example, the literary Ephemerides, which were printed in Rome from 1772 to 1795 and contained reviews of new books; the scientific and literary Ephemerides for Sicily, which were published from 1832 to 1840.
3. Table or group of numerical tables, called e. astronomical (or even nautical, as they mainly serve the needs of navigation), which provide the coordinates of the stars (or other astronomical data variable over time) at pre-established and equal intervals, for example. from day to day or from hour to hour. By extension, also the books, generally published annually, which contain such collections.

Each of the three definitions contains an element that we felt close to us: the daily recording of documents, which reminds us of an ideal journey into pathology; the periodic publication, which responds to our wishes; the table that provides the coordinates, our aspiration and intent in the publication of these brochures.

The relative rarity of the use of this term, its feminine connotation, its originality given that the last person who used it dates back to 1840 for literary or scientific publications further convinced us that we were made for each other for the other: Federation and effemèride, community of people with rare diseases and periodic publication that recounts a journey and tries to guide its route.

Here is therefore the beginning of a series that will follow the federation's activity by giving an account of the meetings and working groups set up on specific topics, and the fruit of their work.

Ad maiora semper.

The Board of Directors

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Rari, mai soli

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