The clinical assessment of studies on orphan drugs in relation to the EMA's authorization marketing decisions

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Abstract

Introduction Clinical evidence on effectiveness and safety for orphan drugs is limited. We aimed to assess the correlation between clinical robustness of studies on orphan drugs and the status assigned by the European Medicines Agency (EMA).

Methods We assessed all medicines with an orphan designation included in the EMA website as of June 1, 2020. Clinical data were collected from the European public assessment report (EPAR) documents for each drug, containing such information as clinical trial characteristics as well as drug safety and efficacy. Data were categorized, and statistical analysis was performed.

Results We identified 968 trials reporting the results of 1342 clinical evaluations of 105 orphan drugs in a total number of almost 130 000 patients. In the multiple regression model analysis, each additional dose-response trial was associated with a 33-fold increase in the odds for the drug being under additional monitoring (p=0.02). Each additional randomized controlled trial was associated with a 91% reduction in the odds for additional monitoring (p=0.02). Each additional 100 patients participating in clinical trials was associated with a 58% reduction in the odds for exceptional circumstances (p=0.04). Each additional percent point for a share of studies with a follow-up longer than 2 years was associated with a 98% reduction in the odds for accelerated assessment (p=0.01).

Conclusions Our quantitative analysis of the EMA authorization decision-making process revealed that the characteristics of a clinical trial and the quality of available evidence can be significantly associated with the odds for a specific status.

1. Background

Orphan drugs are drugs that are designed specifically to treat rare diseases. A medicine is classified as an orphan drug if it complies with the guidelines primarily outlined in the Orphan Regulation [1] and implementing acts. According to the European Medicines Agency (EMA), to qualify for orphan designation, a medicinal product has to meet the following criteria: 1) it must be intended for diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition; 2) the condition must affect less than 5 in 10 000 people in the European Union and drug would provide adequate profits to justify the investment required to develop it; (EU); and 3) the available therapeutic, diagnostic or preventive method can be replaced by a new and more effective one with significant benefits for patients [1].

It is estimated that there are between 5 000 and 8 000 different rare diseases and they affect between 6% and 8% of the EU population, which is between 27 and 36 million people [2]. The most common groups of rare diseases treated with orphan drugs are oncological and metabolic diseases [3]. Moreover, about 80% of rare diseases are of genetic origin and affect 3–4% of newborns. Other rare conditions are caused by bacterial or viral infections, allergies, or degenerative and proliferative factors (abnormalities during cell multiplication) [4].

To authorize an orphan drug, a marketing authorization holder (eg, a company or research institute) must fulfill several specific criteria, such as provide the complete report of research studies that indicate the clinical efficacy and safety of the drug. Holders are obligated to share their clinical trial data with the EMA, but they are not currently required to publish comprehensive data to receive a marketing approval [5].

Clinical data submitted to the EMA are automatically made accessible to external parties via a European public assessment report (EPAR), that is, a set of documents containing detailed information on the medicines assessed by the Committee for Medicinal Products for Human Use (CHMP). The EPAR is prepared using a centralized procedure and includes information about medicinal products published publicly on the EMA website. Moreover, it provides a comprehensive overview of the medicinal product, authorization details, and assessment history [6].

Sharing clinical trial data is important in that the results can be verified and pooled for a meta-analysis; new trends can be identified, enabling further research; and, finally, physicians and patients can stay up to date and make their decision based on clinical evidence. Transparency also builds trust in the results of clinical studies, potentially attracting more people to participate in future trials [7, 8]. Finally, data from clinical trials can be a valuable source of information for policymakers when deciding on whether to authorize or reimburse a medicine in a particular EU Member State.

A marketing authorization holder that has conducted well-documented clinical trials and intends to obtain authorization for an orphan drug must undergo a specific approval process [9]. Through authorization, the EMA can assign a status (type of authorization, required supervision, or registration procedure) to a medicine depending on the data submitted by the holder and several additional factors, such as the type of substance, side effects, or disease severity. Orphan drugs can be granted two types of authorization statuses (conditional approval or exceptional circumstances) and other statuses (additional monitoring and/or accelerated assessment) [10].

The CHMP may grant a conditional marketing authorization (also known as conditional approval) to an orphan drug with missing clinical data if, despite the risks, the benefits of its use outweigh potential harms. Such a decision is made in specific situations when there is a strong need for immediate therapy. The marketing authorization holder is expected to complete missing information after authorization. This status is valid for one year and can be renewed annually [11]. Another type of marketing authorization is so called exceptional circumstances. This authorization is granted to medicines when the applicant is unable to provide comprehensive data on efficacy and safety under normal conditions of use. This can happen when the condition to be treated is rare, or when it is not possible (or not entirely ethical) to collect full information [12, 13].

Authorization under additional monitoring is different from conditional approval and exceptional circumstances. Most importantly, it is not a type of authorization under certain conditions. Rather, it entails some additional responsibility on the part of the holder because the EMA will monitor such a medicine with greater attention. This most often applies to situations when the medicine has biological

components, there is no clinical evidence on longer-term use, or there are rare side effects. Drugs under additional monitoring are often those that already have a conditional approval or have been approved for use under exceptional circumstances. The decision is based on advice from the Pharmacovigilance Risk Assessment Committee of the EMA. If granted this type of authorization, a company is specifically required to record suspected adverse drug reactions [14, 15].

The evaluation of a marketing authorization application under the centralized procedure can take up to 210 days (about 7 months), excluding clock stops when applicants have to provide additional information. On request, the CHMP can reduce the timeframe to 150 days (5 months) if the applicant provides sufficient justification for an accelerated assessment procedure. Applicants requesting an accelerated assessment should substantiate their submission that the medicinal product is expected to be of significant public health importance, especially from the perspective of therapeutic innovation [13, 16].

The robustness of clinical trials on orphan drugs is an interesting topic. Research shows that the available evidence on the effectiveness, cost-effectiveness, and budget impact of most orphan drugs is limited compared with that for common drugs (non-orphan drugs). Moreover, it often does not meet standard quality criteria [17]. These differences result from the challenges inherent to studies on rare diseases, such as low disease prevalence, small and heterogeneous patient populations with recruitment problems (high failure rates), disease severity, and limited knowledge of the disease [18, 19]. In addition, there are important ethical concerns (particularly in pediatric trials), and pharmaceutical companies come under reimbursement scrutiny [20]. Finally, it was shown that although there are post-marketing data available for oncological orphan drugs, a large number of these drugs have failed to demonstrate a clinically relevant increase in overall survival in real-world conditions [21].

The aim of this study was to evaluate the clinical robustness of studies on orphan drugs in relation to assigned statuses during the process of granting the marketing authorization decision by the EMA.

2. Methods

The list of authorized drugs with current orphan designation was obtained from the EMA's website on 1 June 2020 (European Medicines Agency, 2020). In the EMA's medicine-related data (called registry) [23], official EPAR documents are assigned to each medicine. We performed a detailed analysis of the information contained in the following documents: "EPAR – Product Information" (latest version) and "EPAR – Scientific Discussion" (pre-authorization version). Based on these documents, it was possible to define the following clinical categories:

- number of patients enrolled in the study;
- type of study: randomized controlled trial (RCT), controlled trials, dose-response study, retrospective study;

- study details: open-label, randomization, blinding, control group, placebo, phase, number of sites, number of arms, last follow-up visit;
- duration of treatment and study;
- safety and efficacy endpoints;
- quality-of-life assessment.

Each category of the clinical trial robustness was assessed in relation to four selected statuses: conditional approval; exceptional circumstances; additional monitoring; and accelerated assessment. To obtain more comprehensive results, an additional analysis was performed for a combination of two statuses: “conditional approval or exceptional circumstances”.

Statistical analysis

Two or more quantitative variables were compared using the Student t-test (or the Wilcoxon sum rank test if assumptions were not met) and the ANOVA test (or the Kruskal-Wallis test if assumptions were not met). The data were summarized using mean and standard deviation or median with the first and the third quartile.

Two nominal variables were compared using the χ^2 test or the Fisher exact test, depending on expected cell counts in contingency tables. The results of the tests were presented as p-values rounded to four decimal places. The data were summarized with counts and percentages.

The impact of the particular components from the clinical robustness on the EMA’s statuses was assessed using the simple logistic regression models and presented as odds ratio (OR). All ORs were presented with 95% CI rounded to two decimal places and corresponding p-values rounded to four decimal places. A p-value of < 0.05 was considered statistically significant. Among all simple models, those with a p-value < 0.2 were selected for the multiple logistic regression analysis. The final models for each of the statuses (conditional approval, exceptional circumstances, additional monitoring, and accelerated assessment) were obtained using the stepwise selection with minimization of the Akaike information criterion as target and adjusted to the type of the disease. Statistical analyses were carried out in the JMP software, version 15.1 (SAS Institute Inc., 2019, Cary, North Carolina 27513, USA).

3. Results

A total of 105 authorized medicines with orphan designation were identified and included in further analysis. Each of the 105 medicines might have had more than one EMA status (Table 1). Under additional monitoring was the most commonly assigned status (n = 72), while the exceptional circumstances status was the least frequent (n = 12). However, some orphan drugs did not require any status to be assigned by the EMA (n = 24) (Table 1).

The specific statuses assigned to each orphan drug, indicated by the trade name, can be found in Table 1 (valid on 1 June 2020).

Table 1
Orphan drug statuses granted by the European Medicines Agency

	Drug name	EMA status			
		CA	EC	AM	AA
1	Adcetris	yes	no	yes	no
2	Adempas	no	no	no	no
3	Alofisel	no	no	yes	no
4	Alprolix	no	no	yes	no
5	Amglidia	no	no	no	no
6	Besponsa	no	no	yes	no
7	Blincyto	no	no	yes	no
8	Brineura	no	yes	yes	yes
9	Bronchitol	no	no	no	no
10	Cablivi	no	no	yes	no
11	Carbaglu	no	no	no	no
12	Cerdelga	no	no	yes	no
13	Chenodeoxycholic acid Leadiant	no	yes	yes	no
14	Coagadex	no	no	yes	yes
15	Cometriq	yes	no	yes	no
16	Cresemba	no	no	yes	no
17	Crysvita	yes	no	yes	no
18	Cystadrops	no	no	no	no
19	Dacogen	no	no	no	no
20	Darzalex	no	no	yes	yes
21	Defitelio	no	no	yes	yes
22	Deltyba	yes	no	yes	no
23	Epidyolex	no	no	no	no
24	Esbriet	no	no	no	no
25	Farydak	no	no	yes	no
26	Firazyr	no	no	no	no

	Drug name	EMA status			
		CA	EC	AM	AA
27	Galafold	no	no	yes	no
28	Gazyvaro	no	no	yes	no
29	Givlaari	no	no	yes	no
30	Granupas	no	no	no	no
31	Hetlioz	no	no	yes	no
32	Holoclar	yes	no	yes	no
33	Iclusig	no	no	yes	yes
34	Idelvion	no	no	yes	no
35	Imbruvica	no	no	no	no
36	Imnovid	no	no	yes	no
37	Insurisa	no	no	yes	no
38	Jorveza	no	no	no	yes
39	Kalydeco	no	no	no	yes
40	Kanuma	no	no	yes	yes
41	Ketoconazole HRA	no	no	yes	yes
42	Kolbam	no	yes	yes	no
43	Kuvan	no	no	no	no
44	Kymriah	no	no	yes	no
45	Kyprolis	no	no	yes	yes
46	Lamzede	no	yes	yes	no
47	Ledaga	no	no	no	no
48	Lutathera	no	no	yes	no
49	Luxturna	no	no	yes	no
50	Mepsevii	no	yes	yes	no
51	Mozobil	no	no	no	no
52	Myalepta	no	yes	yes	no
53	Mylotarg	no	no	yes	no

	Drug name	EMA status			
		CA	EC	AM	AA
54	Namuscla	no	no	no	no
55	Natpar	yes	no	yes	no
56	Nexavar	no	no	no	no
57	NexoBrid	no	no	yes	no
58	Ninlaro	yes	no	yes	no
59	Ocaliva	yes	no	yes	no
60	Ofev	no	no	no	yes
61	Onivyde pegylated liposomal	no	no	no	no
62	Onpattro	no	no	yes	yes
63	Opsumit	no	no	no	no
64	Orphacol	no	yes	yes	no
65	Oxervate	no	no	yes	yes
66	Palynziq	no	no	yes	no
67	Plenadren	no	no	no	no
68	Polivy	yes	no	yes	no
69	Poteligeo	no	no	yes	no
70	Prevymis	no	no	yes	no
71	Procysbi	no	no	no	no
72	Qarziba	no	yes	yes	no
73	Ravicti	no	no	yes	no
74	Raxone	no	yes	yes	no
75	Revestive	no	no	yes	no
76	Rydapt	no	no	yes	no
77	Scenesse	no	yes	yes	no
78	Signifor	no	no	no	no
79	Sirturo	yes	no	yes	no
80	Soliris	no	no	no	yes

	Drug name	EMA status			
		CA	EC	AM	AA
81	SomaKit TOC	no	no	yes	no
82	Spinraza	no	no	yes	yes
83	Strensiq	no	yes	yes	no
84	Strimvelis	no	no	yes	no
85	Sylvant	no	no	no	yes
86	Symkevi	no	no	yes	no
87	Takhzyro	no	no	yes	yes
88	Tegsedi	no	no	yes	yes
89	Tobi Podhaler	no	no	no	no
90	Translarna	yes	no	yes	no
91	Trepulmix	no	no	no	no
92	Verkazia	no	no	no	yes
93	Vimizim	no	no	yes	no
94	Votubia	no	no	no	no
95	Vpriv	no	no	no	yes
96	Vyndaqel	no	yes	yes	no
97	Vyxeos liposomal	no	no	no	no
98	Wakix	no	no	yes	no
99	Waylivra	yes	no	yes	no
100	Xaluprine	no	no	no	no
101	Xermelo	no	no	yes	no
102	Xospata	no	no	yes	no
103	Yescarta	no	no	yes	no
104	Zejula	no	no	yes	no
105	Zynteglo	yes	no	yes	no

[EC] exceptional circumstances [CA] conditional approval [AM] additional monitoring [AA] accelerated assessment

Characteristics of studies on orphan drugs

During the analysis, 968 separate studies were extracted from EPAR documents. Phase III studies were the most common (n = 227, 23%), followed by phase II and phase I studies (n = 208, 21% and n = 143, 15%, respectively). The number of patients was reported in 937 studies and totaled 129 660 patients. The maximum number of patients reported per study was 4 439, and the mean (SD) number of patients per study was 138 (292). There were 447 open-label studies (46%), 178 dose-response studies (18%), 151 RCTs (16%), and 37 retrospective studies (4%). The remaining studies could not be classified based on EPAR data. Single or double blinding was used in 209 trials (22%), placebo in control groups was used in 180 trials (19%), and 294 trials (30%) had at least one control group.

There is a distinction between study duration (ie, duration of the entire study) and treatment duration (ie, duration of treatment/dosing). However, information on study duration was not commonly reported. Of the assessed studies, 94 (10%) lasted more than two years, while 69 studies (7%) had a duration of up to two years. Data on study duration was missing for 805 records. More information was available for treatment duration. In 192 studies (20%), the treatment lasted up to three months; in 212 studies (22%), from three to 12 months; and in 178 studies (18%), the duration was more than 12 months. Data were missing for 386 studies. A safety endpoint was defined in 891 studies (92%), and efficacy endpoint, in 586 studies (61%). However, data on the timepoint of the safety and efficacy assessment were reported much less often. Only 127 studies (13%) reported the quality-of-life assessment.

Clinical robustness of studies depending on the classification of orphan drugs

Based on the Anatomical Therapeutic Chemical codes used in the EMA website (and indications from other studies [3, 24]), orphan drugs were classified into three groups: metabolic diseases, oncological diseases, and other diseases (non-metabolic and non-oncological). The characteristics of studies on orphan drugs for metabolic, oncological, and other diseases depending on the presence or absence of a given status are summarized in Tables 2–4. A comparison of study characteristics between the three groups of orphan drugs is presented in Tables 5–6.

There were 23 drugs assigned to the group of metabolic diseases (Table 2). In this group, additional monitoring was the most common status, reported for 17 drugs. The exceptional circumstances status was noted for eight drugs; accelerated assessment, for four; and conditional approval, for one drug. The median number of enrolled patients was lower for drugs with exceptional circumstances than for those without (181.00 [141.25; 285.00] vs 507.00 [392.00; 753.00], p = 0.03). Orphan drugs for metabolic diseases granted the exceptional circumstances status were characterized by a much smaller percentage of RCTs when compared with drugs without this status (0% [0%-9%] vs. 13% [0%-30%]). The median number of studies assessing efficacy after the follow-up of at least 6 months was more than twice as high for drugs with accelerated assessment than for those without this status (2.50 [1.25; 4.50] vs 1.00 [0.00; 2.00], p = 0.04), which shows that the status was also influenced by the timepoint of safety and efficacy assessment.

Table 2
Characteristics of studies on orphan drugs for metabolic diseases depending on the presence or absence of exceptional circumstances, conditional approval, additional monitoring, and accelerated assessment status.

exceptional circumstances	No (n = 15)	Yes (n = 8)	p-value
Total number of patients enrolled in all studies	507 (392; 753)	181(141.25; 285)	0.0332*
Share of RCTs	13% (0%; 30%)	0% (0%; 9%)	0.0364*
Number of studies with safety endpoint at up to 2 months follow-up	1 (0; 2)	0 (0; 0.75)	0.0371*
Share of studies with safety endpoint at up to 2 months follow-up	13% (0%; 21%)	0% (0%; 9%)	0.0930
Number of studies with safety endpoint at 2–6 months follow-up	1(0; 1)	0.5 (0; 1.75)	0.9446
Share of studies with safety endpoint at 2–6 months follow-up	4% (0%; 14%)	6% (0%; 25%)	0.8107
Number of studies with safety endpoint assessed at later than 6 months follow-up	1 (0; 1)	0.5 (0; 1.75)	0.9446
Share of studies with safety endpoint assessed at later than 6 months follow-up	10% (0%; 36%)	19% (0%; 63%)	0.6886
Number of studies with efficacy endpoint assessed at later than 6 months follow-up	1 (0; 2)	1 (0; 2.75)	0.9732
Share of studies with efficacy endpoint assessed at later than 6 months follow-up	10% (0%; 25%)	19% (0%; 63%)	0.5930
conditional approval	No (n = 22)	Yes (n = 1) **	
Total number of patients enrolled in all studies	393.5 (167.25; 649)	1244	-
Share of RCTs	5% (0%; 25%)	56%	-
Number of studies with safety endpoint at up to 2 months follow-up	0.50 (0; 1.25)	1	-
Share of studies with safety endpoint at up to 2 months follow-up	5% (0%; 18%)	11%	-
Number of studies with safety endpoint at 2–6 months follow-up	0.5 (0; 1)	5	-
Share of studies with safety endpoint at 2–6 months follow-up	2% (0%; 15%)	56%	-

*statistically significant, **without measure of dispersion because n = 1

exceptional circumstances	No (n = 15)	Yes (n = 8)	p-value
Number of studies with safety endpoint assessed at later than 6 months follow-up	1 (0; 3)	0	-
Share of studies with safety endpoint assessed at later than 6 months follow-up	13% (0; 39%)	0%	-
Number of studies with efficacy endpoint assessed at later than 6 months follow-up	1 (0; 2.25)	0	-
Share of studies with efficacy endpoint assessed at later than 6 months follow-up	13% (0%; 28%)	0%	-
additional monitoring	No (n = 6)	Yes (n = 17)	
Total number of patients enrolled in all studies	410 (132.75; 610.25)	395 (166.5; 705.5)	0.6744
Share of RCTs	0% (0%; 41%)	13% (0%; 25%)	0.6083
Number of studies with safety endpoint at up to 2 months follow-up	1 (0; 3.75)	0 (0; 1)	0.2744
Share of studies with safety endpoint at up to 2 months follow-up	13% (0%; 64%)	0% (0%; 13%)	0.2646
Number of studies with safety endpoint at 2–6 months follow-up	0 (0; 0.25)	1 (0; 2.5)	0.0419*
Share of studies with safety endpoint at 2–6 months follow-up	0% (0%; 4%)	13% (0% 25%)	0.0584
Number of studies with safety endpoint assessed at later than 6 months follow-up	0.5 (0; 2)	1 (0; 3)	0.4450
Share of studies with safety endpoint assessed at later than 6 months follow-up	5% (0%; 37%)	14% (0%; 43%)	0.4468
Number of studies with efficacy endpoint assessed at later than 6 months follow-up	0.5 (0; 2)	1 (0; 2.5)	0.4657
Share of studies with efficacy endpoint assessed at later than 6 months follow-up	5% (0%; 37%)	14% (0%; 31%)	0.4911
accelerated assessment	No (n = 19)	Yes (n = 4)	
Total number of patients enrolled in all studies	441 (174; 753)	275.5 (144; 419)	0.1944
Share of RCTs	7% (0%; 25%)	6% (0%; 59%)	1.0000
Number of studies with safety endpoint at up to 2 months follow-up	1 (0; 1)	0 (0; 2.25)	0.4579
*statistically significant, **without measure of dispersion because n = 1			

exceptional circumstances	No (n = 15)	Yes (n = 8)	p-value
Share of studies with safety endpoint at up to 2 months follow-up	11% (0%; 17%)	0% (0%; 56%)	0.5465
Number of studies with safety endpoint at 2–6 months follow-up	1 (0; 1)	0.5 (0; 2.5)	0.9652
Share of studies with safety endpoint at 2–6 months follow-up	4% (0%; 19%)	7% (0%; 32%)	0.8974
Number of studies with safety endpoint assessed at later than 6 months follow-up	1 (0; 2)	2.5 (1.25; 4.5)	0.0700
Share of studies with safety endpoint assessed at later than 6 months follow-up	8% (0%; 25%)	48% (25%; 74%)	0.0359*
Number of studies with efficacy endpoint assessed at later than 6 months follow-up	1 (0; 2)	2.5 (1.25; 4.5)	0.0425*
Share of studies with efficacy endpoint assessed at later than 6 months follow-up	8% (0%; 25%)	48% (25%; 74%)	0.0234*
*statistically significant, **without measure of dispersion because n = 1			

– data presented as median with the first and the third quartile Me(Q1; Q3)

The oncological diseases group included 35 medications (Table 3). As in the metabolic diseases group, the most common status was additional monitoring. On the other hand, the exceptional circumstances status was the least frequent. More specifically, additional monitoring was reported for 22 drugs; accelerated assessment, for six; conditional approval, for four; and exceptional circumstances, for one drug. This again confirmed the considerable effect of RCTs on the EMA's status, in this case – additional monitoring. Orphan drugs for oncological diseases under additional monitoring were characterized by a smaller percentage of RCTs than those without additional monitoring (0% [0%-10%] vs. 13% [0%-54%]). The study and treatment duration were another variable that affected the status. Drugs with an accelerated assessment status had a higher percentage of studies with a treatment duration over 12 months compared with drugs without this status (25% [10%-43%] vs. 8% [0%-14%]).

Table 3
Characteristics of studies on orphan drugs for oncological diseases depending on the presence or absence of exceptional circumstances, conditional approval, additional monitoring, and accelerated assessment status.

exceptional circumstances	**No (n = 34)**	**Yes (n = 1)**	**p-value**
Share of RCTs	0% (0%; 16%)	0% (0%; 0%)	-
Number of studies with study duration over 2 years	1 (0; 2)	2 (2; 2)	-
Share of studies with study duration over 2 years	11% (0%; 22%)	33% (33%; 33%)	-
Number of studies with treatment duration over 12 months	1 (0; 1.25)	0 (0; 0)	-
Share of studies with treatment duration over 12 months	10% (0%; 20%)	0% (0%; 0%)	-
conditional approval	No (n = 31)	Yes (n = 4)	
Share of RCTs	0% (0%; 17%)	12% (3%; 15%)	0.4101
Number of studies with study duration over 2 years	1 (0; 2)	0.5 (0; 1.)	0.2520
Share of studies with study duration over 2 years	11% (0%; 25%)	5% (0% 13%)	0.2549
Number of studies with treatment duration over 12 months	1 (0; 1)	0.5 (0; 1.75)	0.7200
Share of studies with treatment duration over 12 months	1% (0%; 20%)	5% (0%; 13%)	0.4692
additional monitoring	No (n = 13)	Yes (n = 22)	
Share of RCTs	13% (0%; 54%)	0% (0%; 10%)	0.0306*
Number of studies with study duration over 2 years	1 (0; 1.5)	1 (0; 2)	0.5534
Share of studies with study duration over 2 years	11% (0%; 19%)	12% (0%; 28%)	0.4965
Number of studies with treatment duration over 12 months	1 (0; 3)	1 (0; 1.)	0.8417
Share of studies with treatment duration over 12 months	11% (0%; 29%)	10% (0%; 20%)	0.8461
accelerated assessment	No (n = 29)	Yes (n = 6)	
Share of RCTs	0% (0%; 15%)	6% (0%; 26%)	0.7465
Number of studies with study duration over 2 years	1 (0; 2)	0 (0; 1)	0.0428*

*statistically significant

exceptional circumstances	No (n = 34)	Yes (n = 1)	p-value
Share of studies with study duration over 2 years	13% (0; 26%)	0% (0%; 6%)	0.0226*
Number of studies with treatment duration over 12 months	1 (0; 1)	2 (1; 5)	0.0105*
Share of studies with treatment duration over 12 months	8% (0%; 14%)	25% (10%; 43%)	0.0198*
*statistically significant			

– data presented as median with the first and the third quartile Me(Q1; Q3)

The last group included 47 drugs intended for other diseases – non-metabolic and non-oncological (Table 4). Most drugs were under additional monitoring (33 drugs), followed by accelerated assessment (10 drugs), conditional approval (8 drugs), and exceptional circumstances (3 drugs). This group of orphan drugs showed significant differences only for additional monitoring (Table 4). On the one hand, studies with a longer treatment duration (over 12 months) were more common for oncological drugs under accelerated assessment (Table 3), while on the other hand, studies with a relatively short treatment duration (3 to 12 months) were less frequent for drugs under additional monitoring included in the other-diseases group (Table 4). Drugs under additional monitoring had a lower percentage of studies with a treatment duration of three to 12 months than drugs without this status (17% [0%-32%] vs. 33% [24%-48%]).

Table 4
Characteristics of studies on orphan drugs for other diseases depending on the presence or absence of exceptional circumstances, conditional approval, additional monitoring, and accelerated assessment status.

exceptional circumstances	**No (n = 44)**	**Yes (n = 3)**	**p-value**
Number of studies with treatment duration 3 to 12 months	2 (0; 3)	2 (2; 5)	0.2570
Share of studies with treatment duration 3 to 12 months	25% (0%; 33%)	17% (13%; 63%)	0.7575
conditional approval	No (n = 39)	Yes (n = 8)	
Number of studies with treatment duration 3 to 12 months	1 (0; 3)	2 (2; 3.75)	0.2535
Share of studies with treatment duration 3 to 12 months	20% (0%; 33%)	31% (20%; 36%)	0.2572
additional monitoring	No (n = 14)	Yes (n = 33)	
Number of studies with treatment duration 3 to 12 months	2 (1; 4.25)	1 (0; 3)	0.0589
Share of studies with treatment duration 3 to 12 months	33% (24%; 48%)	17% (0%; 32%)	0.0050*
accelerated assessment	No (n = 37)	Yes (n = 10)	
Number of studies with treatment duration 3 to 12 months	2 (0.5; 3)	1 (0; 4)	0.5415
Share of studies with treatment duration 3 to 12 months	25% (6%; 33%)	19% (0; 31%)	0.3043
*statistically significant			

– data presented as median with the first and the third quartile Me(Q1; Q3)

A comparison of clinical categories between the three types of orphan drugs is shown in Table 6. The highest number of patients participated in studies on oncological orphan drugs, and the lowest, in those on metabolic diseases. Drugs for metabolic diseases were characterized by a much smaller mean average of patients when compared to drugs for oncological diseases (51 [23.50; 98.00] vs. 166 [117.74; 289.44]) – for other diseases, it was 89 (50.33; 227.00). The most significant difference was noted between oncological and metabolic diseases ($p < 0.0001$), followed by other diseases vs oncological diseases ($p = 0.007$) and other diseases vs metabolic diseases ($p = 0.05$). This difference may be due to the low prevalence of the disease group on the one hand and the availability of the patient group on the other, but other reasons cannot be excluded.

The distribution of study types (dose-response and RCT) differed among the three drug groups. Dose-response studies were most common for oncological diseases, while RCTs, for other diseases. The

percentage of dose-response studies was 24% (12%-33%) for oncological diseases, 22% (0%-50%) for metabolic diseases, and 14% (0%-29%) for other diseases. However, the difference was significant only for oncological vs other diseases (p = 0.05). The percentage of RCTs was 0% (0%-16%) for oncological diseases, 7% (0%-25%) for metabolic diseases, and 18% (0%-33%) for other diseases, with a significant difference only between oncological and other diseases (p = 0.04). In addition, we noted differences in the duration of studies only for those lasting longer than 12 months. Drugs for metabolic diseases showed a higher percentage of studies with a study duration over 12 months compared with drugs for oncological diseases (33% [14%-50%] vs. 10% [0%-20%], p = 0.002). The category of safety and efficacy assessment also showed some differences indicating a heterogeneity of studies on orphan drugs. For instance, studies evaluating safety endpoints after the follow-up of at least 6 months were most frequent among drugs for metabolic diseases (13% [0%-36%], followed by drugs for oncological diseases (0% [0%-11%]) and other diseases (0% [0%-25%]). However, a significant difference was observed only between oncological and metabolic diseases (p = 0.05).

Table 5
Relation between EMA status and type of disease

Variable/Type	Metabolic diseases	Oncological diseases	Other diseases	p-value
Number of orphan drugs	23 (22%)	35 (33%)	47 (45%)	-
Number of drugs with exceptional circumstances	8 (8%)	1 (1%)	3 (3%)	0.0003*
Number of drugs with conditional approval	1 (1%)	4 (4%)	8 (8%)	0.3119
Number of drugs under additional monitoring	17 (16%)	22 (21%)	33 (31%)	0.6397
Number of drugs with accelerated assessment	4 (4%)	6 (6%)	10 (10%)	0.8717
*statistically significant				

– percentages do not add up to 100%; one drug could have more than one status

Table 6
Relation between clinical variables and type of disease

Variable/Type	Metabolic diseases	Oncological diseases	Other diseases	p-value
Total number of patients enrolled in all studies	395.00 (170.00; 658.00)	1338.00 (745.50; 2906.25)	686.00 (351.00; 1624.00)	< 0.0001*
Average number of patients per study	51.25 (23.50; 98.00)	166.29 (117.74; 289.44)	89.14 (50.33; 227.00)	< 0.0001*
Share of dose-response studies	22% (0%; 50%)	24% (12%; 33%)	14% (0%; 29%)	0.0498*
Share of RCTs	7% (0%; 25%)	0% (0%; 16%)	18% (0%; 33%)	0.0405*
Number of studies with treatment duration over 12 months	2 (1; 3)	1 (0; 1)	1 (0; 2)	0.0193*
Share of studies with treatment duration over 12 months	33% (14%; 50%)	10% (0%; 20%)	18% (0%; 33%)	0.0024*
Number of studies with safety endpoint assessed at later than 6 month follow-up	1 (0; 3)	0 (0; 1)	0 (0; 1)	0.0494*
Share of studies with safety endpoint assessed at later than 6 month follow-up	13% (0%; 36%)	0% (0%; 11%)	0% (0%; 25%)	0.0475*
Number of studies with safety endpoint at 2–6 months follow-up	1 (0; 1)	0 (0; 1)	1 (0; 2)	0.0304*
Share of studies with safety endpoint at 2–6 months follow-up	4% (0%; 19%)	0% (0%; 11%)	11% (0%; 25%)	0.0150*
Number of studies with efficacy endpoint at 2–6 months follow-up	0 (0; 1)	0 (0; 1)	1 (0; 2)	0.0534
Share of studies with efficacy endpoint at 2–6 months follow-up	0% (0%; 19%)	0% (0%; 11%)	11% (0%; 25%)	0.0233*
*statistically significant				

– data presented as median with the first and the third quartile Me(Q1; Q3)

Analysis of multiple regression model for the clinical robustness of the studies

The multiple regression model analysis showed some robust outcomes depending on the EMA status (Table 7). The most significant results for the exceptional circumstances status were observed for the number of patients, number of sites, treatment duration, and safety endpoint assessment. Each

additional 100 patients participating in clinical trials was associated with a 58% reduction in the odds for exceptional circumstances (OR = 0.42, 95% CI: 0.11–0.95; p = 0.04). Each additional multicenter study was associated with a 96% reduction in the odds for exceptional circumstances (OR = 0.04, 95%CI: 0.00-0.46; p = 0.01). Each additional percent point increase in a share of studies with a treatment duration between three and 12 months was associated with a 50-fold increase in the odds for exceptional circumstances (OR = 49.88, 95%CI: 2.22-2011.15; p = 0.01). Finally, each additional safety endpoint assessed within two months was associated with a 63% reduction in the odds for exceptional circumstances (OR = 0.37, 95%CI: 0.10–0.93; p = 0.03).

The multiple regression model did not indicate any significant results for separate conditional approval; therefore, in this case, we used the combined category “conditional approval or exceptional circumstances”. A correlation between these two statuses was found for treatment duration and safety assessment. Each additional percent point increase in a share of studies with a safety endpoint assessed within two months was associated with a 99.8% reduction in the odds for conditional approval or exceptional circumstances (OR = 0.002, 95%CI: 4.562e-6-0.15; p = 0.002). Each additional percent point for a share of studies with a treatment duration between three and 12 months was associated with a 29-fold increase in the odds for conditional approval or exceptional circumstances (OR = 29.03, 95%CI: 2.70-413.70; p = 0.005).

For drugs under additional monitoring, we noted an association for the type of study (dose-response studies and RCTs) and treatment duration. Each additional dose-response study was associated with a 33-fold increase in the odds for additional monitoring (OR = 33.1, 95%CI: 1.90-833.99; p = 0.02). Each additional RCT was associated with a 91% reduction in the odds for additional monitoring (OR = 0.09, 95%CI: 0.01–0.71; p = 0.02). Finally, each additional percent point increase in a share of studies with a treatment duration longer than 12 months was associated with a 13-fold increase in the odds for additional monitoring (OR = 13.32, 95%CI: 1.31-188.38; p = 0.03).

The analysis of orphan drugs reviewed under accelerated assessment revealed only one correlation for study duration. The multiple model regression showed that each additional percent point increase in a share of studies with a study duration longer than two years was associated with a 98% reduction in the odds for accelerated assessment (OR = 0.02, 95%CI: 0.00-0.50; p = 0.01).

We also investigated the effect of adjustment for the type of disease on the results of the regression model (Table 7). Although the effect of disease type was not significant in any of the separate analyses, its overall impact was noted. An increase by one percent point for a share of the number of studies with a treatment duration between three and 12 months increased the odds for orphan drugs being granted exceptional circumstances. However, after adjustment for the type of disease, a 13-fold reduction in the impact was noted, resulting in a 37-fold increase in the odds for exceptional circumstances (OR = 36.62, 95%CI: 1.26-1962.64; p = 0.04). Additionally, there were cases in which adjustment for the type of disease significantly increased the effect. Each additional percent point increase in a share of studies with a treatment duration between three and 12 months was associated with a 37-fold increase in the odds for

conditional approval or exceptional circumstances (OR = 36.56, 95%CI: 2.84–679.50; p = 0.005), which was 8-fold higher than in the unadjusted regression model. Finally, each additional dose-response study was associated with a 52-fold increase in the odds for additional monitoring (OR = 51.84, 95%CI: 2.63-1610.63; p = 0.01), which was 19-fold higher than in the unadjusted regression model.

Table 7

Relation between clinical variables and EMA status using Simple and Multiple Regression Model

Variable	Simple Models		Multiple Model (AUC = 0.88)		Multiple Model adjusted for type of disease[!] (AUC = 0.89)	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
exceptional circumstances						
Total number of patients enrolled in all studies per drug, per 100 patients	**0.45** (0.16–0.45)	0.0270*	**0.42** (0.11–0.95)	0.0356*	**0.66** (0.18-1,32)	0.3223
Share of mean multicenter studies for a specific drug, per drug	**0.03** (0.00-0.29)	0.0023*	**0.04** (0.00-0.46)	0.0096*	**0.06** (0.00-0.81)	0.0337*
Fraction of studies with treatment duration between 3 and 12 months for a specific drug, per 1 p.p.**	**6.43** (0.56–70.90)	0.1310	**49.88** (2.22-2011.15)	0.0130*	**36.62** (1.26-1962.64)	0.0358*
Fraction of studies with timepoint safety up to 2 months for a specific drug, per drug	**0.49** (0.16–1.01)	0.0503	**0.37** (0.10–0.93)	0.0319*	**0.34** (0.08–0.92)	0.0298*
conditional approval or exceptional circumstances						
Fraction of studies with treatment duration between 3 and 12 months for a specific drug, per 1 p.p.**	**6.21** (0.94–43.91)	0.0577	**29.03** (2.70-413.70)	0.0048*	**36.56** (2.84–679.50)	0.0050*
Fraction of studies with treatment duration up to 3 months for a specific drug, per 1 p.p. **	**0.06** (0.00-0.72)	0.0239*	-	-	-	-
Fraction of studies with timepoint safety up to 2 months for a specific drug, per drug	**0.57** (0.30–0.93)	0.0199*	-	-	-	-

* statistically significant

** p.p. percent point – when a covariate is measured in precents

[!] the type of disease (oncological, metabolic, other) was not significant in any of the models

Variable	Simple Models		Multiple Model (AUC = 0.88)		Multiple Model adjusted for type of disease[!] (AUC = 0.89)	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Fraction of studies with timepoint safety up to 2 months for a specific drug, per 1 p.p. **	**0.01** (0.00-0.32)	0.0076*	**0.002** (4.562e-6-0.15)	0.0018*	**0.001** (8.414e-7-0.08)	0.0007*
Fraction of studies with timepoint efficacy up to 2 months for a specific drug, per drug	**0.60** (0.32–0.99)	0.0448*	-	-	-	-
Fraction of studies with timepoint efficacy up to 2 months for a specific drug, per 1 p.p.**	**0.01** (0.00-0.53)	0.0196*	-	-	-	-
additional monitoring						
Share of mean dose-response studies for a specific drug, per drug	**10.99** (0.84-185.02)	0.0678	**33.1** (1.90-833.99)	0.0154*	**51.84** (2.63-1610.63)	0.0085*
Share of mean RCTs for a specific drug, per drug	**0.12** (0.01–0.70)	0.0197*	**0.09** (0.01–0.71)	0.0221*	**0.06** (0.01–0.56)	0.0125*
Fraction of studies with treatment duration over 12 months for a specific drug, per 1 p.p.**	**6.37** (0.82–62.20)	0.0771	**13.32** (1.31-188.38)	0.0278*	**13.05** (1.12-213.71)	0.0400*
accelerated assessment						
Fraction of studies with study duration over 2 years for a specific drug, per 1 p.p.**	**0.08** (0.00-1.93)	0.1322	**0.02** (0.00-0.50)	0.0147*	**0.01** (0.00-0.47)	0.0137*

* statistically significant

** p.p. percent point – when a covariate is measured in precents

[!] the type of disease (oncological, metabolic, other) was not significant in any of the models

Variable	Simple Models		Multiple Model (AUC = 0.88)		Multiple Model adjusted for type of disease[!] (AUC = 0.89)	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Fraction of studies with treatment duration over 12 months for a specific drug, per drug	**1.19** (1.00-1.47)	0.0478*	-	-	-	-
* statistically significant						
** p.p. percent point – when a covariate is measured in precents						
[!] the type of disease (oncological, metabolic, other) was not significant in any of the models						

4. Discussion

The objective of this study was to evaluate the clinical robustness of studies on orphan drugs. We were able to collect the following clinical data for orphan drugs from the EMA na publicly available database: the number of patients; duration of treatment/study; type of clinical trials; study details including open-label, randomization, blinding, control group, placebo, phase, number of sites; safety and efficacy endpoints; and quality-of-life assessment. The extracted data allowed us to describe the characteristics of clinical trials on orphan drugs from a different perspective and investigate the strength of associations with the status.

Our study revealed some interesting correlations that provide some clues as to what criteria are considered by the EMA when granting a status to orphan drugs. It appears that multicenter studies had an important impact on marketing authorization decisions made by the EMA regarding orphan drugs. This can be explained by the fact that multicenter studies tend to include more patients and provide more representative results. Therefore, the registration authority was less likely to see the need to monitor such studies. Furthermore, we revealed that a higher number of patients included in a study on an orphan drug was associated with more reliable results, because they reported a satisfactory safety and efficacy profile. However, some criteria clearly motivated the EMA to exercise greater caution in terms of the requirement for a formal status. A treatment duration between three and 12 months was less acceptable by the EMA. It was associated with a necessity for additional review and increased the odds of being granted exceptional circumstances. Additionally, if the treatment duration for a given drug was longer than 12 months, the EMA was more likely to monitor such treatment process, possibly for safety reasons. Our study suggests that safety follow-up assessed after a short period of time were more valuable in orphan drug studies from the perspective of the EMA. A shorter time is associated with a lower risk of treatment failure compared with a longer time. If an effect is not seen after a short time, there is still time

to switch to another treatment. The results also showed that dose-response studies were not valued highly by the EMA because they increased the chances of granting under additional monitoring. On the other hand, RCTs reduced the chances of additional monitoring most likely due to the fact that they are considered as highly reliable studies. By applying for accelerated assessment, holders wish to reduce the time to evaluate a marketing-authorization application when a drug is in high demand and patients are awaiting treatment. Therefore, for longer studies, the need was less relevant, and holders less frequently applied for accelerated assessment.

Our literature review of publications assessing the clinical robustness of studies on orphan drugs in reference to the EMA status revealed only three relevant studies. This indicates that our analysis is quite innovative.

The first study focused on similar issues but was limited to a single country [25]. The authors aimed to assess reimbursement dossiers of orphan drugs in Belgium and to compare them with the clinical evidence submitted to the EMA. Some differences were observed between the clinical evidence submitted to the EMA and that submitted to the Belgian Drug Reimbursement Committee (primary endpoints, number of patients, time for follow-up duration). This indicates the difficulty of data extraction from the EMA registry, but data extraction still works according to EMA policies: only certain types of variations (such as variations in the therapeutic indication) trigger a revision of the EPAR document. The study concluded that there seemed to be a need for European cooperation in sharing clinical evidence on orphan drugs [25]. We can agree with this conclusion because data extraction from the EMA registry is indeed complicated due to the data structure in multipage documents. This structure also makes it difficult to update the data and add more recent study results.

The second publication [24] focused on other clinical characteristics that may influence the authorization marketing decisions made by the EMA and their future implications for reimbursement of drugs in EU countries. For instance, drugs for metabolic diseases were more likely to be approved under exceptional circumstances but less likely to be conditionally approved compared with other orphan drugs. The authors explained this by the inability to collect comprehensive efficacy and safety data. On the other hand, oncological orphan drugs were more often approved under conditional marketing authorization to quickly provide patients with therapy even if clinical data were undeveloped or incomplete. In addition, the same study demonstrated that the registration status (conditional approval) in some European countries reduced the probability of public funding by up to 80% [24]. Our study was similar in that we investigated what might affect the EMA authorization decision for orphan drugs. One of our analyses also showed that there were possible differences between the three groups of drugs (oncological, metabolic, and other diseases). Malinowski et al. [24] indicated the need to investigate new aspects that may affect the registration status granted by the EMA. Considering the rapidly changing conditions for the registration and reimbursement of orphan drugs, we can conclude that our study addresses these needs. First, using more recent data, we assessed which clinical aspects differed between disease groups. Second, we were the first to examine the correlations between the characteristics of clinical trials and the type of the marketing authorization decision.

The third publication addressed the role of clinical robustness in the orphan drug evaluation process in Spain [26, 27]. There was a potential link between clinical and regulatory variables and the reimbursement status of orphan drugs. In May 2013, a major change was introduced to the pricing and reimbursement process, the so called therapeutic positioning report (TPR). In brief, the TPR provides a thorough review and summary of the relative efficacy and safety data available for a new orphan product that has been authorized by the EMA. Orphan drugs with a positive conclusion in the TPR would be more likely to be reimbursed in Spain ($p < 0.0001$). This not only shows that the assigned registration status is important and has implications for reimbursement decisions, but also that the registration authorities make decisions using the clinical data of orphan drugs. Based on our findings, we agree that the available clinical data (with some limitations) can be used to make comparisons and draw conclusions that can inform further decisions on reimbursement policy.

An innovation of our research is the use of a data source. So et al. [28] reported that data sharing from clinical trials could be a key to the development and approval of medicines for rare diseases. Other investigators claimed that it can increase investment in the treatment of rare diseases [29]. However, the advantage of our study was at the same time a limitation. The indicated data source had some flaws such as a variation in data structure depending on the study drug and the occasional inconsistency of data provided by pharmaceutical holders. Our results were incomplete due to some missing information on drug studies. This was due to the selectivity of the data presented by the holder and the lack of precision in describing specific studies.

The pharmaceutical industry is reluctant to share data transparently for various reasons. First, there are concerns about the use of data by competitors to advance their development programs. Second, prior public disclosure of data may lead to some patent rights issues. Finally, the confidentiality of personal patient data is threatened. As the populations of patients with rare diseases are small, identification of patients is much easier [28, 30].

Another limitation is data format standardization, which makes data extraction difficult. This becomes a problem when pharmaceutical companies use different data collection methodologies and start sharing their data. For some investigators, it becomes necessary to compare different types of data for the same drug or disease. Studies indicated that harmonization, if not standardization, of data formats is critical [28]. Obviously, however, it may not be feasible to conduct standard and complete clinical trials for orphan medicines because of a small sample size or the fact that the medical conditions in question are often heterogeneous and poorly understood [31].

We agree that specific tools need to be developed that reflect the priorities and perspective of stakeholders, who have to consider the factors relevant to orphan drug availability and financing at the national level. Some investigators proposed that concerns about data quality may be resolved by the Multi-Criteria Decision Analysis (MCDA) [32]. The MCDA is a set of methods and tools to support complex decision-making that overcomes the limitations inherent to the treatment of rare diseases and improves the quality, ethics, and transparency of decisions regarding prioritization, treatment inclusion, and funding

[32]. This is in line with another study indicating that the MCDA methodology can be used as an add-on to the decision-making process for determining the clinical added value of orphan drugs [33]. However, in our opinion, before implementing such a tool, it would be necessary to update the (orphan) drug registry with clinical data and improve data extraction.

Last but not least, we agree that marketing authorization for orphan drugs is a complex process. Throughout the years 2000–2016, the average time from designation as an orphan medicinal product to authorization in the EU was four years and seven months. This was later reduced to just over 15 months for orphan drugs that were approved in 2014 [34]. We believe that the results of this and similar studies, together with the increasing availability of electronic data and transparency of clinical data, can help further reduce this time, resulting in a higher accessibility to orphan drugs, which is crucial for the effective treatment of patients.

We comprehensively assessed those aspects of clinical trials that are important for studies on marketing authorization of orphan drugs. Our results showed that the status granted by the EMA may differ depending on the robustness of clinical trials for orphan drugs and disease groups. In our opinion, our study opens up the possibility for other investigators to explore also other categories of clinical trials for orphan drugs. Assessment of the new aspect of orphan drugs, namely, the clinical robustness, fills the information gap on the factors that are significant for evaluating the marketing authorization of orphan drugs.

5. Conclusions

Factors associated with the reduced chances of the drug being under exceptional circumstances included a higher number of patients in the study, multicenter design, and a safety endpoint assessed within two months, while factors associated with higher chances included a treatment duration between two and 12 months. In the case of conditional approval or exceptional circumstances, an additional study with a safety endpoint assessed within two months decreased the odds, while a study with a treatment duration between three and 12 months increased the odds. An additional dose-response study and a study with a treatment duration longer than one year increased the odds for a drug to be under additional monitoring, while an additional RCT reduced these odds. An additional study with a duration longer than two years reduced the odds of receiving accelerated assessment.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials All materials were obtained through publicly available sources

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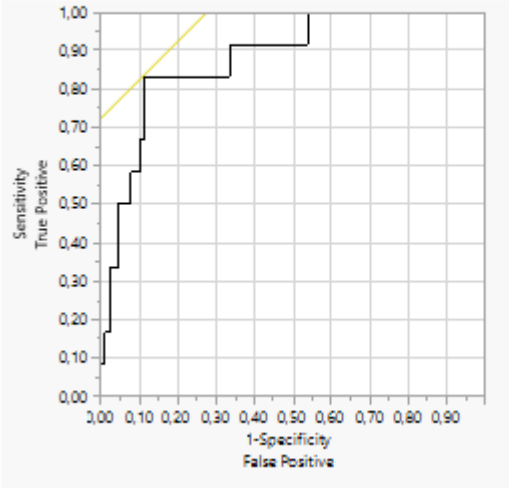
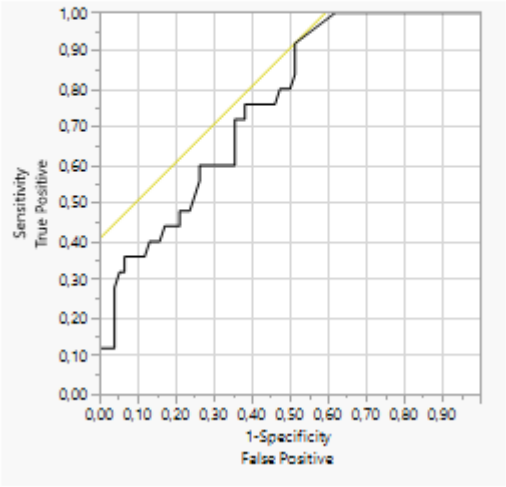
Figures

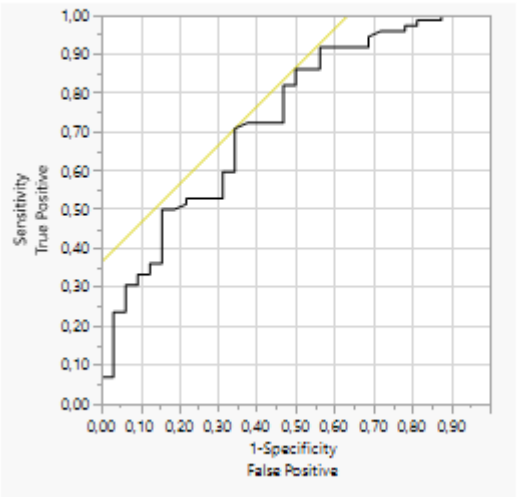
Graph a. Exceptional circumstances



Graph b. Exceptional circumstances or conditional approval



Graph c. Additional monitoring



Graph d. Accelerated assessment

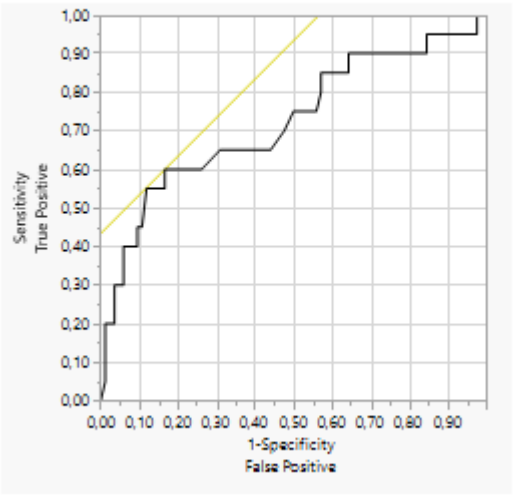
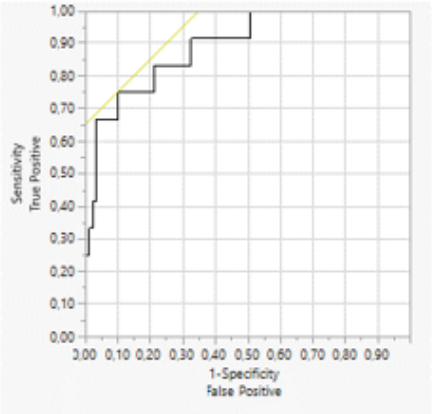


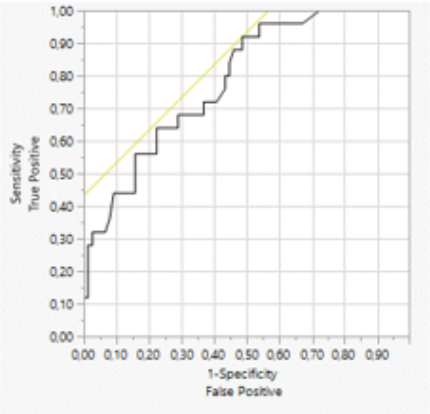
Figure 1

Receiver Operating Characteristic for EMA's statuses

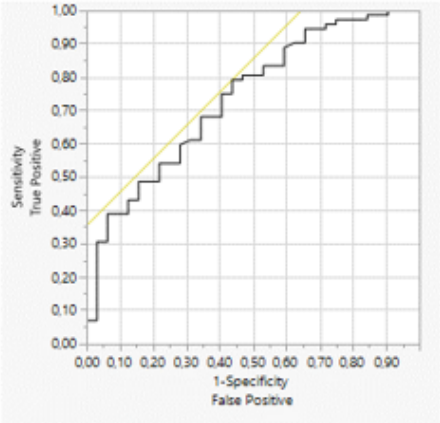
Graph a. Exceptional circumstances



Graph b. Exceptional circumstances or conditional approval



Graph c. Additional monitoring



Graph d. Accelerated assessment

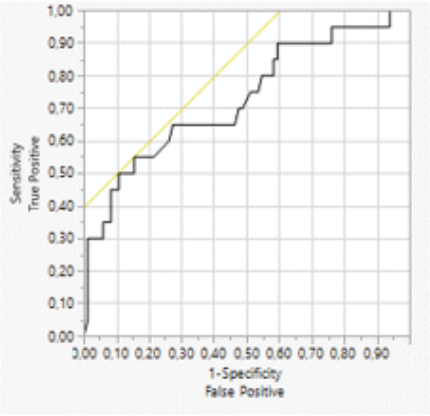


Figure 2

Receiver Operating Characteristic adjusted the type of the disease for EMA's statuses