Universitat Autònoma de Barcelona

Estudi de caracterització del disseny d'assajos clínics realitzats amb medicaments orfes

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Memòria presentada per Juan Manuel Fontanet Sacristán

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Barcelona, June 2017

If you want to build a ship, don't drum up the men to gather wood, divide the work and give orders. Instead, teach them to yearn for the vast and endless sea.

Antoine de Saint-Exupery

1. SUMMARY

Background: Research and development of new orphan medicinal products has been limited because of lack of knowledge on the diseases, anticipated lack of return of investment in absence of incentives, and lack of methodologies to deal with small populations. Ten years after the European Orphan Drug Regulation the number of medicines for orphan diseases has increased significantly. The analysis of the type of scientific evidence and clinical trials conducted to support the marketing authorisation of orphan medicines in Europe will allow to analyse if alternative methodologies aimed to increase efficiency of clinical studies in small populations are applied, to have a reference to explore the applicability of such methodologies, and to compare the current methods used to conduct clinical trials in the rare diseases field versus the alternative methods proposed.

Objective: To analyse the characteristics of the main clinical trials conducted with the orphan drugs authorised in Europe since the European regulation on orphan medicinal products entered in force in year 2000, in order to explore if there is room for application of alternative methodologies in the conduction of clinical trials.

Methods: A review of administrative, pharmacological, regulatory and clinical data for the first 100 orphan medicinal products approved in Europe since the entry into force of the specific European regulation (ER 141/2000) to December 2014 has been conducted and systematized.

Results: Since the European regulation on orphan medicinal products entered in force in year 2000 and up to December 2014, 100 orphan medicinal products have been approved for 125 indications in Europe covering 84 different diseases. Oncology is the area with higher number of orphan medicines authorised. Alternative methodological designs are seldom used. Overall, data suggest that the current methodological robustness of the evidence supporting approval of indications for orphan medicinal products is generally low. The rareness degree and the type of conditions influenced the characteristics of clinical trials conducted.

Conclusions: The characteristics of the main clinical trials conducted with the orphan drugs authorised in Europe since the European regulation on orphan medicinal products entered in force in year 2000 suggest that there is room to explore the application of alternative methodologies in the conduction of clinical trials in rare diseases.

2. ACKNOWLEDGEMENTS

Als meus directors de tesi, la Cari i el Pep, els mestres i companys de qui més he aprés.

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4. INTRODUCTION

4.1. Orphan medicinal products and rare diseases

Orphan drugs are all those medicinal products aimed to diagnosis, prevention or treatment of rare diseases. In the European Union, rare diseases are the medical conditions which have a prevalence figure of not more than 5 cases per 10,000 inhabitants(1).

This prevalence figure is arbitrary and established to determine the threshold below which the market conditions are no longer conventional and special needs are displayed for drug development. In this sense, regulations approved in other geographical and legislative areas could show differences in the prevalence threshold that defines what a rare disease is(2).

In order to envision and put into perspective the magnitude of a rare disease, in the European Union (EU 28), Norway, Iceland and Liechtenstein where 515,700,000 inhabitants are settled down(3), the maximum number of patients affected by a particular rare disease would be 257,850.

Nonetheless, the estimated overall numbers of existing rare diseases range from 6,000 to 8,000 different diseases(4,5). In this way, despite the fact that the number of patients affected by a particular rare disease is sparse, the global number of patients affected by rare diseases is very significative. Thus, approximately around 27 – 36 milions of people living in Europe are affected by a rare disease(5,6).

Rare diseases are a heterogeneous group of medical conditions that potentially could affect any organ or anatomic system of the human body, and they could appear at any age. Despite this fact, a high proportion of rare diseases appear in paediatric populations because frequently they have a genetic origin, usually congenital. This pattern of inheritance causes that many of them begin at early stages of life and lead to premature mortality, shortened life expectancies or affect severely the quality of life of vulnerable populations (7).

Moreover, rare diseases are commonly life-threatening or chronically debilitating conditions, they decrease the quality of life and performance status of patients affected, and generally cause long-term disabilities and dependence. This fact conditions that not only the patient affected by the disease, but also the whole family and environment is concerned and involved in management and patient care(8).

Rare diseases require a multidisciplinary approach to their management, because of their wide range of needs: genetic diagnosis, pharmacological treatment, surgical interventions, nutritional support, physical rehabilitation, specific learning and pedagogic strategies, psychological help and social assistance, could all be required in order to achieve the best healt state possible(9).

On the other hand, rare diseases have been invisible for society and unknown for health professionals for many years, due to the low number of patients who suffer each particular disease. Fortunately, in last years, rare diseases have become an important issue for health systems and have been included on the political agenda to improve quality of life of people affected and their families(10,11).

4.2. Peculiarities of orphan drug development

Generally, the drug development process is a complex procedure, long, risky and economically expensive.

Before reaching the market, a drug must overcome different stages which include drug discovery, preclinical development, different clinical phases (phase I, phase II and phase III) and, finally, the submission of a marketing authorisation application (MAA) to the regulatory agencies.

In these stages the sponsor carries out the complete characterisation of the properties of the molecule, and qualifies the efficacy and safety in a specific diseased population which will become the intended therapeutic indication of the drug.

After the approval, additional stages have to be addressed by the companies holding the marketing authorisation. These include pharmacovigilance studies and continuous safety surveillance, as well as therapeutic positioning studies required for better

documentation of the actual product benefits and value, among others. All these studies are conducted after a medicinal product have been already launched to the market(12).

The whole process to complete the discovery and development process could last an average of 12-13 years. A big capital investment is needed and only a few projects finally succeed(13). The process is characterised by high investment requirements and high risk of failure, both before reaching the market and even after the marketing approval.

Drug discovery	Preclinical development	Clinical development			Regulatory & Pricing	Market
		Phase I	Phase II	Phase III		Phase IV
Target selection Hit to lead Lead optimization Lab synthesis Profiling	P.kinetics P.dynamics Short term toxicology Formulation Pilot synthesis	Clinical pharmacol P.kinetics Tolerability Safety in 10-100 healthy volunteers	Exploratory activity Dose finding in 100 to 1000 patients Long term toxicology	Confirmatory efficacy Exposure >1500 patients Safety Risk/benefit	Submission of application Dossier review Authorization Pricing & reimbursement	Pragmatic trials Safety surveillance Observational studies Therapeutic positioning
2-5 years	1.5 years	5-7 years			1-2 years	decades
100 projects	20 compounds	10	5	2	1.2	1

Figure 1. The phases of drug discovery and development process.

Modified from Rang and Dale. 6th Edition.

After the marketing authorisation by regulatory agencies which determine the quality, efficacy and safety of products to conclude on favourable benefit/risk balance, a necessary step is the assignement of price, which is also regulated, and decisions on reimbursement by public health systems. Health Technology Assessment (HTA) agencies are generally involved in such decisions, through an evaluation of medicines that takes into account additional factors to those considered by regulators. These include factors such as the clinical added value compared with current treatments available, budgetary impact and pharmacoeconomic analysis of value, or the affordability for the national health system concerned. From this evaluation, an appraisal suggesting drug therapeutic positioning and prioritization, as well as the proposed access system and funding of the treatment is released.

From a general perspective, the drug discovery and development process is very burdensome, risky and expensive for all types of products, but the development for orphan medicinal products is even more difficult and challenging because of the low prevalence and type of diseases, that determine many additional hurdles that sponsors must overcome in order to complete the process in a successful way(5,14).

A listing of additional obstacles that hamper the development of new medicines aimed to treat rare disease could include the following:

- Scarce knowledge about the physiopathology of the disease, that reduces the identification of possible drug targets and difficults the design of clinical trials, in particular regarding the choice of the primary objective, inclusion/exclusion criteria, selection of relevant endpoints, or trial duration, among others.
- Lack or shortage of preclinical models. This paucity hinders the conduction of predictive preclinical studies and, consequently, increases the uncertainties at the time of decision to advance to the clinical phases of drug development.
- Absence or paucity of clinical experts or reference hospitals. Physicians with a high degree of expertise are not always available for some rare diseases and, as a consecuence; a lower number of investigators can be involved in clinical trials design and recruitment.
- Scarcity of patient registries. Registries have been proposed as a useful tool to build up the knowledge about the natural history and clinical course of rare diseases, through collection of the data obtained from patients affected. Moreover, a registry of a specific disease could potentially help to identify possible candidates to be enrolled in a clinical trial, as long as the legal requirements are fulfilled.
- Geographical dispersion. The dispersion of patients across the different regions or countries difficults the conduction of clinical trials from an operational point of view.
- Underdiagnosis. The lower knowledge and number of experts for some rare diseases cause underdiagnosis or severe delays to get the right diagnosis, thus

difficulting proper and timely management and patient access to treatments, but also reducing availability of patients for participation in clinical trials.

- Heterogeneity of patients within the same rare condition. The frequent lack of knowledge about the phenotype-genotype relation, or the different clinical expression of the conditions across patients with the same rare disease may increase the methodological complexity of clinical trials.
- Adequate use of comparators. Very often there are no alternative treatments authorised for a given condition suitable to be used as active comparators, but also patients may be reluctant to the use of placebo because of their bias towards action and willingness to face the risk of any innovation, or placebo use may result ethically conflictive due to the vulnerability of the patients, the severity of diseases treated and the fact that often the diseases are paediatric and decisions to participate are surrogate.
- Difficulty on the selection of clinically relevant endpoints. The lack of knowledge about the disease, lack of previous reference data on clinical parameters and variables, the fact that often conditions have an slow progressive course that may be heterogeneous across patients, and reluctances to use proper controls and/or to the conduction of prolonged studies derive in the use of surrogate and non-validated endpoints, that make difficult the interpretation of the outcomes in terms of clinical relevance.
- Reduced sample size. The low number of patients affected by a particular rare disease causes a lower sample size included in clinical trials and, therefore, increases the difficulties to obtain statistically significant results, especially if the magnitude of the effect is modest.
- Small market size. Low number of patients affected also supposes a reduced market size for an orphan medicinal product. As mentioned before, in the European Union, the maximum market size for a particular rare disease would be 257,850 patients to be treated.

As observed, the nature of rare diseases leads to additional difficulties on the drug development process which an orphan drug will have to overcome in order to obtain the marketing authorisation and, afterwards, that patients affected could access to these orphan medicines(15,16).

4.3. Why a specific regulation about orphan medicinal products?

During decades the orphan medicinal product development was seriously forgotten by the pharmaceutical companies, because the huge efforts required to carry out the whole development process and the low number of patients susceptible to be treated after the approval made the investment on rare diseases non-profitable.

Proof of this fact is that, before the year 2000, very few medicines were authorised to treat rare diseases in Europe (only 8 orphan drugs were approved prior to 2000)(17). Contrarily, a large number of medicines were approved yearly for conventional diseases.

This historical deficit in research about orphan drugs and consequently, the limited number of medicines developed and authorised aimed to treat rare diseases is driven by a main point, as described in the introduction to the European regulation on orphan medicinal products(1), *"some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions; these medicinal products are called 'orphan'".*

But, despite this fact, the European regulation on orphan medicinal products (1) also states that *"patients suffering from rare conditions should be entitled to the same quality of treatment as other patients*".

In this scenario, special measures were needed to stimulate the interest on research and development of orphan medicines by the pharmaceutical companies. Inspired by the previous positive experience in the United States of America, where the FDA

approved in 1983 the Orphan Drug Act (18) that resulted in an increase in the availability of orphan drugs (19,20), an specific regulation on orphan medicinal products was created and entered into force in the European Union in year 2000 (1,21).

4.4. The legal framework of orphan medicinal products

The goals of the European regulation on orphan medicinal products (1) included to give incentives to companies in order to adapt the "conventional" market conditions for medicines aimed to treat rare diseases. Such measures should pave the way and help sponsors to overcome the hurdles of orphan drug development process, so that the balance between the investment and efforts required during the development process and the financial return obtained from it would improve, and thus would incentivate the research in the rare disease field.

The first and more important law approved in the European Union which constituted the main milestone in the enhancement of orphan drug development, was the "*Regulation (EC) No 141/2000 of the European Parliament and of the Council*"(1) approved on 16th December 1999 and which was published and entered into force in January 2000 .

This document regulated the following aspects:

- A procedure to obtain the orphan drug designation (ODD).
- Incentives for the development and benefits in marketing conditions for designated orphan medicines.
- Creation of the Committee for Orphan Medicinal Products (COMP) within the European Medicines Agency (EMA).

A subsequent law was approved on April 2000: *"Commision Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority'"*(21), that aimed to

develop and allow the implementation of some articles included in the Regulation 141/2000 (specifically articles 3 and 8). The document assists potential sponsors, the COMP, and competent authorities in the interpretation of Regulation about the following aspects:

- Criteria for designation: prevalence, potential return on investment, description of methods of diagnosis, prevention and treatment, and general provisions.
- Definitions of significant benefit, similar medicinal product and clinical superiority.

The Regulation 847/2000 entered into force in April 28th 2000. After this date the sponsors began to submit the applications to obtain an Orphan Drug Designation (ODD).

These two regulations are the main legislations implemented about orphan medicinal products and constitute the major legal basis regarding the impulse on research and development of medicines for rare diseases in the European Union.

Later legislations have been approved, which have different degrees of implications on the regulation of orphan medicinal products.

- The Regulation (EC) No 726/2004(22) approved on March 2004, established that all the medicinal products designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000 must be authorised mandatory by the centralised proceduce. Decentralised procedures to obtain the marketing authorisation in the European Union are not available to orphan medicinal products. Also, the legal ground for the authorisation under “exceptional circumstances” is also laid down in this Regulation 726/2004.
- The Regulation (EC) No 507/2006(23) was approved on March 2006, and legislated about “conditional marketing authorisation” in order to allow the authorisation of submissions with less complete data to favour the early treatment of patients with unmet medical needs. Missing required data at the moment of granting a “conditional authorisation” should be generated in the postmarketing period in order to keep the authorisation in force.

In this sense, in accordance with this Regulation 507/2006, the human medicines candidates to apply for the "conditional authorisation" are medicines for seriously debilitating diseases or life-threatening diseases, medicines to be used in emergency situations, and medicinal products designated as orphan medicinal products.

- The Regulation (EC) No 1901/2006 (24) approved on December 2006, also known as paediatric regulation, included an extension of the market exclusivity period for orphan medicines which fulfilled the requirements for generation of data regarding their potential use on paediatric population. In this way, the market exclusivity period is enlarged two additional years for orphan medicines submitting data about their use in paediatric populations.
- The Regulation (EC) No 2049/2005 (25) approved on December 2005, established that the Scientific Advice procedure requested by Small and Medium Enterprises (SMEs) for orphan medicinal producted designated by the COMP would be fully free of charge.

All these legislations have entered into force during the last 15 years, and constitute the juridic grounds adopted in the European Union to spur and facilitate the development of orphan medicinal products.

4.4.1. The Committee on Orphan Medicinal Products (COMP)

The Committee on Orphan Medicinal Products (hereafter called COMP), was created in 2000 after the entered into force of the European Regulation 141/2000.

The COMP is one of the scientific committees forming part of the European Medicines Agency which, together with the EMA staff and working parties, lead the scientific work carried out by the EMA.

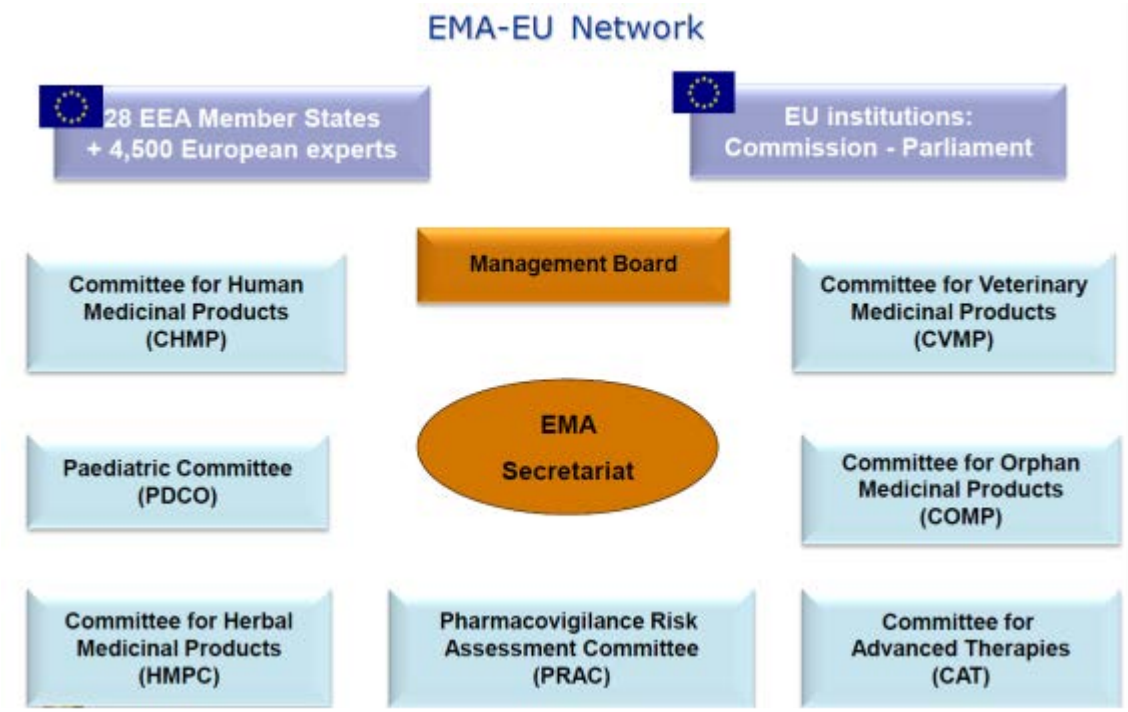


Figure 2. EMA Network.

Modified from slides presented by Nathalie Bere (*How medicines are approved in the EU: role of patients, healthcare professionals and academics*) and available at Eurordis Website(6).

The COMP has several functions according to the regulation. The main and more relevant function is the evaluation of the applications submitted to the EMA in order to obtain an Orphan Drug Designation. Like the other committes of the EMA, the COMP issues opinions about the appropriateness of accepting or denying the concession of the Orphan Drug Designation. Later, the European Comission is the organism who takes the actual decision about the grant of the Orphan Drug Designation, based on COMP recommendations.

In addition, the COMP is also responsible to advice the European Commission about the establishment and development of polices on orphan medicinal products for the European Union, to assist the Commission in liaising internationally on matters related to orphan medicinal products, and in liaising with patient support groups; an finally, to assist the Commission in drawing up detailed guidelines.

The COMP is constituted by one member nominated by each of the 28 European Union Member States, one member nominated by Iceland and Norway (who don't have right

to vote), three members nominated by the European Commission on the Agency's recommendation, and three members representing patients' organisations, also nominated by the European Commission. All members serve on the committee for a renewable three year period and the chair is elected by and from amongst the COMP members.

It is noteworthy that the COMP was the first scientific committee within the EMA where patients' representatives had a role as full members(26). Later, influenced by the positive experience observed in the COMP, patients became part of other scientific committees of the EMA.

4.4.2. Criteria for orphan drug designation

The criteria that a drug must fulfill in order to obtain an orphan drug designation are the following (1):

1. **Rareness / Insufficient return of investment**

   The drug which aims to be designated has to be intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that affects not more than 5 in 10,000 inhabitants in the European Community at the time the application is made ('prevalence criterion') or,

   Alternatively, it has to be intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment ('insufficient return on investment criterion').

2. **Severity of medical conditions**

   The drug must be aimed to treat life-threatening or chronically debilitating conditions.

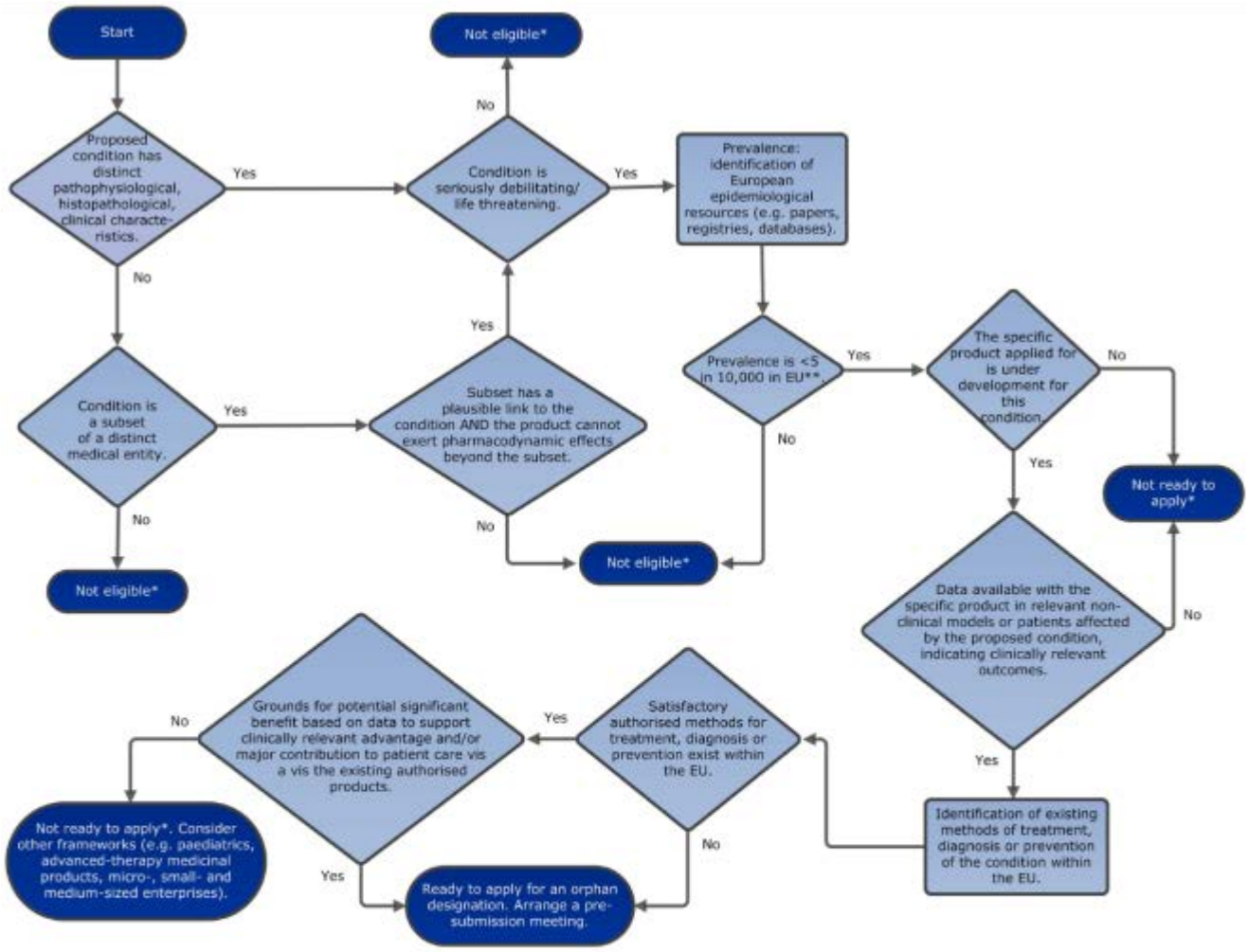
3. **Lack of alternative methods or "significant benefit" versus the existing methods**

There exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the Community ('no satisfactory method criterion') or,

Alternatively, if such a method exists, the medicinal product will be of significant benefit to those affected by that condition ('significant benefit criterion').

In relation with the prevalence of the diseases, it should be taken into account that doing subsets of more prevalent medical conditions to reduce the prevalence figures below the threshold that defines what is a rare disease (this is 5 cases per 10,000 inhabitants), also known as "salami-slicing strategy", is not ordinarily acceptable. Only if the subset has a plausible link to the overall condition and the drug which aims to be designated can not be useful for the whole medical condition, the product would be susceptible to be designated(27).

Regarding the ´significant benefit criterion`, the Regulation 847/2000 (21) defined this concept as a "clinically relevant advantage or a major contribution to patient care". The practical interpretation and further considerations about the fulfilment of the "significant benefit" criteria is carried out by the COMP in a case by case basis.



Disclaimer: The flowchart presented should be interpreted as a tool to guide potential sponsors through the orphan designation eligibility criteria. The flowchart is not used for the assessment of orphan designation, it is non-binding and it does not pre-empt any of the opinions obtained by the Committee for Orphan Medicinal Products.

*Contact the EMA orphan medicines office for more guidance.

**Article 3(1)(a) of Regulation (EC) No 141/2000 provides an alternative criterion to the prevalence number, based on evidence of insufficient return to justify the necessary investment.

Figure 3. Flowchart to check eligibility for Orphan Drug Designation

Obtained from EMA Website (27).

Other characteristics related with the orphan drug designation and its charactersitics that must be considered by sponsor before submit applications include the following:

- Only human medicinal products are elegible to receive the Orphan Drug Designation, unlike what happens in the USA where the FDA also endorsed orphan designations to medical devices.

- No fees are charged to sponsors in relation with the orphan drug designation request, so that the procedure of application for an orphan drug designation is completely free of charge.
- The orphan drug designation can be requested at any stage of drug development, but always before the submission of a marketing authorisation application.
- Scientific evidence must be submitted in order to substantiate the medical plausibility of a designation application for a given product(28). An important proportion of sponsors request the orphan drug designation in early stages of drug development in order to obtain the incentives included in the regulation from the very beginning. Because of this, most of applications are supported by preclinical data only (17).
- The applicant of the orphan drug designation submissions must be any company or individual settled down in the European Community. This fact indicates that there is room for academia, public institutions or researchers to apply in order to obtain an orphan drug designation; designation helps to value their research and facilitates further licensing agreements.
- According to the European legal framework, the COMP only issues scientific opinions. Later, COMP opinions must be ratified by the European Comission. In this sense, the European Comission decisions are the key which gives the right to receive incentives to sponsors.

4.4.3. Procedure

In order to obtain an orphan drug designation, sponsors must submit an application to the EMA following the template available in the EMA website (27).

The template contains the following sections:

A. Description of the condition

B. Prevalence of the condition

C. Potential for return of investment (only applicable in case of medical conditions with prevalences higher than 5 cases per 10,000 inhabitants that apply for orphan drug designation based on the scenario of unlikeliness of sufficient return to justify the necessary investment).

D. Other methods for diagnostic, prevention or treatment of the condition.

E. Description of the stage of development.

F. Bibliography

Additionally, some indications and recommendations are specially addressed to complete some of these sections. In this line, recommendations are available and strongly recommended to follow about how to calculate adequately the prevalence of the medical condition, how to substantiate the medical plausibility of the applications and also how to support the potential significant benefit when alternative methods exist for the condition. Following recommendations increase the chances to obtain the orphan drug designation (27,29–31).

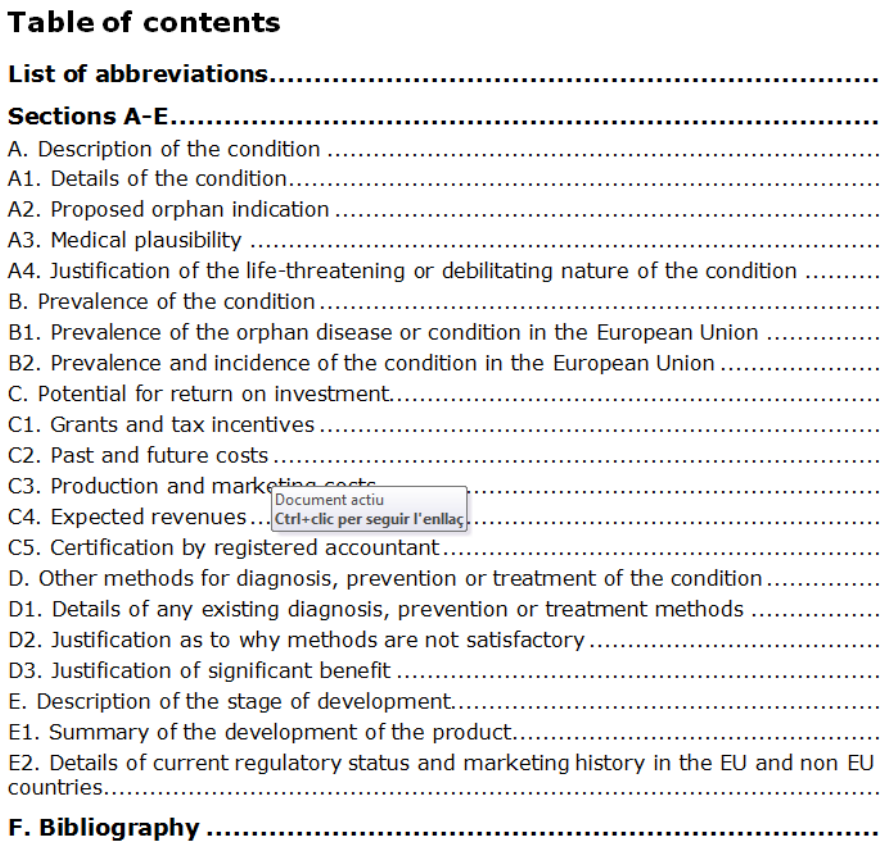


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Figure 4. Sections the application template for orphan drug designation.

Obtained from EMA Website (27)

Applications for orphan drug designations can be submitted directly to the EMA. However, pressubmissions meetings or teleconferences with the EMA staff are also possible, and greatly recommended, because the procedure does not have “clock stops”. In case of lack of any information needed to endorse an orphan drug designation, a negative opinion must be given by the COMP. In presubmission meetings, amendements may be proposed to ensure that the application is thorough and correct.

Two rapporteurs are assigned for each received application: one member of the COMP and one member of the EMA staff. The application is validated for completeness and formal correction, and then a 90 days procedure is started.

The rapporteurs elaborate a summary report which is presented for discussion within a COMP session on day 60. If the COMP reaches an agreement, an opinion is issued. In

case of the COMP needs further information or additional issues must be clarified, a list of questions addressed to the sponsor is prepared and issued to the applicant to be responded in writing, and if required in a discussion meeting. The answers to the list of questions are brough back to the COMP for discussion on the day 90, and a final opinion is given. Finally, the European Comission decides to endorse or not the COMP opinion within the following 30 days.

After an Orphan Drug Designation is given, the EMA publishes this information on its website (27) and the European Commission enters the orphan designation into the Community register of designated orphan medicinal products (32).

As mentioned before, the procedure to obtain the orphan drug designation is completely free of charge.

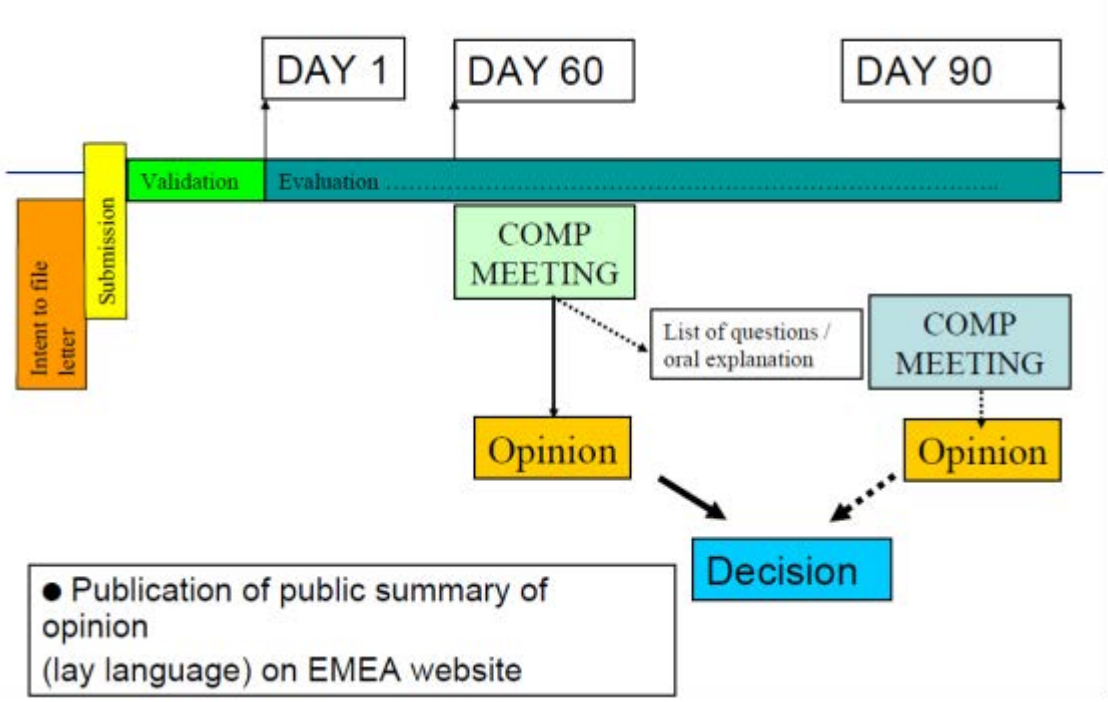


Figure 5. Orphan drug designation procedure followed by the COMP.

Modified from slides presented by Jordi Llinares (*Orphan designation: Key concepts and evaluation criteria*) and obtained from EMA Website(27)

Finally, a relevant action developed in order to reduce the administrative burden for sponsors is that a parallel application process with the FDA is available.

4.4.4. Incentives

One of the cornerstones of the European regulation about orphan drugs is the incentives given to the sponsors that obtain an orphan drug designation. These incentives seek to modify the conventional market rules, in order to facilitate the return of the investment also for the orphan drug development.

Several sort of incentives are available for designated orphan medicinal products(26,27):

- **Scientific advice to the orphan drug development: Protocol Assistance.**

  The Protocol Assistance procedure is a scientific advice specially addressed for orphan drug. Sponsors requesting protocol assistance have fees reductions according to the company size. Furthermore, sponsors can ask for protocol assistance as many times as they need.

  This incentive is aimed to assist the sponsors to overcome the scientific difficulties inherent to the orphan drug development, and also to increase the predictability of regulatory decisions in an area where guidance is scarce and generic only.

  Parallel scientific advice with the FDA is also possible, and strongly recommended for products intending to apply for authorisations to both regulatory bodies.

- **Fee reductions**

  Designated orphan medicinal products can benefit from fee reductions in several procedures of the EMA, such as advice procedures, inspections, marketing authorisation application or annual fees. The percentage of reduction depends of the company size(33).

- **Market exclusivity**

  Designated orphan medicines which are authorised are granted by the European Commision a period of 10 years of market exclusivity. This fact means that no similar medicines for the same indiciation can be authorised during 10 years since the orphan drug approval. This period can be enlarged by two additional years in case that an agreed Paediatric Investigation Plan has been complied(24).

Market exclusivity rule can be broken if a new product demonstrates clinical superiority to the commercialised product (significant benefit), or is being considered as no similar(21).

Market exclusivity can also be lost if the first marketing authorisation holder results unable to provide sufficient quantities of drug to treat all the population affected. Also, exclusivity can be refused by the first marketing authorisation holder to allow the entry of new products in the market.

In summary, the market exclusivity rules avoid commercialisation of new similar medicines which do not contribute to improve the disease management. Likewise, this incentive allows to the sponsors stability and predictability of the market conditions that may allow recovering the investment and made profitable returns.

- **Priority in research programms in the European Union**

The European Comission does not give direct grants or credit to the sponsors. Nonetheless, medicinal products holding an orphan designation have had priority in some research programmes funded by the European Commisison, such as the Seventh Framework Programme or Horizon 2020 Programme.

- **National incentives**

Besides the incentives given at European level, additional incentives could be given by the Member States. These incentives differ among Member States and may include measures such as fee reductions, scientific support or price and reimbursement advantages(34,35).

Fee Reductions for centrally (EU) authorised designated orphan medicinal products

Procedure or service	Fee reduction applicable to	Percentage fee reduction
Protocol assistance, initial and follow-up requests	SME sponsors for all assistance	100%
	Non-SME sponsors for non-paediatric-related assistance	75%
	Non-SME sponsors for paediatric-related assistance[1]	100%
Pre-authorisation inspection	All sponsors	100%
Initial marketing authorisation application	SME sponsors	100%
	Non-SME sponsors	10%
Post-authorisation applications and annual fee, specified in Council Regulation (EC) No 297/95, in the first year from granting of a marketing authorisation	SME sponsors	100%
Pharmacovigilance fees, specified in Regulation (EU) 658/2014[2]	All sponsors	n/a

Table 6. Fee reductions for designated orphan medicinal products.(33)

Obtained from EMA Website (27)

4.4.5. International regulations on orphan medicines

The orphan drug regulation approved in Europe seeks to promote the orphan drug development by helping sponsors to overcome the hurdles found in the rare disease field that are due to the nature of these kind of medical conditions.

In this sense, the definition of rare disease is arbitrary and directly related with the prevalence below which the market size is deemed as insufficient to compensate the financial investment required for drug development. Thus, medicines aimed to treat conditions with a reduced market size need additional incentives in order to become profitable for companies, but also to achieve that patients affected by low prevalence diseases may have therapeutic options to be treated.

The European Union has defined that the threshold of prevalence below which it is estimated that the cost of developing a medicine would not be recovered by the expected sales is 5 cases per 10,000 inhabitants. As a consecuence, all medical

conditions with prevalence not higher than 5 cases per 10,000 inhabitants are considered rare diseases and would be theoretical candidates to apply for an orphan drug designation, and consequently for the associated incentives.

However, the prevalence threshold is somehow arbitrary, and thus prevalence thresholds for orphan conditions in other regulatory environments may differ. The different definitions of rare diseases in other regions are shown in the next table (2):

Region /Country	Orphan drug legislation	Rare disease definition	Prevalence threshold
Europe	Regulation EC No. 141/2000	A life-threatening or chronically debilitating condition affecting no more than 5 in 10,000 persons, in the community; or life-threatening, seriously debilitating or serious chronic condition in European Union and without incentives the Sponsor would develop the medicine; and there are no other satisfactory method of diagnostic, prevention or treatment of the condition	5 / 10,000
United States of America	Orphan Drug Act of January 1983 and amendments	A disease or a condition, which affects fewer than 200,000 patients in the US	Approx. 7.5 / 10,000
Japan	Law 145 – 10 August 1960 (revised in 1993)	A disease that affects fewer than 50,000 patients in Japan	Approx.3.9 / 10,000
Australia	Therapeutic Goods Act in 1989 (revised in 1997)	A disease that affects fewer than 2,000 patients per year	Approx. 1 / 10,000
Singapore	Medicines Act Chapter176, section 9	A life-threatening and severely debilitating illness affecting fewer than 20,000 patients	Approx. 39.4 / 10,000

Table 7. Regulatory definitions of rare diseases in different regions

The European regulation 141/2000 was inspired by the positive results achieved in the US with the Orphan Drug Act approved in 1983, aimed to stimulate the development of medicines for rare diseases by favouring the return of the investment made by the sponsors, and thus was developed following its spirit (19,20,36). However, there are a

number of differences between both regulatons. As an example, the US Orphan Drug Act included incentives for drugs intended for diseases affecting less than 200,000 patients in the USA. Other differences affecting the type of products, scope of the regulation and incentives given are summarized in the table below (2,37):

	Europe	**USA**
Legal basis	Regulation EC 141/2000	Orphan Drug Act (1983)
Responsible Authorities of the orphan designation	Committee for Orphan Medicinal Products (COMP – EMA)	Office of Orphan Products Development (FDA)
Criteria for designation		
Scope of regulation	Medicinal products for human use	Medicinal products for human use. Furthermore, the act also includes medical devices and dietary or diet products
Prevalence threshold	5 per 10,0000	Approx. 7.5 per 10,000
Severity of the disease criteria	Yes. Life-threatening or chronically debilitating nature of the condition	No
Non return on investment criteria	Yes. It is improbable marketing a medicinal product in European Union without incentives	Yes. Lack of economic viability when the prevalence exceeds 200,000 patients
Significant benefit criteria	Yes. No satisfactory method of diagnosis, prevention or treatment exist, or if exist, the new medicinal product will be of significant benefit to the patients	No
Incentives		
Market exclusivity	10 years, plus two additional for medicines complying the agreed paediatric investigation plan (PIP)	7 years
How to break the market exclusivity for similar medicinal products	Clinical superiority, or First MAH are unable to provide sufficient quantities, or Consent of the first MAH	Clinical superiority, or First MAH are unable to provide sufficient quantities, or Consent of the first MAH
Scientific advice (protocol assistance or consultation for development)	Yes	Yes

	Europe	USA
Legal basis	Regulation EC 141/2000	Orphan Drug Act (1983)
Fee reduction for marketing authorisation	Yes	Yes
Marketing authorisation review process	Allows sponsor to apply for accelerate review	Allows sponsor to apply for accelerate review
Grants form regulatory competent authorities	Indirect. Some incentives by Member States and EC-Community Research Programmes	Yes. Direct
Financial incentives	Not direct. Depends of Member States initiatives	50% federal tax credit for clinical research

Table 8. Differences between European and American orphan regulations

4.5. Marketing authorisation of orphan medicinal products in Europe

The regulatory process for orphan medicinal products may start with an Orphan Drug Designation application. As already described, the orphan drug designation application is evaluated by the COMP; the applicant has to demonstrate the medical plausibility for the orphan drug, and, if granted, the designation gives the right to the sponsors to receive some incentives. For this reason, the COMP sometimes has been described as the "gate opener" to the research in the rare disease field. However, the Orphan Drug Designation is not assuring that drugs will be authorised.

4.5.1. Evaluation process

As stated in the European regulation, patients affected by rare diseases deserve medicines which fulfill the same criteria to be approved equally than the medicines aimed to treat conventional diseases(1). In this sense, orphan medicinal products must provide evidences to support the guarantees of quality, efficacy and safety required for accessing the market, and, obviously, they need to show a positive benefit/risk balance, in order to be authorised.

The procedure for assessment of marketing authorisation applications for orphan medicinal products is similar to that of any other medicinal product. Applications are evaluated by the scientific committee within the EMA issuing opinions on acceptability of approval of human medicinal products: the Committee for Human Medicinal Products (CHMP).

The CHMP analyses the dossier and concludes on whether the required requirements for quality, efficacy, safety and positive benefit/risk balance are demonstrated based on solid scientific evidence, and recommends the European Commission to grant or not a marketing authorisation valid across all the European Union for the approved therapeutic indication.

4.5.2. Marketing authorisation under special conditions

When evidences suggest that there are many reasons to allow access to the market for a product, but evidence is yet incomplete, the opinion of the CHMP may recommend some special types of approvals especially designed to deal with clinical uncertainties. These have been frequently used for orphan medicinal products as a consecuence to the difficulties found to generate strong scientific evidence because the nature of rare diseases(27):

- Marketing authorisation under “exceptional circumstances” can be granted when the applicant can demonstrate that comprehensive data on the efficacy and safety under normal conditions of use cannot be provided because of:
    - the indications for which the product is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
    - in the present state of scientific knowledge, comprehensive information cannot be provided, or
    - it would be contrary to generally accepted principles of medical ethics to collect such information.

  The legal basis for this type of authorisation is the Article 14 (8) of the Regulation (EC) No 726/2004 (22), and the relevant documentation for applications in

exceptional circumstances are laid down in Part II of Annex I of Directive 2001/83/EC, as amended.

- A “conditional approval” can be granted to medicines aimed to treat urgent unmet medical needs of patients when a full demonstration of efficacy and safety is not yet available. This special authorisation is given when lower level of evidence is available but the available evidence reasonably suggests that benefits outweight the risks.

  The medicines candidates to be given a conditional authorisation should be:

  - aimed at treating, preventing or diagnosing seriously debilitating or life-threatening diseases;
  - intended for use in emergency situations (also less comprehensive pharmaceutical and non-clinical data may be accepted for such products) or;
  - designated as orphan medicines.

The conditional approval is valid for 1 year, which can be renewed annually conditioned to the fulfilment by the holder of the marketing authorisation of specific obligations and commitments aimed to obtain comprenhensive data confirming the positive benefit/risk balance of the product.

The legal basis of this type of authorisation is included in the Regulation 507/2006(23).

4.5.3. Review of Orphan Drug Designation

An additional issue that should be reminded is that, when a sponsor submits a marketing authorisation application, a review of the orphan drug designation granted previously is conducted by the COMP.

The review of the orphan drug designation is carried out by the COMP in parallel to the evaluation of the marketing authorisation application conducted by the CHMP. In this review, the COMP checks that the criteria to be designated as orphan (rarity, severity and lack of alternatives/significant benefit) are maintained at the time of marketing authorisation. It should be highlighted the importance to mantain the orphan drug

designation at time of marketing authorisation because it is needed to benefit from market exclusivity.

4.5.4. Additional indications

After an initial approval, changes to the terms of a marketing authorisation can be requested through variation application procedures. Additional orphan indications may be incorporated into the product labelling in successive type II variations, by providing application dossiers follow an initial marketing authorisation with additional information on new drug uses including additional studies and information. The applications are assessed in an abbreviated procedure also by the CHMP, who issues recommendations to the European Commission on compliance of approval criteria (38).

However, the European regulation does not allow that orphan medicinal products may be authorised simultaneously for both orphan and non-orphan conditions. Thus, all therapeutic indications included in the labelling of a branded medicinal product must hold the orphan drug designation, in order to maintain the regulatory benefits and incentives for the product.

Any therapeutic indication without orphan designation should be commercialized in a different medicinal product with a different brand name, or, alternatively, for those holding an orphan drug designaton the orphan status will be withdrawn.

4.5.5. Milestones of the European Regulation on orphan medicinal products

From 2000 to February 2017, up to 2,734 Orphan Drug Designation applications have been submitted to the COMP, of whose 1,860 (72%) were granted a positive opinion (39) (Table 9). Thus, up to 1,860 research projects have been developed for rare diseases from 2000 till nowadays; 129 of these projects have later resulted in marketing authorisations for medicinal products in the European Union, as compared to only 8 medicines that had been authorised for orphan diseases in Europe before the regulation about orphan medicinal products was in force. This may be a reflection of

the role of the COMP as a gate opener paving the way for research in rare diseases(17), and of the success of the European regulation to both stimulate research and to increase the availability of orphan medicines as new alternatives intended to treat patients affected by rare diseases (26,37).

Overview for orphan medicinal product designation procedure since 2000

Please also refer to the Community Register of orphan medicinal products for human use.

Year	Applications submitted	Applications discussed in reporting year	Positive COMP opinions	Applications withdrawn[2]	Final negative COMP opinions	EC designations	Orphan medicinal products[3] authorised
2017	19	50	33 (66%)	17 (34%)	0	20	1
2016	330	304	220 (72%)	82 (27%)	2	209	14
2015	258	272	177 (65%)	94 (35%)	1 (1%)	190	14
2014	329	259	196 (76%)	62 (24%)	2 (1%)	187	15
2013	201	197	136 (69%)	60 (30%)	1 (1%)	136	7
2012	197	192	139 (72%)	52 (27%)	1 (1%)	148	10
2011	166	158	111 (70%)	45 (29%)	2 (1%)	107	5
2010	174	176	123 (70%)	51 (29%)	2 (1%)	128	4
2009	164	136	113 (83%)	23 (17%)	0 (0%)	106	9
2008	119	118	86 (73%)	31 (26%)	1 (1%)	73	6
2007	125	117	97 (83%)	19 (16%)	1 (1%)	98	13
2006	104	103	81 (79%)	20 (19%)	2 (2%)	80	9
2005	118	118	88 (75%)	30 (25%)	0 (0%)	88	4
2004	108	101	75 (74%)	22 (22%)	4 (4%)	73	6
2003	87	96	54 (56%)	37 (40%)	1 (1%)	55	5
2002	80	75	43 (57%)	32 (42%)	2 (3%)	49	4
2001	83	90	62 (70%)	26 (29%)	1 (1%)	64	3
2000	72	32	26 (81%)	3 (10%)	0 (0%)	14	0
Total	**2734**	**2589**	**1860 (72%)**	**706 (27%)**	**23(1%)**	**1825**	**129**

Table 9. Orphan medicinal products designated and approved up to February 2017.

Taken from European Medicines Agency (39).

Despite the praised effects achieved with the orphan drug regulation in Europe, some voices have also expressed their concerns about the low number of medicines authorised compared with the very high number of designations granted (40,41). About this issue, it should be remembered that orphan designations are often granted with only preclinical data and, consequently, a proportion of these drug development processes fail in the same way and proportion than non-orphan drugs also fail.

On the other hand, a lower proportion of regulatory success has been reported for orphan drug applications as compared to applications for non-orphan medicines, and claimed to be due to the difficulties to generate robust scientific evidence for small

populations(42,43). Similarly, approval under special conditions has been reported to be more frequently applied for orphan medicines than for medicines aimed to treat conventional diseases: a study reported that 3.7% of all European authorisations (orphan and non-orphan) were “under exceptional circumstances” or “conditional approvals” between 2008 and 2010, but 21.1% for the orphan medicinal products(42).

Both observations are consistent with the hyphotesis of lower strength of scientific support for orphan products, since comprenhensive data is not always provided at time of the marketing application submission.

In the US, the number of designations and authorisations granted by the FDA since the Orphan Drug Act was enacted has been higher than in Europe. The Orphan Drug Act was enacted 17 years before the European regulation, but even since 2000, when both legislations were in force, a higher yearly number of designations and approvals have been granted in the US(37). Several reasons have been proposed as an explanation for these differences: the higher prevalence limit accepted in US to consider a disease as rare, the fact that in US medical devices and nutraceuticals are suitable to be designated or the direct grant and tax credits might explain the differences(44,45).

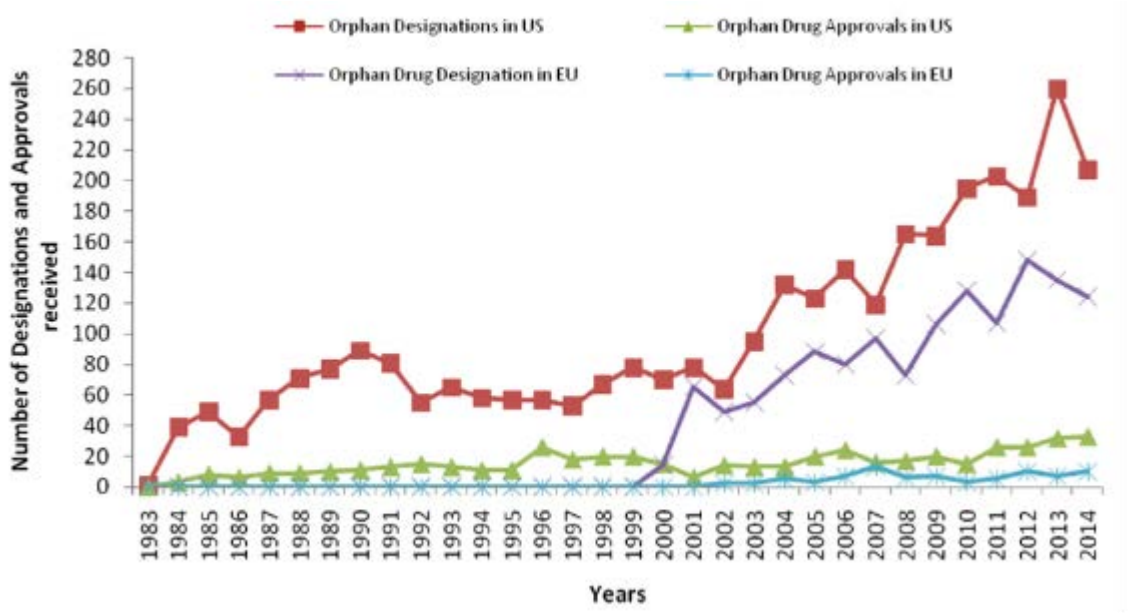


Figure 10. Comparison of orphan medicinal products designated and approved in Europe and US.

Modified from Tiwari J.(37)

4.6. Acces policies to orphan medicinal products

4.6.1. Setting for pricing and reimbursement decisions

In Europe, the centralised procedure is mandatory for orphan medicinal products, so that the European Comission decides and grants the marketing authorisation valid throughout all Europe based on the CHMP opinion(22). However, after the marketing authorisation is granted, each Member State is competent on the decision about pricing and reimbursement conditions for each medicinal product, according to national legislation, economic capacity and prioritisation criteria.

In some Member States, after national decisions, the regions also have competences in health policies which might include decisions about the priorities for use, purchasing conditions and systems for financing of medicines, frequently with the advice of Health Technology Assessment (HTA) agencies. Thus, the regulatory procedure in Europe is fragmented in the late stage of access, after the marketing authorisation is granted to the sponsors.

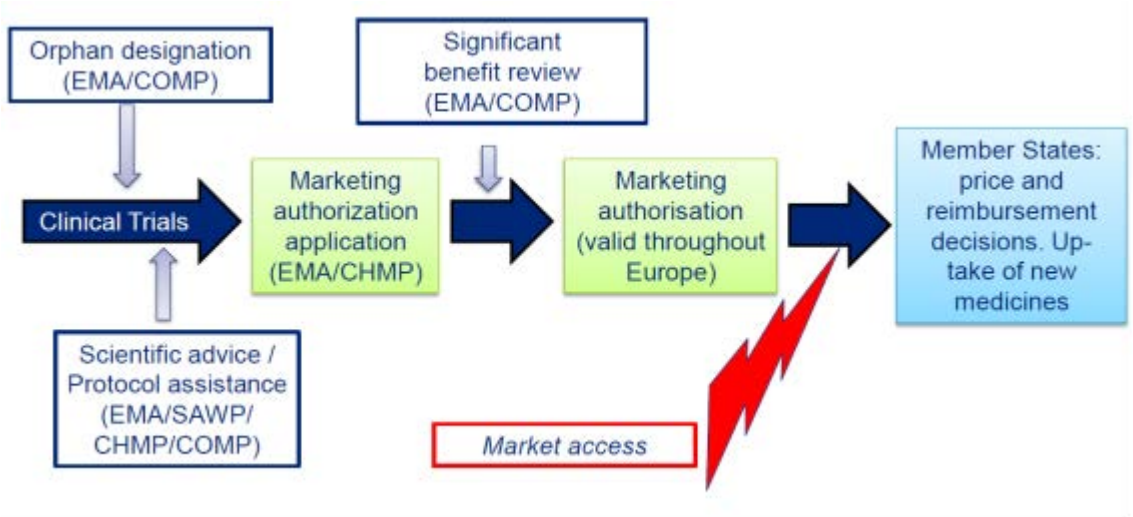


Figure 11. Regulatory procedure for orphan medicinal products in Europe.

While the grounds of the evaluation conducted by the CHMP are focused on quality, safety and efficacy in absolute terms, HTAs assessments are made on comparative terms and relative value to position new treatments in the background of already

available therapies, so that priorities can be set. Thus, additional criteria are applied in their appraisals such as clinical added value (in relation with the alternative treatments for a specific disease), efficiency (cost of the drug in relation with the benefit provided) or the affordability for the public health system, amongst others.

4.6.2. Heterogeneity of criteria across countries or regions

Different HTAs can get to different recommendations, being the assessment of the clinical benefit different according to local standards, because of differences in the finantial capacity of the Member States or regions, or because of different proritisations in health policies.

Such discrepancies can be maximised for orphan medicinal product, because of many reasons, including (46–49).

- Scientific evidences supporting their approval often display uncertainties.
- The prices requested for orphan drugs by marketing authorisation holders could be very high.
- Systems for co-payment may be substantially different across countries.
- Weight of other factors such as prioritisation of minorities, distributive equity or the rule of rescue may diverge.

In this scenario, the access of the patients to the ophan drugs could be hampered and relevant delays may occur. Inequalities in access have been observed across the different European countries. For instance, a survey conducted in 2010 by the European Organisation for Rare Diseases (EURORDIS) checked the availability of some orphan medicines in several countries. They described that the level of accessibility to orphan drugs ranged from 34% to 98% across countries (50), highlighting the problems existing in equity regarding access to orphan drugs (51,52).

As mentioned, access to orphan medicines may often be hampered or delayed, and inequity may occur due to a number of potential barriers, including:

- Decentralization of access steps after marketing authorisation.
- Lower level of scientific evidence that substantiates the marketing authorisations.

- Controversies about the cost-effectiveness
- High prices approved for orphan medicinal products.
- High and growing budgetary impact for the public health systems.

Some depend on the lack of uniform assessment criteria due to national or regional diferences, while others depend on uncertainties depending on poor amount or quality of cumulated evidence supporting authorisation procedures.

4.6.3. Heterogeneity in assessment criteria

While decentralisation is the consequence of the political organization of the European Union, there is room for coordination and sharing of experience between countries to reach a reasonable degree of consensus on the way to approach access decisions for a given product. In this way, the EMA initiative on early dialogue with regulators and HTA bodies may allow some alignement of criteria regarding value assessment and acceptability of evidence to support pricing and reimbursement decisions (53).

This is further difficulted by the relatively high frequency of special approvals ("under exceptional circumstances" and "conditional approval") granted to orphan medicines, as compared with non-orphan medicines (42), since such approvals mean that enough comprenhesive data are not available, although the current benefit/rik balance is considered positive and the medicinal product evaluated is considered to be needed, since it is aimed to treat an unmet medical need.

Judging the value a product that is considered needed, but is not fully measured yet, is difficult and prone to subjectivity, since gaps in information need to be fulfilled based on extrapolations and inferences that accept many assumptions. Such lack of information is frequently a reason for concern and a severe difficulty in HTA assessments. Uncertainties on the robustness and validity of data may generate doubts about the clinical relevance of the outcomes obtained, thus leaving room for subjective assessments that will be influenced by cultural, ethical and social factors, as well as by experience of assessors.

4.6.4. Amount and quality of data

Scientific evidence that support the marketing authorisation application for an orphan drug has in general lower quality than that of non-orphan medicines. The type of evidence and characteristics of the clinical trials that support marketing authorisations for orphan products have been described; the level and quality of evidence were frequently low, and a lack of robustness was often observed in the scientific data submitted to obtain the marketing approval (54). Pivotal clinical trials often displayed many weaknesses, and their characteristics increased the risk of biases or had methodological flaws. Specifically, lack of blinding, no use of control arm, absence of randomization, high use of surrogate endpoints, absence of quality of life endpoints or methodological design shortcomings have been repeatedly described(55). Also, as expected, the number of patients enrolled in clinical trials is low or very low.

Besides, other studies compared the characteristics of clinical trials conducted with orphan medicinal products with the characteristics of clinical trials for non-orphan medicines. In this wise, use or type of control groups, randomized assignation to treatment arms, blinding of treatments, type of main endpoints used to measure treatment effects, or the sample size included in clinical trials conducted with orphan medicinal products showed lower methodological strength as compared to non-orphan trials(56–59).

However, it should be taken into account that, because of the nature of rare diseases, regular clinical trials often are unfeasible and can not be conducted. Thus, what would be nice to know versus what is really possible to know should be clearly understood by regulators and HTAs, and it should be assumed that some types of decisions will be taken based on the best possible available data, but a need for inference and extrapolation of information will be often present in the orphan setting.

4.6.5. High prices and budgetary impact for orphan medicinal products

The price of orphan medicinal products is usually high, or even very high for ultra rare diseases, in order to compensate the reduced market size for each orphan drug conditioned by the rarity of the medical condition(50,60–63).

As a proof of this fact, data provided by Forbes and Pharmaceutical Commerce in 2010 showed that the first 9 most expensive drugs in the world were all aimed to treat rare diseases, reaching the most expensive one a price of 409,500$ yearly per patient (64).

Drug	Indication	Annual cost in US dollars	Company
Soliris (eculizumab)	Paroxysmal nocturnal hemoglobinuria	$409,500	Alexion
Elaprase (idursulfase)	Hunter's syndrome	$375,000	Shire
Naglazyme (galsulfase)	Maroteaux-Lamy syndrome	$365,000	BioMarin
Cinryze (C1 esterase inhibitor)	Hereditary angioedema	$350,000	ViroPharma
Myozyme (alglucosidase alpha)	Pompe disease	$300,000	Genzyme
Arcalyst (rilonacept)	Cryopyrin-associated periodic syndromes	$250,000	Regeneron
Fabrazyme (agalsidase beta)	Fabry disease	$200,000	Genzyme
Cerezyme (imiglucerase)	Gaucher disease	$200,000	Genzyme
Aldurazyme (laronidase)	Hurler syndrome	$200,000	Genzyme, BioMarin Pharmaceutical

Figure 12. The most expensive drugs in the world.

Modified from Winquist et al.(64)

Some authors have studied which are the factors that determine the price that an orphan medicinal product will be granted. The prevalence of the rare disease for which the orphan medicinal product has been approved is the factor more often and consistently identified as predictive of the product price, and is inversely related with the disease prevalence, so that higher prices are given to orphan medicines aimed to treat the rarest diseases. Other factors that have been described to influence product price include the lack of therapeutic alternatives, whether the product is or not a repurposed drug, the ATC class of the product, and the magnitude of the benefit provided by the drug (50,54,65,66).

In order to decide on price and reimbursement, HTAs assess the clinical added value but also the cost-effectiveness and the affordability of drugs for the public health system. Thus, the review of cost-effectiveness becomes a relevant part of the decision process. However, cost-effectiveness studies are usually relying on the clinical evidences obtained during clinical development. Considering that orphan

developments may have weak scientific evidence, strong and reliable cost-effectiveness studies are not always feasible (67–70).

Furthermore, even when cost-effectiveness assessments are available, the outcomes obtained often lead to estimates of cost-efectiveness well above the conventional thresholds established by HTAs to decide on budgetary assignements for these interventions. This fact is due both to the high prices granted to orphan medicines, but also to small sizes of effect or to lack of demonstration of significant improvements in relevant outcomes during clinical development (71–73). However, despite HTAs may conclude lack of cost-effectiveness based on conventional thresholds, many countries decide to pay for orphan medicinal products. Discussions about utilitarianism and equity in treatment access are commonly raised in this setting, and ethical considerations have also an important role(74,75), but again discussions are made based on extrapolation and inference, in absence of standard data an information. In any case, it seems that additional efforts and alternative methods would be needed to conduct pharmacoeconomic studies with orphan medicines(76).

These hurdles have to be set in the context of a rapidly growing cumulative number of orphan medicinal products approved, many claiming high prices, so that the budgetary impact of orphan medicines has become an important portion of the total pharmaceutical expenditure of the public health systems, and is growing in relevance(77–80). A study calculated that the expenditure in orphan drugs might represent about 5% of the total pharmaceutical spending in 2016. Despite that this figure may not seem extraordinay in a first glance, it should be reminded that this expenditure is addressed to treat a very small proportion of patients.

Many companies have found a profitable business approach in focusing their activity into rare diseases, since despite in theory they face similar development risks than in non-orphan settings, regulatory advantages -including possibility of early access and approval under special situations- and high prices in a closed and small target population may make an interesting business case.

The industrial trend to seek “niche buster” drugs should be considered positive from a societal perspective, because leads to an increase of drugs intended to treat rare

diseases. However, should the economical impact to treat rare diseases keep on growing at the same rate, with current parameters the resulting scenario would eventually threaten the economic sustainability of the public health systems(81,82), and become one of the main hurdles for the patients' acces to treatments for rare diseases (52,83).

In this situation, some voices demand more transparency and specific frameworks for the price and reimbursement decision procedures for orphan medicinal products (54,84–86), and some readjustment in the rules of the orphan market can be expected in the upcoming years.

4.6.6. Patient expectatives and empowerment

Patients' advocacy groups have grown in last years in number and empowerment, to defend patient's rights and fighting to achieve improvement of the quality of life of patients affected by rare diseases(6,87). Patients' associations raise their voice to claim an adequate acces to orphan medicinal products, without inadequate delays and inequities in accessibility (88).

As one consequence of this movement, patients' advocacy groups have been progressively recognised in Europe as an active stakeholder in the process of drug regulations, and they have been involved at all levels of the regulatory processes and scientific committees discussions. Their involvement from early drug development stages to final access decisions both at European level as at national level has enriched the discussions and integrated patients' views and preferences into the factors involved in decision making in many different procedures.

Simultaneously to increasing lobbing and influence, and taking into account that some patients' advocacy groups may receive economical and logistic support from pharmaceutical industry through donations aimed to conduct their associative activities, a need of systems to address conflicts of interest and transparency has also appeared. Similar to what is already in place for expert clinicians of medical associations, conflicts of interest should be handled properly in order to avoid misunderstandings when patients take part of making-decision processes about access to specific drugs(89). While there is consensus on the need to control potential

influences of third parties through conflicts of interest, a remaining issue scarcely discussed is the balance between legitimity of affected individuals to provide opinion on treatments intended for them, and the extent of conflict during decision making derived from the fact of being personally affected by the disease being assessed, or a close relative of an affected person.

4.6.7. Regulatory actions aimed to improve orphan drug access

The regulatory bodies have been sensitive in the last years to claims on the need to accelerate regulatory procedures and achieve an adequate and equitable access for patients to innovative orphan drugs. A number of initiatives or mechanisms have been launched or piloted to facilitate rapid and equitable access to innovative treatments aimed to responde to urgent medical needs.

Some of the most relevant projects are the following:

- **PRIME –Priority Medicines**

  The PRIME project is a scheme designed by the EMA to give support to the sponsors in the development process of medicines aimed to treat unmet medical needs (90).

  This program can be requested by the sponsors and is based on early dialogue, scientific advice, continuous support by the EMA staff and accelerated assessment at the time of marketing authorisation application.

  Despite the fact that the PRIME project is not restricted to orphan medicines, these kinds of medicines would be especially adequate for eligibility because most of rare diseases do not have available treatments.

- **Adaptive pathways**

  The adaptive pathways approach is a pilot project that has been lead by the EMA to propose changes to the paradigm of marketing authorisation for medical products which are aimed to treat high unmet medical needs and for whose the full drug development process until gathering complete and comprenhensive data for submission of marketing application would excessively delay patients' access to

the treatment. For these products, an early approval would be granted and afterwards progressive data generation would be required. Thusly, real-life data to expand the knowledge about medicines and early involvement of patients and health-technology-assessment bodies in discussions on a medicine's development would be also principles to be applied.(91)

As happens in PRIME project, despite adaptive pathways are not exclusive for orphan medicinal products, they would be adequate candidates for elegibility.

- **Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow.**

  As has been described in previous section, after the marketing approval, price and reimbursement procedures are conducted at the national level, and different level of access to orphan medicines can be observed among Member States. In addition, due to the lower level of evidence for orphan medicines, the determination of clinical added value for these drugs is often hindered.

  On this wise, the European Union Committee of Experts of Rare Diseases (EUCERD), created by the European Commission, made recommendations for facilitating the exchange of scientific information on orphan medicinal products that would support the clinical added value appraisals across Member States(92). Through information flow, it would be easier to achieve alignment of assessment criteria, and indirectly accelerate the patients' access to approved orphan medicinal products, encourage pricing and reimbursement decisions based on the value of the orphan medicinal procucts, and avoid inequities in accessibility among different European countries.

- **Mechanism of Coordinated Access to orphan medicinal products (MoCA)**

  MoCA is a working Group that was created within the "Process on Corporate Responsibility in the Field of Pharmaceuticals" launched by the European commission in 2010, and was intended to map innovative ways to provide real-life access to orphan medicines, in an affordable and sustainable way. The main recommendation of the group was to develop a coordinated mechanism between volunteering Member States and orphan medicine developers to evaluate the value of an orphan medicinal product, which could be based on a transparent value

framework, in order to support the exchange of information aimed at enabling informed decisions at Member State level on pricing and reimbursement. This, ultimately, should lead to more rational prices for payers, more predictable market conditions for industry and more equitable access for patients.

A pilot project was developed to improve access to orphan medicinal product in Europe where all stakeholders should be involved.

Currently MoCA provides a unique mechanism for European countries to collaborate on coordinated access to orphan medicines in a voluntary, dialogue-based approach, intended to create a fluid set of interactions between key stakeholders, across all aspects of a product.

4.6.8. Other methods to improve access to orphan medicinal products

On the other hand, other measures have been proposed by the stakeholders involved in the assessment of value of orphan medicines, pricing and reimbursement decisions, and on finantial agreements with the pharmaceutical industry, in order to facilitate the evaluation of orphan medicines, facilitate the patients' access and to guarantee the sustainability of the public health systems. These include, amongst others, the following:

- **Multicriteria decision analysis (MCDA)**

Multicriteria decision analysis is a tool aimed to determine the value of medicines taking into account all the criteria that influence decision-making processes(48,93–97) MCDA allows a systematic and explicit evaluation of multiple criteria in several dimensions, some quantitative and some qualitative, that might impact in the drug value concept. Each criterion is weighted and a final score for each medicine may be obtained.

Beyond the meaning and repercussions of the actual score obtained for a given product and its implications regarding the final decisions adopted, this methodology facilitates a structured, predictable, complete and holistic discussion of the clinical value of new medicines, allowing quantitation and transparency of the main determinants of decision making.

Despite such criteria (ethical, political, social and so on) always play a role in any decision process, they are classically not reported in conventional appraisals, since decisions are generally argued on the basis of quantitation of value based on clinical and economical grounds. On last years, the MCDA has been proposed as a good mechanism to be used for orphan drugs assessment, because the characteristics of scientific evidences and the nature of rare diseases preclude conclusive decisions based on quantitation of clinical and economical value, so that additional criteria become key in decision making.

- **Frameworks and methodologies for drug value assessments and pricing decisions**

Taking into account that the hurdles in the patients' acces to orphan drugs is frequently linked to the difficulties to determine the added value of medicines and to the high prices not always properly justified, several authors have proposed different frameworks and criteria both to help to estimate the clinical relevance of new orphan drugs as also to establish the pricing and reimbursement conditions for these (64,85,98–102). Most of the frameworks are proposed after an analysis of the relevant factors involved in the decision-making process, by grouping these factors into general dimensions of assessment, and sometimes proposing a flow of decision process for evaluation of value where the different factors should be considered and discussed. A thorough summary of these initiatives has been recently published by *Annemans et al* (98).

- **Managed entry agreements**

Due to the uncertainties existing with the real clinical benefit provided by some orphan medicines and the accurate epidemiology of some rare diseases, together with the very high budgetary impact caused by these drugs, some authors and public administrations have proposed to used managed entry agreements in order to limit the economical burden and also to share the uncertainties and doubts existents with the pharmaceutical industry through several kind of financial and performance-based schemes(103,104).

Despite few experience is available with this agreements in the rare disease field, it could be a possible option to improve the patients' acces to orphan drugs. A taxonomy of managed entry agreements has been proposed by *Morel et al*.(103).

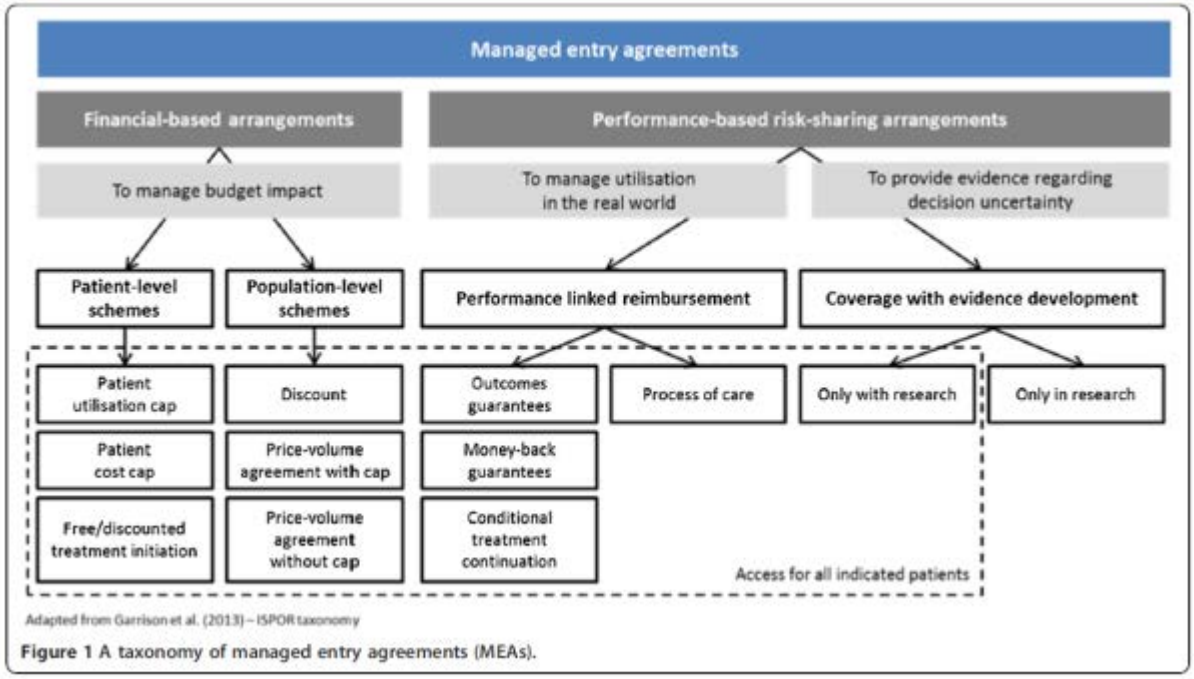


Figure 13. Types of managed entry agreements.

Modified from Morel et al.(103)

4.7. New methodological approaches for clinical trials

One of the main barriers in the orphan drug development are the difficulties to conduct clinical trials, mainly because the number of patients affected by a particular rare disease is low, but also because of reduced knowledge of the conditions, paucity of available expertise, lack of appropriate and validated tools to measure outcomes, and ethical concerns, amongst other factors.

Clinical trials with small sample size may hinder the reaching of conclusive outcomes when conventional designs are used, because of insufficient protection against type 1 and type 2 errors precludes obtaining significant results from a statistical point of view.

However, clinical trials are the standard tool to study causality, and thus regarded as the most robust way to study the efficacy and safety of an experimental treatment

reducing as far as possible the biases on the outcomes assessment, and the one preferred from a regulatory point of view.

For this reason, alternative and unfamiliar trial designs have been proposed by researchers to be used for rare diseases, in order to maintain the methodological rigor in the clinical trials conduction with lower sample sizes than those required for conventional designs(105–115). An example of some of the main alternative designs to the conventional parallel clinical trials with frequentist predetermined design are described briefly hereafter, according to *Gupta et al* (105):

4.7.1. Designs aimed to reduce variability and optimise sample size

- Crossover designs: Patients receive both of two treatments in a pre-specified sequence. At the end of each period of treatment the main endpoint is measured. Patients act as theis own control

  Advantages:

  - Reduced variability requires smaller sample size than parallel designs
  - Results depend only on within-patient variability
  - To guarantee that all patients will receive the active treatment estimulates recruitment.

  Disadvantages:

  - Only useful for chronic stable diseases
  - Requires absence of carry over effect (or alternatively a wash out period is needed between treatments)
  - Less robust and longer than conventional desigsn
  - Very susceptible to dropouts

- N-of-1-trials: Only one patient receives the different therapeutic alternatives in different consecutive periods.

  Advantages:

- Patient enrolled acts as his or hes own control, minimizing counfounding and reducing variance (high internal validity).
- To guarantee that patient will receive the active treatment estimulates the recruitment.

Disadvantages:

- Usuful at the patient level but less applicable to inference for populations
- Needs chronic and stable diseases.
- Requires absence of carry over effect, and a wash out period is needed between treatments
- Very sensitive to patient dropouts
- Less external validity to extrapolate outcomes.
- Meta-analysis of N-of-1 trials might be limited by heterogeneity of outcomes.

4.7.2. Designs allowing adaptions based on trial informations

- Adaptive designs - response-adaptive randomization: Results obtained guide the subsequent allocation of patients to maximize the pacients enrolled in the most active treatment arm.

Advantages:

- Higher number of patients receives the most effective treatment, so that chances to obtain significant results are maximized by favouring the test of wining strategies.

Disadvantages:

- Requires fast and simple measure of outcomes.
- May lead to overestimated results
- Risk of biases if integrity of blinding is not preserved.
- Complex designs form an operational point of view.

- Adaptive designs: ranking and selection: These designs are usually formed by two stages. In the first stage several treatments are administrated. At the end of the first stage, a comparation is conducted (usually without statistical testing) and the treatment with best results is selected for the second stage ("pick-the-winner" or "drop-the-loser" strategies). In the second stage, the treatment chosen is compared with placebo or alternatives and, in this case, a statistical testing must be conducted. They are also called seamless designs.

  Advantages:

  - Allows comparison among several treatments options with reduced sample sizes.
  - Reduces operational gap between development phases

  Disadvantages:

  - Risk of choose an inadequate treatment during the first phase.
  - Delay to receive the effective treatment for patients randomized to ineffective treatment arms, unless rescue procedures are in place.

- Adaptive designs- internal pilot: When pilot phases are conducted before the definitive trials, the patients enrolled in the pilot phases are generally not included in the definitive studies, to avoid carry over, training effect or selection biases. Internal pilot designs are aimed to allow that the outcomes obtained during the pilot phase of clinical trials can be also included in the final analysis of the definitive studies.

  Advantages:

  - Avoid loss of patients because they have been enrolled in the previous pilot.

  Disadvantages:

  - If not properly conducted, may increase the risk of type I error.

4.7.3. Flexible designs aimed to use only the minimum required sample size

- Sequential designs: Designs that allow repeated interim analysis to lead to premature termination for futility or efficacy. Sample size is unkown at the beginning of the trial, and repeated interim analysis guide the final sample size.

  Advantages:

  - They take advantage of emerging outcomes to enable early study termination, for futility or efficacy.

  Disadvantages:

  - Treatment outcomes must be quickly measurable.
  - In certain circumstances the fnal sample size may be higher than with conventional trials.
  - Risk of biases if integrity of blinding is not preserved.
  - Complex design: timings of interim analysis, optimal number of interim analysis, multiplicity correction or methods to calculate the study power are difficult to establish.

4.7.4. Designs aimed to integrate all available information

- Bayesian designs: Group of designs that use the previous available information to obtain an estimation of outcomes resulting of weighing previous knowledge with that obtained in the trial. Conclusions are drawn from the combination of past and current outcomes, taking profit of all available information.

  Advantages:

  - Allows the use of previous available information.
  - Higher potency to provide results in a natural and intuitive manner.

  Disadvantages:

  - Strong reliance on quality and reliability of prior estimations

- Doubts about the validity of data coming from external sources to the current trial.
- Complexity in design and computational analysis.

4.7.5. Applicability of designs

Nontheless, the described examples of alternative designs are only some of many existing unfamiliar designs suitable to be applied in the setting of rare diseases.

Many others are available, such as those aimed to reduce sample size by maximisation of treatment effect through population enrichment, or those aimed to improve ethical acceptability by treating all potential patients and then randomising treatment withdrawal with a clear rescue procedure.

Many others are being developed, including desings aimed to provide methodological solutions to multiplicity of assessments, integration of data or adaptions to ongoing information, amongst others. Moreover, the combination of several of these methodologies would be also feasible.

The choice of the best methodology will depend of the nature of each specific rare disease, the drug characteristics or the main endpoint or duration applied in the clinical trials.

In this regard, the EMA published in 2016 the Guideline on clinical trial on Small Populations in which some of these alternative methods are described, stating that they can be useful when large clinical trials are not feasible to be conducted(116). However, the guideline only includes general recommendations, and no specific guidances are available that provide advice on neither the conditions where the trials are suitable according to disease features and drugs studied, nor the practicalities of their design and analysis.

4.8. Justification of the project

The European Comission has repeatedly recognised that the development of treatments for rare or neglected conditions is a clear priority, and has taken actions to promote the development of new treatments in the field.

4.8.1. Policies developed to improve the health of patients affected by rare diseases

Regarding the policies developed in the rare disease field, it should be highlighted that a relevant step ahead has been produced since the European regulation entered into force in year 2000.

In this way, the rare diseases have been recognized by public institutions as a challenge to be faced up in order to improve the quality of life of people affected and their families(117).

Thus, several actions have been started up on last decade on several issues to increase the visibility and recognition of rare diseases, to strength the coordination at European Union level, to guarantee the access to orphan medicines, to include rare conditions within the international classification of disease, to improve the social attention, to disseminate the knowledge about the rare diseases or to foster the research, among others.

These actions have been developed both at European level as also at national level where strategies about rare diseases in the national health services have been planned(11,118).

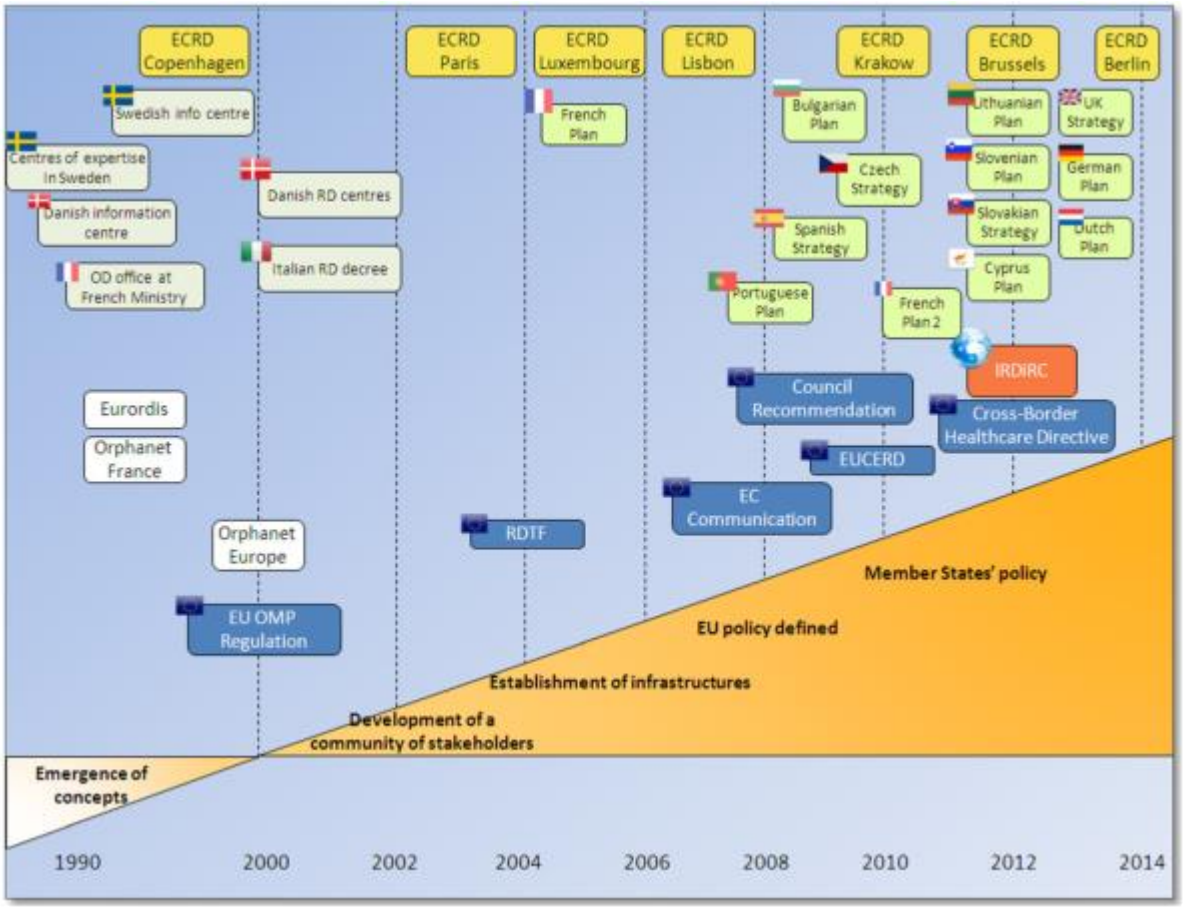


Figure 14. Evolution of policies in the rare disease fied.

Modified from Ayme S et al.(11)

4.8.2. Research opportunities on rare disease field

During the last decade, the rare disease field has become one of the niches of opportunities for research groups which have guide their efforts to the basic medical research of rare medical conditions (119).

In this sense, and understanding the high compleixity of basic research in this area, several public institutions and public-private consortiums have potentiated the research on rare disease and orphan medicines to achieve that basic research advances do translate into factual progresses and improvements for patients affected and their families. Examples of these initiatives include the Horizon 2020 program developed by the European Commission, the IRDiRC consortium or the IMI project.

These projects frequently engage the different stakeholders involved (public institutions, industries and patients' advocacy groups), and in this way they assure coordination among them, improve the quality of their production, and avoid unnecessary and worthless duplicities in projects.

The European Comission has recognised the need to take into consideration that one of the main hurdles in the drug development for small populations is the difficulties to conduct adequate and feasible clinical trials. Also, it is recognised that conventional trial designs have been traditionally preferred to new designs by regulators, because they are well-known and allow a more confident decision making. The FP7 Call – Health.2013.4.2-3 was issued specifically to foster innovative approaches to adapt and assess clinical trials on small populations and rare diseases, with a focus in achieving not only development, but applicability and implantation of new methods into the development of new orphan medicinal products.

4.8.3. The ASTERIX project

ASTERIX (Advances in Small Trials dEsign for Regulatory Innovation and eXcellence, FP7 HEALTH 2013 – 603160)(120,121) is one of the 3 multinational projects funded by the European Commission with the aim to develop innovative approaches to adapt and assess clinical trials on small populations and rare diseases, by means of the FP7 Call – Health.2013.4.2-3. The other 2 projects are IDEAL (Integrated Design and Analysis of small population group trials, FP7 HEALTH 2013 – 602552) and InsPIRe (Innovative methodology for small population research, FP7 HEALTH 2013 – 602144).

The Universitat Autònoma de Barcelona is one of the partners in the project ASTERIX, leading the working package number 5. The aims are to translate into regulatory recommendations and proposals the findings and results obtained by other groups, who develop statistical approaches to the design or analysis of clinical trials in diseases characterised by difficulties to recruit enough subjects.

The first objective at Universitat Autònoma de Barcelona consisted of setting a framework able to simplify the descritption of medical conditions into groups sharing similar methodological characteristic, so that the applicability of methodologies, designs and statistical approaches could be analysed, generalised and addressed in

aggregate for groups or clusters of conditions. This objective led to the proposal of a clustering of conditions that is summarised in the figure below (122).

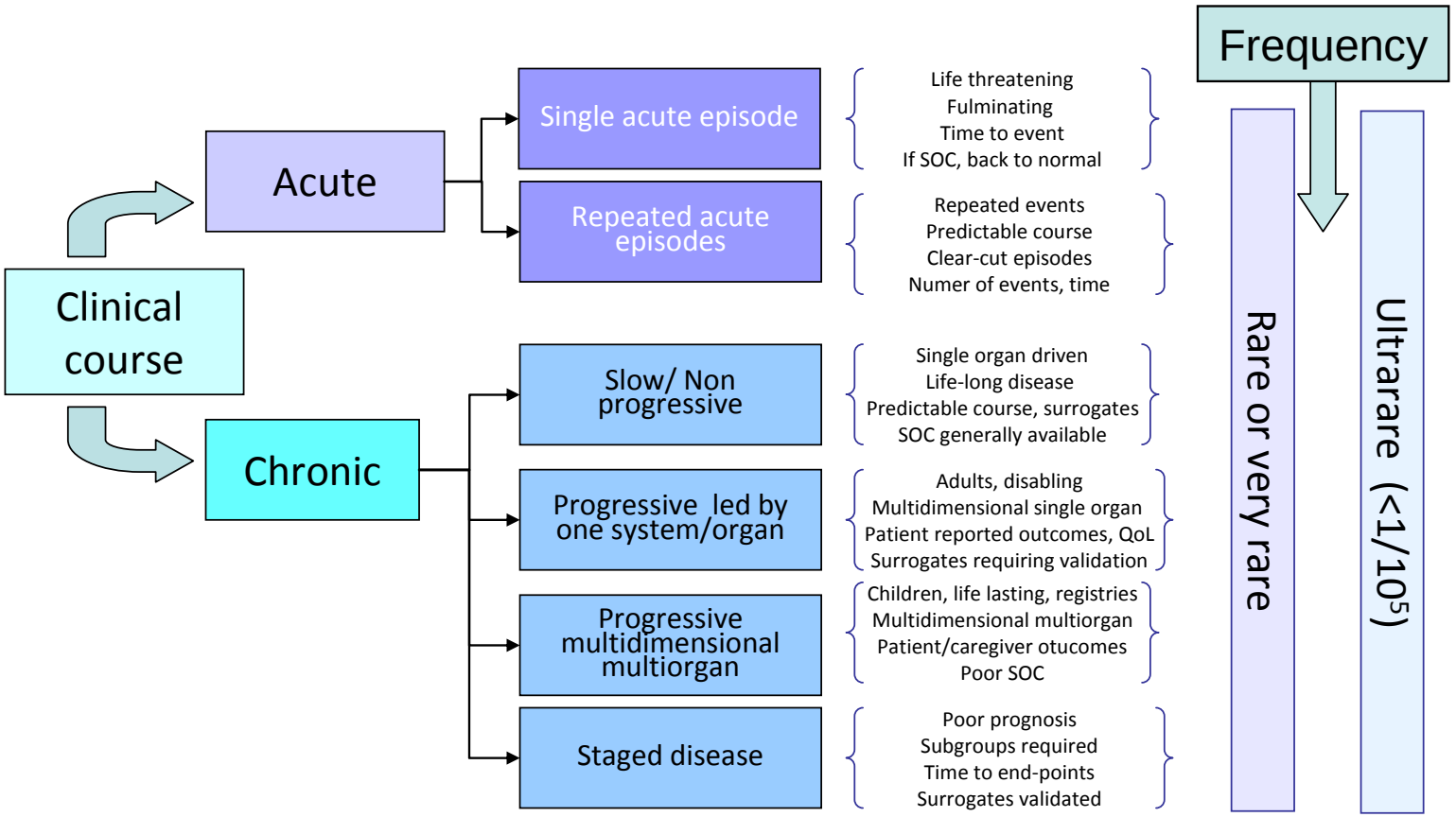


Figure 15. Clustering of orphan and/or rare conditions based on clinical characteristics that determine the applicability of different research methods to their study

As a second step, the objectives included the description of the current state of the art regarding clinical trial design and characteristics of the data that is currently used as supportive evidence to apply for marketing authorisation of orphan medicinal products, and used to support regulatory decision making. Such detailed description should allow describing a regulatory standard against which the clustering proposal could be validated, and also new methods could be checked for applicability and efficiency. This is the focus of the present project and report.

Finally, the third objective, still in progress, will be to issue some clustered regulatory recommendations based on the testing of new proposals against the current regulatory standard for each cluster of conditions.

The final aim and goal will be to set the framework to improve the specificity of references for regulators and sponsors on the most suitable methods for clinical development of orphan medicinal products or products aimed to treat of a wide range of rare conditions or small populations.

4.8.4. Setting a regulatory standard for orphan medicinal products in Europe

The present work is a part of the ASTERIX project (Advances in Small Trials dEsign for Regulatory Innovation and eXcellence, FP7 HEALTH 2013 – 603160), and aims to provide a regulatory standard that summarises the current state of the art regarding the regulatory information supporting marketing authorisation of orphan medicinal products. The project is a necessary intermediate step between the proposal of clustering of conditions and the issue of specific recommendations to the application of innovative statistical and methodological approaches to the study of rare conditions within the ASTERIX project.

In this regard, the characteristics of the scientific dossiers submitted to the EMA to apply for marketing authorisation of orphan medicinal products have been thoroughly described, focusing specially on the type and strength of scientific evidence, the characteristics of the clinical trials conducted and the type of outcomes measured in

the trials, in order to issue a regulatory standard suitable to proceed to validation of cluster and to test applicability of new statistical methods.

5. HYPOTHESIS

The analysis of the type of scientific evidence underpinning the marketing authorisation of orphan medicines in Europe and the characteristics of the main clinical trials conducted for these medicinal products will allow: determining which is the quality and strength of the scientific evidence for the orphan drugs approved in Europe since the specific regulation for orphan medicinal products entered into force; to have a reference to explore the applicability of alternative methodologies in the conduction of clinical trials; and to compare the current methods used to conduct clinical trials in the rare diseases field versus the alternative methods proposed in the frame of the ASTERIX project (Advances in Small Trials dEsign for Regulatory Innovation and eXcellence, FP7 HEALTH 2013 – 603160).

6. OBJECTIVES

6.1. General objective

The main objective is to analyse the characteristics of the main clinical trials conducted with the orphan medicinal products authorised in Europe since the European regulation on orphan medicinal products entered in force in year 2000, in order to explore if there is room for application of alternative methodologies in the conduction of clinical trials.

6.2. Specific objectives:

- To review all the orphan medicinal products approved in Europe since the European regulation on orphan medicinal products entered in force in year 2000 and up to December 2014, and to describe the main characteristics of these medicinal products.
- To analyze the source and type of the scientific evidence that substantiates the marketing authorisation endorsement for these orphan medicinal products.
- To describe the features of the main or pivotal clinical trials conducted with orphan medicinal products, focusing especially on the characteristics that are relevant to the clinical trial design and methods.
- To conduct a subgroup analysis of the characteristics of the clinical trials conducted with orphan medicinal products aimed to treat conditions with ultrarare prevalences.
- To conduct a subgroup analysis of the characteristics of the clinical trials conducted with orphan medicinal products accoding to the clustering of medical conditions defined previously in the ASTERIX project.
- To discuss if there is room to apply new methodologies in the design of clinical trials with small populations.

7. METHODS

7.1. General approach

In a first stage, a comprehensive review of the European regulation concercing the orphan medicinal products and rare diseases was conducted in order to have a general overview about this kind of medicines.

Afterwards, all the orphan medicinal products approved in the European Union from the entry into force of the European regulation 141/2000 about orphan medicinal products in year 2000 to December 2014 were identified.

In this way, all the medicines approved following the centralised procedure that had the Orphan Drug Designation at the moment to be authorised by the European Commission were considered as orphan medicinal products and, consequently, selected for our study.

On the other hand, medicines aimed to treat rare diseases which did not have the Orphan Drug Designation at the moment to be authorised were ruled out. Additionally, medicines aimed to treat rare diseases that were authorised before the European regulation 141/2000 was in force of were also excluded form our study.

Finally, for each one of the orphan medicinal products included in our analysis, all their therapeutic indications approved were identified. In this sense, each medical condition designated as orphan by the COMP constituted a therapeutic indication.

All the data that are part of this work were registered in a database and statistical analysis was performed using SPSS version 21.0 (IBM Corp, 2012) and Microsoft Excell version 14.0.

7.2. Description of orphan medicinal products approved

In a first phase, for each one of the orphan therapeutic indications approved for orphan medicinal products (n=125), information regarding the pharmacological

properties of the drug, the characteristics of the disease for which is targeted and regulatory procedure features were wrapped up.

On this wise the information compiled was the following:

Scope	Features analyzed
Drug properties	• Active principle • Brand name • Type of drug (Chemical / Biological / Advanced therapy) • Mechanism of action • ATC code
Disease characteristics	• Orphan medical condition designated by the COMP • Therapeutic indication approved by the CHMP • Population included within the therapeutic indication label (Adults/ Paediatric / Both) • Therapeutic field according the ICD-10 • Overall prevalence of the orphan medical condition
Regulatory features	• Originator of the molecule and size of the company • Applicant of the Orphan Drug Designation and size of the company • Date of Orphan Drug Designation • Current status of Orphan Drug Designation (Active / Withdrawn / Expired) (on data December 2014) • Number of transfers among companies of the Orphan Drug Designation • Marketing authorisation holder and size of the company • Date of marketing authorisation

Table 16. General characteristics of EPAR described

Mostly, these data was collected from the public information available on the EMA Website (27), including the summary of product characteristics, the European Public Assessment Report, Orphan Designation, and the product assessment history amongst other documents.

Additionally, some specific features were obtained from other sources. In this sense, therapeutic field of the diseases for which orphan drugs were authorised were

classified according the ICD10 (123). Futhermore, the originator of the molecules was consulted in the Integrity database (124). And the size of the companies was consulted in the registry of Small and Medium Enterprises (SMEs) of the EMA.

Finally, some clarifications about the characteristics described would be needed.

- The mechanism of action was consulted in the Summary of Products Chracteristics available on the EMA Website and described in a broder manner to allow a grouping of indications.

- On the other hand, the population included within the therapeutic indication was obtained from the wording of the therapeutic indication described at the time of the extraction.

- Finally, the prevalence figure reported was the prevalence figure accepted by the COMP at time of granting the orphan drug designation, and refers to the prevalence for the overall medical condition designated.

7.3. Description of characteristics of the scientific evidence supporting the marketing authorisation

In a second phase, for each therapeutic indication approved for an orphan medicinal product a wide description of the characteristics of the scientific evidence submitted to substantiate the marketing authorisation was conducted.

In this sense, the study of the characteristics of the main trials was only conducted for therapeutic indications approved with scientific evidence coming from clinica trials.

The information collected was the following:

Scope	Characteristics analyzed
For each therapeutic indication approved	• Active principle • Brand name • New medicine or Extension of therapeutic indication • Orphan medical condition

	• Type of scientific evidence supporting the marketing approval • Number of main clinical trials conducted (if exist) • Number of supportive clinical trials conducted (if exist) • Overall number of patients exposed to the orphan medicinal product • Longest follow up time period available • ASTERIX project Identification Number
For each main clinical trial being part of the application submitted to the EMA to obtain the marketing authorisation **(only anlayzed for therapeutic indications approved based on clinical trials)**	• Study name • Type of phase • Type of blinding • Existence or absence of randomization • Existence or absence of stratification in the randomization process • Type of control (if exist) • Experimental treatment used as add on treatment or not • Number of arms included in the clinical trial • Number of arms included in the clinical trial that received the experimental treatment • Uninational or multinational trial • Uncentric or multicentric trial • Overall population enrolled in the clinical trial • Population enrolled in the clinical trial whom received the experimental treatment • Clinical trial following a Survival design (Yes/Not) • Duration of primary endpoint • Type of methodological design applied in the clinical trial • Description of the primary endpoint • Type of statistical analysis conducted for the primary endpoint • Key secondary endpoints • Description of the outcome for the primary endpoint • Fulfillment of the primary objective

	• Pre-specified subgroup analysis conducted • Marketing authorisation based on subgroups analysis • ASTERIX project Identification Number

Table 17. Information described on characteristics of main clinical trials

The description of all these features is defined in the Annex 1.

All this information was extracted from the European Public Assessemnt Reports (EPARs) published on the EMA Website. Furthermore, if some feature was not found, it was consulted on the clinical trials database of the National Institutes of Health (www.clinicaltrials.gov). Finally, the information not located was classified as "Not described".

The compilation of the whole information was carried out by a single investigator. Afterwards, some of these characteristics were validated one by one in a peer review process by a second investigator of the ASTERIX project. In this sense, the characteristics validated were the following:

- type of scientific evidence supporting the marketing approval;

- type of blinding;

- existence or absence of randomization;

- type of control;

- overall size of population enrolled on the clinical trial;

- time to assessment of primary endpoint (duration);

- description of the primary endpoint

- type of methodological design applied in the clinical trial.

The discrepancies were solved through a specific meeting and amendments were done if necessary.

7.4. Description of the primary endpoint in pivotal trials

In a third phase, the description of characteristics of the primary endpoint used in each main clinical trial was conducted.

Features analyzed are displayed in the table below:

Scope	Characteristics analysed
Primary endpoint chosen in each clinical trial	• Single or several components analyzed • Objective or subjective • Final or Intermediate • Inclusion of overall survival within the primary endpoint definition • Inclusion of biomarkers within the primary endpoint definition • Inclusion of Patient Reported Outcome Measures (PROMs) within the primary endpoint definition

Table 18. Characteristics described for main end-points in pivotal trials

The description of all these features is defined in the Annex 1.

As done for characteristics of the scientific evidence, a peer review was conducted. In this case, all the charactersitics were validated by a second investigator and discrepancies were solved through a specific meeting.

7.5. Subgroup analyses of trial characteristics

A subgroup analysis was carried out to study the influence of the prevalence in the study design.

In this sense, medical conditions were classified in rare or ultrare. All medical conditions with a prevalence figure below the threshold of 0.1 cases per 10,000 inhabitants were considered ultrarare. On the other hand, medical condictions with prevalences equal or higher than 0.1 cases per 10,000 inhabitants and below 5 per 10,000 inhabitants were considered as rare.

Furthermore, a different subgroup analysis was conducted according to the ASTERIX clustering of medical conditions.

As mentioned in the introduction section ("Justification of the project"), the ASTERIX project carried out a clustering of diseases following a consensus process that used a base-case built through an analytic process based on a Multiple Correspondence Analysis (MCA). As a result, six different groups of medical conditions were proposed which would share the applicability of similar methodologies to their trials.

The clusters proposed were as follows:

1. Conditions with single acute episode
2. Conditions with repeated acute episodes
3. Chronic non-progressive conditions
4. Chronic progressive conditions led by one system-organ
5. Chronic progressive multidimensional conditions
6. Staged conditions

The characteristics of each cluster are described in the table below. The subgroup analysis of the design of trials was conducted according these clusters of rare diseases indentified in the framework of the ASTERIX project.

Cluster	Description	Implications
(1) Single acute episode	Incident cases with single acute episode, with rapid onset and rapid endpoint. Well-known and predictable course in absence of treatment, often serious or life-threatening. Recovery generally returns to baseline health status with or without sequels. Generally led by one organ/system that then derives into multiorganic impairment. Comparison must consider whether there is an effective SOC. Add-on designs. Generally single hard objective and clinically relevant end-point, often dichotomic.	Studies with longer recruitment than follow-up for a given subject, thus application of sequential and adaptive methods may optimise the trial size. Time to event may be applied. If SOC available, then placebo could be applicable in parallel, add-on designs with non-inferiority or superiority objective. Single hard objective end-point may allow unblinded designs. Lack of SOC may ease recruitment, but comparisons against placebo generally not acceptable unless add-on designs to e.g. best supportive care. Placebo may be used for limited time in non life-threatening conditions. For disease without SOC or trials in patients who have exhausted all SOC options, controls may be historical, external or even uncontrolled trials assessing change from baseline or superiority to substantiated expectations may be justified. Rescue strategies generally required during patient follow-up.
(2) Repeated acute episodes	Prevalent subjects who suffer clear-cut repeated episodes separated by relatively healthy periods. The condition has a well known predictable clinical course, with repeated clinical episodes led by one organ/system, which are generally due to a single biological or physiological abnormality which -if severe or immunological- may derive into multiorganic impairment. Baseline status may deteriorate slowly along years due to repeated episodes. Generally there are clinically relevant time-related end-points, measuring the underlying activity of the abnormality through number of episodes by time. If the condition is mild, variables may be based on patient reported outcomes. If the condition is serious, then dichotomic clinical end-points can be used.	Generally two different indications: treatment of acute episodes and prevention of new episodes. If condition is returning to normal after acute episode, start-stop designs (withdrawal, cross-over and intrasubject comparison) may be applicable for both indications. For treatment of acute episodes, variables generally include remission of the episode (dichotomic), time to remission of the episode (time to event) or intensity of the episode. For prevention of the episodes, variables generally rely on number of episodes per time. Longitudinal designs with repeated measurements may be applied. Response may be based on clinical assessments supported by lab/biological/imaging data. Multiple assessments are generally feasible. Use of placebo generally limited in time for non life-threatening conditions or when lack of prognostic consequences for periods without treatment. Rescue plan needed (either for placebo or for experimental treatment)

Cluster	Description	Implications
(3) Chronic non-progressive	The condition is life-long and affects mainly a single system/organ, with constitutive activity due to deficiency or impairment of function and a predictable well-known clinical course. May be adult or both pediatric and adult. In general, it does not rapidly deteriorate the subject function or life-expectancy with current standard of care, which is generally available but not always evidence based. However, if SOC is not optimal, further deterioration may occur in years. Prevalence is higher than incidence, and often there are available surrogates which measure the underlying defect or deficiency directly.	Recruitment may be more rapid than subject follow-up, potentially limiting the role for sequential designs and some adaptions. Start – stop based methods (crossover, withdrawal) may be applicable. Intrasubject comparisons generally feasible. Double blind would be generally required, and because SOC is generally available, designs would generally be add-on, unless treatments share mechanism of action – then direct comparison may be required with non-inferiority approach. Surrogates would generally be available and often easily validated. Safety requirements must be widely assessed due to chronicity and relative mildness of conditions with current SOC.
(4) Chronic progressive led by one system-organ	Initial impairment of one system/organ, which may or not involve others along time Clinical course is longer than acute conditions, usually year(s). Progressively reducing life quality and/or quantity of life, typically subjects are seriously disabled due to disease. Current standard of care is generally symptomatic or supportive, but not curative. Variables are often relying on patient reported outcomes, and patient perceptions on the disease; disability and QoL may be relevant for decision-making.	Due to progression, start stop methods and intrasubject comparison generally not feasible. Parallel trials needed when heterogeneity or poor predictability of clinical course are present, with add-on to SOC. Enrichment designs may reduce heterogeneity. Disease assessment often highly dependent on patient inputs, with (time to change in) function(s) and QoL being key components of the efficacy measures; multiple end-points usually in the same domain may be acceptable/required. Often using surrogates that allow early (interim) results used for decision making. Some adaptions can be applied along the trial. When severe, classical parallel sequential designs with long term comparison may not be applicable, unless early rescue / crossing over. Patient input on clinical relevance required. High willingness to accept trials even if SOC available. Unbalanced randomization may be useful. Thorough safety requirements may be delayed if substantial effect is observed

Cluster	Description	Implications
(5) Chronic progressive multidimensional	Life-lasting diseases, often inherited starting as paediatric and, if mild or available SOC, affecting (young) adults. Often SOC is poor or not available. Highly variable clinical course, with impact in multiple system/organs, requiring multidimensional assessment and endpoints relying on subjective assessments from caregivers/patients on clinical or functional status and QoL. Previous data on event/response rate or variance is often available for current SOC. Prevalent cases much more frequent than incident cases. If not rapidly life-threatening, prospective registries often feasible and available If inherited, known physiopathology allowing development of targeted therapies and options for genetic approaches.	Prevalent cases in paediatric population may be identified from registries, speeding recruitment. Parallel designs will be generally needed, due to progression and intersubject variability. Enrichment /stratification may be useful to control heterogeneity. Previous information on the clinical course can be suitable for bayesian approaches and planning of adaptions. Designs generally add-on to supportive SOC;reluctance to placebo may occur because of paediatric population, concern on progression and lack of effective SOC. Unbalanced randomisation, delayed start and early escape/crossing-over may be useful to limit placebo exposure and cover ethical concerns. Multiple variables applicable to cover the multidimensional nature. Function and quality of life would generally be regarded as key assessments, including patient/ caregiver's input on reported outcomes and clinical relevance. Surrogates may be useful for early (interim) decision-making, and may be validated along clinical development. For gene-therapy trials, generally a single chance is possible by subject, so that early participation preclude future options.
(6) Staged conditions	The condition initially is mild/limited to one system/organ and then progresses/expands impairment into other system/organs, with clearly defined clinical stages which cannot be studied together. Conditions are not age-specific. Different severities or extensions of disease have different prognosis and treatment approaches; disease extension is a key variable, either time dependent or not. For those neoplastic, imaging is preferred method for staging; haematological conditions also assess tumour burden, and non-malignant conditions generally measure subject function. Quality of life relevant for all. Outcomes are generally referred to progression, stagnation or reversal of the condition, with time in each stage as a relevant measure of disease. Complete healing may be possible, but requires long term confirmation. If reversal is not feasible, late stages have poor (fatal) prognosis.	Prevalent diseases with subjects identified at any stage. Registries available for slow progressive conditions, or subjects diagnosed in early stage. Well documented case series on natural course available for many conditions favouring bayesian approaches and allowing external/historical controls for ultrarare/poor prognosis. Long follow-up is required. Stage determines both design (through stratification of pre-defined subgroups) and variables (main variable being different in each stage); a variable may be change of status. Enrichment designs may use biomarkers selecting potential respondes. Multidimensional and multiple objective measurable end-points would be acceptable in milder conditions; if progression is ràpid, hard end-points may be accessible. Designs often include survival. Repeated measurements applicable along follow-up. High willingness to accept trials even if SOC available; when poor prognosis, methods to limit placebo exposure required to cover ethical concerns. Unbalanced randomization may be useful. Safety requirements may be less stringent or delayed if progression is rapid and severe, but should consider impact on QoL.

Table 19. Description of clusters and implicatons for study design.

Taken from Gòmez-Valent M.(122)

8. RESULTS

8.1. Overall description of the EPARs

8.1.1. Medicines and therapeutic indications approved

Following the search of orphan medicinal products authorised in the European Union from January 2000 to December 2014, a total of 100 different orphan medicines were identified. These 100 medicines accounted for 125 different therapeutic indications, since some medicines were approved for more than a single indication (*Annex 2*).

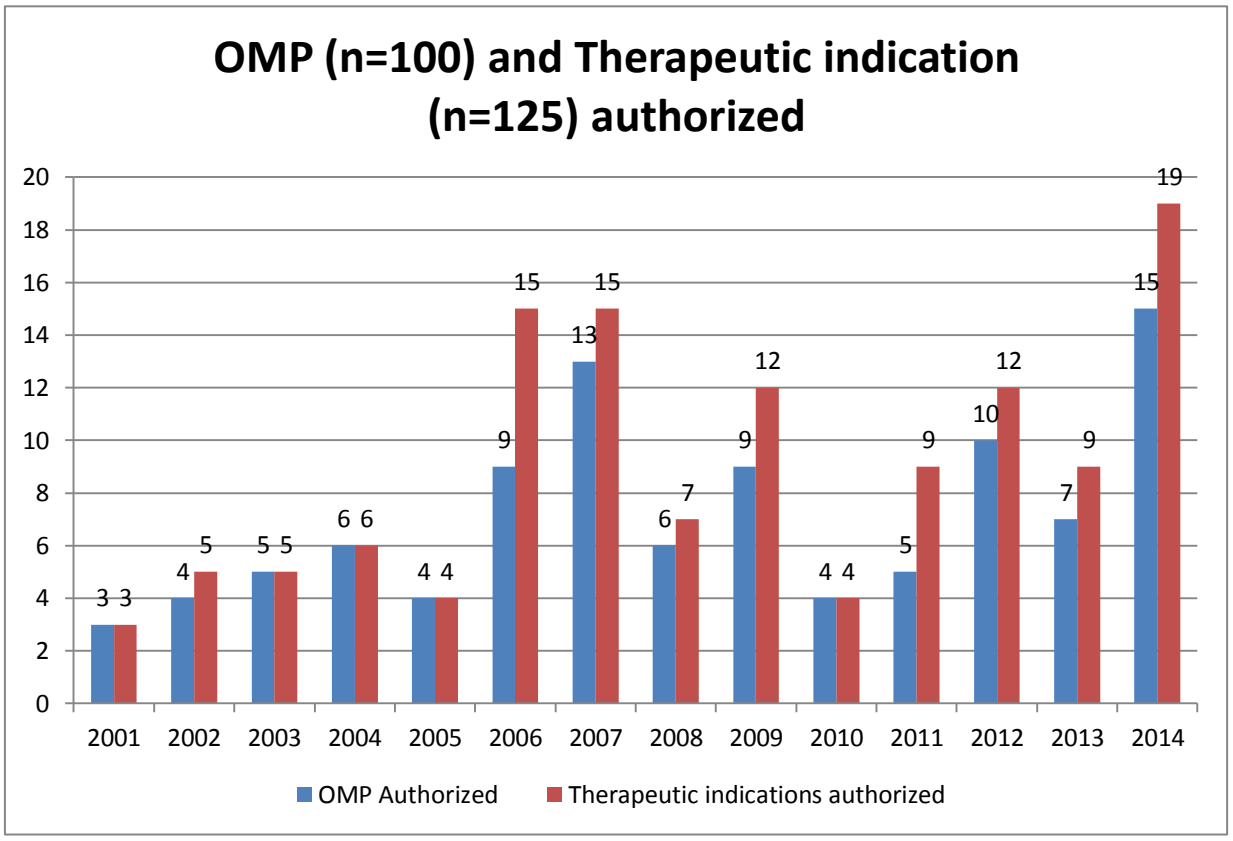
Two exceptions were produced for selection criteria because the scope of the medical condition designated by the COMP included more than a single therapeutic indication authorised with different drug development programmes for each therapeutic indication. Thus, riociguat (Adempas®) designated by the COMP with the labelling "Treatment of pulmonary arterial hypertension including treatment of chronic thromboembolic pulmonary hypertension", was authorised for the treatment of the pulmonary arterial hypertension and for the treatment of thromboembolic pulmonary hypertension with different drug development programmes and different clinical trials were conducted for each setting. Likewise, everolimus (Votubia®), designated by the COMP with the labelling "Treatment tuberous sclerosis", was authorised for the treatment of subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex and for the treatment of renal angiomyolipoma associated with tuberous sclerosis complex with different drug development programmes.

Also, two therapeutic indications were covered by two orphan designations each one because a single clinical development was conducted for both orphan designations involved, and the EMA accepted a single wording for the therapeutic indication encompassing the scope of both orphan designations. These therapeutic indications were the treatment of myelofibrosis due to different causes with ruxolitinib (Jakavi®) and the treatment of papillary and follicular thyroid carcinoma with sorafenib (Nexavar®).

Thus, from January 2000 to December 2014, 100 different orphan medicinal products were authorised which held an Orphan Drug Designation at the time of the marketing approval. Furthermore, these 100 orphan drugs accounted up to 125 different therapeutic indications.

The number of orphan medicines and therapeutic indications approved per year by the EMA throughout the period of time considered (from 2000 to 2014) increased along time up to a maximum of 15 different medicines and 19 different therapeutic indications in 2014 (*Figure 20*).

Figure 20. Orphan medicines and therapeutic indications approved yearly from January 2000 to December 2014



Overall, the approved orphan medicinal products were aimed to treat 84 different rare medical conditions. In this sense, up to 21 rare medical conditions had more than a single medicine authorised for their treatment.

The medical condition that had more orphan medicinal products approved was "Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension" which had 8 different medicines approved in the European Union, followed by "Acute lymphoblastic leukaemia" which had 6 different medicines approved, "Chronic myeloid leukaemia" which had 5 different medicines in the market and "Renal cell carcinoma" which had 4 orphan medicines authorised. The remaining rare medical conditions had 3 or fewer medicines approved. All rare medical conditions with at least one orphan medicinal product approved in Europe with EMA orphan designation and the number of authorised orphan medicinal products for each condition are displayed in Annex 3.

8.1.2. Type of rare diseases covered by therapeutic indications approved

All therapeutic indications included in the authorisation of orphan medicinal products approved during the studied period were classified according its ICD-10 group. Most of therapeutic indications were aimed to treat "Neoplasms" (Group II of ICD-10 classification) which accounted for 41.6% out of the 125 therapeutic indications followed by "Endocrine, nutritional and metabolic diseases" which accounted for 28.6%, and "Diseases of the circulatory system", "Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism", and "Diseases of the nervous system" with 6.4%, 5.6% and 4% respectively. The rest of groups of diseases entailed equal or less than 2.4% of therapeutic indications studied. The total number and proportion of therapeutic indications approved for each ICD-10 group is shown in *Table 21*.

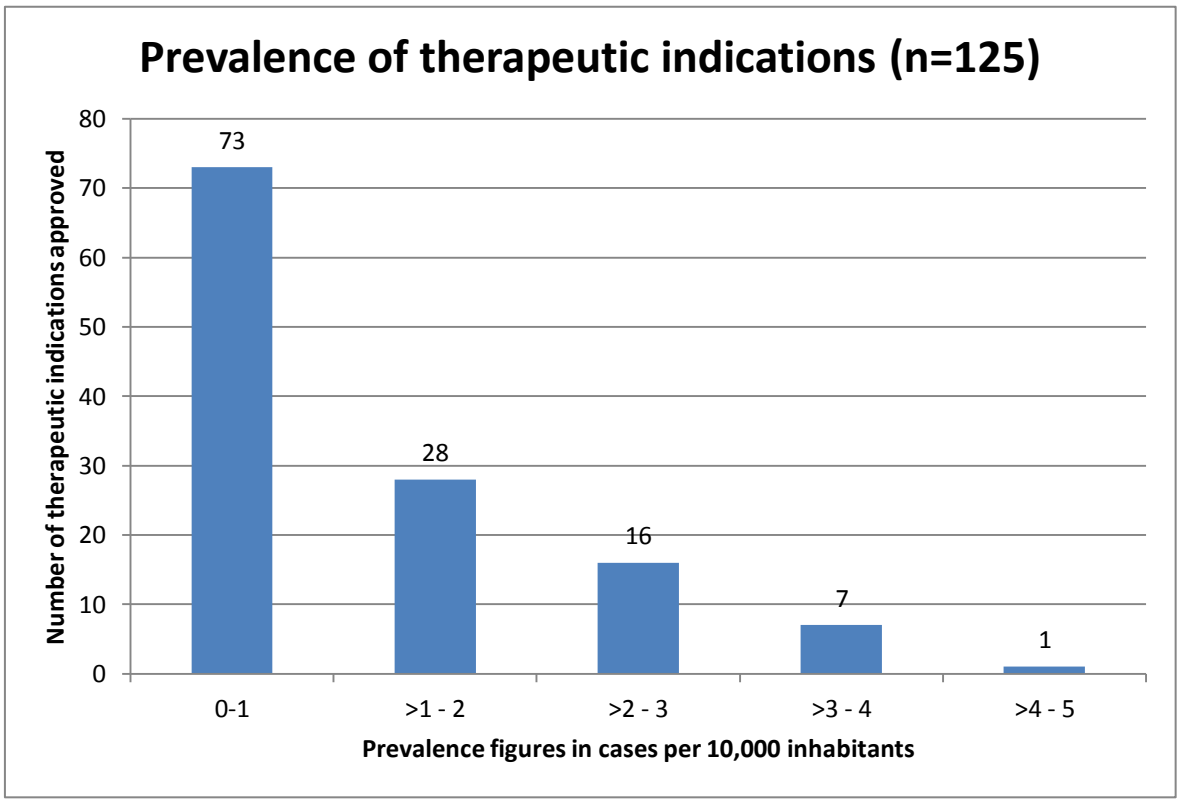
Table 21. Total number of therapeutic and proportion of therapeutic indications approved for each ICD-10 group.

ICD-10 Group	Number of therapeutic indications	Rate
II Neoplasms	52	41.60%
IV Endocrine, nutritional and metabolic diseases	36	28.80%
IX Diseases of the circulatory system	8	6.40%

III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	7	5.60%
VI Diseases of the nervous system	5	4.00%
I Certain infectious and parasitic diseases	3	2.40%
XI Diseases of the digestive system	3	2.40%
XVII Congenital malformations, deformations and chromosomal abnormalities	3	2.40%
XIX Injury, poisoning and certain other consequences of external causes	2	1.60%
XXI Factors influencing health status and contact with health services	2	1.60%
X Diseases of the respiratory system	1	0.80%
XIII Diseases of the musculoskeletal system and connective tissue	1	0.80%
XVI Certain conditions originating in the perinatal period	1	0.80%
XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1	0.80%
Total	**125**	**100.00%**

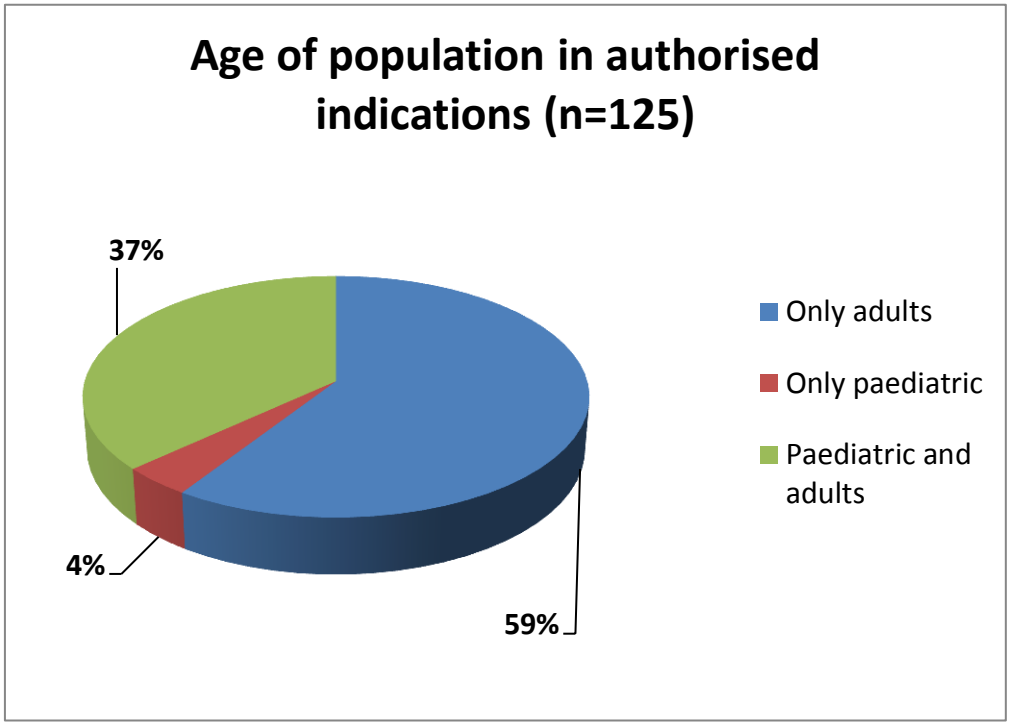
All approved therapeutic indications (n=125) were also classified regarding the overall prevalence of the umbrella medical condition under which each therapeutic indication could be included (expressed in cases per 10,000 inhabitants in the European Union). In this sense, most of indications were aimed to treat diseases in the lowest range of prevalence permitted (78 therapeutic indications had prevalences between 0 to 1 cases per 10,000 inhabitants) and only one therapeutic indication was approved to treat a disease with a prevalence between 4 and 5 cases per 10,000 inhabitants, that is, in the highest range of prevalence allowed by the European Regulation on orphan medicinal products ER 141/2000. The prevalence of undelying medical conditions for the 125 authorised therapeutic indications is displayed in *Figure 22*.

Figure 22. Ranges of prevalence of the authorised indications.



Whether the wording approved in labelled indications at the time point of December 2014 included or not paediatric population, defined by age below 18 years, was analysed. The results showed that 74 (59%) of therapeutic indications approved were authorised only for adult populations, 46 (37%) of therapeutic indications were approved for both adult and paediatric population, and 5 (4%) of therapeutic indications were approved exclusively for paediatric populations. The age scope of authorisations is shown in *Figure 23*.

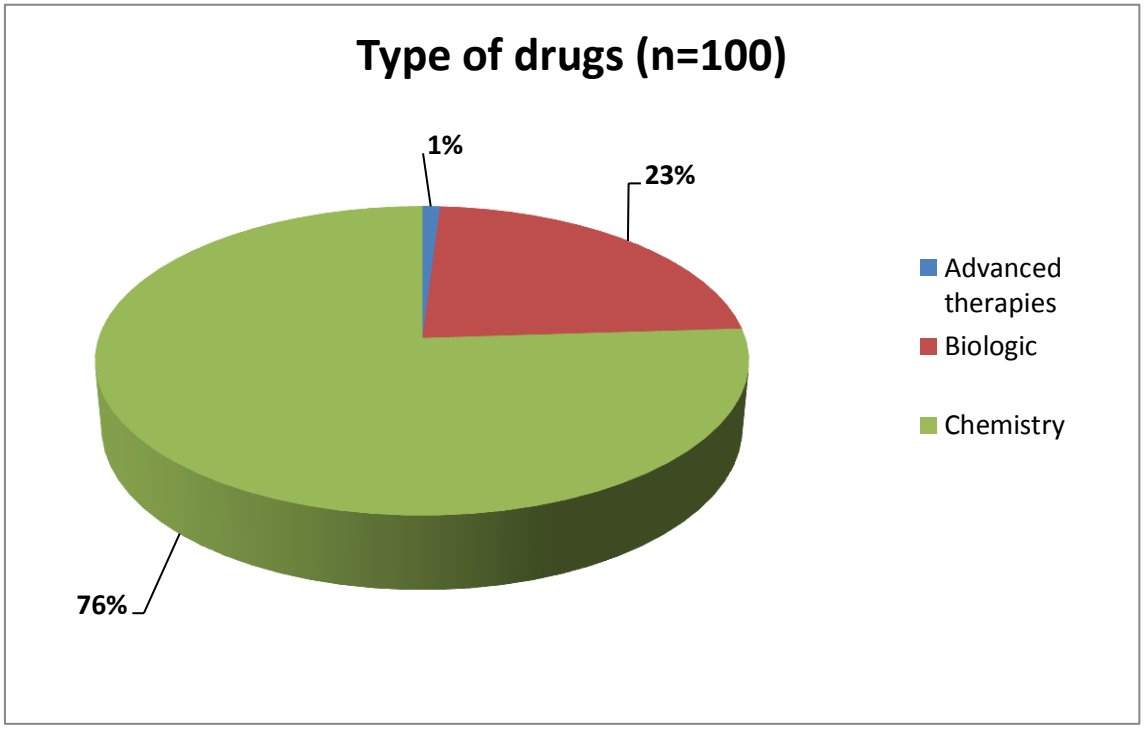
Figure 23. Age of population of therapeutic indications approved.



8.1.3. Type of drugs approved

Most of orphan medicinal products approved were considered small molecules or "Chemical" molecules (n=76; 76%), 23 (23%) orphan medicinal products were "Biological" molecules (excluding advanced therapies), and only one (1%) orphan medicinal product was qualified as an "Advanced therapy". Distribution of type of molecule can be observed in *Figure 24*.

Figure 24. Type of molecule of the first 100 orphan medicines approved in Europe



Regarding the mechanism of action, up to 9 different drugs had a tyrosin kinase inhibition action and 8 orphan medicinal products were enzyme replacement therapies. Other types of mechanisms of action frequently observed were the following: 6 were antimetabolite chemotherapies, 4 were described as "immunomodulator chemotherapy", 4 acted as endotelin receptors antagonists" and 3 were mTOR inhibitors. The mechanisms of action for all orphan medicinal products are detailed in Annex 4.

8.1.4. Transfers of ODD among holders

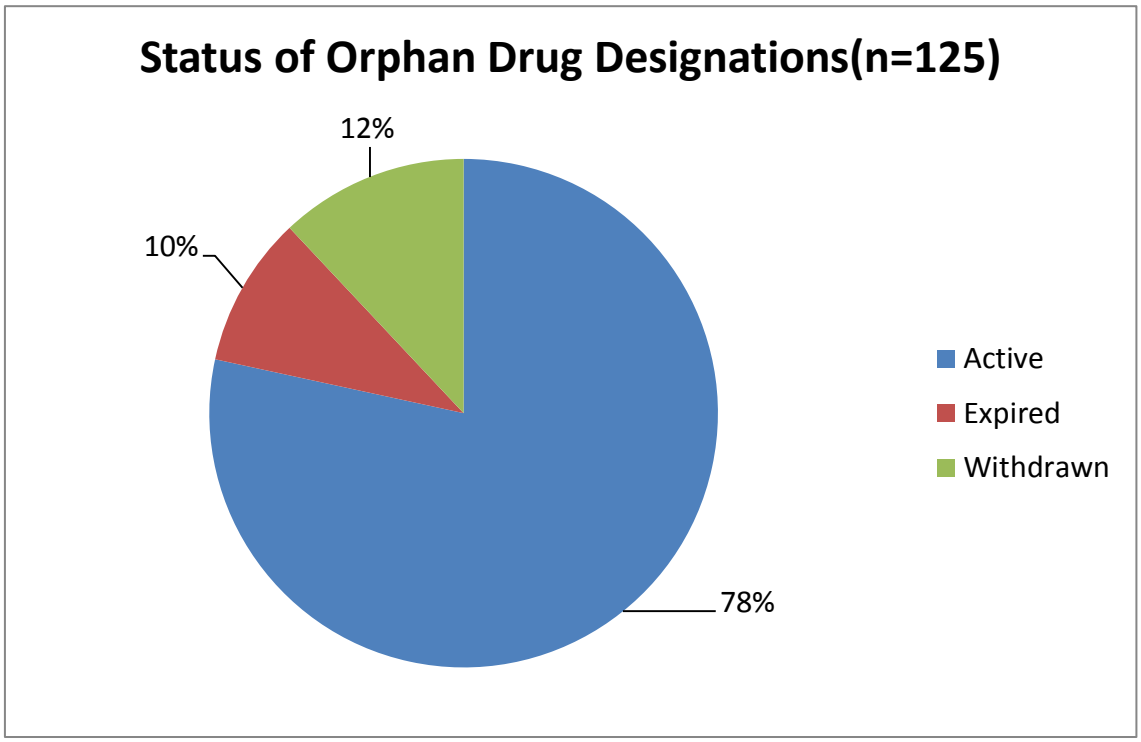
As previously mentioned in the introduction section, to be formally considered an orphan medicine, the Orphan Drug Designation (ODD) should be applied by a sponsor and concealed by the EMA before the marketing authorisation.

In this regard, the time lapsed from the Orphan Drug Designation to the Marketing Authorisation have been studied for each therapeutic indication approved (n=125), taking into account that Orphan Designation must be requested for each different

medical condition. The median time from Orphan Drug Designation to Marketing Autorisation for the 125 therapeutic indications approved was 1,229 days (3.36 years) (IQR: 752-1,878) and the mean was 1,421.84 days (SD=925 days). Nonetheless, a big variation was observed among the different therapeutic indications with a range of lapsed time going from 77 days for the shortest procedure up to 3.864 days for the longest one.

Regarding to expiry of the orphan drug designation (ODD) market exclusivity period, by December 2014 98 (78%) had its ODD active, 12 (10%) had its ODD expired because the time of market exclusivity had elapsed and finally, for 15 (12%) indications its ODD was withdrawn at request of the sponsor. The status of orphan designation by December 2014 is shown in *Figure 25.*

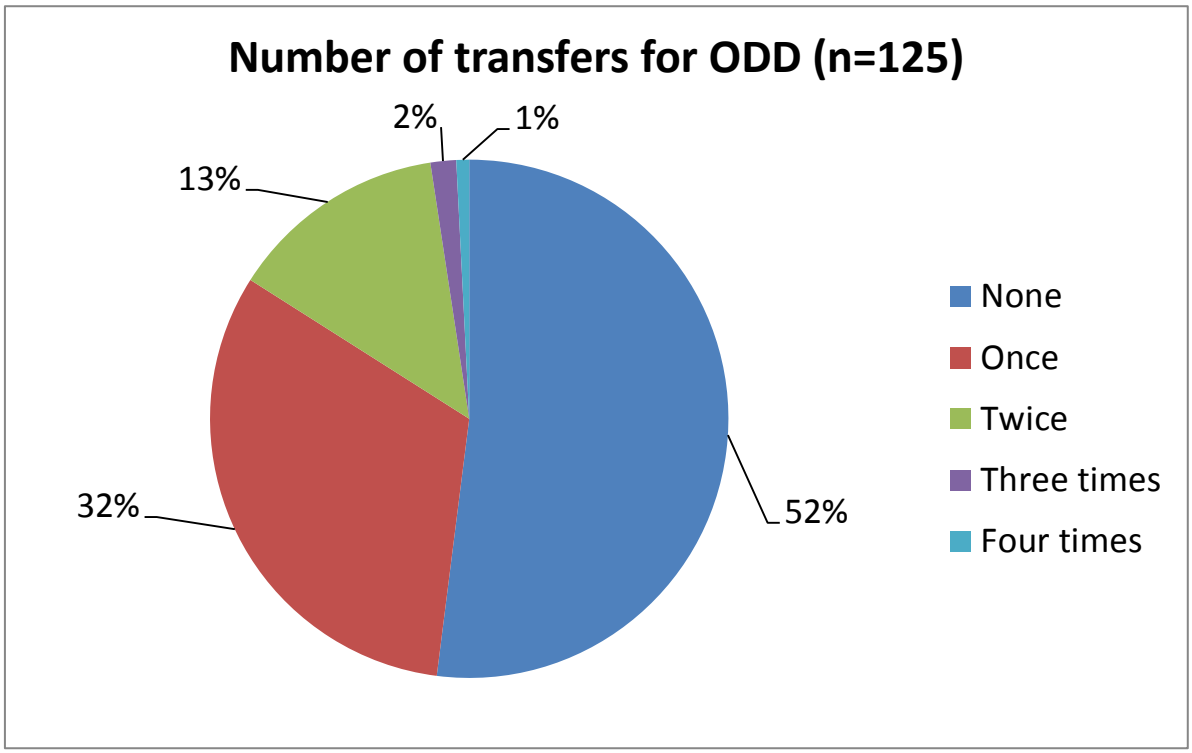
Figure 25. Proportion of orphan designation status of approved orphan medicinal products in December 2014.



The number of transfers among different companies for each ODD was analysed. By December 2014, in 65 (52%) therapeutic indications the holder of the orphan designation had not changed, in 40 (32%) therapeutic indications the holder of the

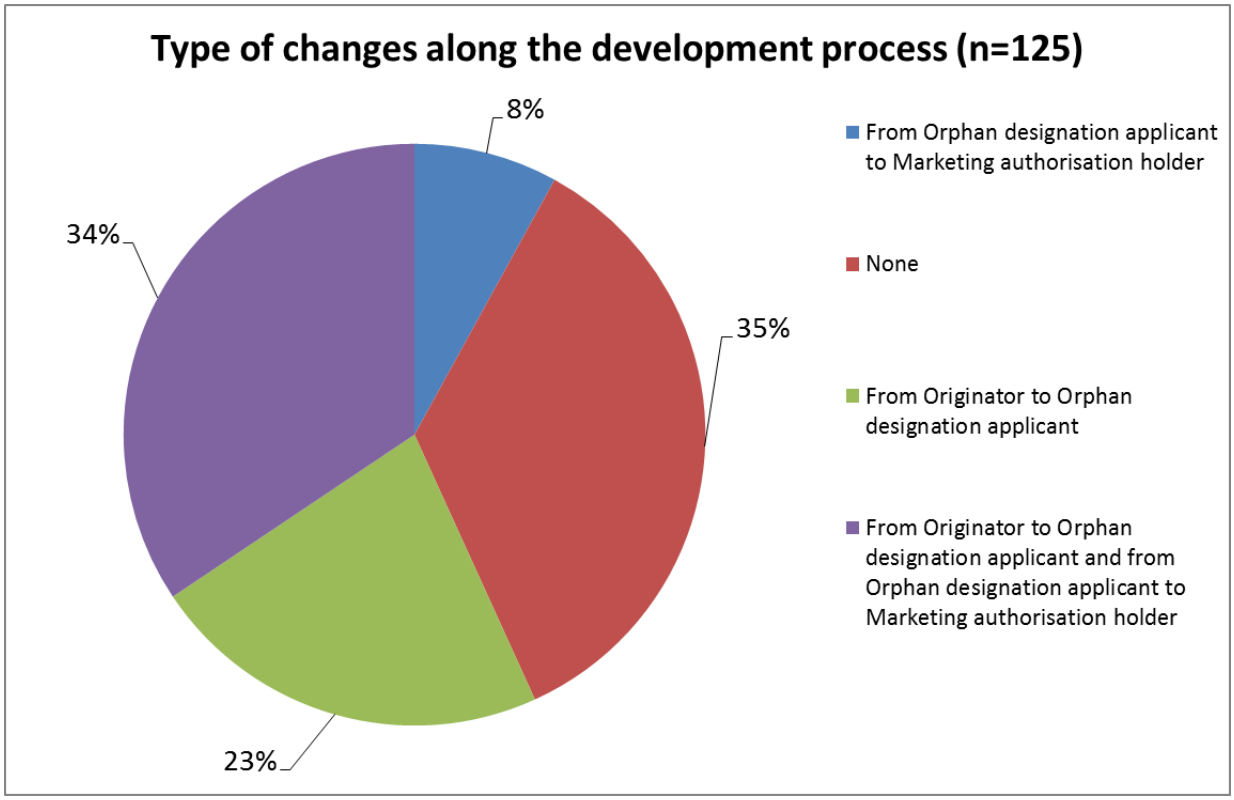
orphan designation changed a single time, for 17 (13%) therapeutic indications the holder of the orphan indication had changed twice, for 2 (2%) the holder had changed three times, and for 1 (1%) changed up to four times. These figures are displayed in *Figure 26*.

Figure 26. Changes of holder for orphan designation.



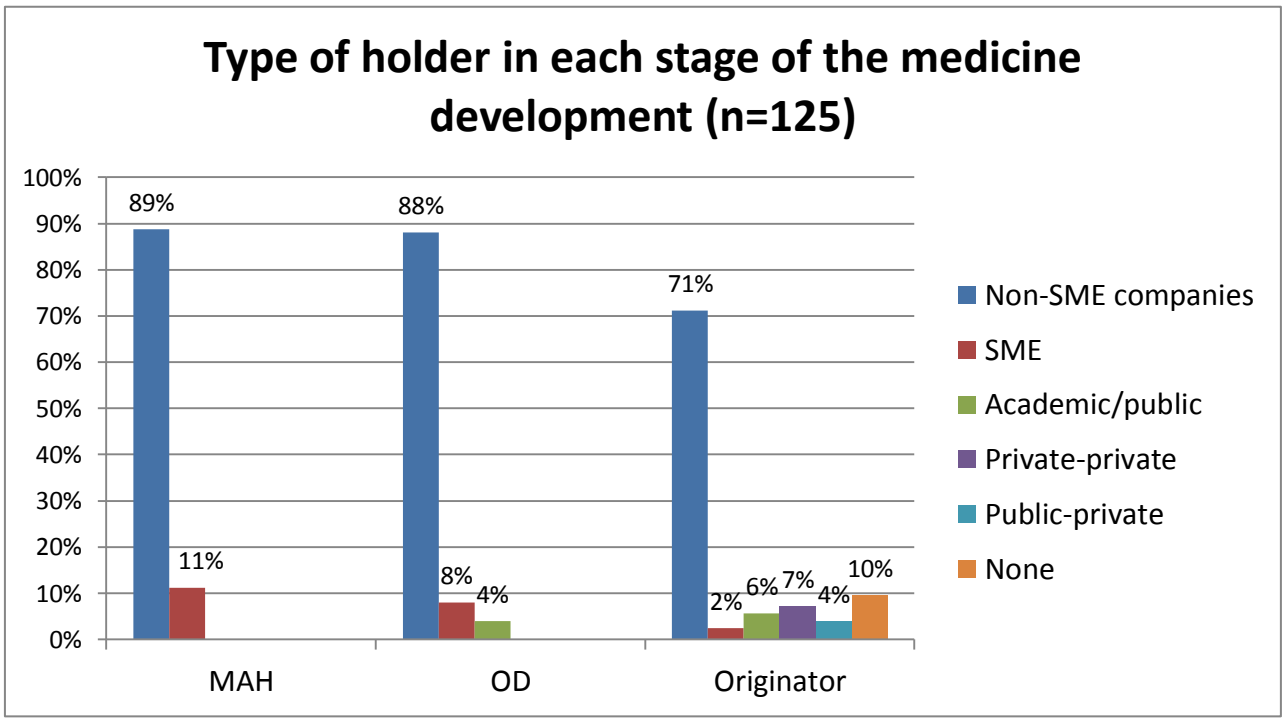
Regarding the transfer of products between holders, changes of holder between three stages (originator of the molecule according to the Integrity database, requester of Orphan Drug Designation, and Marketing Authorisation Holder by December 2014) was described for the 125 authorised indications. The same entity was involved in all stages in 35% (n=44) of indications, and 65% (n=81) indications changed of holder at least in one of the steps: 23% changed from Originator to Orphan Drug Designation applicant, 8% from Orphan Drug Designation applicant to Marketing Authorisation Holder and 34% from Originator to Orphan Drug Designation applicant to Orphan Drug Designation applicant and also to Marketing authorisation holder. The changes are described in *Figure 27*.

Figure 27. Type of transfers among holders during development



Likewise, the type of holder in each step included several types of companies or consortiums. While non-SME enterprises were the most frequent type of entity at all stages (71% of originators, 88% of ODD applicants and 89% of MAH), the proportion of other types of entities changed along phases: SME companies were originators in 2% of indications, ODD applicants in 8% of indications and MAH for 11% of indications. Other types of entities did not act as MAH, and only public or academic institutions acted as ODD applicants in 4% of indications. Originators included private-private consortiums in 7% of cases, public or academic institutions in 6% of cases and public-private consortiums in 4% of cases. In 10% of indications no originator could be identified. The type of holder in each step of the orphan medicine development is represented in *Figure 28*.

Figure 28. Type of holder in each step of the orphan medicine development.

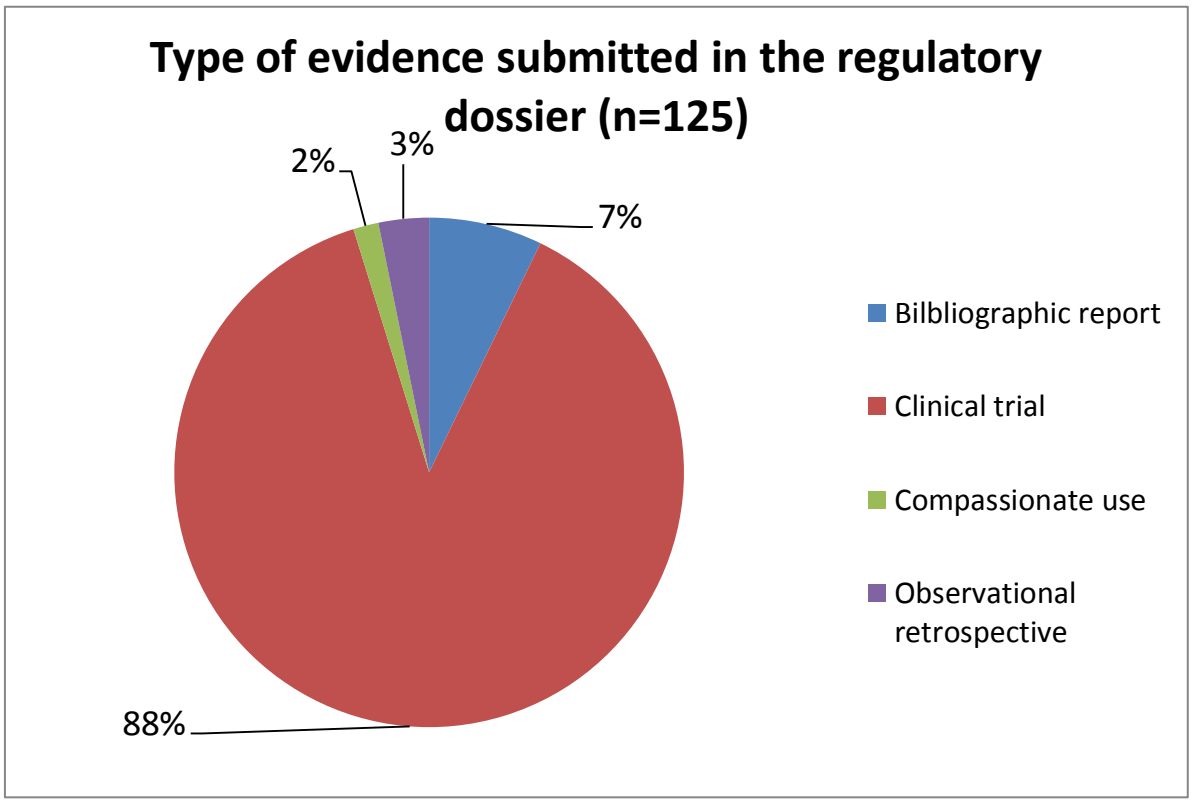


8.2. Description of the EPARs

8.2.1. Type of scientific evidence

Of 125 therapeutic indications approved, in 110 (88%) the scientific evidence referred in the EPAR as supporting the positive balance/benefit risk of the product was based on "Clinical Trials". The remaining 15 therapeutic indications (including 12 different orphan medicinal products) were based on "Bibliographic reports" (9 indications, 7%), on "Observational retrospective studies" (4 indications, 3%) and on data coming from "Compasisonate use studies" (3 indications, 2%). The type of evidence supporting the authorisation decision is summarised in *Figure 29*.

Figure 29. Type of evidence supporting MAA



For the 110 therapeutic indications with scientific evidence arising from clinical trials, up to 159 main or pivotal clinical trials were identified in the EPARs. The mean (SD) number of clinical trial conducted for each indication was 1.45 (0.73), and the median (interquartile range) was 1 (IQR: 1 - 2) clinical trial, with a range between 1 and 5 trials.

The number of supportive studies included in the 110 EPARs was 339, with a mean (SD) number of 3.08 (2.25), a median (interquartile range) of 3 (IQR: 2 - 4) supportive studies and a range between 0 to 15 supportive trials.

Regarding the type of scientific evidence included in the dossiers submitted to obtain the marketing approval in function of the type of molecule, all advanced therapies and biological drugs submitted scientific evidence coming from clinical trials. Dossiers submitted to get the marketing approval based on scientific evidence generated from different sources like bibliographic reports, compassionate use studies or observational retrospective studies were limited to chemical entities. Results are shown in *Table 30*.

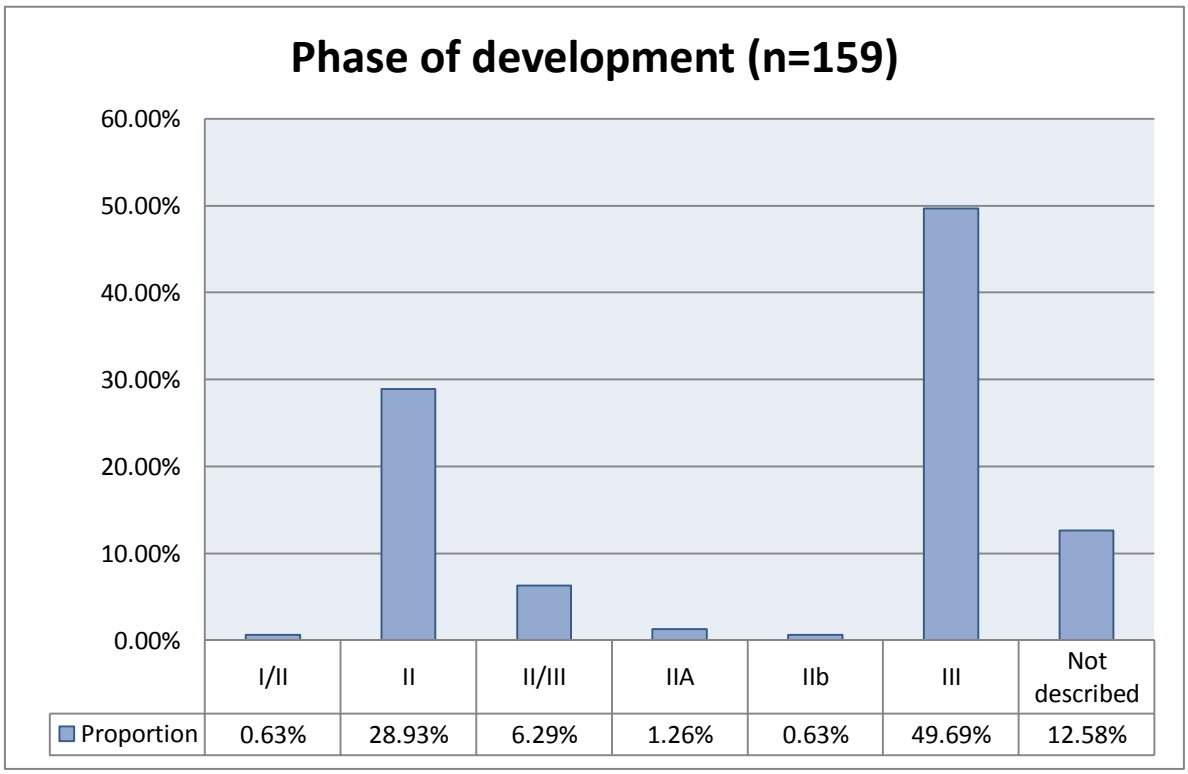
Table 30. Type of supportive evidence by type of molecule.

Type of drug / Type of dossier	Clinical trial	Bibliographic report	Compassionate use	Observational retrospective	Total
Advanced therapies; n (%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Biologic; n (%)	25 (100%)	0 (0%)	0 (0%)	0 (0%)	25 (100%)
Chemistry; n (%)	84 (84.8%)	9 (9.1%)	2 (2.0%)	4 (4.0%)	99 (100%)
Overall; n (%)	110 (88%)	9 (7.2%)	2 (1.6%)	4 (3.2%)	125 (100%)

8.2.2. Type of trials

Regarding the phase of the 159 pivotal trials, 79 (49.7%) were phase III and 60 were diffferent types of phase II trials: 46 (28.9%) trials were classified as Phase II, 1 (0.6%) as a Phase IIb trial, 2 (1.3%) trials as Phase IIa, 10 (6.3%) trials were considered Phase II/III, , and 1 (0.6%) trial was considered Phase I/II. On the other hand, 20 (12.6%) different trials were not cathegorized for development phase in the European Public Report Assessment. The development phase of the pivotal trials is summarised in *Figure 31*.

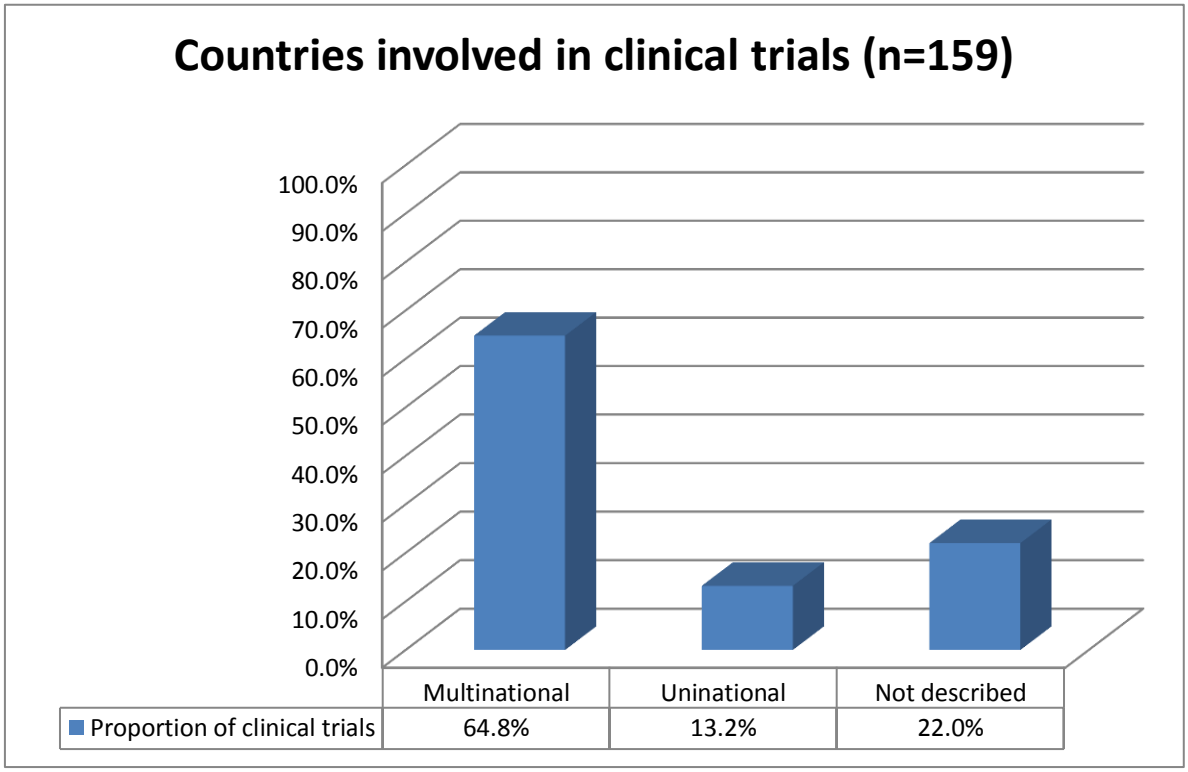
Figure 31. Phase of development of pivotal trials.



Out of the 110 different therapeutic indications that were approved in Europe based on evidence coming from clinical trials, 61 (55.5%) counted with at least one Phase III trial in its development programme, as opposed to 49 (44.5) therapeutic indications that did not have any Phase III pivotal trial at the time of marketing authorisation.

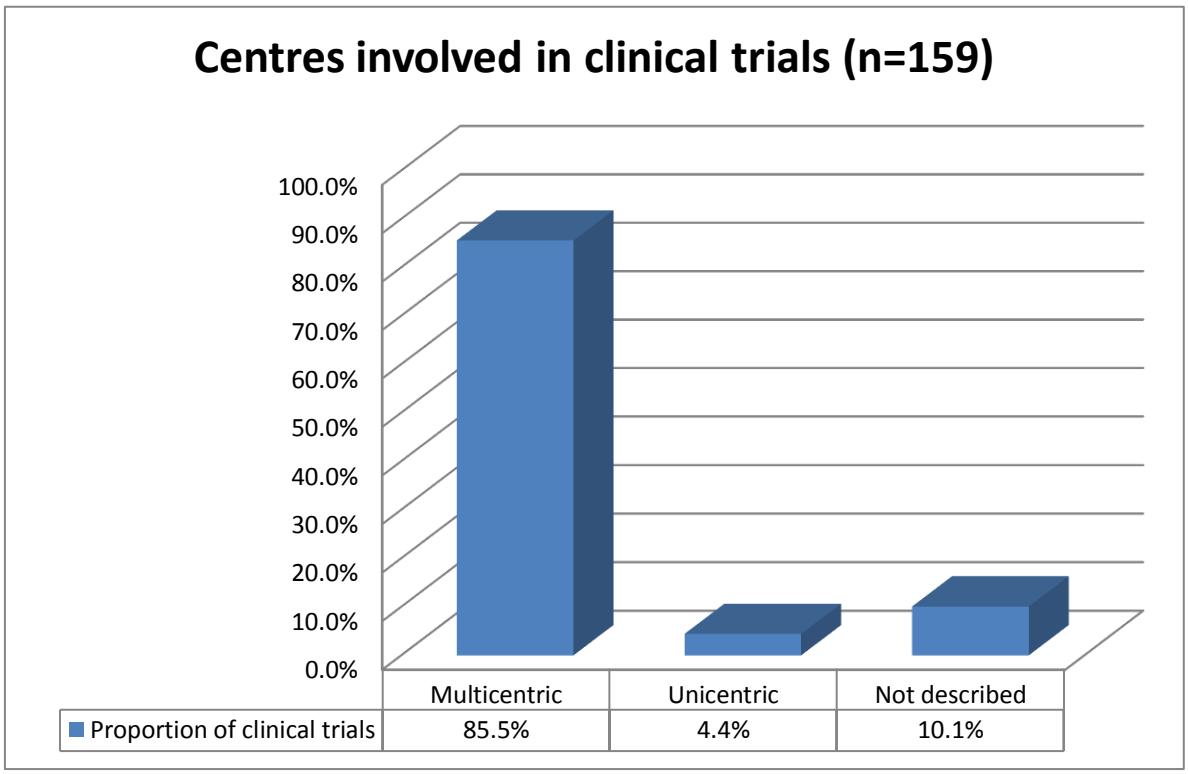
Overall, 103 (64.8%) pivotal clinical trials were multinational studies and 21 (13.2%) were conducted in a single country. For 35 (22%) trials the number of countries involved were not described in the European Public Assessment Reports. Results are represented in *Figure 32.*

Figure 32. Number of involved countries in pivotal trials.



On the other hand, 136 (85.5%) pivotal clinical trials were multicentric studies and 7 (4.4%) trials were unicentric; for 16 (10.1%) trials the number of centres participating in the trial was not reported in the corresponding European Public Assessment Report. These findings are summarised in *Figure 33*.

Figure 33. Number of participating sites in pivotal trials

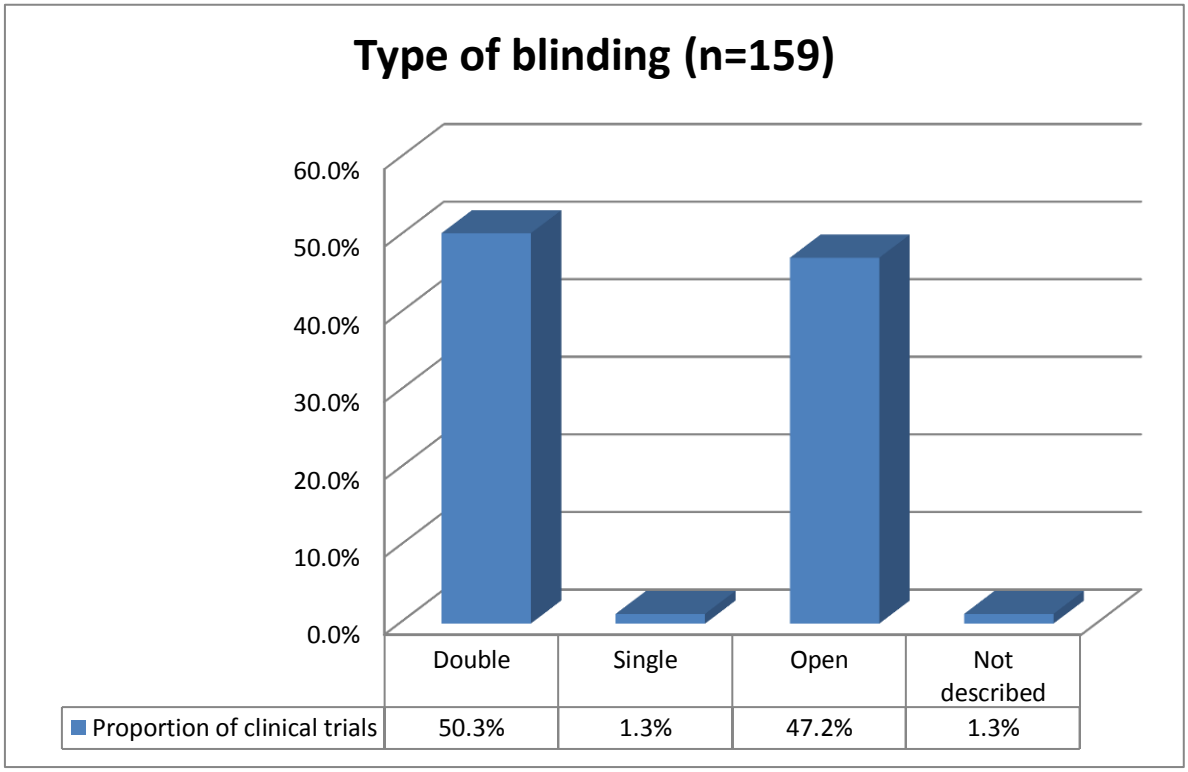


8.3. Design of pivotal trials

8.3.1. Assignation and blinding

Out of the 159 pivotal clinical trials, 80 (50.3%) were double blinded, 2 (1.3%) trials were single blinded and 75 (47.2%) were open label studies; in 2 cases (1.3%) blinding was not described in the EPAR. Type of blinding in pivotal trials is shown in *Figure 34*.

Figure 34. Blinding in pivotal clinical trials.



In 109 (68.6%) of pivotal clinical trials the population included was randomized, and in 50 (31.4%) trials no randomization was done. For those randomized, in 74 (67.9%) of clinical trials a stratification system was applied (*Figure 35* and *Figure 36)*.

Figure 35. Randomization in pivotal clinical trials

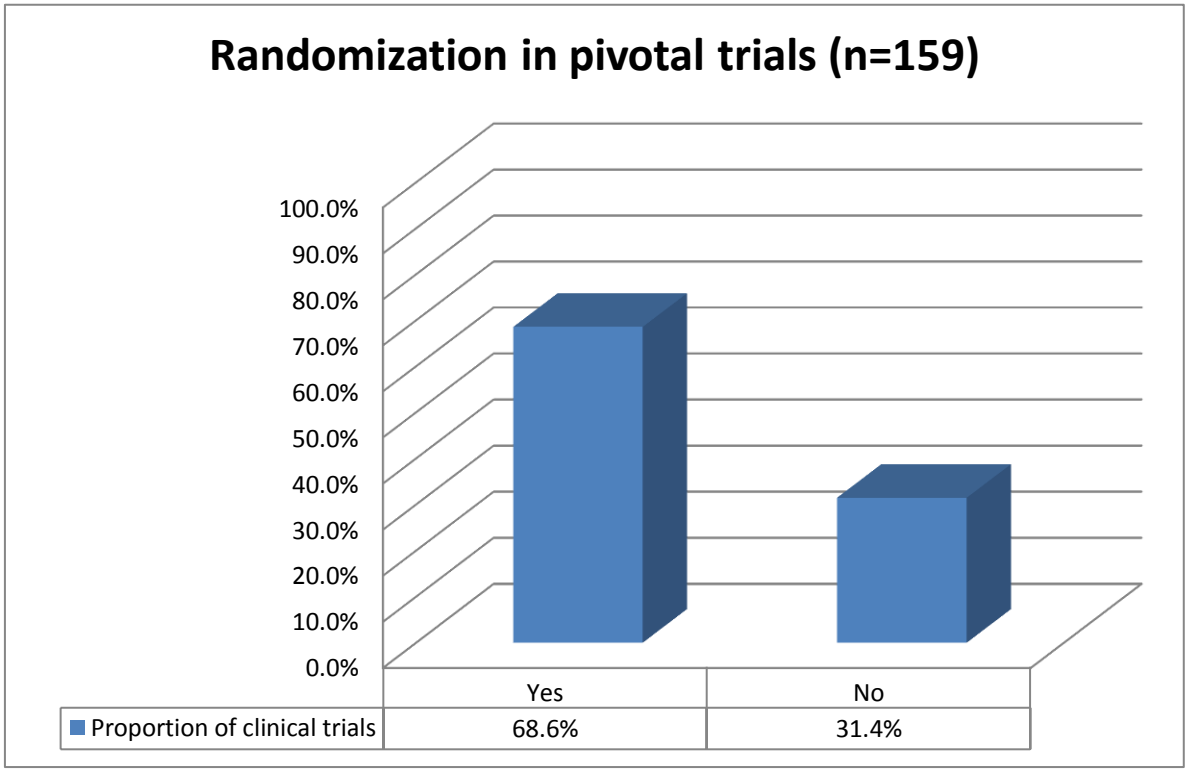
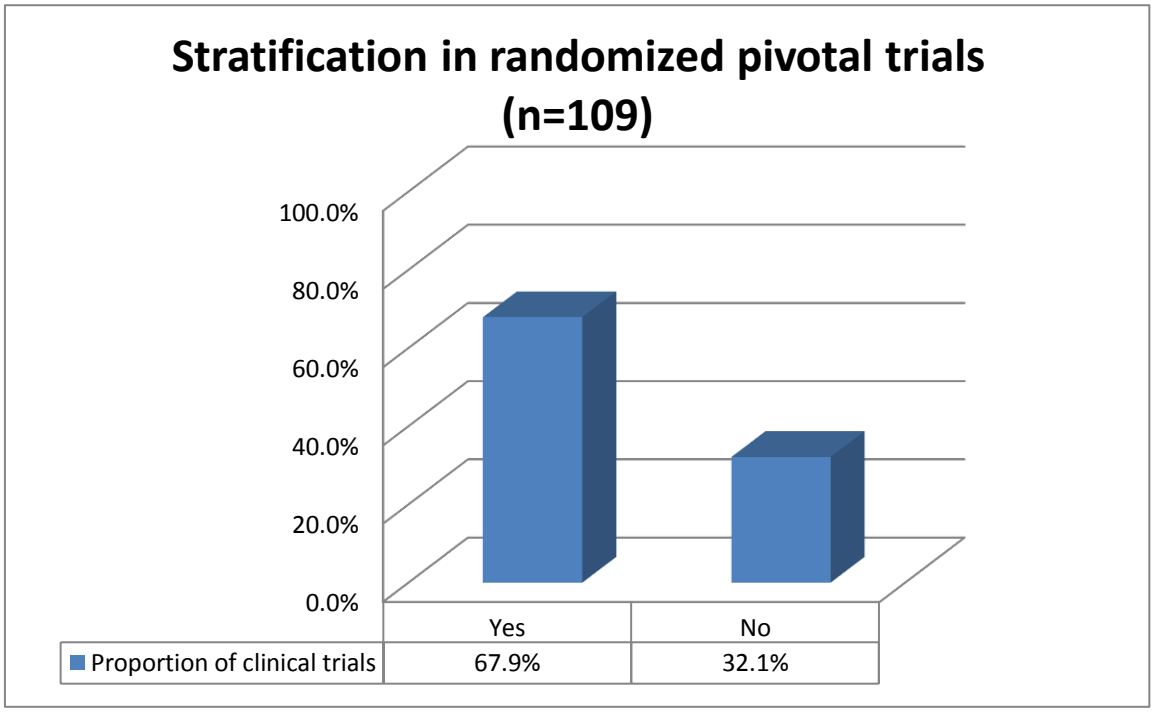


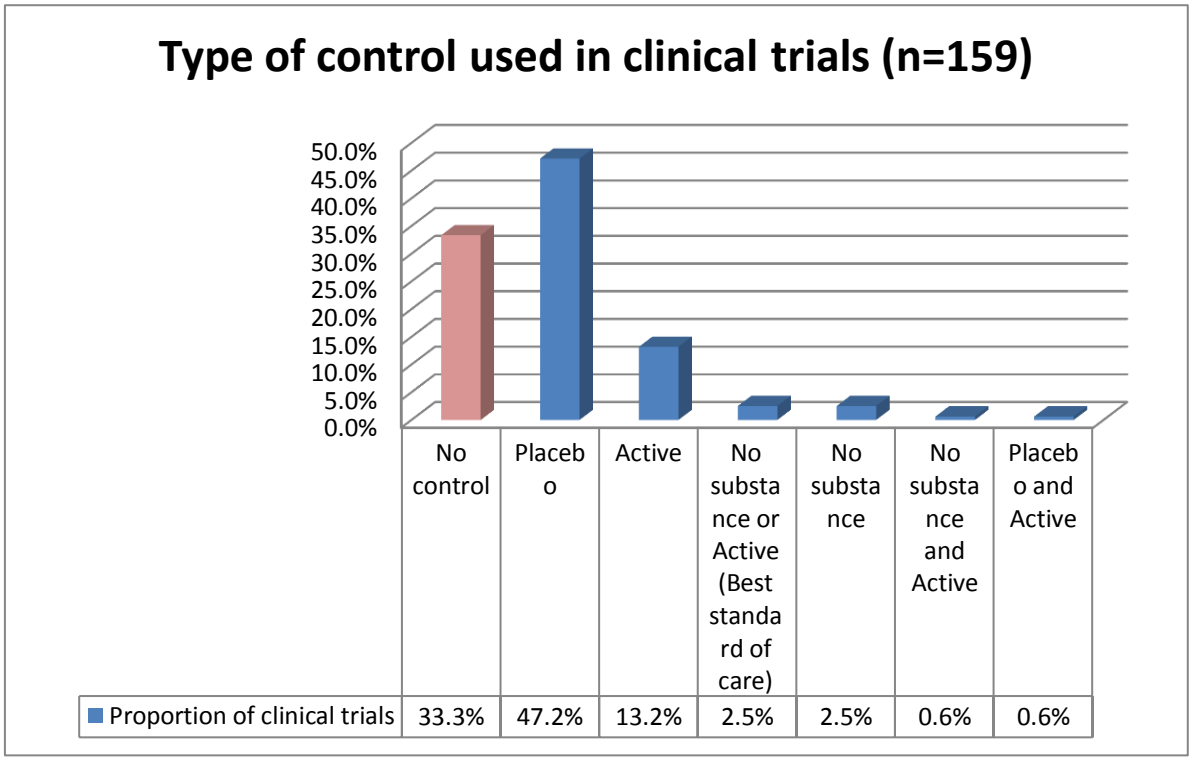
Figure 36. Stratification in randomized pivotal trials.



8.3.2. Control groups

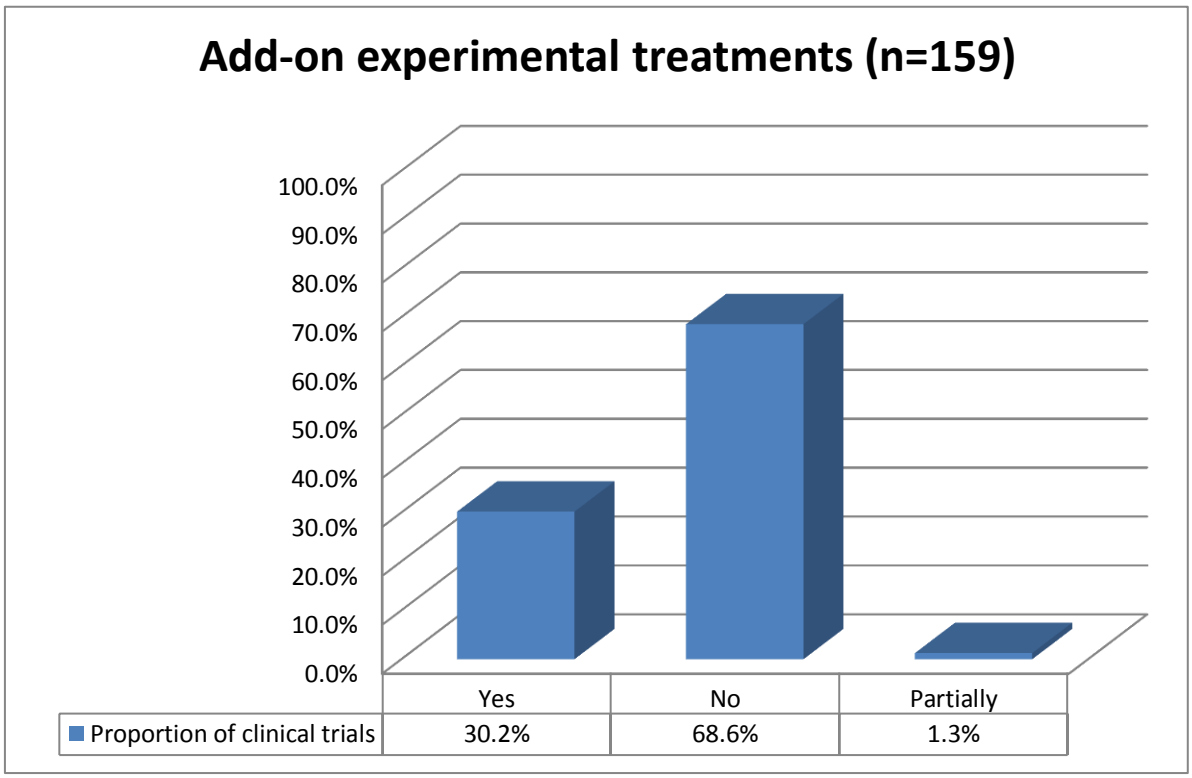
Regarding the existence or absence of comparators and the type of comparators used, 53 (33.3%) of clinical trials were not controlled and 106 (66.7%) had some type of control. Overall, 75 (47.2%) of trials used placebo as control and 21 (13.2%) of trials used an active control; in 4 (2.5%) trials the comparator was the best standard of care, in 4 (2.5%) trials the control arm did not receive any substance, in two trials (1.2%) there were two comparator arms; in one trial one arm did not receive any substance and one received an active control, and the other trial had one placebo arm and one active control arm. Comparators are summarised in *Figure 37.*

Figure 37. Type of comparators used in pivotal trials



In 48 (30.2%) trials the experimental orphan drug was an add-on treatment to standard of care or baseline treatment, while in 109 (68.6%) of pivotal trials the experimental orphan drug was not incremental to any background therapy. Finally, in 2 (1.3%) cases the experimental orphan drug was an add-on therapy only in some study arms. Results are represented in *Figure 38*.

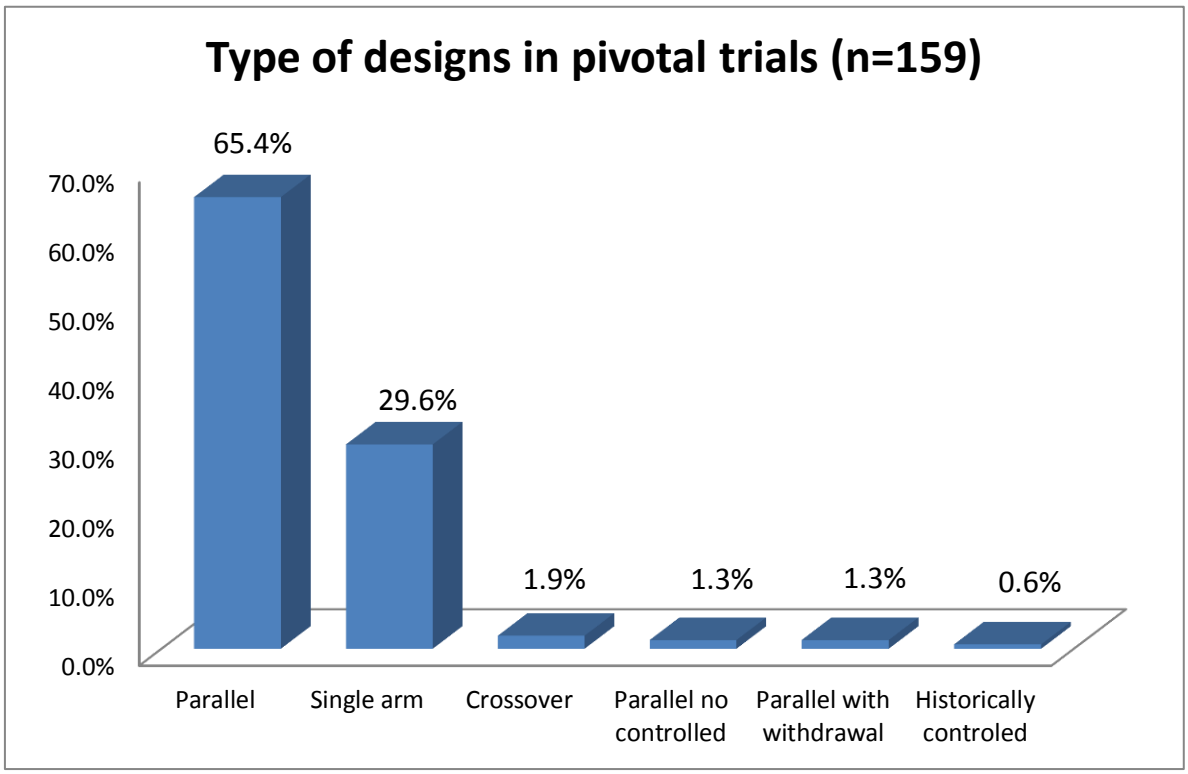
Figure 38. Add-on therapy designs in pivotal trials.



8.3.3. Trial arms and setting

Regarding the methodological design, 104 (65.4%) trials had a conventional parallel arms design, 47 (29.6%) trials were single arm studies, 3 (1.9%) were crossover design studies, 2 (1.3%) trials were considered as uncontrolled parallel studies since all arms received the experimental drug in different ways or doses, 2 (1.3%) trials were parallel studies with periods of drug withdrawal, and a single trial (0.6%) was controlled with historical data. The designs are summarised in *Figure 39*.

Figure 39. Type of designs in pivotal clinical trials



As regards to the number of treatment arms included in the trial design, the median of arms included in the trials was 2, ranging from 1 arm up to 4 different arms. The median of experimental arms (arms assigned to the experimental treatment) was 1 (ranging from 1 arm to 3 different experimental treatment arms).

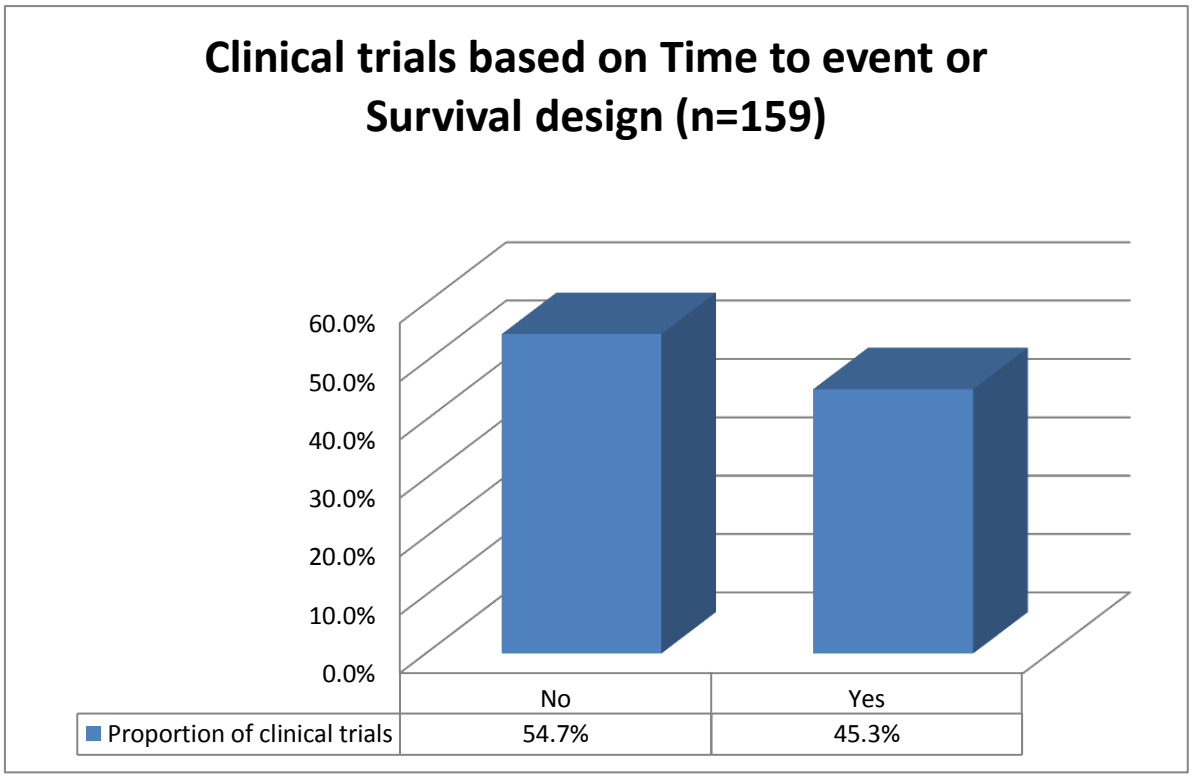
8.3.4. Sample size and study duration

The mean (SD) and median (interquartilic range) size of the sample of patients enrolled in the pivotal clinical trials was 198.51 (193.9) and 134 (IQR: 55.5 - 288), respectively, with values ranging from 5 patients to 934 patients. Besides, the mean (SD) and median (interquatilic range) of the subgroup of patients enrolled in the arms assigned to to the experimental drugs was 131.31 (132.48) and 100 (IQR: 40.5 - 176), respectively, ranging from 5 to 934 patients.

The mean (SD) and median (Interquartilic range) duration of the trials, as regards to the time point established to mesure the main endpoint of the study, was 27.95 weeks (32.72) and 21 weeks (IQR: 8.14 - 33.87), respectively, ranging from 0.01 to 221 weeks. In this aspect, the analysis was limited to 139 clinical trials because in 20 trials the

duration was not described. There were 72 (45.3%) trials designed with time to achieve an event or survival as main end-point, or for which the time point to analyse the main endpoint was not pre-specified (*Figure 40)*. When these trials were excluded, the mean (SD) and median (interquartilic range) point time to determine the main endpoint results was 25.05 weeks (21.21) and 24 weeks (IQR: 12 - 26) weeks, respectively, with a range from 0.85 to 102 weeks. In the same way, one trial was excluded from the analysis because the duration was not described.

Figure 40. Proportion of trials which design was based on time to event or survival.



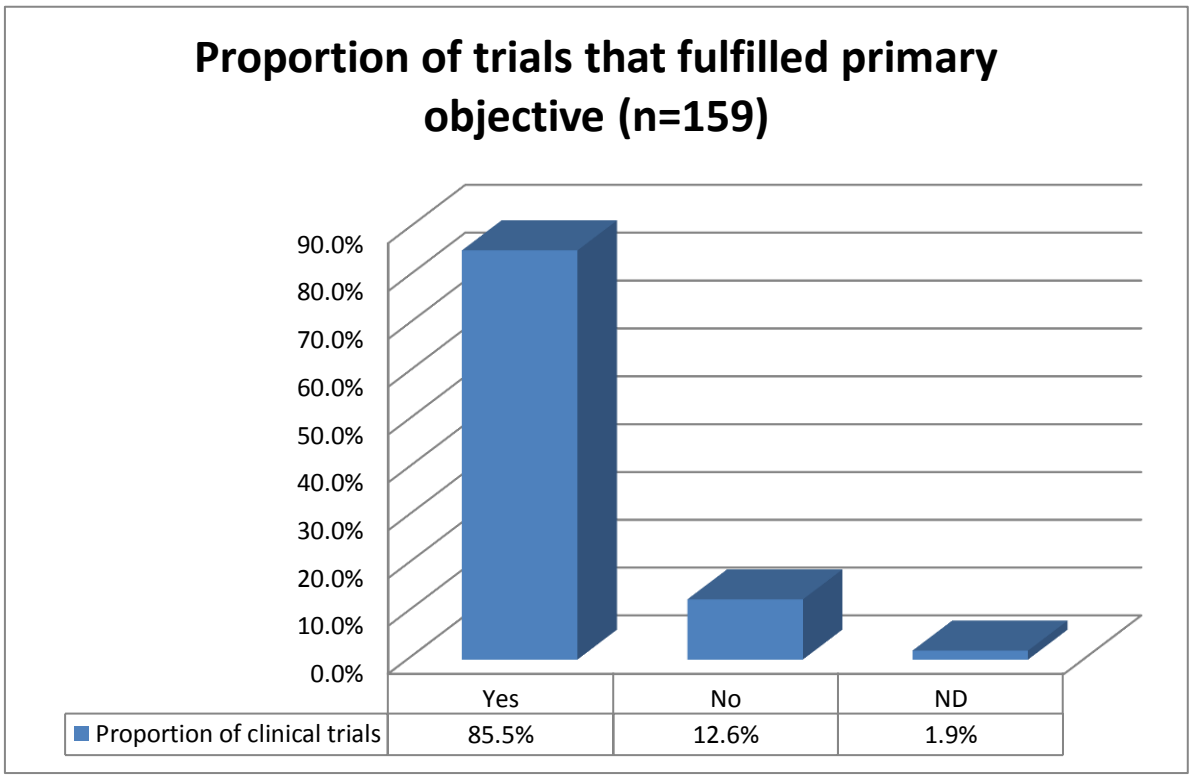
The mean (SD) and median (interquartilic range) number of patients exposed to the experimental orphan treatment across the different studies (not only main trials) included in the European Public Assessment Report was 893.53 (1,647.25) and 511 (IQR: 256.25 -896), ranging from 27 patients to 15,715 different patients.

The longest follow up time available for each orphan drug was considered; the mean (SD) and median (interquartilic range) of the longest follow up period was 162.39 weeks (158.73) and 110 weeks (IQR: 77 -182.85), ranging from 24 weeks to 959 weeks.

8.3.5. Study results

The number of trials that fulfilled the primary objective of the study was 136 (85.5%), while 20 (12.6%) trials did not achieve their primary objective and in 3 (1.9) cases the definition of the objective or outcomes did not allow to clarify the goals. The proportion of trials that fulfilled their primary objective is displayed in *Figure 41*.

Figure 41. Proportion of trials that fulfilled their primary objective.



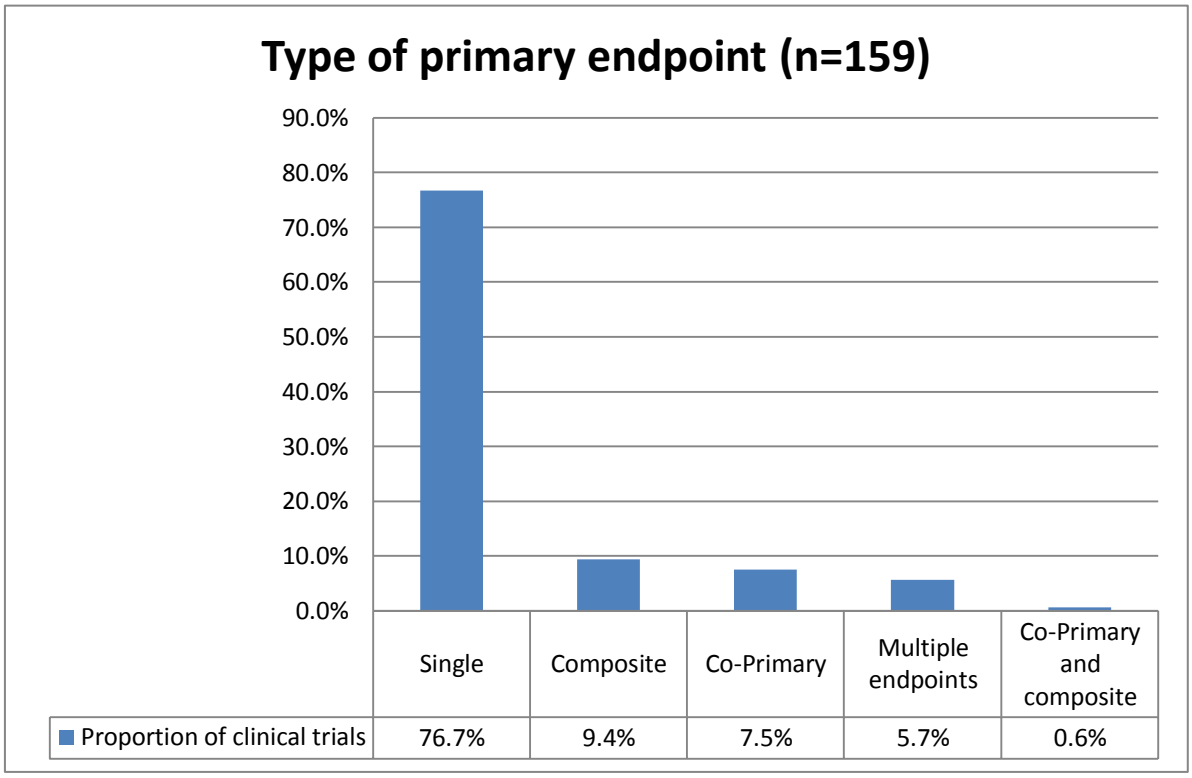
Up to 11 different therapeutic indications out of the 110 indications supported on data coming from clinical trials were approved without any clinical trial meeting its primary objective, in 9 cases because primary objective was not reached and in 2 cases because it was not possible to identify the study goal. Amongst these 11 approvals, 4 were based on subgroup analysis, with 2 approvals being supported by subgroup analysis not pre-specified before the trial begun.

8.3.6. Primary endpoints

In 122 (76.7%) trials the main study variable was a single endpoint; 15 (9.4%) trials used composite end-points, 12 (7.5%) studies used co-primary endpoints, 9 (5.7%)

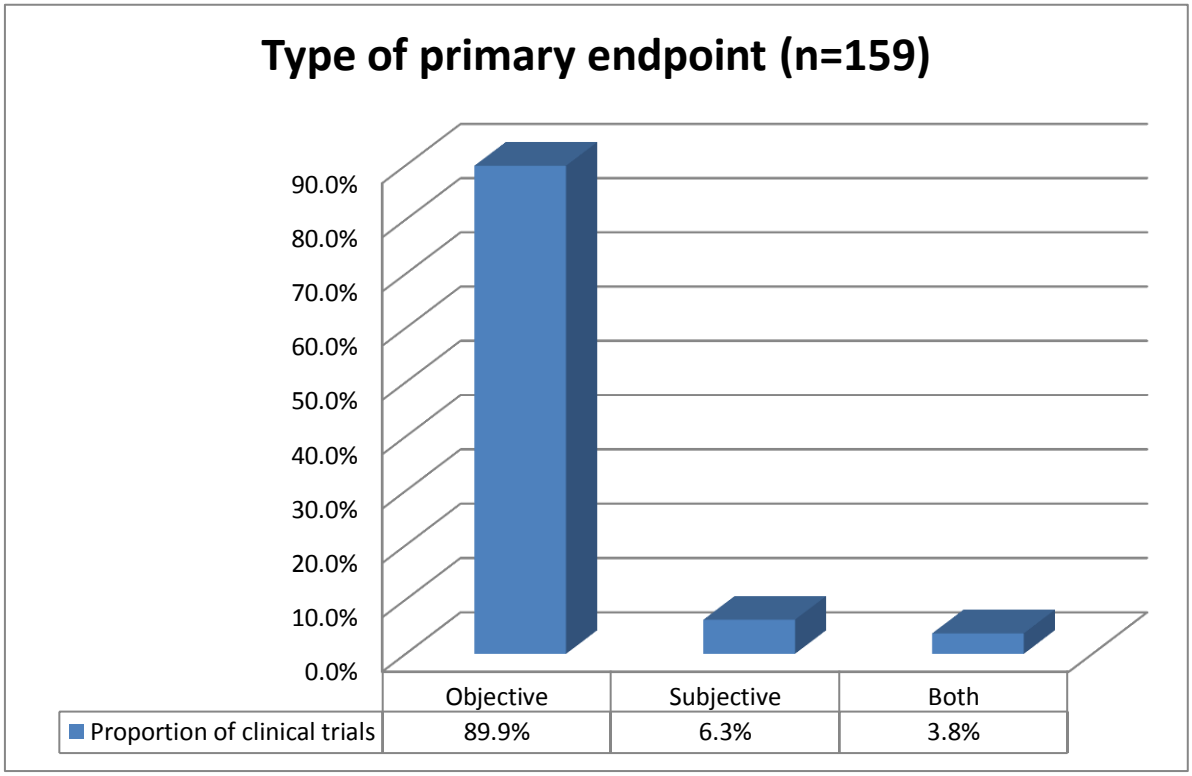
trials measured multiple endpoints and one (0.6%) trial used a co-primary endpoint that incuded a composite variable as one of these co-primary end-points. The type of primary endpoints used is summarised in *Figure 42.*

Figure 42. Type of primary endpoints used in clinical trials.



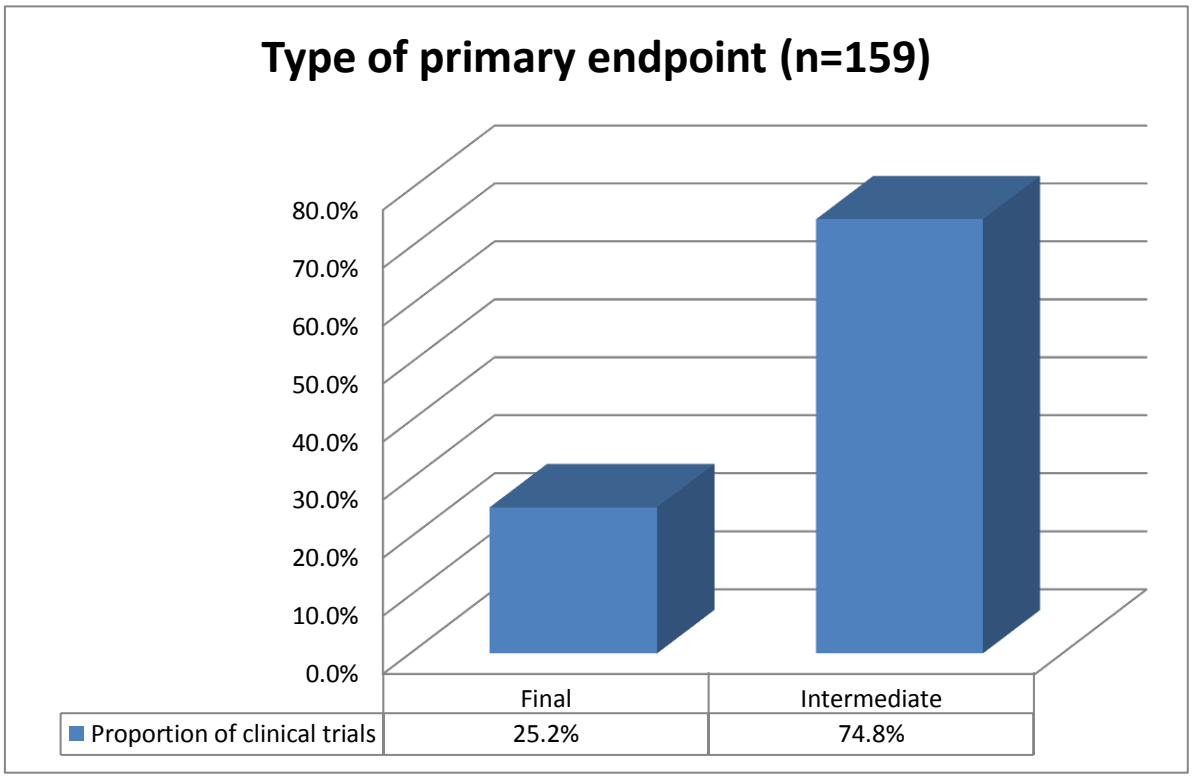
In 143 (89.9%) trials the primary endpoint was an objectivable measure, while in 10 (6.3%) studies the primary endpoint were subjective assessments; in 6 (3.8%) trials main endpoint included both objective an subjective determinations. Results are shown in *Figure 43*.

Figure 43. Objective or subjective primary endpoints in pivotal trials



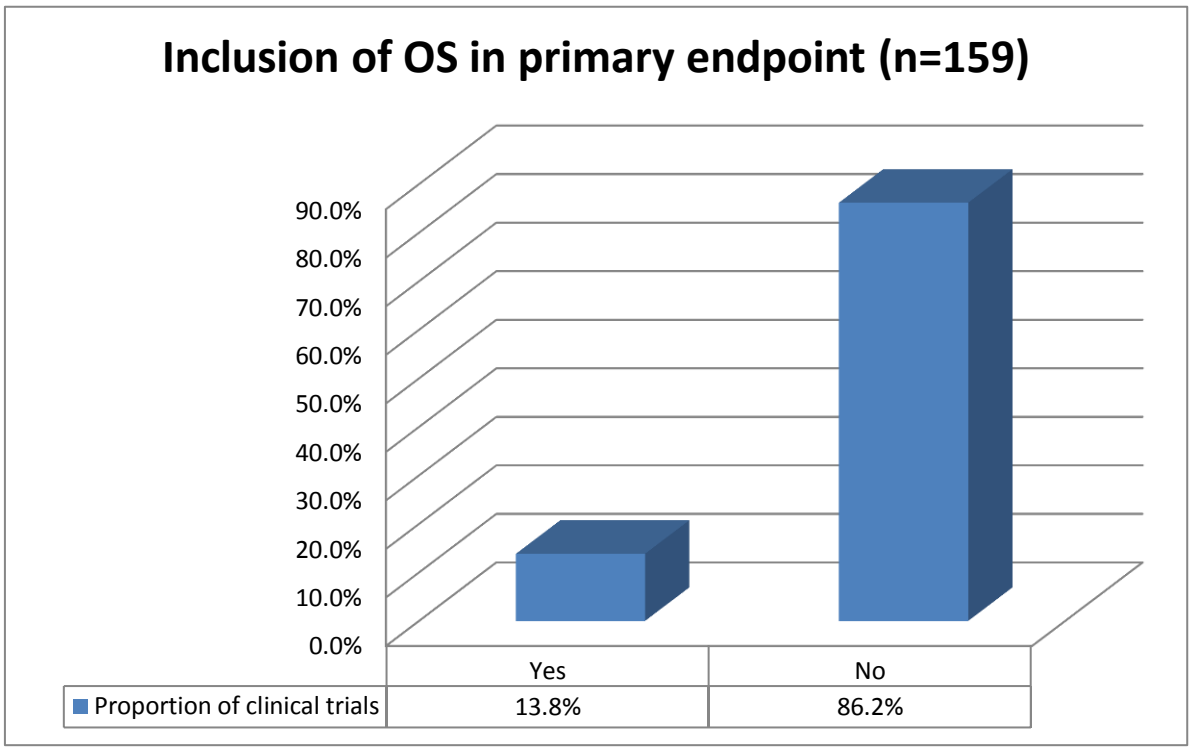
In 40 (25.2%) of trials the main endpoints were considered finalist end-points, as opposed to 119 (74.8%) trials in which primary endpoint was considered as an intermediate measure. The frequency of use of final or intermediate endpoints is displayed in *Figure 44*.

Figure 44. Frequency of use of final or intermediate endpoints in main clinical trials conducted with orphan drugs.



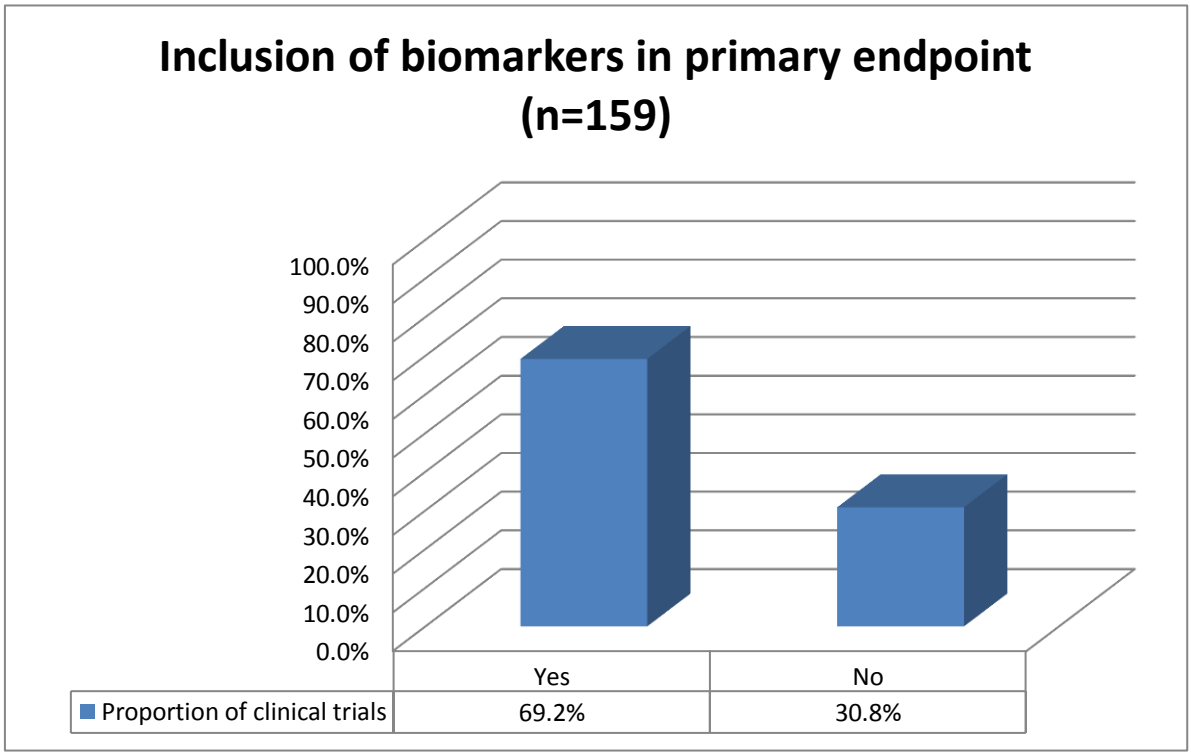
Primary endpoints were also studied regarding if they included the overall survival, biomarkers or Patient Reported Outcomes Mesures (PROM) in its definition. In 22 (13.8%) trials the primary endpoint was the overall subject survival, or overall survival was a component of a composite primary endpoint (*Figure 45)*.

Figure 45. Overall Survival inclusion in the primary endpoint.



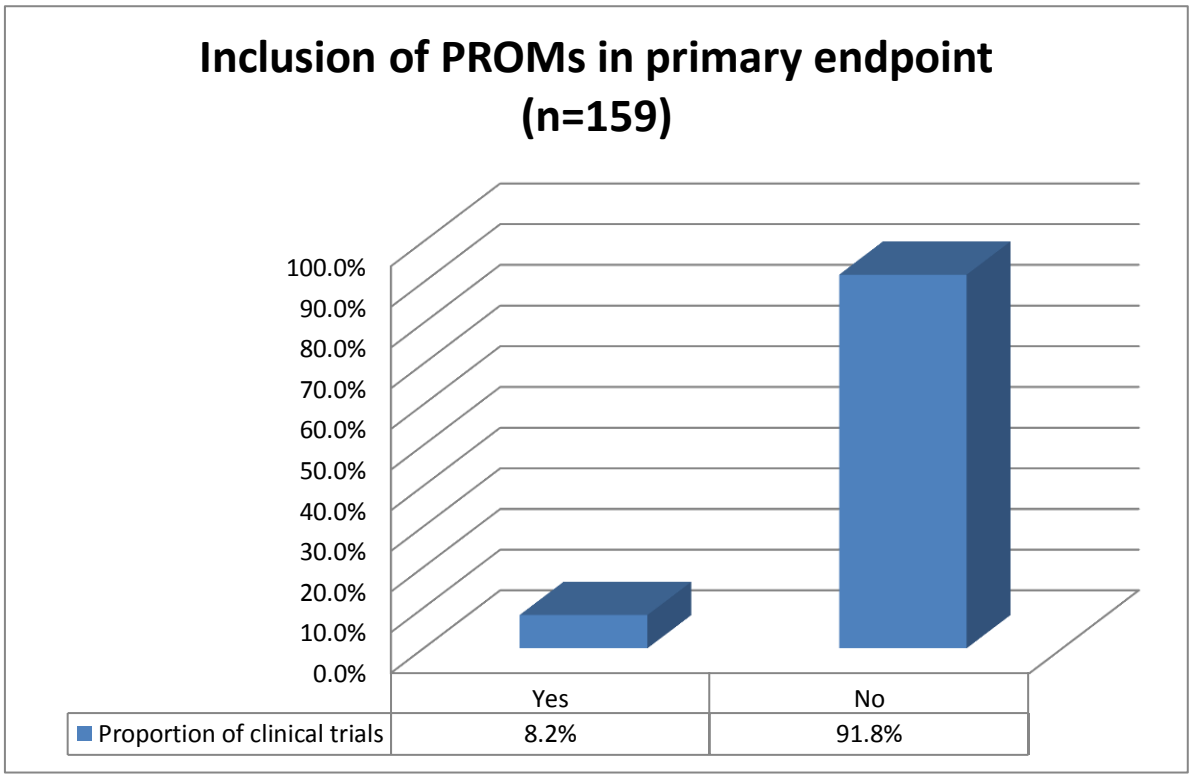
In 110 (69.2%) trials the primary endpoint included a biomarker, either as a single end-point or as part of composite end-points (*Figure 46)*.

Figure 46. Proportion of Biomarkers inclusion in the primary endpoint.



In 13 (8.2%) trials a PROM was the primary endpoint or a component of the main endpoint, while 146 (91.8%) trials did not include PROMs as a primary endpoint. Proportion of PROM inclusion in primary endpoint is exposed in *Figure 47*.

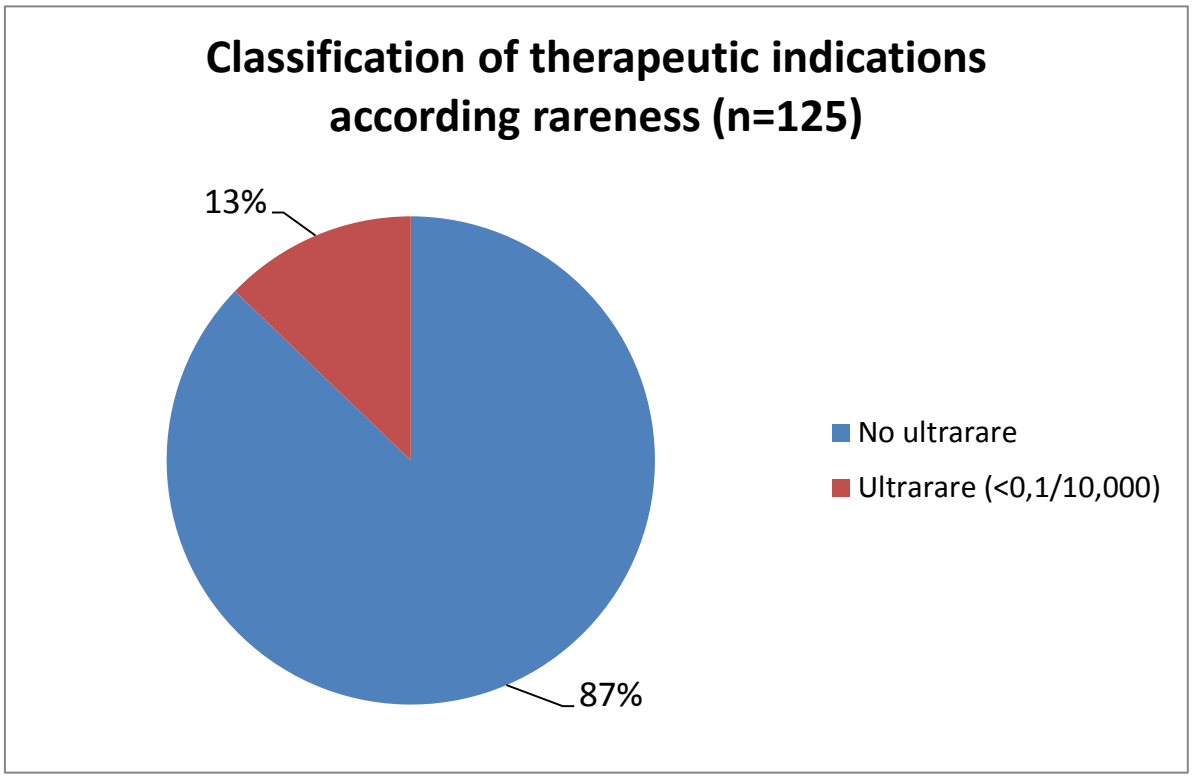
Figure 47. Use of Patient Reported Outcome Measurement in primary endpoints.



8.3.7. Influence of the prevalence of the condition in study design

To explore if type of evidence generated for orphan medicines was influenced by rareness degree, rare medical conditions (prevalence ≥0.1/10,000; 109 (87%) therapeutic indications) and ultrarare medical conditions (prevalence <0.1/10,000; 16 (13%) therapeutic indications) were analysed separately (*Figure 48)*.

Figure 48. Proportion of therapeutic indications approved aimed to treat rare or ultrarare medical conditions.



The type of scientific evidence which supported the application (obtained from clinical trials, bibliographic reports, compassionate use studies or observational retrospective studies) regarding the rareness degree is shown in Table *49*.

Table 49. Type of evidence supporting authorisation by prevalence of condition.

Rareness degree/ Type of dossier	Clinical trial	Bilbliographic report	Compassionate use	Observational retrospective	Total general
Rare; n (%)	100 (91.7%)	8 (7.3%)	1 (0.9%)	0 (0%)	109 (100%)
Ultrarare; n (%)	10 (62.5%)	1 (6.3%)	1 (6.3%)	4 (25%)	16 (100%)
Overall; n (%)	110 (88%)	9 (7.2%)	2 (1.6%)	4 (3.2%)	125 (100%)

Amongst the 110 authorisations based on clinical trials, 100 were for rare conditions and 10 for therapeutic indications aimed to treat ultrarare medical conditions.

The 100 therapeutic indications intended to treat rare conditions accounted for 145 different pivotal clinical trials, with a mean (SD) of 1.45 (0.74) trials per indication and a median (interquartilic range) of 1 (IQR: 1 - 2) clinical trial per indicaton, (range from 1 to 5). The mean (SD) and median (interquartilic range) number of different supportive studies included in the dossiers of rare conditions were 3.19 (2.32) and 3 (IQR: 2 - 4) different supportive studies for each indication approved, ranging from 0 to 15.

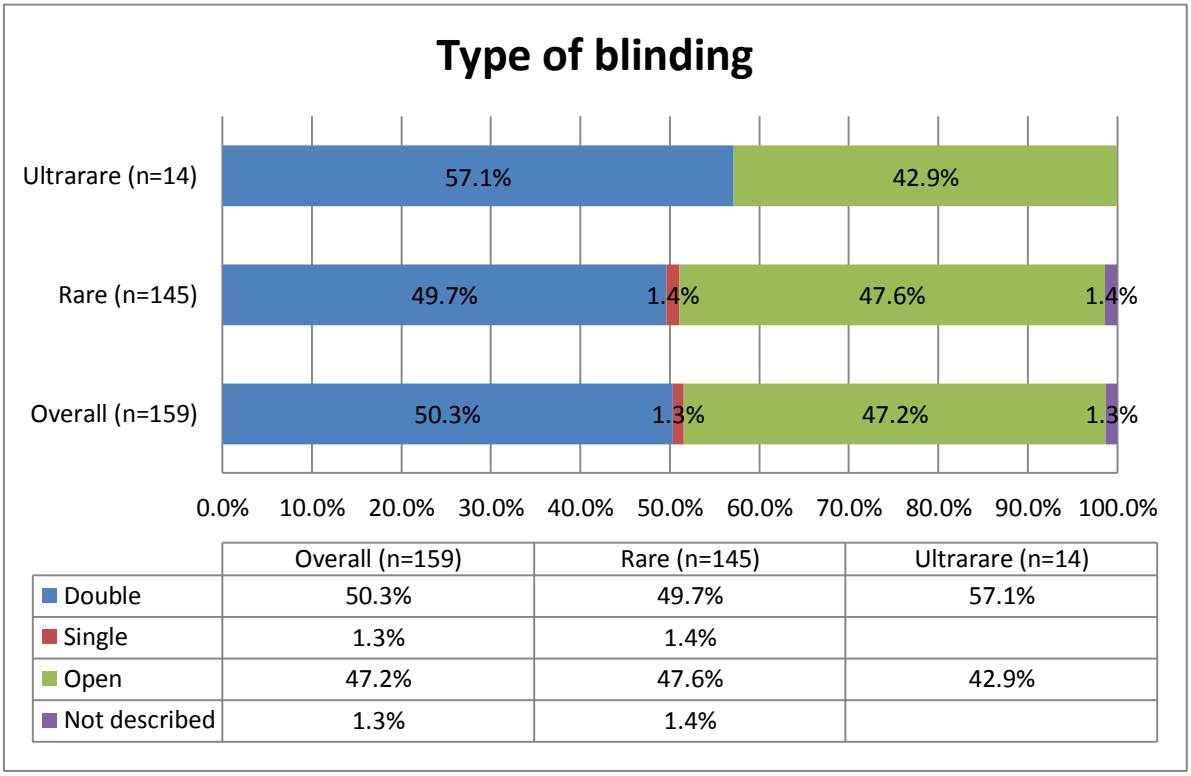
For the 10 therapeutic indications approved to treat ultrarare medical conditions, there were 14 different pivotal clinical trials. This figure supposed a mean (SD) of 1.4 (0.69) different main clinical trials and a median (interquartilic range) of 1 (IQR: 1 – 1.75) for each therapeutic indication, ranging from 1 to 3. The mean (SD) and median (interquartilic range) number of different supportive studies submitted in the dossiers for the subgroup of ultrarare conditions were 2 (0.94) and 2 (IQR: 1.25 - 2), range going from 1 to 4. These results are showed in *Table 50*, also compared with overall results for the entire set of 110 therapeutic indications approved based on clinical trials.

Table 50. Number of pivotal trials and supportive studies in the EPARS by prevalence of condition, subset authorised based on clinical trials.

		Overall (110 Therapeutic indications)	**Rare** (100 Therapeutic indications)	**Ultrarare** (10 Therapeutic indications)
Main studies	**Overall number of clinical trials conducted (n)**	**159**	**145**	**14**
	Mean (n)	**1.45**	**1.45**	**1.4**
	Median (n)	**1**	**1**	**1**
	Range (n)	**1 - 5**	**1 - 5**	**1 - 3**
Supportive studies	**Overall number of supportive studies conducted (n)**	**339**	**319**	**20**
	Mean (n)	**3.08**	**3.19**	**2**
	Median (n)	**3**	**3**	**2**
	Range (n)	**0 - 15**	**0 - 15**	**1 - 4**

The type of blinding used in clinical trials was similar regardless of the prevalence of the condition (*Figure 51)*.

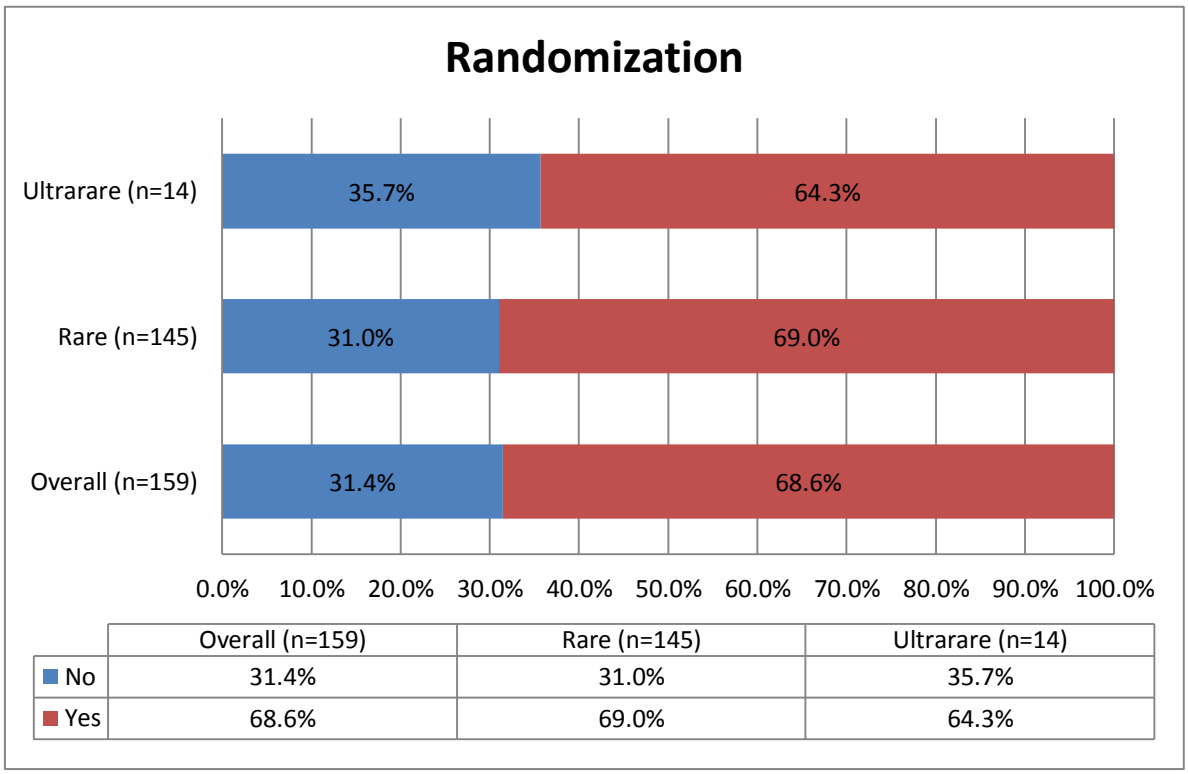
Figure 51. Blinding of pivotal trials according to prevalence of condition



	Overall (n=159)	Rare (n=145)	Ultrarare (n=14)
Double	50.3%	49.7%	57.1%
Single	1.3%	1.4%	
Open	47.2%	47.6%	42.9%
Not described	1.3%	1.4%	

The number of randomised trials was similar regardless of the prevalence of the condition (*Figure 52).*

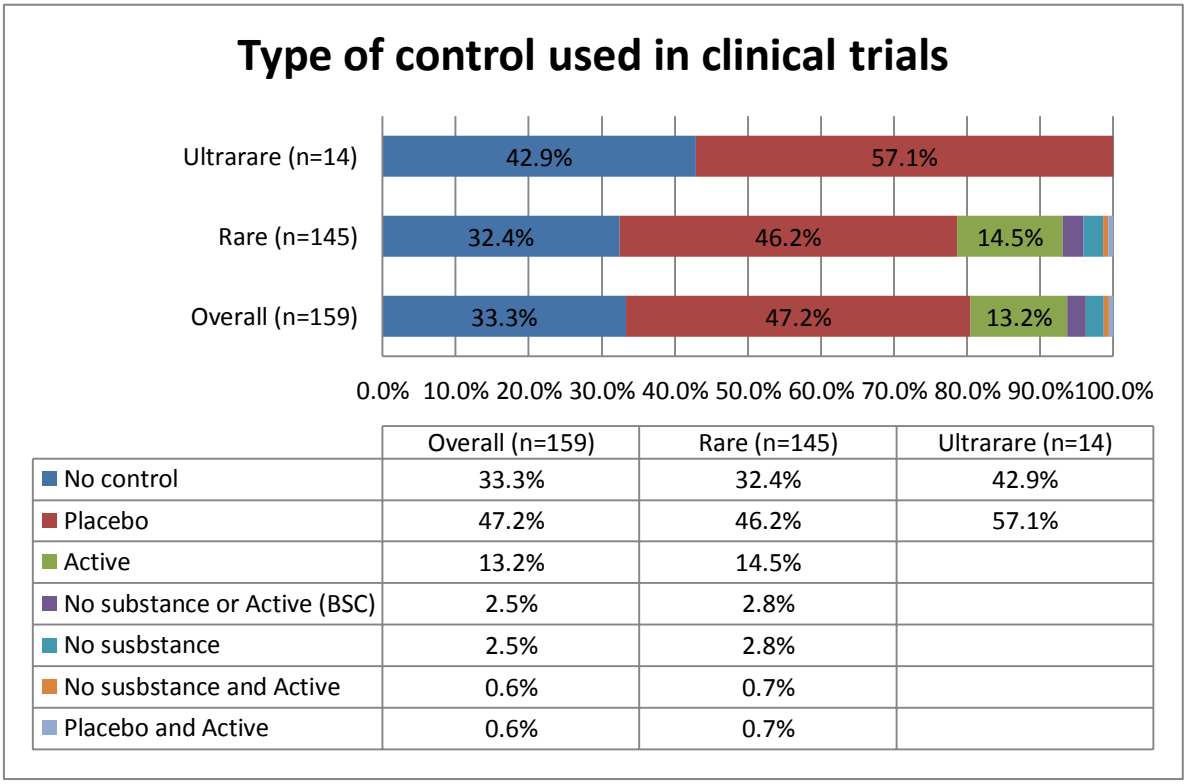
Figure 52. Type of assignation in pivotal trials according to prevalence of condition



	Overall (n=159)	Rare (n=145)	Ultrarare (n=14)
No	31.4%	31.0%	35.7%
Yes	68.6%	69.0%	64.3%

The proportion of placebo controlled studies was a little higher amongst ultrarare conditions (46,2% in rare conditions vs 57.1% in ultrarare), as well as the proportion without control treatment (32.4% in rare vs 42.9% in ultrarare); this was mainly at the expense of higher number of trials with active control treatment in rare than in ultrarare conditions (14.5% vs 0%, respectively) (*Figure 53)*.

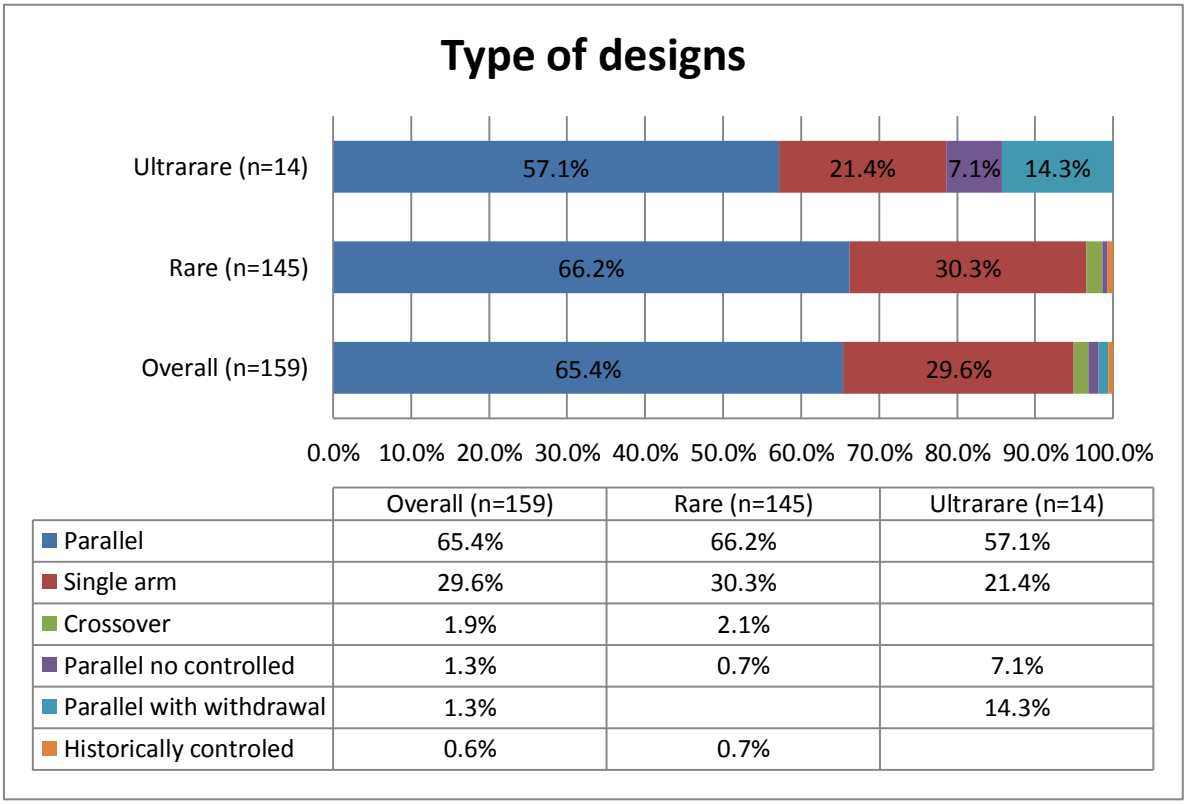
Figure 53. Type of control in pivotal trials according to prevalence of condition.



	Overall (n=159)	Rare (n=145)	Ultrarare (n=14)
No control	33.3%	32.4%	42.9%
Placebo	47.2%	46.2%	57.1%
Active	13.2%	14.5%	
No substance or Active (BSC)	2.5%	2.8%	
No susbstance	2.5%	2.8%	
No susbstance and Active	0.6%	0.7%	
Placebo and Active	0.6%	0.7%	

Alternative or less-known trial designs (crossover, trials with withdrawal periods and historically controlled) were used more often in ultrarare conditions than in rare conditions (2.8% in rare vs 14.3% in ultrarare conditions) (*Figure 54)*.

Figure 54. Type of design of pivotal trials according to prevalence of condition.



	Overall (n=159)	Rare (n=145)	Ultrarare (n=14)
Parallel	65.4%	66.2%	57.1%
Single arm	29.6%	30.3%	21.4%
Crossover	1.9%	2.1%	
Parallel no controlled	1.3%	0.7%	7.1%
Parallel with withdrawal	1.3%		14.3%
Historically controled	0.6%	0.7%	

8.3.8. Influence in study size and population exposure of the prevalence of the condition

The sample size included in pivotal trials was around 4 to 5 fold higher in rare than in ultrarare conditions, as was also the overall population assigned to the active treatment (Table *55)*.

Table 55.Sample size in pivotal trials according to prevalence of condition

		Overall (159 Clinical trials conducted)	Rare (145 Clinical trials conducted)	Ultrarare (14 Clinical trials conducted)
Overall population enrolled	Mean (n)	198.51	213.46	43.64
	Median (n)	134	154	35
	Range (n)	5 - 934	7 - 934	5 - 147
Population enrolled who received the experimental treatment	Mean (n) Ratio to sample size	131.31 0.661	140.90 0.660	31.93 0.731
	Median (n) Ratio to sample size	100 0.746	106 0.688	20.5 0.585
	Range (n)	5 - 934	7 - 934	5 - 147

Also, the duration of the time from inclusion to the assessment of the primay endpoint outcome of the main studies, the mean values were slightly longer for rare than for ultrarare conditions (28,48 weks vs 22.31 weks, but medians were slightly longer in ultrarare conditions (20.57 weeks and 24 weeks, respectively), but were quite similar around 24 weeks in all cases when the analysis excluded trials with time to event or survival, and those with no pre-specified time to assessment of outcomes (*Table 56)*.

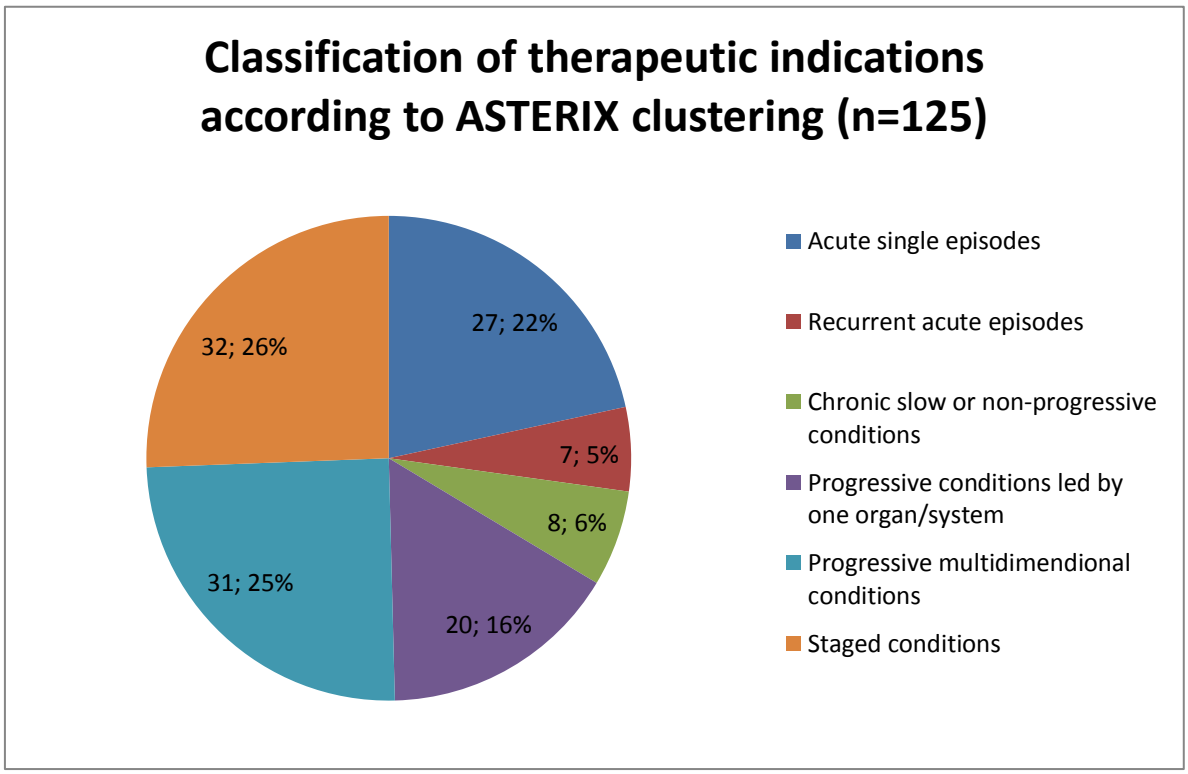
Table 56. Time frame for main endpoint in pivotal trials according to prevalence of condition.

		Overall (139 Clinical trials analyzed)	**Rare** (127 Clinical trials analyzed)	**Ultrarare** (12 Clinical trials analyzed)
Time point established to mesure the main endpoint	**Mean (weeks)**	**27.95**	**28.48**	**22.31**
	Median (weeks)	**21**	**20.57**	**24**
	Range (weeks)	**0.011 – 221.14**	**0.011 – 221.14**	**12- 53**
Time point established to mesure the main endpoint, excluding the "time to event, survival or time point for the analysis not pre-specified" trials	**Mean (weeks)**	**25.05**	**25.33**	**23.18**
	Median (weeks)	**24**	**24**	**24**
	Range (weeks)	**0.85 – 102.85**	**0.85 – 102.85**	**12 - 53**

8.3.9. Trial characteristics according to ASTERIX clustering

All the indications were classified according to the clustering of medical conditions resulting from the work in the frame of the ASTERIX project (122): 1) Acute single episodes; 2) Recurrent acute episodes; 3) Chronic slow or non-progressive conditions; 4) Progressive conditions led by one organ/system; 5)Progressive multidimensional conditions; and 6) Staged conditions. Staged conditions and progressive multidimensional conditions were the most frequently representedclusters, followed by acute single episodes (*Figure 57)*.

Figure 57. Therapeutic indications according to ASTERIX project clustering



Progressive multidimensional conditions had the higher proportion of authorisations based on evidences other than clinical trials (7/31; 22.6%), at the expense of retrospective studies (N=4; 12.9%), bibliographic based applications (N=2; 6.5%) and reports from compassionate access programs (N=1; 3.2%). Acute episodes also had a relevant proportion of bibliographic applications (N=4; 14.8%) (*Table 58).*

Chronic slow or non-progressive conditions had the higher mean and median number of pivotal trials supporting applications (18 trials supporting 7 therapeutic indications, mean (SD) 2.57 (1.27) and median 3 (IQR: 1.5 – 3.5), ranging from 1 to 4). The mean (SD) number of supportive studies was higher for the cluster of recurrent acute episodes, with 4.57 (3.6) trials per application and median 3 (IQR: 2 – 6.5), ranging from 1 to 11 (*Table 59)*.

Table 58. Therapeutic indications according to the type of evidence and the ASTERIX clustering

Cluster / Type of dossier	Clinical trial	Bilbliographic report	Compassionate use	Observational retrospective	Total
Acute single episodes; n (%)	23 (85.2%)	4 (14.8%)	0 (0%)	0 (0%)	**27 (100%)**
Recurrent acute episodes; n (%)	7 (100%)	0 (0%)	0 (0%)	0 (0%)	**7 (100%)**
Chronic slow or non-progressive conditions; n (%)	7 (87.5%)	1 (12.5%)	0 (0%)	0 (0%)	**8 (100%)**
Progressive conditions led by one organ/system; n (%)	18 (90%)	1 (5%)	1 (5%)	0 (0%)	**20 (100%)**
Progressive multidimensional conditions; n (%)	24 (77.4%)	2 (6.5%)	1 (3.2%)	4 (12.9%)	**31 (100%)**
Staged conditions; n (%)	31 (96.9%)	1 (3.1%)	0 (0%)	0 (0%)	**32 (100%)**
Overall; n (%)	**110 (88%)**	**9 (7.2%)**	**2 (1.6%)**	**4 (3.2%)**	**125 (100%)**

Table 59. Pivotal clinical trials and supportive studies in the EPARS of orphan medicinal products approvals based on clinical trials (n=110) according to ASTERIX clustering

		Overall (110 Therapeutic indications)	Acute single episodes (23 Therapeutic indications)	Recurrent acute episodes (7 Therapeutic indications)	Chronic slow or non-progressive conditions (7 Therapeutic indications)	Progressive conditions led by one organ/system (18 Therapeutic indications)	Progressive multidimensional conditions (24 Therapeutic indications)	Staged conditions (31 Therapeutic indications)
Main studies	Overall number of clinical trials conducted (n)	159	32	11	18	27	33	38
	Mean (n)	1.45	1.39	1.57	2.57	1.5	1.38	1.23
	Median (n)	1	1	2	3	1	1	1
	Range (n)	1 - 5	1 - 2	1 - 2	1- 4	1 - 5	1 - 2	1 - 3
Supportive studies	Overall number of supportive studies conducted (n)	339	84	32	21	44	70	88
	Mean (n)	3.08	3.65	4.57	3	2.44	2.92	2.84
	Median (n)	3	3	3	3	2	2,5	3
	Range (n)	0 - 15	1 - 15	1 - 11	1- 7	1- 8	1- 6	0 - 7

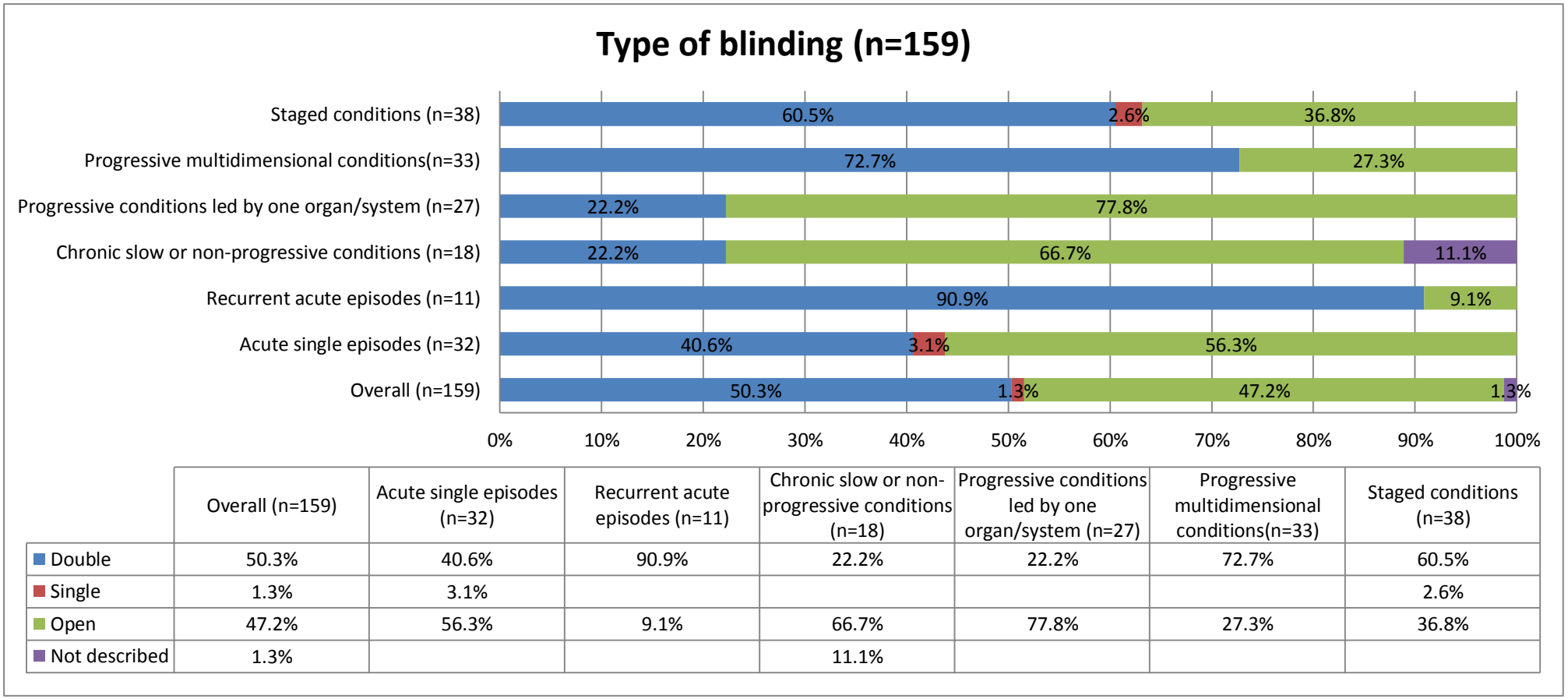
Trials were more frequently designed as open label in progressive conditions led by one organ/system (77.8%) and in chronic or slow progressive conditions (66.7%). Recurrent acute episodes were almost always (90.9%) using double blind designs. Single blind trials were infrequent, only used in staged conditions and in acute single episodes (*Figure 60*).

Non randomised designs were used frequently for pivotal trials in progressive conditions led by one system/organ and in chronic slow or non-progressive conditions (55.6% for both groups), and also in acute single episodes (40.6% of trials). All trials in conditions within the recurrent acute episodes were randomised, as were more than 80% of the trials within the staged conditions and the progressive multidimensional conditions clusterings (*Figure 61*).

Regarding the type of controls, placebo was widely used as a control (90.9%) for the conditions included in the progressive multidimensional clustering. For staged conditions and for progressive conditions led by one organ/system, placebo was used in more than 50% of the pivotal trials. More than half of the pivotal trials done for chronic slow or non progressive conditions and for conditions with recurrent acute episodes did not use any control treatment, and in these clusters the use of placebo was limited to one third or less of the pivotal trials. Active controls were used in less than 20% of trials in all clusters *(Figure 62).*

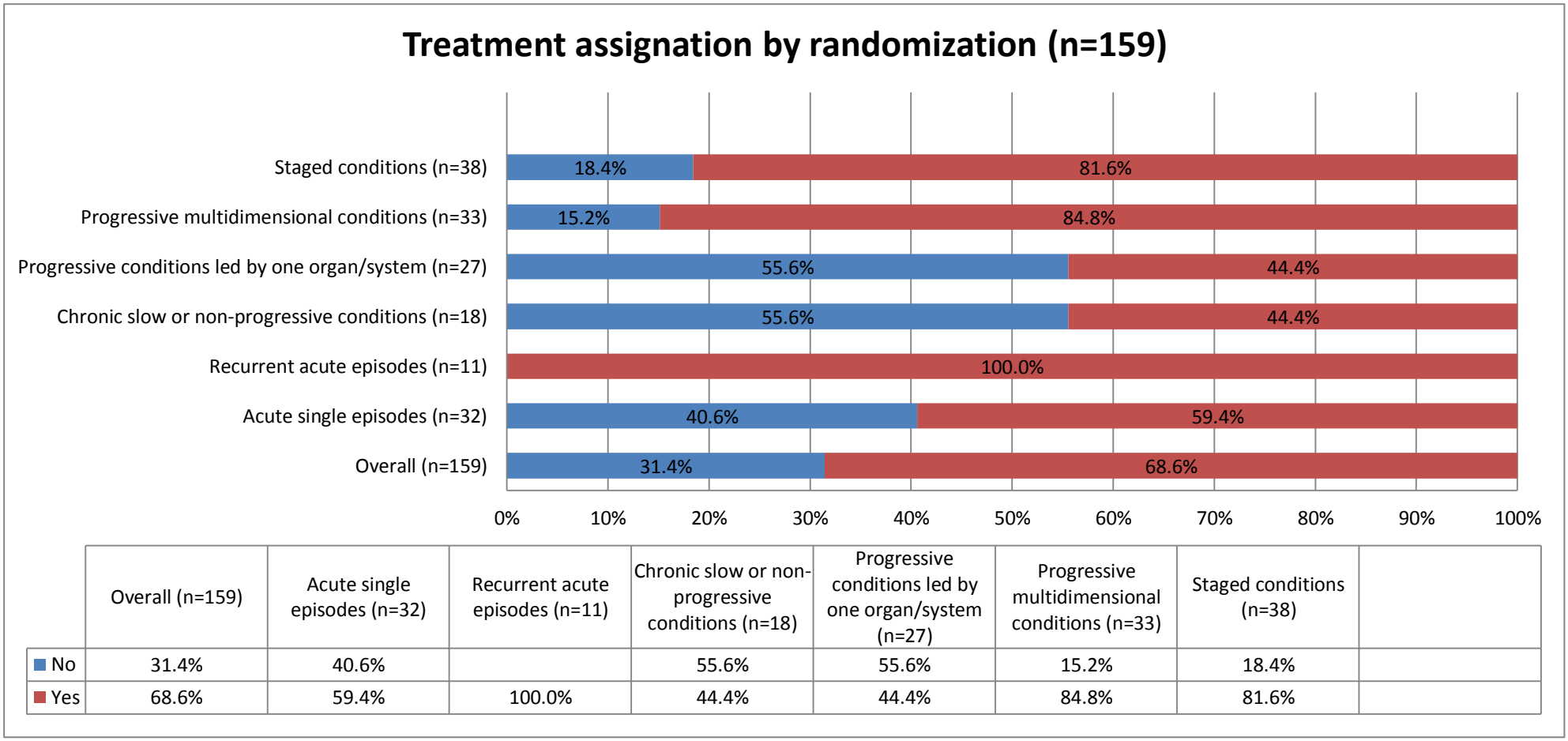
Parallel trials were the most frequently used design across all clusters except for chronic slow or non progressive conditions and progressive conditions led by one organ/system, which used mainly single arm pivotal trials. In the latter cluster, parallel trials comparing arms all receiving the experimental treatment with different doses or posologies, but with no negative nor positive control group, was used in up to 7.4% of trials. Crossover trials were used mostly in chronic slow or non progressive conditions, as the design for 11.1% of the pivotal trial in this cluster. Trials using historical controls were limited to conditions within the acute single episodes cluster (*Figure 63)*.

Figure 60. Study blinding in pivotal clinical trials according to ASTERIX clustering



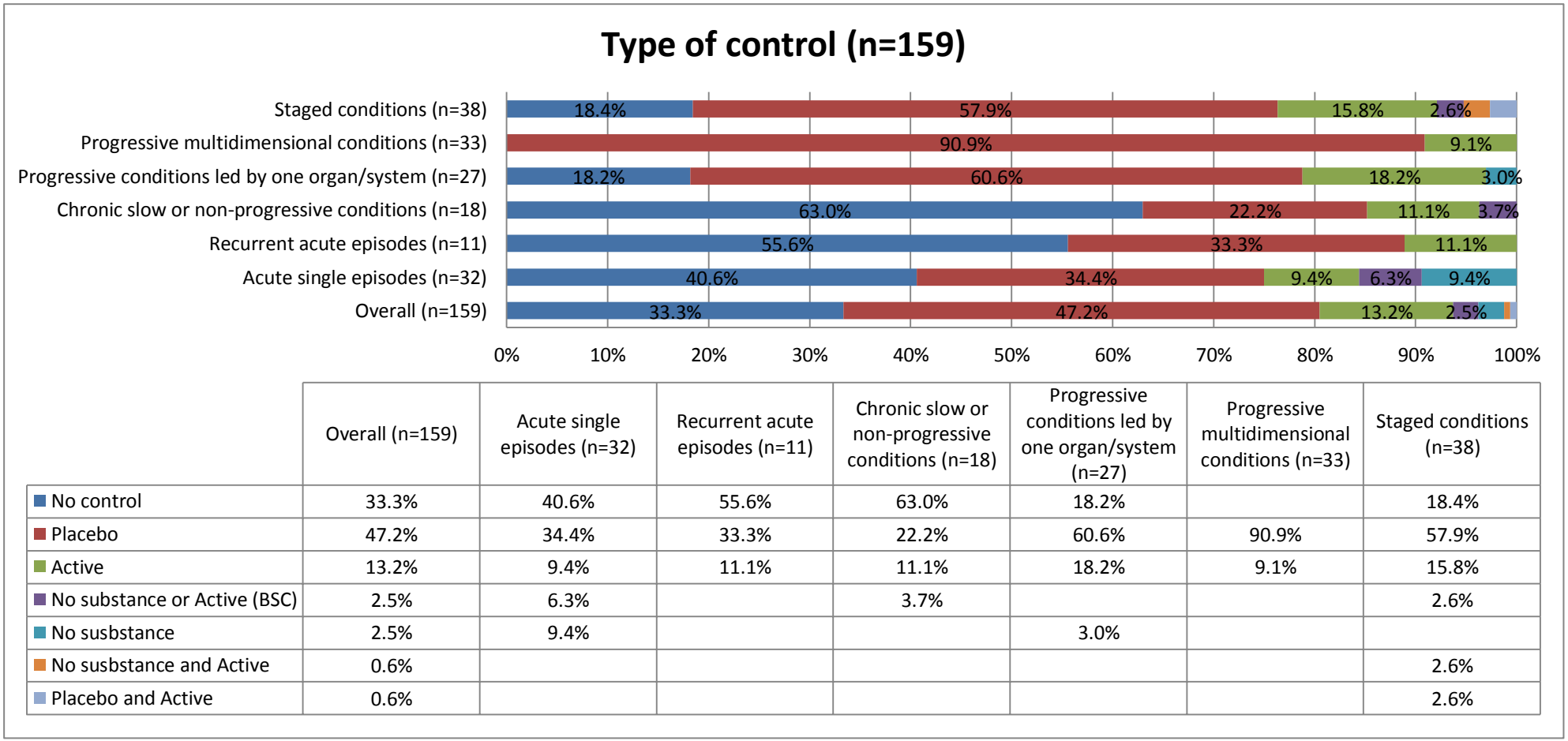
	Overall (n=159)	Acute single episodes (n=32)	Recurrent acute episodes (n=11)	Chronic slow or non-progressive conditions (n=18)	Progressive conditions led by one organ/system (n=27)	Progressive multidimensional conditions(n=33)	Staged conditions (n=38)
Double	50.3%	40.6%	90.9%	22.2%	22.2%	72.7%	60.5%
Single	1.3%	3.1%					2.6%
Open	47.2%	56.3%	9.1%	66.7%	77.8%	27.3%	36.8%
Not described	1.3%			11.1%			

Figure 61. Treatment randomizaton in pivotal trials according to ASTERIX clustering



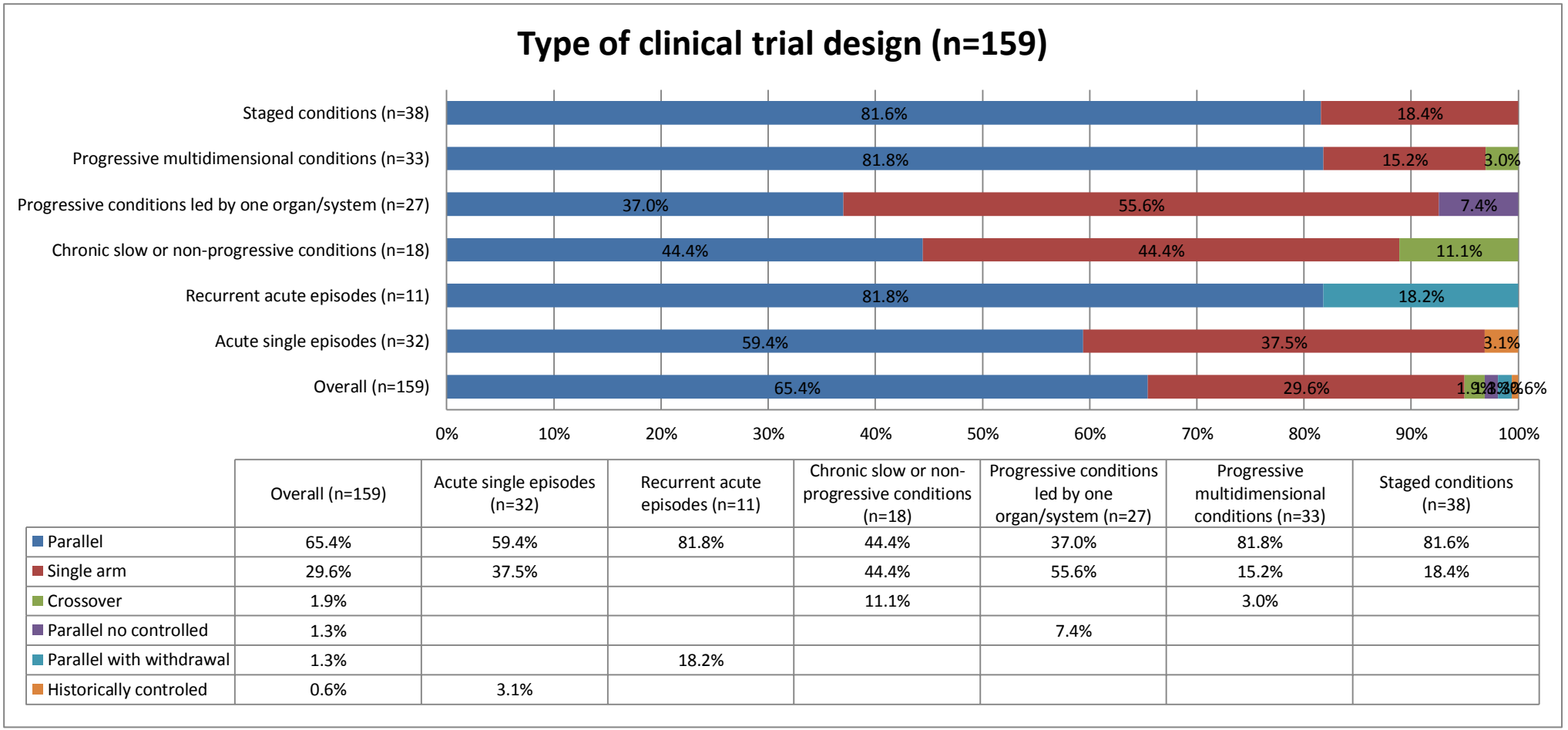
	Overall (n=159)	Acute single episodes (n=32)	Recurrent acute episodes (n=11)	Chronic slow or non-progressive conditions (n=18)	Progressive conditions led by one organ/system (n=27)	Progressive multidimensional conditions (n=33)	Staged conditions (n=38)	
No	31.4%	40.6%		55.6%	55.6%	15.2%	18.4%	
Yes	68.6%	59.4%	100.0%	44.4%	44.4%	84.8%	81.6%	

Figure 62. Type of control in pivotal trials according to ASTERIX clustering



	Overall (n=159)	Acute single episodes (n=32)	Recurrent acute episodes (n=11)	Chronic slow or non-progressive conditions (n=18)	Progressive conditions led by one organ/system (n=27)	Progressive multidimensional conditions (n=33)	Staged conditions (n=38)
No control	33.3%	40.6%	55.6%	63.0%	18.2%		18.4%
Placebo	47.2%	34.4%	33.3%	22.2%	60.6%	90.9%	57.9%
Active	13.2%	9.4%	11.1%	11.1%	18.2%	9.1%	15.8%
No substance or Active (BSC)	2.5%	6.3%		3.7%			2.6%
No susbstance	2.5%	9.4%			3.0%		
No susbstance and Active	0.6%						2.6%
Placebo and Active	0.6%						2.6%

Figure 63. Type of pivotal study design according to ASTERIX clustering



	Overall (n=159)	Acute single episodes (n=32)	Recurrent acute episodes (n=11)	Chronic slow or non-progressive conditions (n=18)	Progressive conditions led by one organ/system (n=27)	Progressive multidimensional conditions (n=33)	Staged conditions (n=38)
Parallel	65.4%	59.4%	81.8%	44.4%	37.0%	81.8%	81.6%
Single arm	29.6%	37.5%		44.4%	55.6%	15.2%	18.4%
Crossover	1.9%			11.1%		3.0%	
Parallel no controlled	1.3%				7.4%		
Parallel with withdrawal	1.3%		18.2%				
Historically controled	0.6%	3.1%					

The mean (SD) and median (interquartilic range) sample size of trials was biggest in the cluster of staged conditions with 318.9 (227.16) and 254.5 (IQR: 156 - 416.75) subjects per trial, respectively, followed by progressive conditions led by one organ/system with mean (SD) 241.9 (178.75) and 219 (IQR: 97.5 - 352) subjects by trial, respectively. Lowest sample sizes were those for progressive multidimensional conditions with mean (SD) and median (interquartilic range) of 100.2 (93.34) and 58 (IQR: 29 - 128) subjects per trial, respectively. The number of subjects assigned to the experimental treatment was consistent with sample size, although the ratio of subjects assigned to experimental groups was highest for the group with chronic slow or non-progressive conditions. (*Table 64)*.

The time frame for assessment of efficacy regarding the main outcome of pivotal trials was shortest for the trials done to study conditions within the cluster of recurrent acute episodes, with mean (SD) and median (interquartilic range) follow-ups of 9.8 (8.8) and 4.3 (IQR: 4 – 16.57) weeks, respectively, followed by those studying acute single episodes with mean (SD) and median (interquartilic range) follow-ups of 17.7 (22.18) and 9.1 (IQR: 2.6 – 25.7) weeks, respectively. Longest mean (SD) and median (interquartilic range) follow-ups were described for the cluster of staged conditions with 36.5 (34.48) and 23.1 (IQR: 12 – 46.78) weeks, respectively, followed by progressive conditions led by one organ/system with mean (SD) and median (interquartilic range) of 36.12 (54.96) and 15.7 (IQR: 8.14 – 36.1) weeks, respectively. When the trials with time to event or survival designs were excluded, chronic slow or non-progressive conditions and progressive conditions led by one organ/system were the two clusters with longer time to primary end-point (*Table 65*)

Table 64. Sample size of pivotal trials by ASTERIX clustering

		Overall (159 Clinical trials conducted)	Acute single episodes (32 Clinical trials conducted)	Recurrent acute episodes (11 Clinical trials conducted)	Chronic slow or non-progressive conditions (18 Clinical trials conducted)	Progressive conditions led by one organ/system (27 Clinical trials conducted)	Progressive multidimensional conditions (33 Clinical trials conducted)	Staged conditions (38 Clinical trials conducted)
Overall population enrolled	Mean (n)	198.51	158.19	136.64	168.78	241.93	100.24	318.95
	Median (n)	134	80.5	102	80	219	58	254.5
	Range (n)	5 - 934	12 - 485	23 - 553	5 - 934	7 - 602	15 - 358	32 - 903
Population enrolled who received the experimental treatment	Mean (n) Ratio to sample size	131.31 0.661	102.25 0.646	78.73 0.576	136.17 0.806	184.33 0.762	60.94 0.608	192.13 0.621
	Median (n) Ratio to sample size	100 0.746	63.5 0.789	48 0.47	66 0.825	148 0.676	42 0.724	151 0.594
	Range (n)	5 - 934	12 - 449	12 - 329	5 - 934	7 - 571	7 - 192	21 - 492

Table 65. Time frame for main endpoint in pivotal trials by ASTERIX clustering

		Overall (139 Clinical trials analyzed)	Acute single episodes (26 Clinical trials analyzed)	Recurrent acute episodes (11 Clinical trials analyzed)	Chronic slow or non-progressive conditions (17 Clinical trials analyzed)	Progressive conditions led by one organ/system (21 Clinical trials analyzed)	Progressive multidimensional conditions (32 Clinical trials analyzed)	Staged conditions (32 Clinical trials analyzed)
Time point established to mesure the main endpoint	Mean (n)	27.95	17.67	9.79	26.57	36.12	29.34	36.53
	Median (n)	21	9.07	4.28	12	15.7	24.85	23.14
	Range (n)	0.011 - 221.14	0.011 - 104.82	2 - 24	0.85 - 102.85	3.71 - 221.14	6 - 77	4 - 154
Time point established to mesure the main endpoint, excluding the "time to event, survival or time point for the analysis not pre-specified" trials	Mean (n)	25.05	17.09	9.46	33.44	30.50	29.89	23.21
	Median (n)	24	19.14	4.14	24	25	25.71	16
	Range (n)	0.85 - 102.85	1 - 36	2 - 24	0.85 - 102.85	24 - 48	6 - 77	12 - 72

Regarding the features of the primary endpoints used in function to the different clusters, the recurrent acute episodes was the group which a higher proportion of single endpoints (90.1%). On the other hand, the cluster with lower percentage of single endpoints was the staged conditions (68.4%) which also displayed the higher proportion of composite endpoints (up to 31.6%) (*Figure 66*).

In relation to the objectivity to the measures, staged conditions, progressive conditions led by one organ/system and acute single episodes had the highest proportion of primary endpoints based on objective assessment with 97.4%, 96.3% and 93.8% respectively. The cluster with the lowest proportion of primary endpoints based on objective measures was the recurrent acute episodes group with only 63.6% (*Figure 67*).

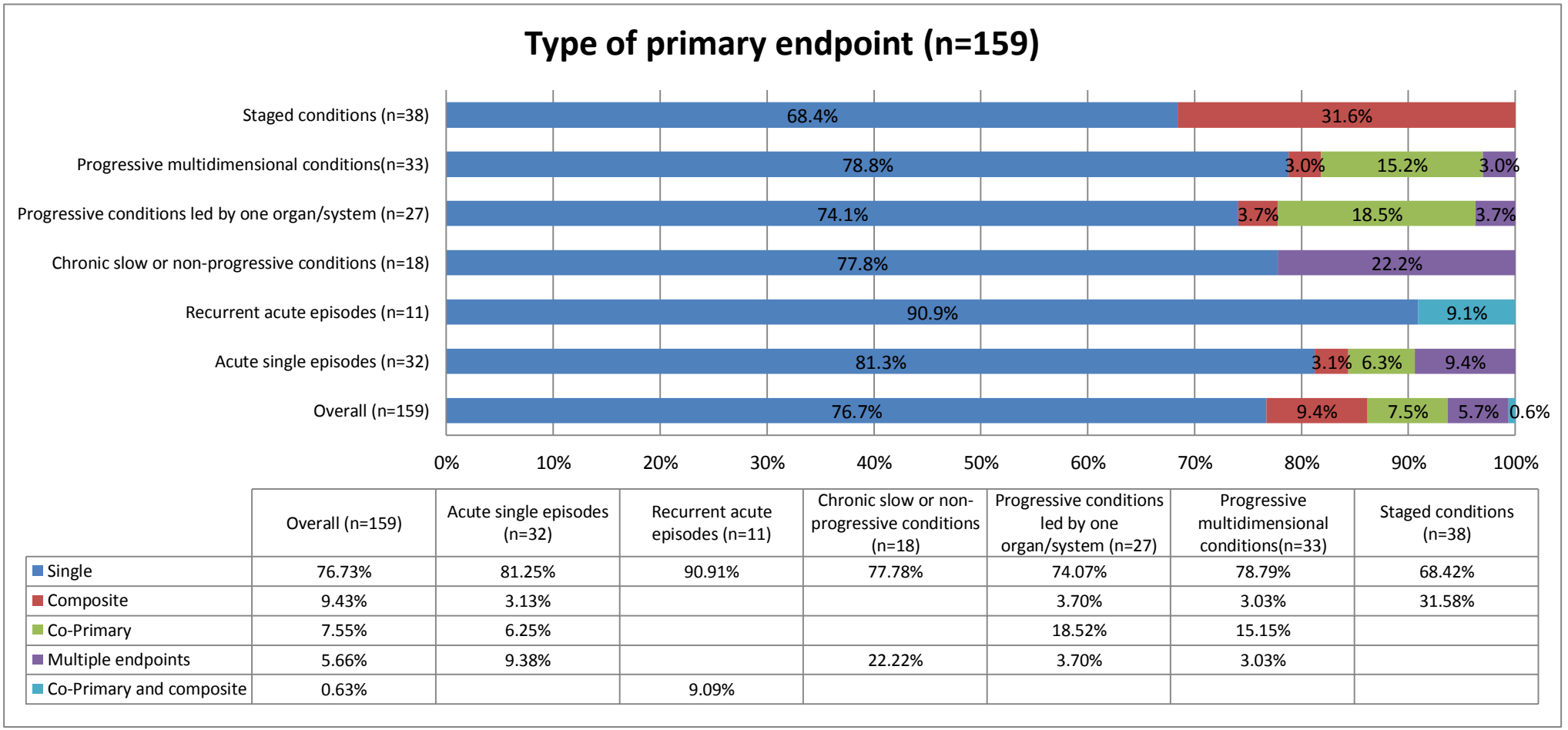
Recurrent acute episodes was the cluster with the larger proportion of final primary endpoints (81.8%) used in their clinical trials, meanwhile progressive condition led by one organ/system was the cluster with the most reduced proportion of final endpoint utilisation with only 7.4% of cases *(Figure 68*).

The overall survival was the primary endpoint or was a component of the primary endpoint in up to the 36.8% of cases in Staged conditions. Otherwise, any trial in Recurrent acute episodes and Chronic slow or non-progressive conditions used overall survival as single or as a component of the primary endpoint (0% for both clusters) (*Figure 69*).

When use of biomarkers regarding the clustering was analyzed, progressive conditions led by one organ /system showed the highest proportion of utilisation (92.6%). On the other hand, in recurrent acute episodes cluster only 27.3% of primary endpoints included a biomarker (*Figure 70*).

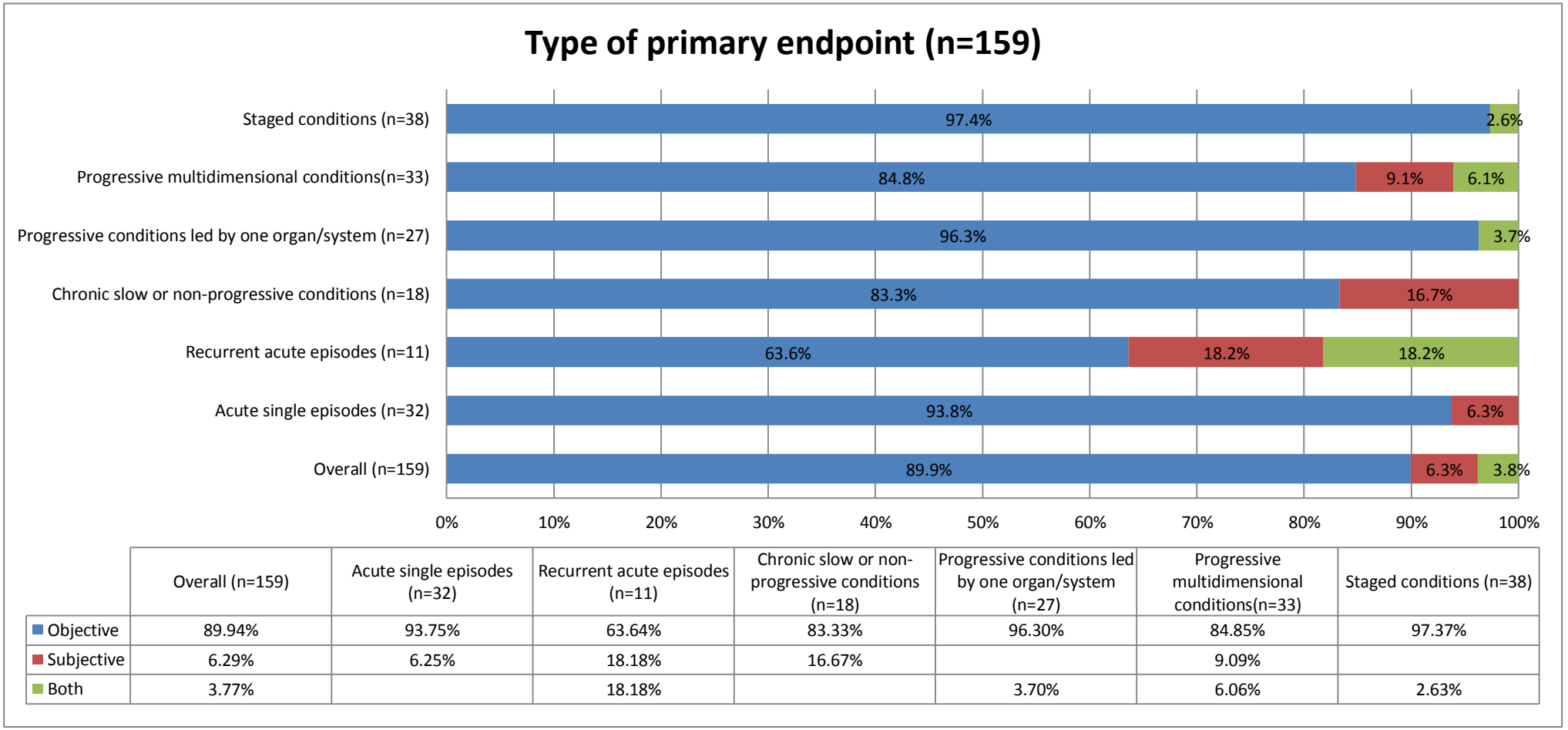
The use of PROMs as a primary endpoint or as a component of the primary endpoint was analyzed. In this regard, the cluster with larger inclusion of PROMs in the primary endpoints was the recurrent acute episodes with the 27.3%. On the contrary, any main clinical trial for the staged conditions used a PROM as primary endpoint (0%) (*Figure 71)*.

Figure 66. Type of primary endpoints used in clinical trials conducted with orphan medicines according to ASTERIX clustering



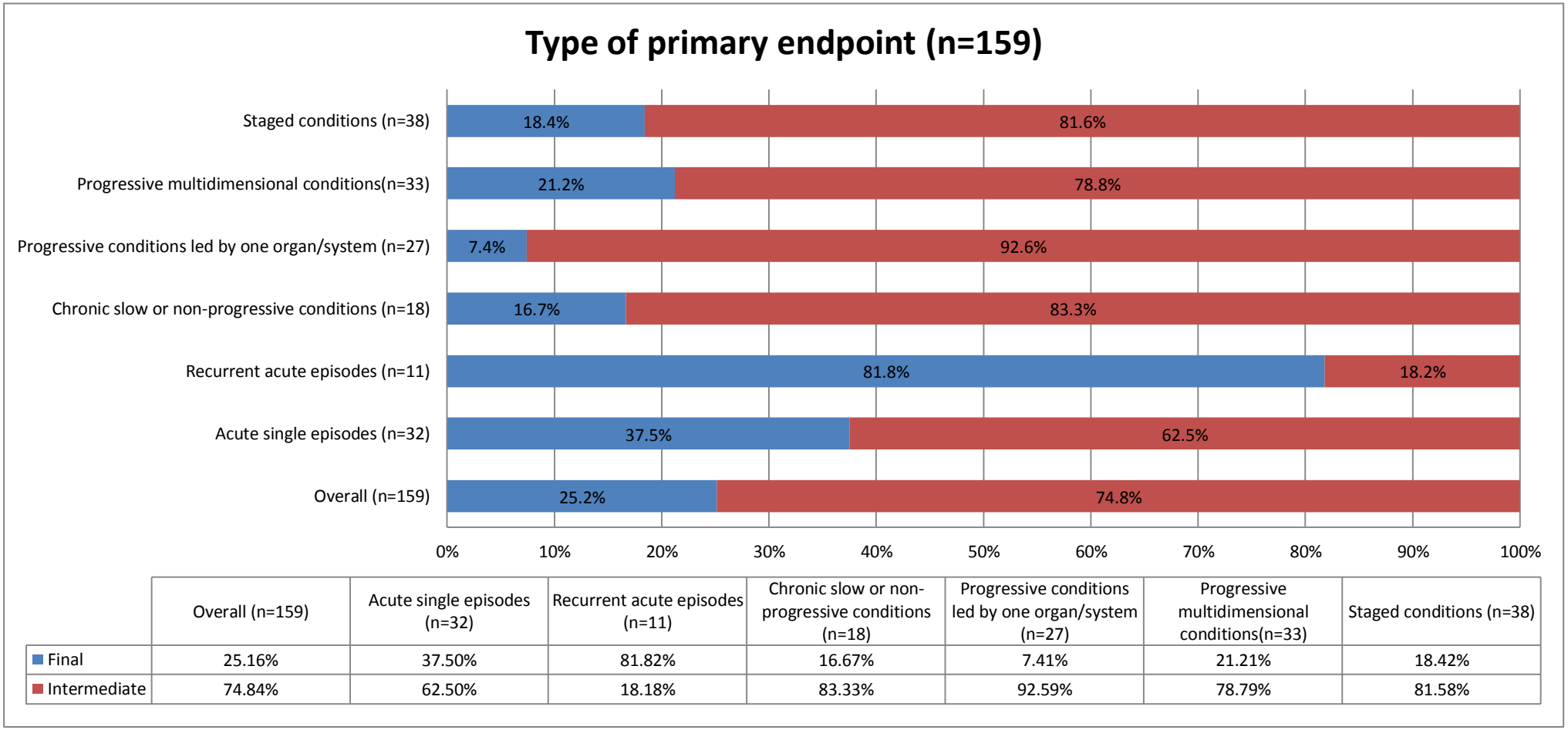
	Overall (n=159)	Acute single episodes (n=32)	Recurrent acute episodes (n=11)	Chronic slow or non-progressive conditions (n=18)	Progressive conditions led by one organ/system (n=27)	Progressive multidimensional conditions(n=33)	Staged conditions (n=38)
Single	76.73%	81.25%	90.91%	77.78%	74.07%	78.79%	68.42%
Composite	9.43%	3.13%			3.70%	3.03%	31.58%
Co-Primary	7.55%	6.25%			18.52%	15.15%	
Multiple endpoints	5.66%	9.38%		22.22%	3.70%	3.03%	
Co-Primary and composite	0.63%		9.09%				

Figure 67. Objective or subjective primary endpoints in pivotal trials according to ASTERIX clustering



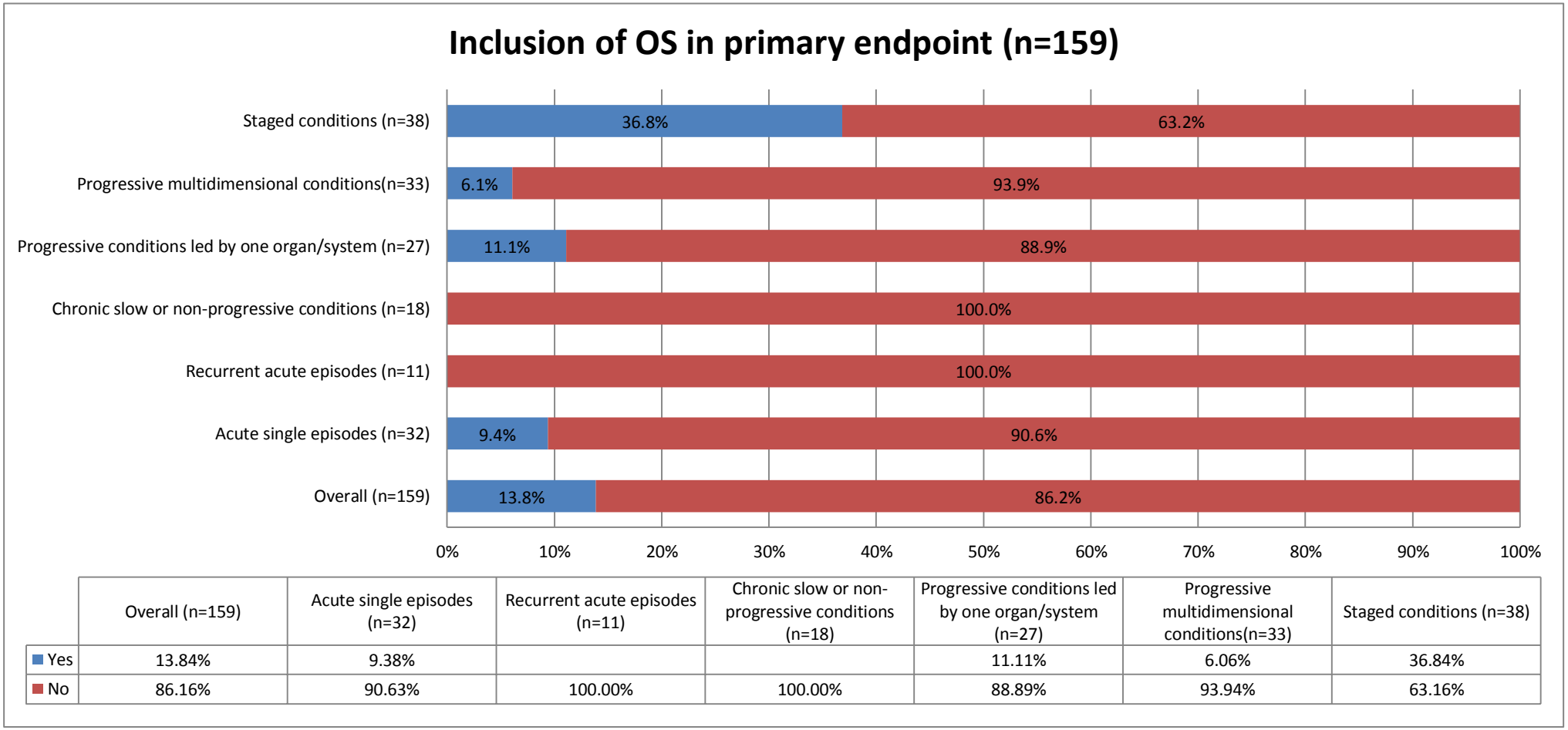
	Overall (n=159)	Acute single episodes (n=32)	Recurrent acute episodes (n=11)	Chronic slow or non-progressive conditions (n=18)	Progressive conditions led by one organ/system (n=27)	Progressive multidimensional conditions(n=33)	Staged conditions (n=38)
Objective	89.94%	93.75%	63.64%	83.33%	96.30%	84.85%	97.37%
Subjective	6.29%	6.25%	18.18%	16.67%		9.09%	
Both	3.77%		18.18%		3.70%	6.06%	2.63%

Figure 68. Frequency of use of final or intermediate endpoints in main clinical trials according to ASTERIX clustering



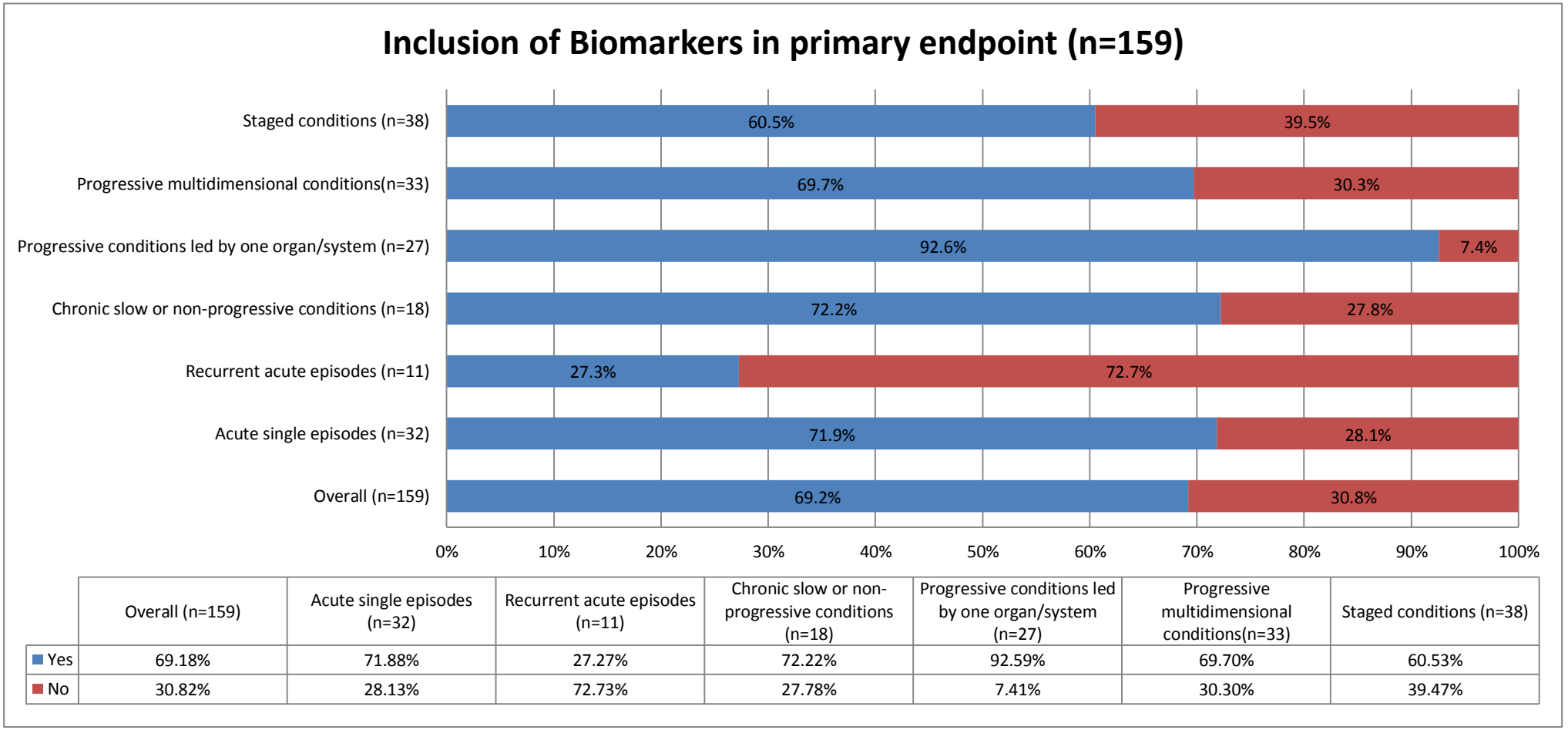
	Overall (n=159)	Acute single episodes (n=32)	Recurrent acute episodes (n=11)	Chronic slow or non-progressive conditions (n=18)	Progressive conditions led by one organ/system (n=27)	Progressive multidimensional conditions(n=33)	Staged conditions (n=38)
Final	25.16%	37.50%	81.82%	16.67%	7.41%	21.21%	18.42%
Intermediate	74.84%	62.50%	18.18%	83.33%	92.59%	78.79%	81.58%

Figure 69. Overall Survival in the primary endpoint according to ASTERIX clustering



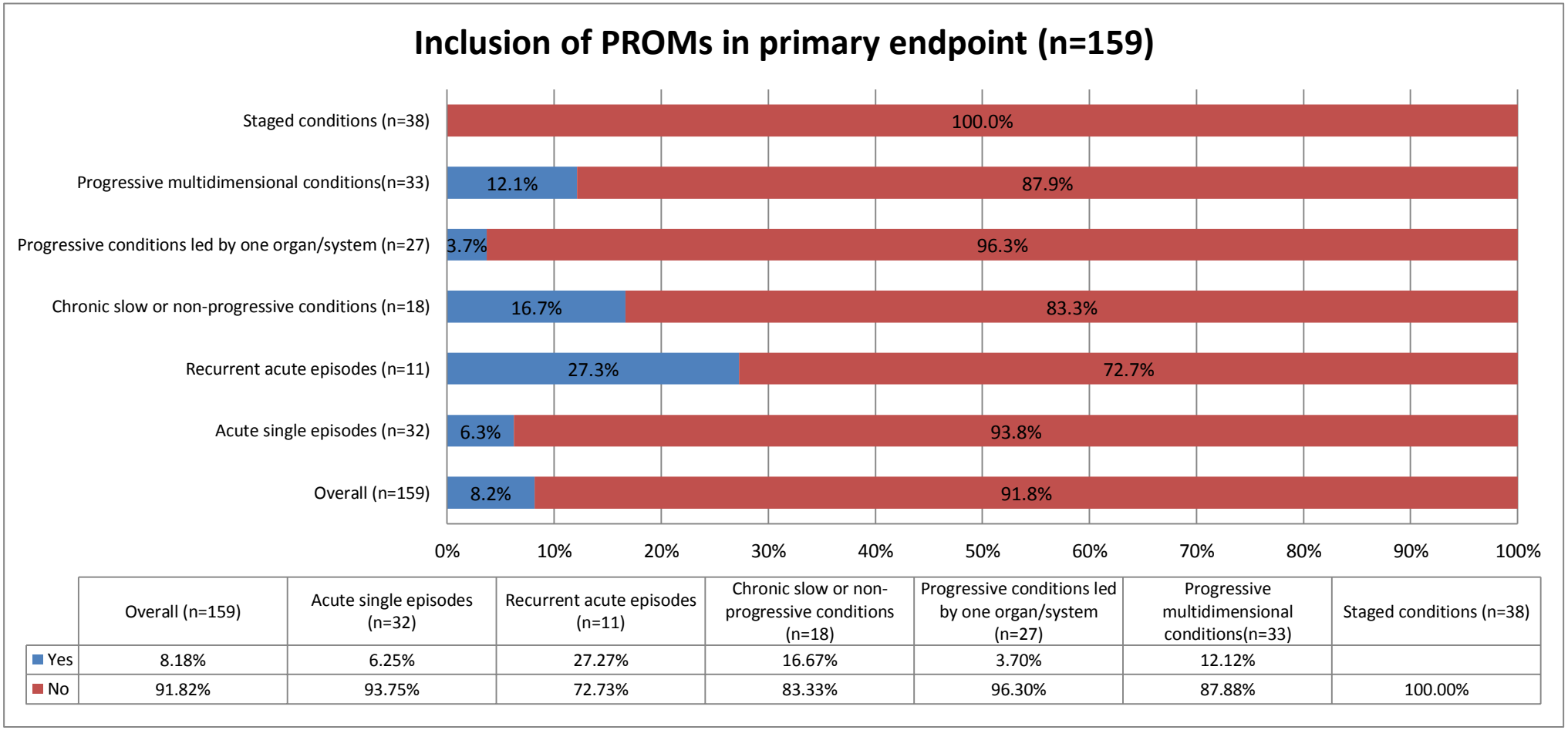
	Overall (n=159)	Acute single episodes (n=32)	Recurrent acute episodes (n=11)	Chronic slow or non-progressive conditions (n=18)	Progressive conditions led by one organ/system (n=27)	Progressive multidimensional conditions(n=33)	Staged conditions (n=38)
Yes	13.84%	9.38%			11.11%	6.06%	36.84%
No	86.16%	90.63%	100.00%	100.00%	88.89%	93.94%	63.16%

Figure 70. Proportion Proportion of primary end-points including biomarkers according to ASTERIX clustering



	Overall (n=159)	Acute single episodes (n=32)	Recurrent acute episodes (n=11)	Chronic slow or non-progressive conditions (n=18)	Progressive conditions led by one organ/system (n=27)	Progressive multidimensional conditions(n=33)	Staged conditions (n=38)
Yes	69.18%	71.88%	27.27%	72.22%	92.59%	69.70%	60.53%
No	30.82%	28.13%	72.73%	27.78%	7.41%	30.30%	39.47%

Figure 71. Use of Patient Reported Outcome Measurement in primary endpoint according to ASTERIX clustering



	Overall (n=159)	Acute single episodes (n=32)	Recurrent acute episodes (n=11)	Chronic slow or non-progressive conditions (n=18)	Progressive conditions led by one organ/system (n=27)	Progressive multidimensional conditions(n=33)	Staged conditions (n=38)
Yes	8.18%	6.25%	27.27%	16.67%	3.70%	12.12%	
No	91.82%	93.75%	72.73%	83.33%	96.30%	87.88%	100.00%

Finally, the clusters with higher proportion of ultrarare conditions were the one for conditions with recurrent acute episodes and the one including progressive multidimensional conditions; with 28.6% and 20.8% of conditions below the prevalence cut-off of 0.1/10,000 subjects. Staged conditions were always above the threshold defined for ultrarare conditions (*Table 72).*

Table 72. Prevalence of conditions with orphan medicinal product approvals based on clinical trials (n=110) by ASTERIX clustering.

Rareness degree / Cluster	Acute single episodes	Recurrent acute episodes	Chronic slow or non-progressive conditions	Progressive conditions led by one organ/system	Progressive multidimensional conditions	Staged conditions
Rare	22 (95.7%)	5 (71.4%)	6 (85.7%)	17 (94.4%)	19 (79.2%)	31 (100%)
Ultrarare	1 (4.3%)	2 (28.6%)	1 (14.3%)	1 (5.6%)	5 (20.8%)	0 (0%)
Total	23 (100%)	7 (100%)	7 (100%)	18 (100%)	24 (100%)	31 (100%)

9. DISCUSSION

9.1. Orphan medicinal products in Europe

The European Regulation on orphan medicines (141/2000)(1) approved by the European Parliament and the Council entered into force in January 2000 with the objective to stimulate the research in drugs for rare diseases and raise the number of medicines marketed.

After 15 years of the application of the European regulation, a retrospective research has been conducted to analyse the results of the regulation from January 2000 till December 2014. During these 15 years, the COMP of the EMA had given a positive opinion to grant 1,430 different Orphan Drug Designations (125), and a hundred of different orphan medicinal products have been approved in the European Union for being used in 125 therapeutic indications; some of these medicines have more than one therapeutic indication authorised.

A strong indicator to demonstrate the positive effect of the regulation on orphan medicines is the number of drugs available before the approval of the European regulation (only 8 medicines)(17) as compared with 15 years after its approval (up to 100 different orphan medicines). These figures, including the number of ODD, of authorised orphan medicinal products and of therapeutic indications approved, show that the European regulation on orphan medicines has supposed a step forward to provide new therapeutic options to people affected by rare diseases and to spur the research on the rare diseases field(26).

The number of Orphan Drug Designations and Marketing Authorisations granted for orphan medicinal products after the approval of the specific orphan regulation has been continuously increasing along these first 15 years. While an increase in availability and access to orphan medicinal products is suggested by the growing trend of ODD, orphan medicinal products approvals and enlargement of available therapeutic indications for treatments for rare diseases in Europe, it must be recognized that the increase can not be considered lineal, and probably a longer

period of time would be required to extract conclusions about this trend. Yet, further to the period of time analysed, 14 new orphan medicinal products were approved on 2015 and 14 more were approved on 2016 (39), suggesting a flattening of the growing curve.

Some voices have alerted on the existing gap between the high figures of Orphan Drug Designations and the low number of orphan medicinal products reaching the market (40,41). To this respect, *Joppi et al.* reported that only around 8% of the Orphan Drug Designations granted by the European Commission had reached the European market during the first decade of orphan drug legislation(42). This figure is also in line with that observed in our study (i.e. 8.7%) for the first fifteen years of orphan drug legislation.

Some reasons proposed to explain this gap include the lower quality of scientific evidence generated for orphan medicines, but other causes can also contribute. A main one is the fact that orphan drug designation can be applied by the sponsor at any stage of drug development previously to the marketing authorisation(28). However, sponsors frequently submit applications on early stages of development, in order to benefit as soon as possible from incentives included in the European regulation, and thus they often apply when only preclinical data support the medical plausibility of the drugs designated.

In this line, orphan drug designation is a tool to stimulate the research in pharmacological treatments for rare diseases, but thereafter a positive benefit /risk balance will be needed to get a marketing authorisation. Since drug development is a high-risk process where a high proportion of molecules don't success, equally for orphan drugs and for drugs aimed to treat common diseases, the attrition rate due to developmental risk is certainly related to the attrition rate of ODD not reaching the market. Consequently, such a low proportion of success for Orphan Drug Designations in relation with orphan medicines approved can be expected to be permanent.

9.2. Overall description of orphan medicinal products authorised in Europe

9.2.1. Selection of orphan medicinal products for the analysis

As mentioned previously, our review includes all medicines approved in the European Union which at time to receive the marketing authorisation from the European Comission had an Orphan Drug Designation. Thus, some medicines aimed to treat rare diseases were excluded because they didn't hold an active Orphan Drug Designation at time to be authorised in Europe.

Mainly, three different groups of medicines have been excluded:

1. Medicines authorised in Europe before the orphan drug legislation entered into force.

   Medicines authorised before 2000, despite being aimed to treat rare diseases, have been not included in the analysis because they couldn't apply to the Orphan Drug Designation, since this regulation was approved later than the medicine approval.

2. Medicines without Orphan Drug Designation because the sponsor did not apply for it.

   The Orphan Drug Designation is a voluntary procedure, and consequently application is not mandatory if the product holder is not interested. It may happen that regardless of incentives offered by the European regulation to drugs getting an Orphan Drug Designation, some sponsors might have commercial or strategical reasons to decide not to apply, although this is not usual. Some reasons may include the strategical decision to expand indications. Since orphan medicinal products with Orphan Drug Designation only can include in their labelling those therapeutic indications qualifying for and with granted orphan designation, should the product holder wish to include other therapeutic indications without orphan designation, a different medicinal product with different brand name must be

authorised. If a single common medical product is preferred by pharmaceutical companies, they may decide not to apply for an Orphan Drug Designation.

3. Medicines that held an Orphan Drug Designation during development, but not at the time of marketing authorisation.

   There are several reasons for withdrawal of the ODD before marketing authorisation. Besides the rareness and the severity of the diseases, a criterion defined to get the Orphan Drug Designation is that no satisfactory methods are available for this disease or, if alternative methods are available, the new orphan drug must demonstrate significant benefit over the existing treatments available. When applicable, the significant benefit criteria must be justified first to obtain the Orphan Drug Designation, and later at the time of the orphan medicinal product marketing authorisation application. Confirmation of significant benefit during the process of assessment of the marketing application is required in order to maintain the Orphan Drug Designation. If significant benefit criteria can not be demonstrated at that time, the Orphan Drug Designation is withdrawn.

   During the assessment process, if any other designated orphan medicinal product is commercialized for the same indication and is still holding its period of “market exclusivity”, a similarity report must be addressed. If the new orphan drug fullfills the “Similarity” criteria(21) to the orphan medicinal product already authorised, the new drug must not be authorised. If “Similarity” criterion is not met, the new orphan drug can be authorised, even if its Orphan Drug Designation has been withdrawn.

In our study, orphan drugs which did not maintain the Orphan Drug Designation at time to get the marketing authorisation were not included in the review, regardless of whether they satisfied the criteria to obtain the marketing authorisation.

Taking into account these considerations, the number of orphan medicines and therapeutic indications included in our analysis might be slightly underestimated regarding the number of therapeutic options for rare diseases authorised during the period of time studied. However, the approach used in our work is reliable, clear and

feasible, and includes most of orphan medicinal products authorised for rare diseases along this period. The alternative was to study all medicines aproved in Europe to check their authorisation details and to search for prevalence data, in order to check if their therapeutic indications included or not any rare medical conditions. However, such an approach was considered to be not reflective of the European regulatory options, and also was deemed as of poor efficiency and unfeasible.

9.2.2. Number of rare medical conditions covered by the therapeutic indications

The 125 different therapeutic indications approved during the period of time studied were aimed to treat only 84 different rare medical conditions. It means that some rare diseases had more than one medicine authorised for their treatment. Yet, if we take into account that the estimations on the actual number of rare medical diseases consider that up to 6,000-8,000 different rare diseases exist (5), it seems clear that a huge quantity of diseases remain without therapeutic options and with unmet medical needs.

We described that 21 conditions had more than one orphan medicinal product authorised for their treatment, including up to 8 orphan medicinal products as in the case of pulmonary arterial hypertension, or up to 6 such as acute lymphoblastic leukaemia, 5 such as chronic myeloid leukaemia or 4 such as renal cell carcinoma. Some questions arise on whether the prevalence of such diseases is related with the number of different drugs authorised to treat them, so that conditions with higher prevalence figures could have more orphan medicines authorised because the market size is bigger and thus more interesting to companies. A study conducted by *Brabers et al.*(126) actually found an association between higher prevalences for a given disease and the likehood to have “follow-on” orphan medicinal products after a first orphan medicinal product had been approved; follow-on orphan medicinal products were defined as: 1) another orphan medicine approved for the same condition (medicine authorised), or 2) another medicine with Orphan Drug Designation for the same condition (medicine not yet authorised).

Despite the limitations due to the fact that we have not checked the medicines designated as orphan but not yet authorised, our data does not confirm such trend; if we focus on the 4 conditions that had 4 or more orphan medicinal products authorised, their prevalences are not close to the upper bound of the cut-off points for accepted prevalences (5/10,000 inhabitants) by the COMP (Table 73).

Table 73. Number of availale orphan medicinal products per condition and prevalence

Condition	Number of available OMPs	Prevalence
Pulmonary arterial hypertension	**8**	**2/10,000 inhabitants**
Acute lymphoblastic leukaemia	**6**	**1/10,000 inhabitants**
Chronic myeloid leukaemia	**5**	**0,8/10,000 inhabitants**
Renal cell carcinoma	**4**	**3.5/10,000 inhabitants**
Acute myeloid leukaemia **Chronic lymphocytic leukaemia** **Multiple myeloma** **Tuberculosis** **Myelodysplastic syndromes**	**3**	**0.7 to 3/10,000 inhabitants**

The reason for such a different conclusion can be related to the definition used by *Brabers et al*. (126), since they used a cut-off limit for low prevalence of “less than 0.1 cases per 10,000 inhabitants” which is an extremely low prevalence which in our work we defined as “ultrarare”. If we apply their threshold, then none of the conditions with several available orphan medicinal products is an ultrarare condition. Thus, it can be concluded that more than one orphan medicinal product is unlikely for extremely rare conditions.

An additional possible hyphotesis to explain why 21 diseases have more than one treatment available may be that the research follows an exponential growth. All advances reached by one specific sponsor in a particular disease increase the knowledge about physiopathology of this medical condition, which can be used by the investigative community as a starting point. Better condition knowledge flattens the way to further research pathways, and eases feasibility of clinical trials. *Brabers et al* (126) also described a direct relationship between a higher frequency of “follow-on” orphan medicinal products and a higher number of articles on the condition and treatment published in the Pubmed database.

Besides prevalence figure and scientific output, other associations described in *Brabers et al* (126) included the turnover of the first orphan medicinal product (market sales higher than 50 milions of US dollars), the disease class (more follow-on medicines for oncologic disorders) and the age of onset (higher chance to obtain a follow-on medicine for disorders which age of onset was in adulthood). However, *Brabers et al* applied only univariate analyses, but some of this factors could be interrelated such as the market sales and prevalence, oncologic disorders and scientific output or adult age. In summary, prevalence may influence the probability that one orphan medicinal product may have one or more "follow-on" orphan medicines, but many different factors may also play a role in determining this fact, such as market size, scientific progress and dissemination and other factors.

An additional concern raised from the approval of the orphan legislation in Europe; whether the market exclusivity for 10 years (plus 2 additonal years in case to conduct a paediatric investigation plan) given to the orphan medicines as an incentive - to guarantee the return of investment in drug development - could discourage the development of new drugs when a first one had been approved.

It has been considered that "Market exclusivity" incentives may represent a threaten to innovation, and may block the development of new drugs(127). Also, the hurdles to approve new drugs for a particular disease when an orphan medicine has been previously authorised, and the market exclusivity is in force, could lead to market monopolies and ease that high prices are granted for orphan medicines(61). However, "market exclusivity" incentives are intended only to avoid that "similar"(21) drugs enter to the market while the exclusivity period is in force. In case that the new drug does not fulfil the "similarity" criterion, the new non-similar drug could be authorised. In addition, a clinically superior drug, despite being classified as "similar" could be also authorised based on the "significant benefit" criteria, as set in the European regulation on orphan medicinal products(17). Consequently, the "market exclusivity" rule only prevents the approval of "similar" new drugs lacking additional benefits over the already authorised therapeutic methods (i e: mainly opportunistic "me too" drugs).

Actually, *Brabers et al*(126) describe that most of medicinal products with Orphan Drug Designation continued its development after a marketing authorisation had been given to an orphan medicine in their intended indication. This fact suggests that the "market exclusivity" is not a disincentive for sponsors to develop new alternative treatments for rare diseases. In our study, 125 therapeutical indications approved during 15 years covered 84 different rare medical conditions, of whose 21 conditions had more than a single medicine authorised, supporting that "market exclusivity" does not fully block the commercialization of new orphan medicinal products after a first one has been approved for the same condition. Only drugs considered similar, and not bringing additional clinical value to existing treatment methods should not be approved.

9.2.3. Type of diseases covered by the therapeutic indications

Considering the type of condition according its ICD-10 group, a high proportion (41.6%) of authorised orphan medicinal products was aimed to treat "Neoplasms", followed by "Endocrine, nutritional and metabolic diseases" (28.6%). Each one of the rest of ICD-10 groups represented less than 6.5% out of all therapeutic indications approved. Our data are consistent with data published by *Westermark et al*. (26), who analyzed the outcomes of the first decade after the approval of the orphan legislation in Europe and described that Neoplasms summed up the 41% of authorisations. The high proportion of therapeutic indications directed to treat rare cancers could be deemed as unexpected, considering that most of rare diseases are not cancers(4).

The intensity of oncological research in the last decades, scientific progresses in the field and the very high number of research projects being developed, regardless on whether they were related to rare conditions or not, may be leading reasons for such a disproportionality. A study conducted to evaluate the new molecular entities approved by the FDA from 1930 to 2013 showed that the target therapeutic class for which more number of new drugs were approved from the year 2000 onwards (the period of time included in our review) was, sharply, oncology(128). The observation has been reported also in Europe, where a high number of drugs have been approved for oncological diseases, both for rare as for non-rare neoplasms: new medicines

approved in Europe in 2015 and 2016 show that oncology is again the most common target therapeutic class(129,130).

An additional circumstance that might help to the development of new orphan drugs in the oncology area is the translational factor. Scientific advances in the rare cancer environment, in which sponsors have some incentives, provide knowledge about cancer physiopathology that can be potentially useful for non-rare cancers. Thus, investments in rare conditions would be widely profitable when translated into non-rare conditions. However, this is only a hyphotesis which can not be confirmed based on our data.

Besides from oncology, the group of endocrine, nutritional and metabolic diseases has been also a driver for the number of orphan medicinal products authorised. The development of substitutive proteins targeting well-known and characterised congenital deficits is a relatively straightforward application from the mechanistical point of view, requiring either biotechnological production of a lacking enzyme or protein, or development of metabolical inhibitors able to block the production of substances that cannot be metabolised. Genetical, biotechnological and analytical developments, allowing identifying the involved genes, manufacturing products and measuring final products of metabolism as intermediate outcomes, respectively, have fostered progress and allowed a substantial growth of this type of orphan medicinal products.

9.2.4. Prevalence of therapeutic indications approved

A theorical risk of the orphan legislation could have been that companies applied for the orphan drug designations mainly for medical conditions in the upper part of the prevalence range considered in the orphan regulation, this is for the “most prevalent” rare diseases, with prevalence figures close to 5 cases per 10,000 inhabitants, in order to obtain the incentives included in the regulation to treat diseases with market sales close to those of conventional diseases.

However, our results showed that most of therapeutic indications (58.4%) approved were aimed to treat diseases with prevalences in the range between 0 and 1 case per

10,000 inhabitants, and only one therapeutic indication was aimed to treat a disease with a prevalence figure in the upper range allowed (between 4 and 5 cases per 10,000 inhabitants). The fact that most of therapeutic indications are aimed to treat the rarest and orphanest medical conditions can be considered a success of the European regulation.

A reason for the focus on low prevalence rare conditions may be related to a choice of the companies, who may be addressing their efforts to search new therapeutic alternatives for the rarest diseases due to research strategies (using rare conditions as proof of concept for new mechanisms), clinical feasibility (conditions with available registries or relatively high cohorts already identified, facilitating conduction of clinical trials), or market convenience (well known rare conditions with organised patients lobbies and concentration of the market).

Also, the focus can be related to a successful strategy of the COMP aimed to stimulate research in those conditions with lower prevalences. In this sense, the analysis of the prevalences of medical conditions designated as orphan during the first decade of the European regulation shows that most of medical conditions designated as orphan (52.6%) had prevalences between 0 and 1 cases per 10,000 inhabitants, and only few medical conditions (2.6%) had prevalences between 4 and 5 cases per 10,000 inhabitants (26).

These data could suggest that, despite the fact that the mission of the COMP is to be the “door opener” to the investigation in the field of rare diseases, as confirmed by the high proportion of positive opinion endorsed (73% of all applications up to December 2014 were resolved with positive opinion (125)), the COMP requires that the criteria established to access to the incentives must be fulfilled rigorously.

It should be highlighted that no orphan medicinal product approval during the 15 first years of European regulation was based on one option considered in the regulation: despite the prevalence is not that of a rare disease “without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment (‘insufficient return on investment

criterion')". Accordingly, all therapeutic indications approved during these 15 years have been targeted to treat only rare diseases.

9.2.5. Type of population covered by the therapeutic indication

In 2006 an specific European regulation was approved to "facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations"(24). The regulation requires a mandatory paediatric investigational plan (PIP) as a requirement for granting a marketing authorisation of a new medicinal product, and compliance with the plan is a requirement to obtain both authorisation and renewals of the marketing authorisation. Waivers to the conduction of a PIP are limited to few circumstances, such as conditions not involving children, or complete unfeasibility of research.

The implementation of the regulation had resulted 10 years later in the authorisation of 238 new medicines for use in children and 39 new pharmaceutical forms appropriate for children in the European Union. Also, around 19,000 reports on completed paediatric studies in about 1,000 active substances have been produced by pharmaceutical companies, resulting in approximately 140 updates of the product information and 16 new paediatric indications in areas where no paediatric medicines were previously approved. Also, by the end of 2015, the PDCO had adopted 860 opinions on the agreement of a PIP and in 421 (33%) cases had granted an exemption from conducting paediatric studies in one or more conditions (131).

Our data shows that for authorised orphan medicinal products, most (59%) therapeutic indications were claimed to treat only the adult population, followed by therapeutic indications covering both adult and paediatric population (37%); 4% of authorisations were limited to paediatric patients. Although, as compared to the results of the implementation of the paediatric regulation, the observed 59% can be regarded as higher to the proportion of waivers granted by the PDCO (33%)

considering all medicinal products. These results may seem inconsistent, considering that bibliography usually reports a high proportion of rare diseases appearing at early stages of life, probably because most of them are congenital(8,9). Moreover, paediatric population is expressly vulnerable to rare diseases, because children must face many complications regarding to their health, education, socialization and so on(7).

Yet, our figures may be biased, considering that we analysed the labelling as approved at the data cut-off by December 2014, and not the initial product labelling at the time of approval of the therapeutic indication. Some therapeutic indications can be extended to paediatrics once in the market if further studies are conducted after the initial marketing authorisation for adults. Yet, the potential resulting bias would be towards better paediatric figures than those at the time of first authorisation, and closer to real life regarding drug availability for paediatric population.

The low ratio of therapeutic indications approved only for paediatric population might be related to the intrinsic difficulty of research in such situations, risk aversion and cautions taken by companies to develop new drugs for children, but also to the fact that such indications are probably of lowest marketing potential. This circumstance is valid both for the drug development for rare diseases such as for conventional diseases.

9.2.6. Type of drugs approved

Related with the type of drugs approved, a high number of chemical entities were approved (76%) versus biological (23%) and advanced therapies (1%)(132).

Consistently, 74.6% of all marketing authorisations applications submitted to the EMA for orphan medicines from 2000 to the end of 2009 were small molecules(133). In a study in which factors associated with success of marketing authorisation applications were reviewed, existing small molecules were related with a higher ratio of success versus biotechnology therapies(43). Repurposing of drugs has become a succesful approach and strategy for some companies in rare diseases(134)(135); many chemical

entities approved in Europe in the 15 years analyzed could be considered repurposed drugs.

Regarding other types of molecules, when the mechanism of action of the 100 different products approved was analysed, inhibition of tyrosin kinases was the most frequent mechanism amongst orphan medicinal products, in particular for orphan medicinal products with oncological therapeutic indications. This result parallels the high number of Tyrosin kinase inhibitors approved in the last years, as reported in an analysis of FDA-approved drugs for oncology, which revealed the emergence of cancer drugs targeting kinases approved in USA from year 2000 onwards(136).

Regarding advanced therapies approved during the period of time studied, only one orphan medicinal product consisting of gene therapy was authorised. To note, this particular gene therapy is yet the single gene therapy that has been authorised in Europe up to the end of the period of time analyzed in our study. Eight years after the adoption of the advanced therapies regulation, only five marketing authorisations have been granted up to October 2015 (137). *(Table 74)*

Table 74. Advanced therapies authorised in the European Union up to October 2015.

Product	Indication	Year of authorisation	Type of therapy
Sipuleucel-T (Provenge®)	metastatic castrate-resistant prostate cancer	2013	Cell therapy
Alipogene tiparvovec (Glybera®)	lipoprotein lipase deficiency (Orphan)	2012	Gene therapy
Autologous cartilage cells expanded *ex vivo* expressing specific marker proteins (Chondrocelect®)	Cartilage defects	2009	Tissue-enginereed product
Matrix applied characterised autologous cultured chondrocytes (MACI®)	Cartilage defects	2013	Tissue-enginereed product
Ex vivo expanded autologous human corneal epithelial cells containing stem cells (Holoclar®)	severe limbal stem-cell deficiency caused by burns to the eyes	2015	Tissue-enginereed product

The fact that the first and only gene therapy authorised in Europe up to December 2014 is addressed to treat a rare disease is consistent, considering that gene therapy has been postulated as one of the most promising therapeutic opportunities for patiens with rare diseases, mainly monogenic diseases(138). Actually, it could seem that monogenic orphan conditions could herald the development of this group of products, and become a driver for change in the development of gene therapies for other non-rare conditions. However, technical and manufacturing progresses are yet not fully mature and the number of opportunities for developing gene therapies is still to be fully uptaken.

9.3. Description of regulatory process

9.3.1. Time lapsed from orphan drug designation and marketing authorisation

The average time lapsed from the obtention of the orphan drug designation to the obtention of an European marketing authorisation for the 125 orphan medicinal product authorisations analysed was 1,229 days (3.36 years). It can be considered a very short time if we assume that most of companies prefer to apply to receive the orphan designation in early stages of drug development, in order to get the incentives as soon as possible, and that in general, the median time required to complete the whole development of a drug is assumed to be around 12-13 years(13). It should be reminded that the orphan drug designation could be applied in any stage of drug development but always before the marketing authorisation.

Thus, the short time to approval amongst orphan medicinal products could be indicative that some products were designated as orphan in advanced phases of drug development, especially during the first years after the implementation of the Orphan directive. This is supported by observations such as the shortest time being only 77 days from granting of designation to granting of marketing authorisation.

Thus, the orphan medicinal products approved close after the approval of the European regulation about orphan medicines should be in last phases of drug development. According to *Westermark et al.*(26), who analysed the first decade of experience after the approval of the European regulation, the time lapse from designation to authorisation was 2.8 years. In our study in which 5 additional years have been included (from 2000 to 2014), the time lapse from designation to authorisation have been enlarged till 3.36 years. Such trend requires further follow-up to conclude whether the time from designation to authorisation will be further augmented in next years.

9.3.2. Transfers of the orphan drug designations among companies

The transfers of the orphan drug designation among companies was studied and revealed that almost half (48%) of Orphan designations which obtained the marketing authorisation changed of hands at least once.

This fact seems to point out that Orphan drug production could be developed in early stages by some companies and afterwards transferred to other kind of companies to develop the lasts phases of drug development in which usually more resources are needed.

We analysed which sponsor was the originator of the molecule (this is who discovered first the molecule), which sponsor was the first holder of the orphan drug designation (this is who submitted the application to the COMP to get the orphan drug designation) and which sponsor was the holder of the marketing authorisation.

We observed that in only 35% of therapeutic indications there were no changes of companies throughout all the the drug development process. Thus, the situation where all the orphan drug development was carried out by the same sponsor/company was not the rule. Also, we observed that big pharmaceutical companies (non-small and medium enterprises) were dominating the scene, so that we observed that in 71% of cases they were originators of molecules, with 29% of originators being small and medium enterprises, academic or public institutions,

private-private consortia or public-private consortia. For some molecules, no originator was found in Integrity database; these were already existing and well known old medicinal products repurposed for new orphan indications.

Initial orphan drug designation holders were again big pharmaceutical companies, who gained space over other type of holders to represent an 88% of holders, followed by small and medium enterprises and in low proportion Academic o public institutions. At the final stages, marketing authorisation holders only included Non-small and medium enterprises (89%) and Small and medium enterprises (11%). This is consistent with the legal requirements of European Legislation for Marketing Authorisation Holders, who are required to be formally commercial companies.

These outcomes showed that despite the fact that in early stages of development smaller companies or institutions have a role in the drug discovery process, the scenario is dominated by bigger companies, specially in advanced stages of drug development. This situation is likely due to the fact that latter stages of medicines development and authorisation require considerable resources which are not available for non-commercial sponsors nor easy to sustain for small companies.

In a similar study, *Lincker et al* (139) analyzed the type of entity acting as originator and marketing authorisation holder for all innovative medicines approved by the centralised procedure in Europe between 2000 and 2012, including both orphan and non-orphan drugs. The results also confirmed that among originators of innovative medicines there were a relevant proportion of small companies (27%) and academic institutions, public bodies and public-private partnerships (17%); meanwhile most of marketing authorisation holders were large and intermediate companies (87%), small and medium enterprises represented only a 13% of marketing authorisation holders and there was a null participation of other kind of entities. A subgroup analysis restricted to orphan medicines showed that 61% of the medicines with an orphan designation originate from SMEs, while SMEs account for only 22% of the marketing-authorisation holders, and 11% of the medicines with an orphan designation originate from academic institutions, public bodies and public-private partnerships, while these

organisations are no longer involved at the stage of marketing-authorisation applications for orphan drugs.

Despite our results and those of *Lincker et al* (139) are not identical, both point in the same direction and tendencies are coincident. Differences might be caused by the distinct period of time analyzed, the way to define the size of companies and the database used to identify the originator of the molecules (they used ADIS insight instead of Integrity, as we did).

Some limitations in our exercise should be mentioned. In one hand, we only used the registry of SMEs of the EMA to consider a company an SME or not. This registry is not mandatory and, despite most of SMEs are included, we can not guarantee that all companies not classified as SMEs are really small companies(140). Besides, we considered product transfers for all cases where the originator, orphan designation holder or marketing authorisation holder were different. In this sense, some transfers happened between different companies belonging to the same business holding (with common shareholders), but yet were accounted as changes of holders.

Results obtained both in our work as in the previous study conducted by *Lincker et al* (139), show that the orphan drug discovery and development process, at least in early stages, can be often led by small companies and even public or academic research institutions. The field of orphan medicines can become an area of work and growth for this sort of groups, and the EMA and the European Union recognise that small and medium enterprises are a motor of innovation in the European Union. Acknowledging their role in the development of new medicines, the EMA has implemented a programme to support small and medium enterprises throughout all stages of medicine development. It has been reported as a priority for EMA to reinforce the support available to small and medium enterprises, and to act as an enabler of development for the smaller actors in the pharmaceutical innovation ecosystem, particularly academia.

In this line, a way to foster the investigation on rare disease field includes training and support programs aimed to provide competences on leading regulatory development

to academic groups and small start-up companies, in order to spur these research groups to investigate on orphan medicines and to apply for orphan drug designations to the EMA. Some public institutions in Spain like the CIBERER have already taken the lead on this sense (141).

Finally, an additional consideration could be done. As it is well-known, the price of orphan medicines is usually, and increasingly, high (60,61,64). Several determinants conditioning the final price approved for orphan medicines have been studied. Up to now, the prevalence of the treated conditon is the one single factor which correlates better with final price of orphan medicines (higher prices for orphan medicines aimed to treat diseases with lower prevalences) (54,65). It could be interesting to check if the number of transfers among different companies has also a direct influence on the final price approved for orphan medicines. It may seem reasonable to think that chained royalty agreements between the successive holders may determine the need for high prices to ensure return of investment and profitability across different entities. In this manner, the number of transferences and consequently the number of purchasing processes might raise the final price of orphan medicines. No data have been found checking this hypothesis, which could be explored in the future as a further line of research.

9.3.3. Comparison with FDA results

As mentioned in the introduction, the European regulation on orphan medicinal products was inspired on the Orphan Drug Act (18) approved in the USA in 1983, which was aimed to promote drug development for rare diseases in the United States (142).

The Orphan Drug Act has been mostly considered a success and an important step ahead regarding the increase in research on rare diseases and as an estimulous for orphan drug development (19). In this manner, after the approval of the Orphan Drug Act, similar initiatives have been taken in other regulatory environments, such as the European Union, Japan, Singapore, Taiwan or Australia (2).

After the Orphan Drug Act approval, by 2006 nearly 300 approved products aimed to treat more than 15 millions of patients with rare diseases in the USA were already

available. The magnitude of the benefits of the Orphan Drug Act can be shown by the fact that only 10 treatments for rare diseases were approved along the decade before 1982 (36). Some other additional impacts of the Orphan Drug Act approval have been reported, such as an increase in biotechnology medicines development, growth of non-big pharma companies which have found in rare diseases a niche research field, or fostering of pharmacogenomics advances.

In 2008, *Braun et al.* (20) conducted a study aimed to analyze quantitatively the outcomes of the first 25 years after the approval of the Orphan Drug Act. In this study, which included the period of time lapsed from 1983 to August 2008, the FDA granted up to 1,892 ophan drug designations, of which 326 subsequently were granted a marketing authorisation. In our study, if we limit the outcomes until August 2008, in the European Union 573 orphan drug designations were granted, of which, 50 different orphan drugs obtained the marketing authorisation (143), that is, in Europe the number of granted ODD was 30.3% of those granted in the USA, and the number of orphan medicinal product authorisations represented 15.4% of those granted in the same period in the USA. Obviously, despite the lenght of the period assessed is the same, the periods are not comparable since the Orphan Drug Act entered into force 17 years before than European Regulation. In this line, it could be interesting to conduct further studies to clarify if orphan medicines approved from 1983 to 2000 in the United States were also approved in Europe, despite not being designated formally as orphan medicinal products because of lack of specific regulation.

Nonetheless, *Tiwari J* (37) observed that since year 2000, when European Regulation entered into force, the yearly number of orphan drug designations and marketing authorisations was always higher in United States as compared to Europe. Despite a review to understand the gap existing between United States and Europe in yearly number of designations and marketing authorisations have not been formaly conducted, some reasons could be suggested.

On one hand, the threshold established to determine what is orphan in the USA is based on the number of patients affected by a particular disease. All diseases which affect less than 200,000 inhabitants are considered rare in the USA. Taking into

account the USA population (144), it would be equivalent approximately to “less than 7.5 cases per 10,000 inhabitants”. Thus, the definition for rare conditions is less stringent than the European definition “less than 5 cases per 10,000 inhabitants”. Thus, the number of potential designations and approvals is higher in the states, involving more prevalent conditions – which may also be more interesting from a commercial point of view. As suggested above, further studies to analyse if orphan drugs approved in USA from year 2000 onwards have also been approved in Europe regardless of their ODD status.

Besides, the Orphan Drug Act allows grantingorphan designation also for medical devices and dietary or dieting products, while in Europe only medicines are suitable to be designated as orphan. Again, this may explain part of the differential number of ODD between both regions.

Another point to consider is the allowance of ODD for subgroups within a given condition, defined based on biomarkers, lines of treatment or other considerations. Differences in criteria for ODD assessments may lead to additional differences in final ODD numbers.

Finally, some authors have suggested that the tax credits and research grants included in the incentives given by the FDA after the orphan drug designations could be also a reason that might explain the higher number of approvals and designations in the USA(44). The easiness for creation of companies, and flexibility amongst academic grounds to create start-up companies and small and medium enterprises may also play a role to this respect.

Coming back to the study conducted by *Braun et al.* (20), they described that both orphan designations and marketing authorisations for orphan products in the USA were also focused on diseases in the low range of prevalence, as we have described in previos sections. It means that most of orphan research is addressed to the rarest diseases. Similary, and again consistent with European findings and our series, cancer was the most common disease category both for designation as for approvals in the USA.

9.4. Type of evidence supporting the approval of orphan medicines in Europe

In our work, the type of scientific evidence submitted to the EMA in order to obtain the marketing authorisation application for the 110 out of 125 (88%) therapeutic indications approved from 2000 to 2014 included scientific evidence coming from clinical trials. On the other hand, up to 12% (n=15) of therapeutic indications were approved on the basis of data obtained from other sources (bibliography, compassionate use programs or retrospective analysis of observational data).

These results are consistent with the outcomes reported by *Picavet et al*.(55), who analysed the type of evidenced submitted to obtain the marketing authorisation for the first 78 therapeutic indications approved for orphan medicinal products in Europe between year 2000 up to July 2012. They also identified that in up to 10 different therapeutic indications, the pivotal scientific evidence in the application dossiers was coming from sources different to clinical trials.

The study conducted by *Picavet et al* displays many similarities to our study, but referred to a shorter period of time. Hereafter it will be used in the discussion section in order to compare results obtained in both studies.

Currently, there is a unanimous consensus about the fact that clinical trials are the best methodological way to evaluate the efficacy and safety of an experimental treatment(145). Thus, from a strict regulatory point of view, all medicines shoud have been tested in appropriate clinical trials previously to be authorised, and no medicine should be endorsed to be commercialized without clinical trials supporting its positive benefit/risk. In such a setting, it could be surprising that up to 15 (12%) of all orphan therapeutic indications approved from 2000 to 2014 were lacking of clinical trials supportive of their efficacy and safety.

However, it is recognised that in some particulars settings it may be difficult or even unfeasible to conduct conventional clinical trials. In particular, orphan medicinal drugs face up several hurdles because the nature of rare diseases, so that different challenges must be tackled: lower knowledge about the disease physiopathology, lack

of preclinical models validated, absence of standardised and validated diagnostic tools, geographical dispersion of patients, disease hetoregeneity, lack of patients registries, scarcity of reference hospitals, reduced available sample size for trials, absence of comparators, absence of validated endpoints and scarcity of reliable surrogates, especially in conditions with slow clinical course, reluctance to randomisation or to use of placebo by patients, ethical considerations on vulnerable populations and on access to treatments, amongst others(5,14,119,122,146).

In this context, other sources of scienfic evidence different of conventional clinical trials could be considered acceptable, recognizing that they may be the only feasible way to show a positive benefit/risk balance of drugs. Further development of methodologies and statistical methods specially suited to deal with small populations and specific problems of orphan conditions may improve in the future the robustness of the scientific evidences in situations where conventional clinical trials are unfeasible(122) .

9.4.1. Number of clinical trials supporting authorisations of orphan medicines

The 110 therapeutic indications approved based on evidence coming from clinical trials accounted for a total of 159 different pivotal clinical trials (mean per therapeutic indication of 1.45 trials, median of 1 trial per indication). These figures are similar those reported by *Picavet et al.*(55), who described that 108 pivotal studies were conducted for 59 orphan medicinal products approved in Europe from 2000 to July 2012 (mean 1.83 trials per product). Despite the paper didn't clarify the number of therapeutic indications approved for these 59 orphan medicinal products, our results are referred to 159 trials for 88 different orphan medicinal products (mean 1.81 trials per product); thus, the outcomes described by *Picavet et al*. may be considered similar.

Our study overcomes the *Picavet et al* report in that it includes an additional factor related with the amount of supportive scientific evidence, that is: the number of supportive studies enclosed in the EPARs. For the 110 therapeutic indications approved with evidence coming form clinical trials, information on 339 different

supportive studies was also included in the EPARs published by the EMA. This represents a mean of 3.08 supportive studies in each indication approved, and a median of 3 studies per indication. However, there was huge variability in this respect, ranging from 0 to 15 supportive studies across indications.

Supportive studies contribute to the assesment of dose ranging, clinical relevance of main end-points, sustainability of effects and safety issues, and are a relevant source of complementary information in a setting of scarcity of pivotal evidence. Thus, a focus on the amount of supportive data can be considered as relevant in the process of regulatory assessment of orphan medicinal products, and in this sense, some structured approach to key assessment rules that take into account the relative scarcity of data in orphan medicinal product dossiers could be regarded as useful for both regulators and applicants.

9.5. Characteristics of the pivotal clinical trials supporting orphan marketing authorisations in Europe

One of the most relevant features described in our work was the type of methodological design applied in main clinical trials conducted with orphan medicines. This issue is closely related with the objective of the European project in which our study is framed. This European project, included in the 7th Framework Programme, and named ASTERIX (Advances in Small Trials dEsign for Regulatory Innovation an eXcellence) was aimed to search of new methodological designs suitable and more feasible to be applied for orphan medicines: the aims also included to asses the applicability of different methods to different orphan conditions in a framework that eases references, and to translate any potential methodological or statistical improvements into specific recommendations that could be easily disseminated and applied by investigators and sponsors, as well as to serve as references to regulators in their assessment activities(120,121). The bulding of a regulatory standard based on the analysis of current characteristics of the orphan medicinal products application dossiers was one of the key deliverables of the project, and the reason for the

structured analysis of the characteristics of the trials providing evidences to product approvals in orphan settings.

The analysis of the characteristics of pivotal studies supporting the marketing authorisation of orphan medicinal products was limited to the 159 main clinical trials included in the EPARs of those orphan medicinal products approved based on clinical evidence generated from clinical trials.

Other sources of evidence (bibliographic reports, compassionate use studies and retrospective studies) were excluded from the description because their characteristics were considered not comparable to those of clinical trials.

9.5.1. Study phase

Regarding the study phase, 49.7% (n=79) of clinical trials were considered as phase III trials; this is similar to the 46.3% (n=50) report in *Picavet et al.* (55). It is noteworthy that most of the pivotal trials for orphan medicinal products were not phase III trials, which has been traditionally considered the standard of confirmatory trial. This is likely one of the key differences to conventional medicinal products, which mainly are based on 2 or more phase III replicated trials.

9.5.2. Number of involved sites

Most pivotal clinical trials analyzed in our study were multicentric (85.5%; n=136) and multinational (64.8%; n=103). *Picavet et al.*(55) refered the same results regarding multicentric trials (84,3%), but much lower proportion of international trials (only 13.9%). The reason for such divergence must be likely related to the definition of multinational; we considered multinational any trial involving patients from more than 1 country, but no information on such definition has been identified in the *Picavet et al* report.

From a theorical point of view, the low number of patients affected by a particular rare disease and the usual geographical dispersion of patients across the territory would lead us to think that involving several centers and nations in a clinical trial would facilitate the patient's recruitment. Thus, fostering international cooperation between

investigators and clinicians based on different countries should be enhanced to increase the feasibility of better trials with wider sample size, statistical power and external validity. Often, trials are claimed to be small sized because of the rarity of condition and scarcity of patients, but then inconsistently they are based on recruitment in one or few countries only. While it is recognised that funding may be a limiting factor to conduct international research, it seems that small geographical approaches should be disincentived both from an ethical point of view and from public funding. Recent programs fostering research in rare conditions across Europe are working in this direction (147).

9.5.3. Type of blinding

The type of blinding of the clinical trials was also studied. We found that up to 47,2% (n=75) of clinical trials were open-label trials, similarly to *Picavet et al*. results, reporting that 40.7% of clinical trials were open-label. Some concerns might arise about the lacking of blinding, because open studies can increase the risk of many biases. It is accepted that un-blinded studies have more chances to show higher clinical improvement (148), thus leading to overestimation of both efficacy and adverse events, and potential biases based on patient's and investigator's expectations, resulting in a decreased study robustness and reliability (145).

9.5.4. Randomization

Regarding the use of randomization for treatment allocation, our study showed that in 30.9% (n=50) of trials patients were not randomized; similarly, *Picavet et al* reported a percentage of non-randomized clinical trials of 35.2%. Lack of randomization may increase the risk of assignation biases, thus resulting again in a decreased study robustness and reliability (145).

9.5.5. Control arm

In 33.3% of trials (n=53), no control arm was used; for the remaining 67.7% of trials, 47.2% (n=75) used placebo as control and 13.2% (n=21) used an active comparator. Again, these results are virtually overlapping with results published by *Picavet et al.*

whom determined that the proportion of no-controlled trials, placebo-controlled trials and trials with active control were 31.5%, 45.4% and 15.7%, respectively. Lack of control arms preclude to establish an estimate for the magnitude of the treatment effect, does not allow to control for spontaneous recovery, fluctuation of disease, regression to the mean, effect of unspecific therapeutic action, patient's response to observation and assessment (Hawthorne effects) and the patient's response to the patient-practitioner interaction. Again, lack of control group may represent a decreased study robustness, and precludes to establish robust causality relationships (145).

9.5.6. Sample size

The analysis of the number of patients enrolled in the clinical trials showed that the median of patients enrolled in main clinical trials conducted with orphan drugs was 134, with a range from 5 to 934 patients; *Picavet et al.* reported a median of 113 individuals included in the main trials, ranging from 7 to 976.

9.5.7. Study duration

Finally, the duration of the main clinical trials showed that the time point established to evaluate the primary endpoint of trials was in average 21 weeks. When we excluded those trials with a non-specified time point to measure the primary endpoint, such as survival designs, the median point time to evaluate the primary endpoint was 24 weeks. These results have some limitations: in one hand, we only determined the time point when the primary endpoint was measured but the overall duration of the main clinical trials was actually longer when clinical trials continued following patients beyond this time point for secondary assesments. Furthermore, in clinical trials where a time point to mesure the primary endpoint was not pre-established such as "survival or time to event studies", we considered the median time to achieve the main endpoint as the time period when primary endpoint was measured, but at least for half of the poplation the actual time point would have been longer than the median. Because of that, we excluded the trials without a preespecified time point to measure the primary endpoint. Finally, the time point established to measure the primary

endpoint was only quantitated, but a qualitative analysis to determine if the duration was long enough regarding the disease and endpoint used was not done. Consequently, the appropriateness of the median observed duration cannot be discussed.

9.5.8. Study setting and design

We observed that 65.4% (n=104) out of all clinical trials conducted for orphan medicinal products used a “Parallel arms” design and 29.6% (n=47) were “Single arm” trials. Adding up both sort of designs (parallel and single arm), conventional designs supposed that in the 95% of cases, the clinical trials adopted a well-know and non-innovative trial design.

On the other hand, only 3.8% (n=6) of trials followed methodological designs considered as alternative.

These outcomes show that, in the vast majority of cases, classic or well-known methodological designs were used in the main clinical trials conducted with orphan medicines. Nontheless, in last years, some voices have suggested that different, alternative and more flexible methodological designs for clinical trials could be used for orphan medicines in order to achieve more feasible, reliable and cost efficient clinical development of treatments for rare diseases(14,15,44,105,106,108–114,149–154).

It is accepted that trial designs for rare diseases must also fulfill the criteria established to avoid biases as much as possible and obtain valid results. In this sense, randomized clinical trials could be considered still the gold standard in clinical trial development, because it is a design that minimizes the bias risk. However, many different types of designs are available and randomized clinical trials could be not always feasible in some situations like rare diseases because the nature and characterstics of these kind of medical conditions(115).

Starting from the premise that “one size does not fit all”, several alternative clinical trial designs might constitute an alternative to applicate for orphan medicinal product development. In this line, among these alternative methodological designs we could

find the sequential methods, adaptive designs, Bayesian trials, N of 1 trials, among others(107).

Likewise, the current Guideline on clinical trials in small populations of the European Medicines Agency also included alternative designs or methodology as an option to be developed when clinical trials for ophan drugs are conducted(116). However, this guideline does not specifiy which designs are more adequate or feasible to be conducted in each particular scenario.

In summary, the almost complete absence of alternative designs used in trials conducted to get the marketing authorisation for the first hundred of orphan medicinal products approved in Europe could be deemed as unexpected, since is the ideal setting to implement any measure aimed to increase robustness and maximize the efficiency of a scarce sample size.

9.5.9. Studies meeting its primary end-point

Finally, regarding the fulfillment of the primary objective of main clinical trials conducted for orphan drugs, up to 11 different therapeutic indications were approved without any clinical trial which accomplished its primary objective. From a strict methodological point of view, clinical trials which did not fulfill the primary objective specified in the trial protocol should be considered failed and the efficacy of drugs studied should be considered as not demonstrated. Otherwise, the conclusions extracted face the risk of being influended by biases and statistical errors.

For this reasons, it is relevant to emphasise that 11 therapeutic indications were approved without any clinical trial attaining its primary objective. Such an scenario would be inconceivable for medicines aimed to treat prevalent diseases, but seems to be acceptable from the regulatory point of view in the rare disease field. The severity of diseases, the unmet medical needs and the feasibility of conducting “classical” clinical trials, push the regulators to make decisions on access to medicines in uncertain scenarios, applying a wider and more flexible evaluation for the applications submitted to achive the marketing auhorisation for orphan medicines.

9.5.10. **Subgroup analysis**

In order to explore if pre-specified subgroup analysis could justify the autorisation for the 11 therapeutic indications where the main trial was inconclusive, whether therapeutic indications were approved based on subgroup analysis pre-specified in the clinical trial protocol was explored. In 2 our of 11 cases (18.2%) the approval of these therapeutic indications was based on subgroup analysis specified a priori in the protocol.

9.5.11. Overall assessment of study designs and regulatory standard

We have used the *Picavet et al.* study (55) to compare our results because we have considered that this is the most similar work published in the literature to our own exercise. Both works analyzed similar design determinants of main clinical trials, and partially referred to the same data source. While *Picavet et al.* analyzed only the first 78 therapeutic indications authorised for orphan medicinal products in Europe, our study widened the number of therapeutic indications studied up to the 125 first therapeutic indications approved for orphan medicinal products.

As a result of the comparisons, we may conclude that the characteristics of pivotal clinical trials conducted to support orphan medicinal product applications, and, consequently, the level and quality of the scientific evidence generated for orphan medicinal products approved in the European Union, seems to be maintained over time.

As we have seen, the characteristics that traditionally determine the quality of the scientific evidence (that is: use of control groups, random assignation to treatments, blinding to the identity of treatments and dimensioning of trials to allow recruitment of appropriate sample size, amongst other characteristics), suggest that the quality of main clinical trials conducted for orphan medicinal products could be lower than desirable, at least from a theorical point of view.

In this sense, blinding, randomization, use of control or sample size could be affected by the own nature of rare diseases. Several studies have demonstrated clearly that these characteristics of clinical trials conducted for orphan medicinal products are

different versus the clinical trials conducted for non-orphan medicines. In this line, higher frequency of open-label study designs, lower use of randomized allocation of patients, higher percentage of clinical trials non-controlled and lower number of individuals enrolled in clinical trials have been repeatedly reported for clinical trials with orphan drugs versus clinical trials with non-orphan drugs in different settings (56–59,155).

We have observed a really low uptake of alternative designs especially suitable for small samples of patients. Also, 11 therapeutic indications were approved based on clinical trials not attaining its primary objective. These data should be placed in the context of the fact that 15 different therapeutic indications were approved based on scientific evidence coming from sources different of clinical trials. If we add these 15 cases with the 11 cases where clinical trials did'nt achieved its primary objective, we notice that 26 out of the 125 therapeutic indications (20.8%) were approved in a setting of low strenght of scientific evidences. Morevoer, if we take into account that the characteristics of clinical trials conducted in support of applications point out to a lower quality of clinical trials, we realize that, on one side, the capacity to generate robust scientific evidence for orphan medicinal product is a hard challenge to be face up, and on the other side, regulators are taking decisions for orphan medicinal products based on very weak scientific evidences (54,56,70).

9.6. Type of endpoints used in pivotal clinical trials supporting orphan authorisations in Europe

9.6.1. Single vs composite end-points

The type of primary endpoints used in the main clinical trials was also analysed. First of all, we could see that most of primary endpoints were "Single" endpoints (76.7%) and the measure of the endpoint was generally considered as "Objective" (89.9% of clinical trials).

9.6.2. Direct vs intermediate end-points

Moreover, when the clinical relevance of the primary endpoint was assessed, most of clinical trials (74.8%) included an "intermediate" primary endpoint. Our results were similar to those observed by *Picavet et al* (55) who reported that 19.4% of all clinical trials with orphan treatments used "hard" endpoints. Additionally, other studies also confirmed a high use of surrogate endpoints in this setting(40).

Another element studied was the percentage of use of biomarkers included in the primary endpoint. In this wise, in 69.2% (n=110) of clinical trials the primary endpoint used a biomarker.

The high ratio of use of biomarker used in our study could be affected by the definition of biomarker adopted in our work. Thus, biomarkers were considered as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives"(156).

This definition also included histologic and radiographic changes and consequently cancer progressions were considered to be biomarkers. This circumstance should be taken into account because in some environments only biochemical or molecular biomarkers are considered.

Hard or final endpoints are measures directly related with clinical benefit, while intermediate (also called surrogate) endpoints are used in clinical trials as a substitute for a direct measure of patients' health or survival. Intermediate or surrogate endpoints do not directly measure the clinical benefit, but should be able to reliably predict clinical benefit through measures plausibly and reliably related with the clinical improvement(157).

Ideally, to ensure that the drug studied truly the expected clinical results, when we use surrogate or intermediate endpoints, these endpoints should be validated. It means that despite there is a rationale that supports that the intermediate endpoint used is

directly related with clinical benefit, we require clinical data that confirm that changes in surrogate endpoint will actually translate into clinical benefit(157).

In this sense, hard or final endpoints are always preferable over intermediate or surrogate whenever feasible, because the clinical benefit obtained with a particular intervention (eg. Orphan drug) is directly determined and thus uncertainty is reduced (158).

However, in rare diseases, due to restrictions on the available sample size or the limited duration of clinical trials, finalist or hard endpoints are difficult to be implemented as primary endpoints.(55)

Despite the fact that the use of intermediate endpoints has allowed that many orphan drugs could have been approved, some criticisms have been raised about the use of intermediate endpoints in rare diseases, because most of them are not validated. The clinical relevance and reproductibility of these endpoints have been strongly questioned, specially when new intermediate endpoints have been proposed(55,159).

Doubts about the clinical relevance of primary endpoints used in some clinical trials for orphan drugs increase the uncertainties about the magnitude of the effect provided by some orphan medicinal products, and joins to the concerns caused by the lower quality of scientific evidence available and before mentioned.

In a context where final endpoints are difficult to implement, to have sensible and validated biomarkers could suppose a step ahead to improve the development of orphan medicines, not only in clinical phases but also in preclinical stages.

9.6.3. Patient reported outcomes

Subsequently, the incorporation of Patient Reported Outcome Measures (PROMs) in the primary endpoint definition was observed only in the 8.2%. (n=13) of main clinical trials conducted.

A Patient Reported Outcome is considered “a report of the status of a patient’s health condition that comes directly from the patient (or in some cases a caregiver, representative or surrogate), without interpretation of the patient’s response by a

clinician or anyone else" and PROMs are the instrument to asses this Patient Reported Outcome(160,161).

Taking into account the difficulties to define intermediate or surrogate endpoints wich have clinical relevance in the rare disease field, PROMs have been proposed as an useful and valuable tool to establish the relevance of the benefit provided by orphan medicines.

However, PROMs face several limitations, like the lack of specific and validated instruments for each disease, the limited ability to capture all relevant features for a given condition or patient, when heterogeneity in disease expression is high, or the risk of biases. These have hampered a wider use of PROMs in the pivotal clinical trials, and may explain the low rate of use in the trials that we have observed in our study(162).

Despite PROMs have been developed over the past decades, their application have not been generally used in clinical trials as a primary endpoint. Some recent changes like the improvement of information and communication technologies have revived the applicability of these tools(163). Proof of this fact is the recent qualification advice given by the Scientific Advice Working Party of the EMA to the Patient Data Platform for capturing patient-reported outcome measures for Dravet syndrome, a type of rare and refractory paediatric epilepsy(164).

Finally, from an overall point of view, the type of primary endpoints used in clinical trials for orphan medicinal products have been compared with primary endpoint used in clinical trials for non-orphan medicines in the literature (56,57). These works showed that strength of primary endpoints used for orphan drugs seemed to be lower, as compared with the ones used for non-orphan drugs(56,57).

9.7. Factors that influence pivotal study designs supporting marketing authorisations in Europe

9.7.1. Analysis of trial characteristics by prevalence of the medical condition

An analysis of the results as a function of the rareness degree of the medical condition was done, in order to check if study designs were substantially different for very rare conditions with severe limitations of potential recruitment and sample size. In this sense, two different categories were established: 1) rare medical conditions, which included the rare diseases with prevalence figures equal o higher than 0.1 cases per 10,000 inhabitants; and 2) ultrarare medical conditions, which included rare diseases with prevalence figures lower than 0.1 cases per 10,000 inhabitants. Despite the concept of ultrare disease is often used in the bibliography, ultrarares diseases are not specifically defined by the different regulations on orphan medicines, neither in USA nor in Europe. Consequently is a concept that does not exist legally (165). Furthermore, no additional incentives are facilitated to sponsors whom develop medicines for diseases with extremely low prevalences. Several prevalence figures thresholds have been used in bibliography to define ultra-rare diseases. A publication by *Richter et al.* (166) found up to 10 definitions of "Ultrarare diseases" worldwide. In this sense, several figures thresholds have been used to define ultrarare diseases (166,167).

The prevalence figure threshold used in our study (<0.1 cases per 10,000 inhabitants) was decided by consensus within the ASTERIX project members after discussion of available options. Taking into account the European population, the threshold used means that the maximal overall population affected by an ultrarare disease will never exceed the 5,100 patients throughout the European Union. ASTERIX members agreed that these extremely low prevalence figures may heavily influence the feasibility of conducting standard clinical trials.

Out of the 125 therapeutic indications approved for orphan medicinal products, 109 (87%) were classified as rare medical conditions and 16 (13%) were considered

ultrarare medical conditions. In this sense, the low number of medical conditions considered ultrarare requires that data must be interpretated with caution. Also, the low number of therapeutic indications that were approved based on scientific evidence coming from clinical trials for ultrarare conditions was the most remarkable finding: 91.7% of rare therapeutic indications as compared to only 62,5% of ultrare medical conditions were approved based on clinical trials.

Regarding the therapeutic indications approved based on clinical trials, there were no differences as regards to the number of main clinical trials conducted, since it could not be lower (median of 1 main clinical trial both for rare and ultrare groups), but the number of supportive studies was a little lower for ultrarare medical conditions (median of 3 supportive studies for rare group versus 2 suportive studies for ultrare group).

When blinding, use of randomization and type of control used were analyzed, only the type of control showed some mentionables findings. In this sense, no active control group was used in any clinical trials conducted in ultrare diseases. This can be reflective of a higher unmet need in ultrarare conditions, whereas in some rare conditions an active treatment may already be available. Regarding the trial design, only a trend showing a lower percentage of parallel design trials in ultrare diseases seems to be suggested.

Finally, as expected, the number of patients enrolled in the clinical trials was significatively lower for the ultrare group (median of 35 patients versus a median of 154 patients enrolled in the clinical trials for ultrarare and rare diseases, respectively). This difference observed sharply conditionates the capacity to generate robust scienfic evidence.

Taking all outcomes together, it seems clear that the lower is the prevalence of a disease, the harder are the difficulties existing to generate solid scientific evidence.

9.7.2. Analysis of trial characteristics by type of disease (clustering)

One of our hypotheses is that the type of disease can influence in a relevant manner the selection of the clinical trial design. In this line, an analysis of trial characteristics as a function of the type of disease treated was conducted.

We chose to group conditions based on 6 different clusters, as proposed by the ASTERIX project: acute single episodes, recurrent acute episodes, chronic slow or non-progressive conditions, progressive conditions led by one organ/system, progressive multidimensional conditions and staged conditions (122).

One of the strengths of these clusters is that they were created based on the applicability of different methodological approaches to the study of medical conditons. The rationale is based on the fact that it is unfeasible from a regulatory point of view to develop practical guidelines on clinical development requriements for each single rare conditions, since there are up to 6000-8000 different rare diseases (4,5). Thus, one of the objectives within the ASTERIX project was to simplify the scenario by providing a tool for grouping medical conditions or regulatory indications in clusters that could share common designs and methodologies for clinical development and trials design. In this way, guidelines issued for one cluster could be proposed, that would be applicable to various conditions. Simplification of the scenario should improve the ability to issue recommendations, ease communication and thus help for the application of alternative designs aimed to improve orphan drug development.

All 125 therapeutic indications approved were classified regarding the clusters defined. During the process, some of the diseases could be classified in more than one clustering, depending on two main determinants of the intended indication for the drug in the EPAR: the clinical course of the medical indication and the therapeutic goal of the experimental drug tested in the clinical trial. All the therapeutic indications or medical conditions fitted within the clusters, and the trial characteristics were described accordingly.

It was interesting to check whether differences in the applied methods to the clinical development of orphan medicinal products were matching the assigned clusters, since

this could serve as a sort of validation of the appropriateness of the clustering, on one side, and at the same time might result in a good reasoned systematization of potential divergences in clinical development approaches.

Noteworthy, our analysis showed differences among the clusters defined in all the characteristics analyzed, this is, in the percentage of approvals based on clinical trials or different sources of scientific evidence, the median number of main clinical trials, type of blinding, use of randomization, type of control, type of clinical trial design, overall population enrolled or time point established to measure the main endpoint. The main results for the analysis are systematized in *table 75*.

Table 75. Main results for the analysis of characteristics of evidence supporting the EPARS according to ASTERIX clustering

Clustering	Main findings	Description of cluster applicability as per ASTERIX definitions
Acute single episodes (Therapeutic indications N=27; 22% of total)	- 23 therapeutic indications approved based on clinical trials (85.2%) - Relevant proportion of bibliographic applications (14.8%) - Overall number of main clinical trials conducted n=32 (mean=1.39; median=1) - Second with shorter time to outcome with median (IQR) follow-ups of 9.1 (IQR: 2.6 – 25.7) weeks - Used single blind trials, although infrequent (3.1%) - Non randomised designs in 40.6% of trials - Most frequent design is parallel (59.4%) - Only cluster using historical controls (3.1%) - High proportion of single primary endpoints (81.25%) - High percentage of primary endpoints based on objective measures (93.75%) - Final primary endpoints used in 37.5% of pivotal trials	- Studies with longer recruitment than follow-up for a given subject, thus application of sequential and adaptive methods may optimise the trial size. Time to event may be applied. - If SOC available, then placebo could be applicable in parallel, add-on designs with non-inferiority or superiority objective. - Single hard objective end-point may allow unblinded designs. - Lack of SOC may ease recruitment, but comparisons against placebo generally not acceptable unless add-on designs to e.g. best supportive care. Placebo may be used for limited time in non life-threatening conditions. - For disease without SOC or trials in patients who have exhausted all SOC options, controls may be historical, external or even uncontrolled trials assessing change from baseline or superiority to substantiated expectations may be justified. - Rescue strategies generally required during patient follow-up.
Recurrent acute episodes (Therapeutic indications N=7; 5% of total)	- 7 therapeutic indications approved based on clinical trials (100%) - Overall number of main clinical trials conducted n=11 (mean=1.57; median=2) - Higher number of supportive studies with median 3 (IQR: 2 – 6.5), ranging from 1 to 11. - Shortest time to main outcome assesment, with median (interquartilic range) 4.3 (IQR: 4 – 16.57) weeks - Almost always (90.9%) using double blind designs	- Generally two different indications: treatment of acute episodes and prevention of new episodes. - If condition is returning to normal after acute episode, start-stop designs (withdrawal, cross-over and intrasubject comparison) may be applicable for both indications. - For treatment of acute episodes, variables generally include remission of the episode (dichotomic), time to remission of the episode (time to event) or intensity of the episode. - For prevention of the episodes, variables generally rely on number of episodes per time. Longitudinal designs with repeated measurements may be applied.

	- Always randomised. - More than 50% of trials did not use any control treatment - The use of placebo was limited to less of 33% of trials. - Most frequent design is parallel (81.8%) - Highest proportion of single primary endpoints (90.91%) - Use of primary endpoints based on objective measures in 63.64% of cases. - Larger use of final primary endpoints (81.82%) - Higher proportion of ultrarare conditions with 28.6% of conditions below 0.1/10,000 subjects.	- Response may be based on clinical assessments supported by lab/biological/imaging data. Multiple assessments are generally feasible. - Use of placebo generally limited in time for non life-threatening conditions or when lack of prognostic consequences for periods without treatment. - Rescue plan needed (either for placebo or for experimental treatment)
Chronic slow or non-progressive conditions (Therapeutic indications N=8; 6% of total)	- 7 therapeutic indications approved based on clinical trials (87.5%) - Overall number of main clinical trials conducted n=18 (mean=2.57; median=3) - Higher median number of pivotal trials supporting applications. Median 3 (IQR: 1.5 – 3.5), from 1 to 4. - Trials designed as open label in 66.7% - Parallel design and single arm design used in the same proportion (44.4% for both) - Crossover trials were used mostly in this cluster (11.1% of trials) - Non randomised designs used in 55.6% - More than 50% of trials did not use any control treatment - Use of placebo less of 23% of trials. - Highest ratio of subjects assigned to experimental groups - High use of intermediate endpoints (83.33%)	- Recruitment may be more rapid than subject follow-up, potentially limiting the role for sequential designs and some adaptions. - Start – stop based methods (crossover, withdrawal) may be applicable. - Intrasubject comparisons generally feasible. - Double blind would be generally required, and because SOC is generally available, designs would generally be add-on, unless treatments share mechanism of action – then direct comparison may be required with non-inferiority approach. - Surrogates would generally be available and often easily validated. - Safety requirements must be widely assessed due to chronicity and relative mildness of conditions with current SOC.

	- Larger proportion of multiple primary endpoints (22.2%) - Wide inclusion of biomarkers as primary endpoint (72.22%) - Use of PROMs in 16.67% of cases as part of the primary endpoint	
Progressive conditions led by one organ/system (Therapeutic indications N=20; 16% of total)	- 18 therapeutic indications approved based on clinical trials (90%) - Overall number of main clinical trials conducted n=27 (mean=1.5; median=1) - Trials were more frequently designed as open label (77.8%) - Non randomised designs were used frequently (55.6%) - Placebo was used as a control in more than 50% of trials - Most frequent design is single arm (55.6%) - 7.4% of trials with all arms assigned to experimental drug (no positive nor negative control) - Second cluster in sample size with median 219 (IQR: 97.5 - 352) subjects by trial - Second longest mean (IQR) time to main end-point with 36.12. Median: 15.7 (IQR: 8.14 – 36.1) weeks - Large proportion of non-single primary endpoint utilization (almost 26% were composite, co-primary or multiple) - Second highest proportion of primary endpoints based on objective asessments (96.3%) - Larger use of intermediate endpoints (92.59%) - Greater percentage of use of biomarkers as primary endpoints (92.59%)	- Prevalent cases in paediatric population may be identified from registries, speeding recruitment. - Parallel designs will be generally needed, due to progression and intersubject variability. Enrichment /stratification may be useful to control heterogeneity. - Previous information on the clinical course can be suitable for bayesian approaches and planning of adaptions. - Designs generally add-on to supportive SOC;reluctance to placebo may occur because of paediatric population, concern on progression and lack of effective SOC. - Unbalanced randomisation, delayed start and early escape/crossing-over may be useful to limit placebo exposure and cover ethical concerns. - Multiple variables applicable to cover the multidimensional nature. Function and quality of life would generally be regarded as key assessments, including patient/ caregiver's input on reported outcomes and clinical relevance. - Surrogates may be useful for early (interim) decision-making, and may be validated along clinical development. For gene-therapy trials, generally a single chance is possible by subject, so that early participation preclude future options.

	- Second lowest use of PROMs (3.7%) as a primary endpoint	
Progressive multidimensional conditions (Therapeutic indications N=31; 25% of total)	- 24 therapeutic indications approved based on clinical trials (77.4%) - Overall number of main clinical trials conducted n=33 (mean=1.38; median=1) - Higher proportion (22.6%) of authorisations not based on clinical trials: retrospective studies (12.9%), bibliographic based applications (6,5%), reports from compassionate access programs (3,2%). - Most frequent design is parallel (81.8%) - Placebo used as a control in 90.9% - More than 80% of trials were randomised. - Lowest sample sizes with median (interquartilic range) 58 (IQR: 29 - 128) subjects per trial. - Frequent use of composite, co-primaty and multiple endpoints (almost 22%) - High use of objective primary endpoints (84.85%) - Low use of overall survival in the primary endpoint (6.06%) - Use of biomarkers in the primary endpoint in 69.7% of cases - 12.2% of use of PROMs - Second higher proportion of ultrarare conditions: 20.8% below 0.1/10,000 subjects.	- Due to progression, start stop methods and intrasubject comparison generally not feasible. - Parallel trials needed when heterogeneity or poor predictability of clinical course are present, with add-on to SOC. Enrichment designs may reduce heterogeneity. - Disease assessment often highly dependent on patient inputs, with (time to change in) function(s) and QoL being key components of the efficacy measures; multiple end-points usually in the same domain may be acceptable/required. Often using surrogates that allow early (interim) results used for decision making. Patient input on clinical relevance required. - Some adaptions can be applied along the trial. - When severe, classical parallel sequential designs with long term comparison may not be applicable, unless early rescue / crossing over. - High willingness to accept trials even if SOC available. - Unbalanced randomization may be useful. - Thorough safety requirements may be delayed if substantial effect is observed
Staged conditions (Therapeutic indications N=32; 26% of total)	- 31 therapeutic indications approved based on clinical trials (96.9%) - Overall number of main clinical trials conducted n=38 (mean=1.23; median=1)	- Prevalent diseases with subjects identified at any stage. Registries available for slow progressive conditions, or subjects diagnosed in early stage. - Well documented case series on natural course available for many conditions favouring bayesian approaches and allowing

	- Used single blind trials, although infrequent (2.6%) - More than 80% of trials were randomised. - Placebo was used as a control in more than 50% of trials - Most frequent design is parallel (81.6%) - Biggest sample size with median 254.5 (IQR: 156 - 416.75) subjects per trial - Second longest median (IQR) time to end-point with 23.1 (IQR: 12 – 46.78) weeks. - Highest use of composite endpoints (31.8%) - Highest use of objective primary endpoints (97.37%) - Relevant use of intermediate primary endpoints (81.58%) - Highest use of overall survival as primary endpoitns or part of it (36.84%) - Use of biomarkers in 60.53% of primary endpoints - No use of PROMs as primary endpoint - No ultrarare conditions	external/historical controls for ultrarare/poor prognosis. - Long follow-up is required. Stage determines both design (through stratification of pre-defined subgroups) and variables (main variable being different in each stage); a variable may be change of status. Enrichment designs may use biomarkers selecting potential respondes. - Multidimensional and multiple objective measurable end-points would be acceptable in milder conditions; if progression is rapid hard end-points may be accessible. Often survival designs. Repeated measurements applicable along follow-up. - High willingness to accept trials even if SOC available; when poor prognosis, methods to limit placebo exposure required to cover ethical concerns. Unbalanced randomization may be useful. - Safety requirements may be less stringent or delayed if progression is rapid and severe, but should consider impact on QoL.

*Active controls were used in less than 20% of trials in all clusters.

These outcomes reinforce the definition and scope of the clusters defined by the ASTERIX group. Probably, within the staged conditions cluster, some discrepancies might be driven by the existence of two blocks of diseases regarding the clinical trial design. In this sense, we hypothesize that oncological diseases could have different sort of designs versus the rest of conditions included in this cluster. Nonetheless, overall, the fact that differences were observed among clusters in all the determinants means that each cluster has particular needs and considerations to be taken into account. Importantly, these differences are consistent with the anticipated aspects issued as part of the descriptions of the ASTERIX clustering (122), thus supporting their accuracy and relevance to actual data.

On the other hand, the exercise had some limitations; the number of therapeutic indications included in each cluster was low, below 10 EPARs for 2 of the proposed clusters, and thus uncertain to some extent. In addition, other characteristics such as rareness of the conditions could strongly influence the observed results, since the percentage of ultrare conditions in the 6 clusters was very different. To note, the ASTERIX clustering recommends to consider ultrarare conditions within each cluster because many of the assumptions may prove unfeasible in an ultrarare setting.

Yet, the results can be deemed as consistent, and thus if guidance documents including recommendations of alternative and innovative clinical trial designs are proposed, it would make clinical and regulatory sense to develop a different guideline for each ASTERIX cluster, according to the present regulatory standard.

9.7.3. Factors associated with successful marketing authorisation

Several publications have adressed in last years both the percentage of marketing authorisation applications which obtained a positive opinion in Europe and the potential predictors associated with the success of these marketing authorisation applications.

The results published by *Joppi et al.*(42) reported that the percentage of approvals for the marketing applications submitted to the EMA from 2000 to 2010 was lower for orphan medicinal products than for non orphan products. In this sense, *Joppi et al.* described that the proportion of positive opinions and marketing authorisations granted by the EMA from 2000 to 2010 were a 58.3% of submissions for orphan medicinal products, as compared to the general figure of 67% when both orphan and non-orphan medicinal products were considered. This fact displayed that the marketing authorisations applications for orphan medicinal products had a higher risk to fail.

Similarly, *Regnstrom et al* (43) analyzed the factors associated with success for all marketing authorisation applications with a CHMP outcome (positive, negative or withdrawal of the application) between January 2004 and December 2007. They described that medicines with an Orphan Drug Designation had significantly lower probability to obtain a positive opinion and thus to get a marketing authorisation than medicines without an Orphan Drug Designation.

Both studies agree on the fact that the probability to obtain a marketing authorisation seems to be lower for orphan medicines. A reason suggested to justify this circumstance is that drug development would be harder compared with the development of drugs for common diseases, thus raising poorer evidence for regulatory purposes. *Joppi et al.*(42) described that 34.9% of orphan medicines were granted “conditional approval” o “approval under exceptional circumstances”, as compared to the overall figure of 3.7% of approvals “conditional” or “under especial circumstances” when orphan and non-orphan medicines were analyzed together. Taking into account that special approvals are generally applied when the available scientific evidence display uncertainties, it can be considered that the fact that a significative higher proportion of authorisations for orphan medicines are granted using such special procedures may be related to a weaker strength of evidence for orphan medicines, due to the difficulties and limitatons to conduct well dimensioned and robustly conclusive clinical trials.

This hypothesis would be in line with the findings observed in our study, since the characteristics of the scientific evidence submitted to obtain the marketing authorisation sometimes included uncontrolled or open label pivotal trials, lack of randomization in one third of trials, and small sample sizes; actually in up to 12.6% of pivotal trials the main end-points were not met, and in 2 cases the authorisation was based on post-hoc analysis of subgroups.

In other study conducted by *Heemstra et al.* (168), characteristics of orphan medicinal products approved from April 2000 to October 2006 were compared with a subset of orphan drugs designated by the COMP but not yet approved. In this study, the main predictors that predisposed to be authorised were the experience of the sponsor in orphan drug development and the type of product.

On one hand, companies with previous orphan medicinal products approved had higher chances to obtain a marketing authorisation. Despite not being exactly the same characteristic, this fact could be also related with the higher number of non-SMEs companies (89%) that hold a marketing authorisarion observed in our study.

On the other hand, already existing synthetic entities that are repurposed were more probable to obtain a marketing authorisation as compared with biotechnology products, although differences between innovative synthetic drugs and biotechnology were not observed. Our review confirmed a relevant higher proportion of syntethic drugs (76%) compared with biological medicines (23%). Moreover, when we analyzed the differences between synthetic drugs and other types of products (biologic drugs and advanced therapies) regarding the type of evidence underpinning the positive benefit/risk balance of the dossiers, only chemical entities displayed authorisations based on sources different from clinical trials. This fact suggests that previous knowledge about a specific substance (like happens with existing synthetic entities) might be a positive predictor to obtain the marketing authorisation.

Another study conducted by *Putzeist et al.* (133) also analyzed predictors for successful marketing authorisations for orphan medicinal products. They used all marketing authorisations applications evaluated by the CHMP from 2000 until the end of 2009,

(N=73) and analyzed determinants that favoured the obtention of the marketing approval by comparing orphan drugs authorised versus those non-authorised. They confirmed the high percentage of special approvals (conditional and under especial circumstances) for orphan drugs already described by *Joppi et al* (42), which were up to the 41.1% of approvals in their longer series. The determinants of success included showing a beneficial effect on the primary endpoint and the use of a relevant clinical endpoint. Nonetheless, as also observed in our study, they described that some orphan medicines (9/73) were approved without convincing results on the primary endpoint. Other factors that favoured to obtain a positive opinion by the CHMP were the conduction of a randomized clinical trial and the lack of alternative treatments for the disease.

Regnstrom et al (43) also described that the company size was a significant predictor of success, so that large industries had higher probabilities to obtain a marketing authorisation than smaller companies. An interesting additional positive predictor to get the approval was the compliance with any received Scientific Advice, so that applicants compliant with the advices given by the SAWP of the EMA were more likely to obtain a product approval. However, orphan medicinal products had lower compliance of Scientific Advice (38%) compared with non-orphan drugs (77% of compliance). While this fact may be reflect a lack of financial resources of small companies to fund the requested development, it might also be the result of too stringent requests by the EMA, and it could be worthy to consider if the advice given to the sponsors by regulators are or not feasible to conduct in the setting of rare diseases.

Finally, a review of applications conducted in USA (169) also pointed out to the clinical trial design, the level of experience of sponsors and the level of early interaction with regulators as key factors influencing the odds to obtain or not a marketing authorisation.

In summary, some of the positive predictors to obtain the approval such as the size of the company or the type of product would be in line with the characteristics of the

orphan drugs approved described in our study. Other type of predictors can not be properly compared because the differences among studies.

9.8. Patient acces and economic burden of rare disease treatments

An additional factor that should be reminded is that the drug cyclelife does not finish with the marketing authorisation given by the regulatory agencies. In Europe, after the regulatory approval, the different Member States must decide about the inclusion of drugs within the positive list of medicines to be paid by the National Health Services and also the price and reimbursement conditions.

The organisms in charge to evaluate and make recomendattions about price and reimbursement are the Health Technology Assessment (HTA) agencies which take into account several factors such as clinical, economic, social, equity and budgetary implications before to do an appraisal. Thus, the evaluation of orphan medicines by the HTAs have been usually conflictive becase the high untertainties that must face up and handle, and because the real access of patients to these therapies depend on their opinions (48–50,170,171).

In this sense, the concerns on the low level of the scientific evidence generated for orphan medicines have been traditionally proposed as one of the main determinants hampering the estimation of the clinical added value of orphan medicines(55). These weaknesses on the scientific evidence available for orphan medicinal products have been confirmed through our study.

On the other hand, the other main reason leading to a difficult evaluation for orphan medicinal products is the economic assessment. In this line, both the lack of precise knowledge about the rare disease as the very high prices approved for orphan drugs to compensate the low market size(54,60,65,66,70,81,172), are hurdles to overcome in order to conduct adequate cost-efficacy analysis(67,69,71–74,76,173–176).

Finally, the percentage of pharmaceutical expenditure intended for orphan drugs is increasing over the last years and have already reached a significative proportion of the total budget aimed to pay medicines of the health systems, focused in providing access to treatment for a low proportion of patients(77–80).

Nonetheless, despite the fact that European regulation could be considered a success, it becomes nonsense if orphan medicinal products developed and approved do not reach the patients, so that they can not have access to the best existing treatments. In this line, different levels of acces to orphan medicines among countries have been evidentiated(51,52,94,177).

For these reasons, several initiatives to better evaluate the clinical added value for orphan medicinal products have been proposed(64,84,85,98–101,103,178,179). In this wise, one of the most innovative tools developed to help the evalution of added value for orphan drugs is the MultiCriteria Decision Analysis (MCDA) in which all criteria that may have a relevant influence on the final decision are measured and scored to provide 360º evaluations, gaining transparency, objectivity and consistency on appraisals and decisions(93–95,97).

To conclude, we hypthotetize that beyond the current initiatives developed to facilitate the determination of the real added value of orphan medicines and to achieve accurate pharmacoeconomics assessments, improving the level of scientific evidence submitted by the sponsors to obtain the marketing authorisation is the key and relevant factor necessary to spur the access for orphan drugs to patients affected by rare diseases, and to ease the assessment of their value and funding requirements. In this context, the use of alternative methodological designs for clinical trials conducted with orphan medicinal products would contribute to attain this goal.

9.9. Summary and prospects

Fifteen years after the entry into force of the European Regulation about orphan medicinal products, an evaluation about the outcomes achieved has been conducted. In this sense, the specific regulation can be considered an important success. From

2000 to December 2014, up to 100 different orphan medicinal products which accounted for 125 therapeutic indications have been authorised in the European Union. This fact has supposed an undoubted progress in order to provide therapeutic interventions to patients affected by rare diseases, even more considering that in the decades previous to the regulation approval only a few medicines for rare diseases were approved in Europe. This progress is especially relevant because currently most of rare diseases do not have medicines approved to treat them and, consequently, they display severe unmet medical needs pending to be solved. Nonetheless, there are about 6,000 – 8,000 diferent rare diseases. Such a high number represents a challenge to provide a predictable framework where the regulatory expectations can be defined and communicated to sponsors. In this situation, additional actions should be taken in order to increase the number of available medicines for rare diseases.

A relevant success of the European regulation that should be mentioned is the very high number of Orphan Drug Designations endorsed by the COMP of the EMA during this first fifteen years after the regulation approval. In this manner, up to 1,430 different Orphan Drug Designations have been granted up to December 2014. Taking into account that the COMP evaluates all the applications submitted by the sponsors, and communication of the scientific data that support the medical plausibility of applications is mandatory, we could say that 1,430 different research projects with orphan drugs have been conducted in these 15 years.

In this regard, some authors have questioned the low number of orphan medicines authorisated conversely to the high number of orphan designations granted. In addition, analysis of the marketing authorisation applications submitted to the EMA showed that the percentage of success to obtain the marketing approval for orphan medicinal products is lower than the percentage of success for medicines aimed to treat common diseases. Thus, it might seem that holding an orphan drug designation is a negative predictor factor to get the marketing authorisation.

In our opinion, one of the main limitants factors to obtain the marketing authorisation for an orphan medicinal product would be the intrinsic difficulties to generate scientific evidence due to the nature of the rare diseases. In this scenario, we think

that the clinical trial must be reinforced as the standard tool to produce scientific evidence, mainly for two reasons. In one hand, clinical trials are considered a robust method to conclude on causality of interventions in order to create scientific evidences, avoiding potential biases. On the other hand, there are published studies that showed that the percentage of positive opinions to obtain the marketing authorisarion rises up in the cases where randomized clinical trials were conducted.

In our work, we have observed that out of the 125 different therapeutic indications approved, 15 (12%) were authorised without clinical trials conducted, on the basis of scientific evidences coming from other kind of sources (bibliographic reports, compassionate use studies or retrospective studies). When clinical trials were the basis to support the marketing authorisation, we noticed that the most of main clinical trials conducted followed well-known or traditional designs (up to 95% of main clinical trials were parallel or single arm trials). Despite this fact, the review of the determinants of the main clinical trials were related with the level of quality of these clinical trials (blinding, randomization, type of control, kind of endpoints), showing that in a large proportion these determinats were not compliant with the gold standard, and consequently the strength of evidence was weak and risk of bias would be increased. Furthermore, as expected, the sample size enrolled in the clinical trials was small, likely related to the low prevalence of the diseases. Finally, up to 11 different therapeutic indications out of the 110 therapeutic indications approved based on clinical trials did not have any pivotal clinical trial achieving its primary objectives.

Since we only analyzed the therapeutic indications approved, therefore, we could be seeing only the “tip of the iceberg”. In this way, it is possible that the drug development for non-authorised orphan medicines (refused, withdrawals or discontinued programs non-submitted to regulatory agencies) could be even of worse methodological quality.

At this point, it seems that there is room to search for distinct approaches in orphan drug development, and maybe the called “alternative” designs and methodologies could be explored to be used in the rare diseases field.

To facilitate the use of alternative designs, the role of regulators is postulated as being key, by setting the rules of acceptable and non-acceptable approaches to design of pivotal experiments. Regulators have been traditionally reluctant to deviate from standards, but could open the floor to accept alternative designs as valid pivotal supports for rare diseases for orphan drug approvals.

From a practical point of view, the EMA has already endorsed the marketing authorisation for some orphan medicinal products which did not have any clinical trial conducted (up to 12% of all therapeutic indications approved according to our study) and the EMA has also authorised some orphan medines which did not have any main clinical trial which fulfill its primary objective (up to 8.8% of all therapeutic indications approved according to our study). Accordingly, a fifth part of the 125 therapeutic indications approved from 2000 to December 2014 showed important deficiencies in terms of lack of strong scientific evidences to support the marketing authorisation.

Therefore, why not accept alternative designs which are adequate and correct from a methodological perspective, if it facilitates conducting clinical trials which are undoubtedly the best available tool to demonstrate the efficacy of an experimental treatment?

Up to the present moment, the recommendations on best methodological choices are made in a case by case way through the Scientific Advice procedure. This is highly effective and provides high quality guidance, but consumes a lot of resources and efforts. Also, situations addressed during the procedure repeat across products from time to time, and the recommendations are made in the frame of lack of general standards and recommendations, thus driving to relatively subjective choices by the assessors. Often, a maximum scenario is drawn to the sponsors, because even though scientific advice compliance is not mandatory, often the marketing authorisation decisions are bound by previous advice issued by the EMA. In this wise, the compliance of the Scientific Advice have been related with a higher probability to obtain the marketing authorisation versus the applications submitted by sponsors whom did not follow the Scientific Advice given.

Paradoxically, despite that the provision of Scientific Advice / Protocol Assistance free of charge or with reduction of taxes is one of the incentives included in the European regulation about orphan medicinal products, a study showed that orphan medicines had a significatively lower proportion of compliance of Scientfic Advice compared with non-orphan medicines. It could be possible than the recommendations followed standard designs and they were not feasible to be applied? In this situation, an additional measure that could be suggested to break hesitation of pharmaceutical industries and give them confidence in this issue, might include the publication by the EMA of guidelines which include the use of alternative designs as options to be used for orphan medicines.

In fact, the EMA have already published a "Guideline on Clinical Trials in Small Populations". However, the current guideline does not specify which design fits better in each clinical situation, and becomes vague in aspects such as design selection for particular clinical situations. A more explicit guideline which suggests definite designs in different scenarios could be more functional.

Clustering of conditions may be the required intermediate step to allow for such explicit guidelins to be feasible. Taking into account that both from a conceptual perspective, as also because in our study we found differences in the charactersitics and clinical trial design regarding the different disease clusters chosen, it might be useful to explore if a different guideline for each different cluster could be proposed suggesting specific designs for each situation. In this line, the guidelines should also include detailed considerations for ultrarare conditions within each cluster, since our work has also identified important differences in orphan drug development in this regard.

On the other hand, medicines cyclelife do not finish with the marketing authorisation. Subsequently, Health Technology Assesment (HTA) agencies determine the clinical added value of medicines and suggest their role in the therapeutic algorithm of the disease taking into account the clinical benefits provided by the drug compared with available alternatives, the budgetary impact and the affordability for the national health systems.

In this line, the HTAs must overcome some hurdles in the orphan drug evaluation process such as the difficulties to conduct cost-effectiveness studies. The poor evidence available, the very high prices and the lack of knowledge on particular rare diseases, hamper the HTAs appraisals about orphan medicines. Thus, generating better scientific evidence, which could be achieved through implementation of alternative designs for clinical trials, through better scientific coordination or funding, might also help to conduct better evaluations, reduce uncertainties and potentially pave the way to improve the patient access to orphan medicines.

Besides of fostering the use of alternative designs for clinical trials, there is room to improve the choice of sensible clinical end-points and, especially, the way to determine the clinical relevance of scientific findings. In this line, another improvement action could be stimulating the development of PROMs as a relevant – even primary - endpoint in clinical trials for rare diseases. Our review has displayed that only a few cases have used PROM as a part of the primary endpoint. In a environment of growing patient empowerment and involvement, and considering the outstanding advances in technology and communication devices, the system may be reaching the required degree of maturity to explore how to formally incorporate the patients to the assessment of the clinical relevance and added value provided by medicines, specially in the orphan drug field.

Finally, in regard to the pricing process of orphan medicines, our study has not been designed to extract conclusions on this matter. Nonetheless, an increasing concern about high prices as a threat to sustainability and patient's access to treatments has been indentified in the bibliography. In this wise, further studies to establish pricing determinants – i ex: if prices are only related with prevalence figures or also with level of evidence or clinical relevance of outcomes - and development of systems to measure added value could be conducted.

10. CONCLUSIONS

1) Since the European regulation on orphan medicinal products entered in force in year 2000 and up to December 2014, 100 orphan medicinal products have been approved for 125 indications in Europe covering 84 different diseases, suggesting that the Orphan regulation has had a positive effect to stimulate research in orphan conditions and to increase the number of available orphan treatments.
2) Oncological diseases and metabolic defects are the two main areas with most available indications approved. Also, 21 conditions had more than one available treatment. Both observations suggest that availability of orphan drugs is increased in areas where the knowledge on the physiopathology has been further developed.
3) Almost half (48%) of orphan designations which obtained a marketing authorisation changed of holder at least once, with holders of authorisation being increasingly big pharmaceutical companies, suggesting that last phases of orphan drug development require trades across companies to achieve the required resources.
4) The main characteristics of EPARs for orphan medicinal products show that:
    - 12% of the indications for orphan medicinal products have been approved on the basis of sources of scientific evidence other than clinical trials, including bibliography, compassionate use programs o retrospective analysis of observational data.
    - Amongst indications for orphan medicinal products approved based on clinical trials, 11 trials were approved without any trial in their dossier having met its primary end-point objective.
    - Amongst pivotal trials supporting approval for orphan medicinal products, non randomised trials accounted for 31.4%, open-label trials for 47.2%, non-controlled trials for 33.3% and single arm trials for 29.6% of the total number of pivotal trials included in the EPARs, suggesting

that the methodological strength of evidence supporting approval was weak.

- Alternative designs especially suited to small populations were seldom used, only in 3.8% of pivotal trials.
- Intermediate endpoints were used as primary end-points in 74.8% of all pivotal trials, suggesting that approvals required a high degree of inference on final outcomes.
- Overall, data suggest that the current methodological robustness of the evidence supporting approval of indications for orphan medicinal products is generally low.

5) The analysis of the clinical trials conducted with orphan medicinal products according to the prevalence of the conditions showed that ultrarareness was associated to higher rates of dossiers based on sources of scientific evidence other than clinical trials; trials had smaller sample size and did not use active controls in any trial.
6) The analysis of the clinical trials conducted with orphan medicinal products according to the clustering of medical conditions defined previously in the ASTERIX project show that trials in the different clusters have different characteristics that relate to their clinical features and applicability of different study designs.
7) The characteristics of the main clinical trials conducted with the orphan medicinal products authorised in Europe since the European regulation on orphan medicinal products entered in force in year 2000, suggest that there is room for application of alternative methodologies especially suited to deal with small populations in the conduction of clinical trials, and of different approaches to gathering of evidence in the assessment of risk-benefit.

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14.1. Annex 1. Definition of the characteristics analyzed

Description of characteristics of the scientific evidence supporting the marketing authorisation

1. **Active principle**

   International non-proprietary name (INN) or common name.

2. **Brand name**

   Brand name of orphan medicinal product.

3. **New medicine / Extension of therapeutic indication**

   It defines if therapeutic indication analyzed applies for a new medicine or for a medicine already authorized and constitutes a variation type II.

4. **Orphan medical condition**

   Medical condition designated as orphan by the COMP.

5. **Type of scientific evidence supporting the marketing approval**

   Source of the scientific evidence included in the dossiers submitted to the EMA by the applicants to obtain the marketing approval (clinical trial, bibliographic report, compassionate use study or observational retrospective study).

6. **Number of main clinical trials conducted**

   Number of main trials conducted.

   Are considered pivotal all clinical trials considered as “main” in the EPAR.

7. **Number of supportive clinical trials conducted**

   Number of supportive trials conducted.

   Are considered supportive clinical trials all the studies included within the clinical development reported in the EPAR except these ones considered main.

Dose finding studies are considered supportive regardless it included patients or healthy volunteers.

8. Overall number of patients exposed to the orphan medicinal product

Total number of patients exposed to the orphan medicinal product in all the studies included in the EPAR. It is obtained from the safety section of the EPAR.

9. Longest follow up period available (weeks)

Longest time exposition to the orphan medicinal product reported for all studies included in the EPAR.

10. "Asterix Project" Identification Number

Internal number for each therapeutic indication approved.

11. Study name

Name of the study

12. Type of phase

Phase of the study.

13. Type of blinding

Type of blinding: open, single or double.

14. Existence or absence of randomization

In case of have an allocation of patients randomized, it is notified as Yes.

In absence of randomization, it is notified as NO.

15. Existence or absence of stratification in the randomization process

If patients are randomized according strata, it is notified as Yes.

In absence of stratification, it is notified as No.

If it is not described in the EPAR, it is reported as No stratification.

16. Type of control

Type of control used in the clinical trial:

No control

Placebo

Active – Control is an active substance for the disease

No substance or Best Standard of Care (BSC) – Patients performing as control cannot receive any substance or can receive the best standard of care in function of the physician choice.

No substance – Patients performing as control do not receive any substance.

No substance and Active – There are at least two control arms, one of them receiving an active substance and the other one do not receive any treatment.

Placebo and Active - There are at least two control arms, one of them receiving an active substance and the other receiving placebo.

17. Experimental treatment used as Add on treatment or not

Experimental treatment is or not an add on treatment to the usual pharmacological

If other treatments are only permitted in some subgroups, it item is notified as "Partially".

18. Number of arms included in the clinical trial

Number of study arms

19. Number of arms included in the clinical trial that received the experimental treatment

Number of arms that received the experimental treatment studied.

20. Uninational or multinational trial

Uninational or multinational

21. Unicentric or multicentric trial

Unicentric or multicentric

22. Overall population enrolled in the clinical trial

Overall population enrolled in the study (regardless if they are assigned to active or control arms).

23. Population enrolled in the clinical trial whom received the experimental treatment

Population enrolled in the study included on experimental treatment arms.

24. Clinical trial following a Survival design

Yes if Duration of primary endpoint is not stablished previously but depends on survival or time to achieve an endpoint.

No if Duration of primary endpoint is stablished in a specific time point.

25. Duration of primary endpoint (weeks)

Time established to evaluate the primary endpoint.

In case of Survival design, it is notified the median to achieve the main endpoint. (mean only is used if median is not notified in EPAR) (in case of comparative trials, it is noted the median to achieve the main endpoint in the experimental arm)

In case of not Survival design, but the endpoint was analyzed when the last patient enrolled completed a specific time of follow up. This specific time is notified as the duration of the primary endpoint.

26. Type of methodological design applied in the clinical trial

Type of methodological design used:

Parallel

Single arm

Crossover

Parallel no controlled: there are several arms but all arms are treated with the experimental treatment.

Parallel with withdrawal: parallel design with periods of withdrawal of the treatments.

Historically controlled: experimental treatment is statistically compared with an historical cohort.

27. Description of the primary endpoint

Description of the primary endpoint.

28. Type of statistical analysis conducted for the primary endpoint

Description of the type of statistical analysis conducted for the primary endpoint.

29. Key secondary endpoints

Description of the key secondary endpoints.

30. Description of the outcome for the primary endpoint

Description of the outcome for the primary endpoint

31. Fulfillment of the primary objective

Primary endpoint achieves statistical significance or not.

32. Pre especified subgroup analysis conducted

Pre specified subgroup analysis is conducted or not.

33. Marketing authorization based on subgroups analysis

Reported as “Yes” if primary objective was not achieved but drug has been approved based on a subgroup.

34. ASTERIX_Project Identification Number

Internal number for each main clinical trial conducted and analyzed.

Description of the primary endpoint used in each main clinical trial conducted with orphan medicinal products

35. Single or several component

Type of endpoint: single, composite, co-primary, multiple endpoints analyzed or co-primary and composite at the same time.

36. Objective or subjective

The measure of the primary endpoint is objective, subjective or both in case of composite primary endpoints.

37. Final or intermediate

The endpoint measure is related with the final objectives expected to be attained with the medicine or is only an intermediate indicator of response.

38. Inclusion of overall survival within the primary endpoint definition

Overall survival is the primary endpoint or is a component of the primary endpoint.

39. Inclusion of biomarkers within the primary endpoint definition

A biomarker is the primary endpoint or is a component of the primary endpoint.

Definition of biomarker: “a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives”

40. <u>Inclusion of Patient Reported Outcome Measures (PROMs) within the primary endpoint definition</u>

A PROM is the primary endpoint or is a component of the primary endpoint.

Definition of PROM: an instrument, scale, or single item measure used to assess the PRO concept as perceived by the patient, obtained by directly asking the patient (or in some cases a caregiver or surrogate) to self-report.

14.2. *Annex 2. List of orphan medicinal products and therapeutic indications approved from January 2000 to December 2014*

Brand name	Drug	MAH holder	Authorised therapeutic indication	Date of authorisation	ATC
Fabrazyme	Agalsidase beta	Genzyme	Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (a-galactosidase A deficiency).	03/08/2001	A16AB04
Replagal	Agalsidase alfa	Shire	Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (a-galactosidase A deficiency).	03/08/2001	A16AB03
Glivec	Imatinib	Novartis	Treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment. Glivec is also indicated for the treatment of adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis. The effect of Glivec on the outcome of bone marrow transplantation has not been determined.	07/11/2001	L01XE01
Trisenox	Arsenic trioxide	Cephalon	For induction of remission and consolidation in adult patients with relapsed/refractory acute promyelocytic leukaemia (APL), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene. Previous treatment should have included a retinoid and chemotherapy. The response rate of other acute myelogenous leukaemia subtypes to TRISENOX has not been examined.	05/03/2002	L01XX27

Tracleer	Bosentan	Actelion	Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III.Efficacy has been shown in: - Primary (idiopathic and familial) PAH. - PAH secondary to scleroderma without significant interstitial pulmonary disease. - PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology. - Some improvements have also been shown in patients with PAH WHO functional class II.	15/05/2002	C02KX01
Glivec	Imatinib	Novartis	Treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).	24/05/2002	L01XE01
Somavert	Pegvisomant	Pfizer	Treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-I concentrations or was not tolerated.	13/11/2002	H01AX01
Zavesca	Miglustat	Actelion	For the oral treatment of mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.	20/11/2002	A16AX06
Carbaglu	Carglumic acid	Orphan Europe	Treatment of hyperammonaemia due to N-acetylglutamate synthetase deficiency.	24/01/2003	A16AA05
Aldurazyme	Laronidase	Genzyme	For long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis I (MPS I; a [alpha]-L-iduronidase deficiency) to treat the non-neurological manifestations of the disease.	10/06/2003	A16AB05

Busilvex	Busulfan	Pierre-Fabre	Busilvex followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option. Busilvex followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation in paediatric patients.	09/07/2003	L01AB01
Ventavis	Iloprost	Bayer	Treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms.	16/09/2003	B01AC11
Onsenal	Celecoxib	Pfizer	For the reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance. The effect of Onsenal-induced reduction of polyp burden on the risk of intestinal cancer has not been demonstrated.	17/10/2003	L01XX33
Photobarr	Porfimer sodium	Pinnacle	Photodynamic therapy (PDT) for ablation of high-grade dysplasia (HGD) in patients with Barrett's Oesophagus (BO).	25/03/2004	L01XD01
Litak	Cladribine	Lipomed	Treatment of hairy cell leukaemia.	14/04/2004	L01BB04
Lysodren	Mitotane	HRA Pharma	Symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma. The effect of Lysodren on non-functional adrenal cortical carcinoma is not established.	28/04/2004	L01XX23
Pedea	Ibuprofen	Orphan Europe	Treatment of a haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age.	29/07/2004	C01EB16
Wilzin	Zinc	Orphan Europe	Treatment of Wilson's disease.	13/10/2004	A16AX05

Xagrid	Anagrelide	Shire	For the reduction of elevated platelet counts in at risk essential thrombocythaemia patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. An at risk essential thrombocythaemia patient is defined by one or more of the following features: >60 years of age or; A platelet count >1000 x 109/l or; A history of thrombo-haemorrhagic events.	16/11/2004	L01XX35
Prialt	Ziconotide	Eisai	Treatment of severe, chronic pain in patients who require intrathecal (IT) analgesia.	21/02/2005	N02BG08
Orfadin	Nitisinone	Swedish Orphan	Treatment of patients with confirmed diagnosis of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.	21/02/2005	A16AX04
Xyrem	Sodium oxybate	UCB	Treatment of narcolepsy with cataplexy in adult patients.	13/10/2005	N07XX04
Revatio	Sildenafil	Pfizer	Treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease.	28/10/2005	G04BE03
Naglazyme	Galsulfase	BioMarin	For long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis VI (MPS VI; N-acetylgalactosamine 4-sulfatase deficiency; Maroteaux-Lamy syndrome). A key issue is to treat children aged <5 years suffering from a severe form of the disease, even though children <5 years were not included in the pivotal phase 3 study. Limited data are available in patients < 1 year of age.	24/01/2006	A16AB08
Myozyme	Alglucosidase alfa	Genzyme	Indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid-glucosidase deficiency). Myozyme is indicated in adults and paediatric patients of all ages. In patients with late-onset Pompe disease the evidence of efficacy is limited.	29/03/2006	A16AB07

Evoltra	Clofarabine	Genzyme	Treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Safety and efficacy have been assessed in studies of patients ≤ 21 years old at initial diagnosis.	29/05/2006	L01BB06
Sutent	Sunitinib	Pfizer	Treatment of advanced and/or metastatic renal cell carcinoma.	19/07/2006	L01XE04
Sutent	Sunitinib	Pfizer	Treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.	19/07/2006	L01XE05
Nexavar	Sorafenib	Bayer	Treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.	19/07/2006	L01XE05
Savene	Dexrazoxane	Norgine	Treatment of anthracycline extravasation.	28/07/2006	V03AF02
Thelin	Sitaxentan sodium	Pfizer	Treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease.	10/08/2006	C02KX03
Exjade	Deferasirox	Novartis	Treatment of chronic iron overload due to frequent blood transfusions (>/= 7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. Treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups: - in patients with other anaemias, - in patients aged 2 to 5 years, - in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells).	28/08/2006	V03AC03

Glivec	Imatinib	Novartis	Treatment of adult patients with unresectable dermafibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not elegible for surgery.	13/09/2006	L01XE01
Glivec	Imatinib	Novartis	Treatment of adults patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy. The effect of Glivec on the outcome of bone marrow transplantation has not been determined.	13/09/2006	L01XE01
Sprycel	Dasatinib	Bristol	Treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.	20/11/2006	L01XE06
Sprycel	Dasatinib	Bristol	Treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate.	20/11/2006	L01XE06
Glivec	Imatinib	Novartis	Treatment of adults patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.	28/11/2006	L01XE01
Glivec	Imatinib	Novartis	Treatment of adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.	28/11/2006	L01XE01
Diacomit	Stiripentol	Biocodex	Indicated for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate.	04/01/2007	N03AX17
Elaprase	Idursulfase	Shire	Elaprase is indicated for the long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). Heterozygous females were not studied in the clinical trials.	08/01/2007	A16AB09

Inovelon	Rufinamide	Eisai	Indicated as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 4 years and older.	16/01/2007	N03AF03
Cystadane	Betaine anhydrous	Orphan Europe	Adjunctive treatment of homocystinuria, involving deficiencies or defects in: - cystathionine beta-synthase (CBS), - 5,10-methylene-tetrahydrofolate reductase (MTHFR), - cobalamin cofactor metabolism (cbl). Cystadane should be used as supplement to other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), folate and a specific diet.	15/02/2007	A16AA06
Tracleer	Bosentan	Actelion	Indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.	07/06/2007	C02KX01
Revlimid	Lenalidomide	Celgene	In combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.	14/06/2007	L04AX04
Soliris	Eculizumab	Alexion	Treatment of patients with paroxysmal nocturnal haemoglobinuria. Evidence of clinical benefit of Soliris in the treatment of patients with PNH is limited to patients with history of transfusions.	20/06/2007	L04AA25
Siklos	Hydroxiurea	AddMedica	Indicated for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in adults, adolescents and children older than 2 years suffering from symptomatic Sickle Cell Syndrome.	29/06/2007	L01XX05

Increlex	Mecasermin	Ipsen	For the long-term treatment of growth failure in children and adolescents with severe primary insulinlike growth factor-1 deficiency (Primary IGFD). Severe Primary IGFD is defined by: • height standard deviation score ≤ –3.0 and • basal IGF-1 levels below the 2.5th percentile for age and gender and • GH sufficiency. • Exclusion of secondary forms of IGF-1 deficiency, such as malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids. Severe Primary IGFD includes patients with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment. It is recommended to confirm the diagnosis by conducting an IGF-1 generation test.	03/08/2007	H01AC03
Atriance	Nelarabine	Glaxo	Treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. Due to the small patient populations in these disease settings, the information to support these indications is based on limited data.	22/08/2007	L01BB07
Gliolan	5-aminolevulinic acid	MEDAC	In adult patients for visualisation of malignant tissue during surgery for malignant glioma (WHO grade III and IV).	07/09/2007	L01XD04
Yondelis	Trabectedin	Pharmamar	Treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.	17/09/2007	L01CX01
Nexavar	Sorafenib	Bayer	Treatment of hepatocellular carcinoma.	29/10/2007	L01XE05

Torisel	Temsirolimus	Pfizer	First-line treatment of patients with advanced renal cell carcinoma who have at least three of six prognostic risk factors.	19/11/2007	L01XE09
Tasigna	Nilotinib	Novartis	Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase.	19/11/2007	L01XE08
Thalidomide Celgene	Thalidomide	Celgene	Thalidomide Celgene in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.	16/04/2008	L04AX02
Volibris	Ambrisentan	Glaxo	Treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity.	21/04/2008	C02KX02
Firazyr	Icatibant	Shire	Indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency).	11/07/2008	C01EB19
Ceplene	Histamine dihydrochloride	Meda AB	Ceplene maintenance therapy is indicated for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy of Ceplene has not been fully demonstrated in patients older than age 60.	07/10/2008	L03AX14
Kuvan	Sapropterin	Merck	Treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients of 4 years of age and over with phenylketonuria (PKU) who have been shown to be responsive to such treatment. Kuvan is also indicated for the treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients with tetrahydrobiopterin (BH4) deficiency who have been shown to be responsive to such treatment.	02/12/2008	A16AX07

Vidaza	Azacitidine	Celgene	Treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with: - intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS), - chronic myelomonocytic leukaemia (CMML) with 10-29 % marrow blasts without myeloproliferative disorder.	17/12/2008	L01BC07
Vidaza	Azacitidine	Celgene	Treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with: - acute myeloid leukaemia (AML) with 20-30 % blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification.	17/12/2008	L01BC07
Zavesca	Miglustat	Actelion	Treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease.	26/01/2009	A16AX06
Nplate	Romiplostim	Amgen	Indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Nplate may be considered as second line treatment for adult non-splenectomised patients where surgery is contra-indicated.	04/02/2009	B02BX04
Mepact	Mifamurtide	Takeda	Indicated in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection. It is used in combination with post-operative multi-agent chemotherapy.	06/03/2009	L03AX15
Peyona	Caffeine	Chiesi	Treatment of primary apnoea of premature newborns.	02/07/2009	N06BC01
Mozobil	Plerixafor	Genzyme	Indicated in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilise poorly.	31/07/2009	L03AX16

Afinitor	Everolimus	Novartis	Treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.	03/08/2009	L01XE10
Torisel	Temsirolimus	Pfizer	Treatment of adult patients with relapsed and/or refractory mantle cell lymphoma.	21/08/2009	L01XE09
Cayston	Aztreonam	Gilead	Suppressive therapy of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged 18 years and older.	21/09/2009	J01DF01
Rilonacept Regeneron	Rilonacept	Regeneron	Treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) with severe symptoms, including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), in adults and children aged 12 years and older.	23/10/2009	L04AC08
Ilaris	Canakinumab	Novartis	Treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 4 years and older with body weight above 15 kg, including: - Muckle-Wells Syndrome (MWS), - Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA), - Severe forms of Familial Cold Autoinflammatory Syndrome (FCAS) / Familial Cold Urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.	23/10/2009	L04AC08
Yondelis	Trabectedin	Pharmamar	In combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.	28/10/2009	L01CX01
Firdapse	Amifampridine	BioMarin	Symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.	23/12/2009	N07XX05

Revolade	Eltrombopag	Glaxo	Indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated.	11/03/2010	B02BX05
Tepadina	Thiotepa	Adienne	Indicated, in combination with other chemotherapy medicinal products: 1) with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients; 2) when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.	15/03/2010	L01AC01
Arzerra	Ofatumumab	Glaxo	Treatment of chronic lymphocytic leukaemia (CLL) in patients who are refractory to fludarabine and alemtuzumab.	19/04/2010	L01XC10
VPRIV	Velaglucerase alfa	Shire	Indicated for long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease.	26/08/2010	A16AB10
Esbriet	Pirfenidone	Intermune	Indicated in adults for the treatment of mild to moderate Idiopathic Pulmonary Fibrosis (IPF).	28/02/2011	L04AX05
Carbaglu	Carglumic acid	Orphan Europe	Treatment of hyperammoniemia due to isovaleric acidaemia.	27/05/2011	A16AA05
Carbaglu	Carglumic acid	Orphan Europe	Treatment of hyperammoniemia due to methylmalonic acidaemia.	27/05/2011	A16AA05
Carbaglu	Carglumic acid	Orphan Europe	Treatment of hyperammoniemia due to propionic acidaemia.	27/05/2011	A16AA05
TOBI Podhaler	Tobramycin	Novartis	Indicated for the suppressive therapy of chronic pulmonary infection due to Pseudomonas aeruginosa in adults and children aged 6 years and older with cystic fibrosis.	20/07/2011	J01GB01

Votubia	Everolimus	Novartis	Indicated for the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.	02/09/2011	L01XE10
Plenadren	Hydrocortisone	Viropharma	Treatment of adrenal insufficiency.	03/11/2011	H02AB09
Vyndaqel	Tafamidis	Pfizer	Treatment of transthyretin amyloidosis in patients with symptomatic polyneuropathy.	16/11/2011	N07XX08
Soliris	Eculizumab	Alexion	Treatment of atypical haemolytic uremic syndrome (aHUS).	24/11/2011	L04AA25
Xaluprine	Mercaptopurine	Nova labs	Treatment of acute lymphoblastic leukaemia (ALL).	09/03/2012	L01BB02
Bronchitol	Mannitol	Pharmaxis	Treatment of cystic fibrosis.	13/04/2012	R05CB16
Signifor	Pasireotide	Novartis	Treatment of Cushing's disease.	24/04/2012	H01CB05
Kalydeco	Ivacaftor	Vertex	Treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene.	23/07/2012	R07AX02
Jakavi	Ruxolitinib	Novartis	Treatment of diseaserelated splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.	23/08/2012	L01XE18
Revestive	Teduglutide	NPS	Treatment of adult patients with Short Bowel Syndrome. Patients should be stable following a period of intestinal adaptation after surgery.	30/08/2012	A16AX08
Dacogen	Decitabine	Janssen	treatment of adult patients aged 65 years and above with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy". It is proposed that Dacogen be prescribed by physicians experienced in the use of chemotherapeutic agents.	20/09/2012	L01BC08

Glybera	Alipogene tiparvovec	uniQ	Glybera is indicated for adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The diagnosis of LPLD has to be confirmed by genetic testing. The indication is restricted to patients with detectable levels of LPL protein.	25/10/2012	C10AX10
Adcetris	Brentuximab	Takeda	Treatment of adult patients with relapsed or refractory CD30+ H83 (HL): 1.following autologous stem-cell transplant (ASCT) or; 2.following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.	25/10/2012	L01XC12
Adcetris	Brentuximab	Takeda	Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).	25/10/2012	L01XC12
Votubia	Everolimus	Novartis	Treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery.	31/10/2012	L01XE10
NexoBrid	Bromelain	Mediwound	Removal of eschar in adults with deep partial- and full-thickness thermal burns.	18/12/2012	D03BA03
Bosulif	Bosutinib	Pfizer	Treatment of myelogenous leukemia.	27/03/2013	L01XE14
Revlimid	Lenalidomide	Celgene	Treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities.	13/06/2013	L04AX04
Iclusig	Ponatinib	ARIAD	Indicated in adult patients with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.	01/07/2013	L01XE24

Iclusig	Ponatinib	ARIAD	Indicated in adult patients with chronic-phase, accelerated-phase or blast-phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.	01/07/2013	L01XE24
Imnovid	Pomalidomide	Celgene	In combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.	05/08/2013	L04AX06
Procysbi	Mercaptamine	Raptor	Treatment of proven nephropathic cystinosis. Cysteamine reduces cystine accumulation in some cells (e.g. leukocytes, muscle and liver cells) of nephropathic cystinosis patients and, when treatment is started early, it delays the development of renal failure.	06/09/2013	A16AA04
Orphacol	Cholic acid	CTRS labs	Treatment of inborn errors in primary bile-acid synthesis due to 3β-hydroxy-Δ5-C27-steroid oxidoreductase deficiency or Δ4-3-oxosteroid-5β-reductase deficiency in infants, children and adolescents aged one month to 18 years and adults.	12/09/2013	A05AA03
Defitelio	Defibrotide	Gentium	Treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstructive syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy.	18/10/2013	B01AX01
Opsumit	Macitentan	Actelion	As monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III.	20/12/2013	C02KX04

Sirturo	Bedaquiline	Janssen	Indicated for use as part of an appropriate combination regimen for pulmonary multidrug resistant tuberculosis (MDR TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.	05/03/2014	J04AK05
Cometriq	Cabozantinib	TMC	Treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.	21/03/2014	L01XE26
Adempas	Riociguat	Bayer	Treatment of adult patients with WHO Functional Class (FC) II to III with inoperable CTEPH or persistent or recurrent CTEPH after surgical treatment, to improve exercise capacity.	27/03/2014	C02KX05
Adempas	Riociguat	Bayer	As monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity.	27/03/2014	C02KX05
Kolbam	Cholic acid	FGK	Kolbam is indicated for the treatment of inborn errors in primary bile acid synthesis due to Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency or Cholesterol 7α-hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years and adults.	04/04/2014	A05AA03
Granupas	Para-aminosalicylic acid	Lucane	For use as part of an appropriate combination regimen for multi-drug resistant tuberculosis in adults and paediatric patients from 28 days of age and older when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.	07/04/2014	J04AA01
Deltyba	Delamanid	Otsuka	For use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.	28/04/2014	J04AK06

Vimizim	Elosulfase alfa	BioMarin	Treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages.	28/04/2014	A16AB12
Sylvant	Siltuximab	Janssen	Treatment of adult patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.	22/05/2014	L04AC11
Nexavar	Sorafenib	Bayer	Treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.	23/05/2014	L01XE05
Gazyvaro	Obinutuzumab	Roche	In combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy.	23/07/2014	L01XC15
Translarna	Ataluren	PTC	Treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older.	31/07/2014	M09AX03
Imbruvica	Ibrutinib	Janssen	Treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).	21/10/2014	L01XE27
Imbruvica	Ibrutinib	Janssen	Treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.	21/10/2014	L01XE27
Signifor	Pasireotide	Novartis	Treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue.	19/11/2014	H01CB05
Ketoconazole HRA	Ketoconazole	HRA Pharma	Treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.	19/11/2014	J02AB02

Lynparza	Olaparib	Astra	As monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.	16/12/2014	L01XX46
Cyramza	Ramucirumab	Lilly	In combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy. In monotherapy is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate.	19/12/2014	L01XC
Scenesse	Afamelanotide	Clinuvel	Prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).	22/12/2014	D02BB02

14.3. Annex 3. Rare medical conditions covered by the 125 therapeutic indications approved and number of orphan medicinal products authorised for each condition

Rare Medical Conditions	Number of OMP Authorised
Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	8
Treatment of acute lymphoblastic leukaemia	6
Treatment of chronic myeloid leukaemia	5
Treatment of renal cell carcinoma	4
Treatment of acute myeloid leukaemia	3
Treatment of chronic lymphocytic leukaemia	3
Treatment of multiple myeloma	3
Treatment of tuberculosis	3
Treatment of myelodysplastic syndromes	3
Conditioning treatment prior to haematopoietic progenitor cell transplantation	2
Treatment of acromegaly	2
Treatment of cryopirin-associated periodic syndromes (Familial Cold Urticaria Syndrome (FCUS), Muckle-Wells Syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID), also known as Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA))	2
Treatment of Cushing's syndrome	2
Treatment of cystic fibrosis	2
Treatment of Fabry disease	2
Treatment of Gaucher disease	2
Treatment of idiopathic thrombocytopenic purpura	2
Treatment of malignant gastrointestinal stromal tumours	2
Treatment of mantle cell lymphoma	2
Treatment of ovarian cancer	2
Treatment of tuberous sclerosis	2
Intra-operative photodynamic diagnosis of residual glioma	1
Mucopolysaccharidosis VI (MPS VI) or Maroteaux-Lamy Syndrome	1
Treatment of angioedema	1
Treatment of acute promyelocytic leukaemia (APL)	1
Treatment of adrenal cortical carcinoma	1
Treatment of adrenal insufficiency	1
Treatment of anaplastic large cell lymphoma	1

Treatment of anthracycline extravasations	1
Treatment of atypical haemolytic uremic syndrome	1
Treatment of Castleman's disease	1
Treatment of chronic eosinophilic leukaemia and the hypereosinophilic syndrome	1
Treatment of chronic idiopathic myelofibrosis / myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia	1
Treatment of chronic iron overload requiring chelation therapy	1
Treatment of chronic pain requiring intraspinal analgesia	1
Treatment of cystinosis	1
Treatment of dermatofibrosarcoma protuberans	1
Treatment of Duchenne muscular dystrophy	1
Treatment of erythropoietic protoporphyria	1
Treatment of essential thrombocythaemia	1
Treatment of Familial Adenomatous Polyposis (FAP)	1
Treatment of familial amyloid polyneuropathy	1
Treatment of follicular/papillary thyroid cancer	1
Treatment of gastric cancer	1
Treatment of Glycogen Storage Disease type II (Pompe's disease)	1
Treatment of gram negative bacterial lung infection in cystic fibrosis	1
Treatment of hepatic veno-occlusive disease	1
Treatment of hepatocellular carcinoma	1
Treatment of high-grade dysplasia in Barrett's Esophagus	1
Treatment of Hodgkin lymphoma	1
Treatment of homocystinuria	1
Treatment of hyperphenylalaninemia	1
Treatment of idiopathic pulmonary fibrosis	1
Treatment of inborn errors of primary bile acid synthesis	1
Treatment of inborn errors of primary bile acid synthesis responsive to treatment with cholic acid	1
Treatment of indolent non-Hodgkin's lymphoma	1
Treatment of isovaleric acidaemia	1
Treatment of Lambert-Eaton myasthenic syndrome	1
Treatment of Lennox-Gastaut syndrome	1
Treatment of lipoprotein lipase deficiency	1
Treatment of medullary thyroid carcinoma	1
Treatment of methylmalonic acidaemia	1
Treatment of Mucopolysaccharidosis type I	1
Treatment of mucopolysaccharidosis, type II (Hunter syndrome)	1
Treatment of mucopolysaccharidosis, type IVA (Morquio A syndrome)	1
Treatment of N-acetylglutamate synthetase (NAGS) deficiency	1
Treatment of narcolepsy	1
Treatment of Niemann-Pick disease, type C	1

Treatment of osteosarcoma	1
Treatment of paroxysmal nocturnal haemoglobinuria	1
Treatment of partial deep dermal and full thickness burns	1
Treatment of Patent Ductus Arteriosus	1
Treatment of primary apnoea of premature newborns	1
Treatment of primary insulin-like growth factor-1 deficiency due to molecular or genetic defects	1
Treatment of propionic acidaemia	1
Treatment of Pseudomonas aeruginosa lung infection in cystic fibrosis	1
Treatment of severe myoclonic epilepsy in infancy	1
Treatment of short bowel syndrome	1
Treatment of sickle cell syndrome	1
Treatment of soft tissue sarcoma	1
Treatment of systemic sclerosis (scleroderma)	1
Treatment of tyrosinaemia type I	1
Treatment of Wilson's disease	1
Treatment to mobilize progenitor cells prior to stem cell transplantation	1
Total	**125**

14.4. Annex 4. List and number of drugs approved according their mechanism of action

Mechanism of action	Drugs	Number of drugs approved
Tyrosin Kinase Inhibitor	Bosutinib, Cabozantinib, Dasatinib, Ibrutinib, Imatinib, Nilotinib, Ponatinib, Sorafenib, Sunitinib	9
Enzyme replacement therapy	Agalsidase alfa, Agalsidase beta, Alglucosidase alfa, Elosulfase alfa, Galsulfase, Idursulfase, Laronidase, Velaglucerase alfa	8
Chemotherapy: antimetabolite	Azacitidine, Cladribine, Clofarabine, Decitabine, Mercaptopurine, Nelarabine	6
Chemotherapy: immunomodulator	Lenalidomide, Mifamurtide, Pomalidomide, Thalidomide	4
Endotelin receptors antagonist	Ambrisentan, Bosentan, Macitentan, Sitaxentan sodium	4
mTOR inhibitor	Everolimus, Everolimus, Temsirolimus	3
Anti CD20	Obinutuzumab, Ofatumumab	2
Chemotherapy: alkylant agent	Busulfan, Thiotepa	2
Chemotherapy: unknown	Hydroxiurea, Mitotane	2
IL-1 blocker	Canakinumab, Rilonacept	2
Inhibition of production of the hepatotoxic bile acid precursors	Cholic acid, Cholic acid	2

TPO receptor agonist	Eltrombopag, Romiplostim	2
Unknown	Defibrotide, Sodium oxybate	2
4-hidroxylfenilpiruvat dioxigenase competitive inhibitor	Nitisinone	1
Adenosine receptor antagonist	Caffeine	1
Aminoglycoside antibiotic	Tobramycin	1
Analogue for GLP-2	Teduglutide	1
Anti IL6	Siltuximab	1
Anti VEGF Receptor 2	Ramucirumab	1
ATP sintetase inhibitor in Mycobacterium	Bedaquiline	1
Bacterial wall synthesis inhibitor	Delamanid	1
Beta lactamic antibiotic	Aztreonam	1
Bradykinin receptor antagonist	Icatibant	1
C5 antibody	Eculizumab	1
Calicum channel type N blockers	Ziconotide	1

CD30-directed antibody	Brentuximab	1
Chemotherapy: pro-apoptotic	Arsenic trioxide	1
Chemotherapy: cell cycle transcription inhibitor	Trabectedin	1
Chemotherapy: photodinamic therapy	5-aminolevulinic acid	1
Cofactor amino-acid hydrolases	Sapropterin	1
Convert cistine to cisteine	Mercaptamine	1
Cortisol replacement	Hydrocortisone	1
Cyclooxygenase inhibitor	Ibuprofen	1
Cupper captation	Zinc	1
CXCR4 antagonist	Plerixafor	1
Cytotoxic: free radical formation	Porfimer sodium	1
Enables ribosomal readthrough of mRNA	Ataluren	1
Enzyme activator	Carglumic acid	1
Enzyme-based debriding agent	Bromelain	1

Gaba increase	Stiripentol	1
Growth factor receptor antagonist	Pegvisomant	1
Growth factor replacement	Mecasermin	1
Guanilate cyclasa stimulator	Riociguat	1
Hyperosmotic compound	Mannitol	1
Immunomodulator	Histamine dihydrochloride	1
inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3)	Olaparib	1
Iron chelation	Deferasirox	1
Iron chelation and topoisomerase II inhibition	Dexrazoxane	1
Janus kinase inhibitor	Ruxolitinib	1
Lipoproteinlipase integration	Alipogene tiparvovec	1
Melanocortin receptor agonist	Afamelanotide	1
Methyl donnor	Betaine anhydrous	1
Na channel blockers	Rufinamide	1

Phosphodiesterase 5 inhibitor	Sildenafil	1
Phosphodiesterase II AMPc-dependent inhibitor	Anagrelide	1
Potassium channel blocker	Amifampridine	1
Prostacyclin analogue	Iloprost	1
Reduce the amount of folic acid produced	Para-aminosalicylic acid	1
Restore the function of the CFTR protein	Ivacaftor	1
Selective COX2 inhibitor	Celecoxib	1
Somatostatin analogue	Pasireotide	1
Steroidogenesis inhibitor	Ketoconazole	1
Substrat reduction therapy	Miglustat	1
Transthyretin specific stabilizer	Tafamidis	1
Unknown. Antifibrotic, antiimmflamatory	Pirfenidone	1
Total		**100**