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POINT OF VIEW

Orphan drugs, orphan diseases. The first decade of orphan drug legislation in the EU

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Abstract
Purpose To assess the methodological quality of Orphan Medicinal Product (OMP) dossiers and discuss possible reasons for the small number of products licensed.
Methods Information about orphan drug designation, approval, refusal or withdrawal was obtained from the website of the European Medicines Agency and from the European Public Assessment Reports.
Results From 2000 up to 2010, 80.9 % of the 845 candidate orphan drug designations received a positive opinion from the European Medicines Agency (EMA)'s Committee on Orphan Medicinal Products. Of the 108 OMP marketing authorizations applied for, 63 were granted. Randomised clinical trials were done for 38 OMPs and placebo was used as comparator for nearly half the licensed drugs. One third of the OMPs were tested in trials involving fewer than 100 patients and more than half in trials with 100–200 cases. The clinical trials lasted less than one year for 42.9 % of the approved OMPs.
Conclusion Although there may have been some small improvements over time in the methods for developing OMPs, in our opinion, the number of patients studied, the use of placebo as control, the type of outcome measure and the follow-up have often been inadequate. The present system should be changed to find better ways of fostering the development of effective and sustainable treatments for patients with orphan diseases. Public funds supporting independent clinical research on OMPs could bridge the gap between designation and approval. More stringent criteria to assess OMPs' efficacy and cost/effectiveness would improve the clinical value and the affordability of products allowed onto the market.

Keywords Orphan drug · Rare disease · Pharmacological research · Drug regulation · Development · Preclinical studies · Clinical trials · Clinical efficacy · Placebo · Outcome measures

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Introduction

There are about 7,000 rare diseases [1] and they affect 30–40 million people in the European Union (EU). The EU legislation encourages pharmaceutical companies to develop drugs for rare diseases, so-called "orphan drugs" [2]. The Committee for Orphan Medicinal Products (COMP) is responsible for reviewing applications from persons or companies seeking 'orphan medicinal product designation' for products they intend to develop for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect not more than 5 in 10,000 persons in the EU. The COMP recognizes orphan drug status mainly on the basis of epidemiological data (prevalence of the disease ≤ 5/10,000), and potential benefit [2]. For officially designated Orphan Medicinal Products (OMP) the centralized procedure is compulsory when an EU-wide marketing authorization is sought. The Committee for Medicinal Products for Human Use (CHMP) is responsible for the initial assessment of the dossier and for deciding whether the medicines meet the necessary quality, safety and efficacy requirements [3].

Orphan status implies incentives for pharmaceutical companies, including 10 years of market exclusivity, protocol

assistance, fee reductions for the European Medicines Agency (EMA) centralized procedures, and specific grants for OMP trials. However, only a small number of OMPs have been developed, and even fewer are the diseases they target, with sometimes scantily documented efficacy and poor cost-effectiveness.

How many orphan drugs have been approved?—And how?

Since 2000, when the OMP legislation [2] came into force, up to 2010, 80.9 % of the 845 candidate orphan drug designations [4] have received a positive opinion on their designation by the EMA's COMP (Table 1). Of the 108 OMP marketing authorizations applied for, 63 were granted, after a mean of 20.5 months from the designation date to the marketing authorization date (range 2–82 months). In the end, of the 684 designated orphan conditions, 73 indications were licensed [5]. Data from two previous reports [6, 7] show that there were no major changes in 2005–2007 compared to 2000–2004, so the two periods can be taken as a whole. Compared to 2000–2007 [7], in 2008–2010, the rate of positive opinions on orphan designation increased, while negative opinions and withdrawals dropped steeply (Table 1). These figures might reflect a better quality of applications for orphan designation in the last few years.

Looking at the marketing authorizations, the proportions of withdrawals and rejections increased, and there were fewer approvals under exceptional circumstances and conditional approvals (Table 1). These figures possibly reflect greater severity in the assessment of OMPs or less complete applications than in the past, and the general attitude of the EMA: 22.1 % of the applications for all drugs, orphan and non-orphan, are withdrawn or rejected, in comparison to 50 % of OMPs; 3.7 % of the overall authorizations are under exceptional circumstances or conditional, in comparison to 21.1 % for OMPs.

To what extent is OMP toxicity assessed?

Preclinical data in the dossiers were fairly satisfactory (Table 2A). Table 3 (see web extra) reports details on preclinical development of authorized OMPs in 2000–2010. Contrary to the requirements established by the EMA itself [8], toxicity studies were not done in two animal species for 11 of the 63 licensed OMPs, including only one from the period 2008–2010. The duration of toxicity studies was also not in line with the EMA requirements [8] for 34 OMPs, including ten from 2008 to 2010. Lack of genotoxicity, carcinogenicity or reproduction toxicity studies is acceptable, or they are not even required [9], for recombinant anticancer agents, or drugs already on the market for more

Table 1 Designations and marketing applications and approvals of orphan medicinal products (OMPs) in the EU and USA

	OMPs 2000–2010	OMPs 2000–2007	OMPs 2008–2010	OMPs and non-orphan drugs
Candidate designations	845	534	311	
	76.8/yr	66.8/yr	103.7/yr	
Positive opinions on "orphan designation"	684	397	287	
	80.9 %	74.3 %	92.3 %	
	62.2/yr	49.6/yr	95.7/yr	
Negative opinions on "orphan designation"	14	11	3	
	1.7 %	2.1 %	0.9 %	
	1.3/yr	1.4/yr	1/yr	
Withdrawn "orphan designations"	147	126	21	
	17.4 %	23.6 %	6.8 %	
	13.4/yr	15.8/yr	7/yr	
Approved indications (products)	73 (63)	49 (44)	24 (19)	
% of designations	8.8 %	9.5 %	7.8 %	
MA granted	63/108	44/70	19/38	297/443
% of MAA	58.3 %	62.9 %	50.0 %	67.0 %
Withdrawals + rejections	45/108	26/70	19/38	98/443
% of MAA	41.7 %	37.1 %	50.0 %	22.1 %
Approvals under exceptional circumstances + conditional approvals	22	18	4	11/297
% of MA	34.9 %	40.9 %	21.1 %	3.7 %

MA Marketing authorization, *MAA* Marketing authorization application

Table 2 Data in the application dossiers of the approved OMPs

Authorized OMPs	OMPs 2000–2010 63	OMPs 2000–2007 44	OMPs 2008–2010 19
A. Preclinical data			
Repeated-dose toxicity	52	34	18
	82.5 %	72.3 %	94.7 %
Genotoxicity	48	34	14
	76.2 %	72.3 %	73.7 %
Carcinogenicity	21	14	7
	33.3 %	31.8 %	36.8 %
Reproductive toxicity	50	35	15
	79.4 %	79.5 %	78.9 %
B. Clinical data			
Dose-finding	38	23	15
	60.3 %	52.3 %	79.8 %
Randomised controlled trials	38	25	13
	60.3 %	56.8 %	68.4 %
Active control	7	3[a]	4[b]
	11.1 %	6.8 %	21.1 %
Placebo	31	22	9
	49.2 %	50.0 %	47.4 %
Placebo as a justified control	11	9	2
	17.5 %	20.5 %	10.5 %
Phase II	11	10	1
	17.5 %	22.7 %	5.3 %
C. Study population			
< 100	21	16	5
	33.3 %	36.4 %	26.3 %
100–200	15	10	5
	23.8 %	34.1 %	26.3 %
200–500	19	13	6
	30.2 %	29.5 %	31.6 %
500–1,000	5	3	2
	7.9 %	6.8 %	10.5 %)
> 1,000	3	2	1[c]
	4.8 %	4.5 %	5.3 %

[a] Two open-label trials

[b] Two open-label and one non-inferiority trial

[c] Based on a literature search

common indications (e.g. busulfan, hydrocarbamide, and mitotane). This is not the case for 5-aminolevulinic acid hydrochloride, aztreonam lysine, dexrazoxane, pegvisomant, and porfimer (the last was withdrawn in May 2012).

Are the OMP clinical profiles evidence-based?

Table 2B summarises the main features of the clinical trials in the OMP dossiers (for details, see Table 4, web extra). Nearly two-thirds of the dossiers included dose-finding studies and the proportion rose in 2008–2010. Similarly, randomized clinical trials were done for 38 OMPs, with a higher proportion in the later period. Placebo was used as a comparator for nearly half the drugs, with no substantial difference in the two periods.

The inappropriate use of placebo in trials with OMPs authorized in 2000–2007 has been discussed [7]. Briefly, in our opinion, placebo was used inappropriately in the case of anagrelide (in place of hydroxyurea), arsenic trioxide (retinoic acid being an adequate control), bosentan, sidenafil and sitaxentan (epoprostenol), cladribine and imatinib (IFN-alpha), ibuprofen (indomethacin), lenalidomide (bortezomib), miglustat (imiglucerase), pegvisomant (somatostatin), rufinamide (benzodiazepines or newer anti-epileptic drugs such as lamotrigine, topiramate or felbamate alone or as add-on to valproate), zinc acetate (tetrathiomolybdate, penicillamine, or trientine), and ziconotide (morphine).

In trials with the molecules licensed in 2008–2010, the use of placebo was questionable in the case of amifampridine (3,4-diaminopyridine), [10] ambrisentan (epoprostenol, bosentan or sitaxentan), [11] romiplostim and eltrombopag (rituximab, mycophenolate mofetil, cyclophosphamide, azathioprine, danazol or dapsone), [12] rilonacept and canakinumab (anakinra) [13].

We are aware that several of the active comparators suggested are not licensed for the indication in question. However, these drugs are commonly employed in clinical practice and should not be ignored.

Ofatumumab was licensed in 2010 only on the basis of an uncontrolled Phase II trial. This follows ten other drugs authorized in 2000–2007 [7]: aglucosidase alpha, anagrelide, dexazoxane, nitisinone and zinc acetate were authorized on the basis of open-label uncontrolled trials; carglumic acid was approved on the basis of a retrospective study; mitotane, betaine and the pediatric indication of hydroxylcarbamide were only supported by a literature analysis. Velaglucerase alfa was approved in 2010 on the basis of its non-inferiority to imiglucerase in Gaucher's disease.

The adoption of a non-inferiority approach to test OMP efficacy is surprising. By definition, medicines aimed at unmet needs should be tested for their superiority over available treatment, if any, or placebo.

One third of the OMPs (21) were tested in trials involving fewer than 100 patients, more than half (36) in trials with 100–200, only three in trials with more than 1,000 (Table 2C; for details, see Table 4, see web extra). As previously discussed for neralabine, miglustat, clofarabine, algasidase alpha and beta [7], for several OMPs approved in 2008–2010, the small number of patients in the trials is not justifiable (Table 4, see web extra). This was the case with eltrombopag and romiplostim, icatibant, and

Table 3 Preclinical development of Orphan Medicinal Products (OMP) approved in EU

Drug	Repeated dose toxicology	Exposure duration	Genotoxicity	Carcinogenicity	Reproduction toxicity
5-aminolevulinic acid hydrochloride	Mice; rats; dogs	1–7 wks	YES (negative in absence of light and positive in presence of light)	Not indicated	Not indicated
Agalsidase alpha	Rabbits; rats;monkeys	2–26 wks	N.R.	Not indicated	YES (not conclusive)
Agalsidase beta	Rats	27 wks	N.R.	Not indicated	Not indicated
Aglucosidase alfa	Rats; mice; Cynomolgous monkey	4–26 wks	N.R.	N.R.	YES (positive)
Ambrisentan	Dogs; Mice; Rats	12–36 wks	YES (negative)	YES (negative)	YES (positive)
Amifampridine	Dogs; rats	4 wks	YES (negative)	N.R.	NO (the applicant has committed to conduct Segment II and prenatal and postnatal studies, as a follow-up measure to determine the po tential for teratogenic effects)
Anagrelide	Rats; monkeys; dogs	12–52 wks	YES (negative)	N.R.	YES (negative)
Arsenic trioxide	Mice; rats; dogs; monkeys	Not indicated	YES (positive)	N.R.	N.R.
Azacitidine	Dogs; mice; rats; Rhesus monkeys	5–14 days	YES (positive)	YES (positive)	YES (positive)
Aztreonam lysine	Dogs; rats	15 min–90 days	YES (negative)	YES (negative)	Not indicated
Betaine hydrochloride	Rats	2–12 wks	YES (negative)	N.R. (natural constitute of mammalian cells)	N.R.
Bosentan	Rats; dogs; marmosets	1–4 wks	YES (negative)	YES (negative)	YES (+ in rats, − in rabbits)
Busulfan	Dogs	4 days	Not indicated	N.R.	YES (positive)
Caffeine citrate	Rats (data from the literature)	7-21 days	YES (negative; data from the literature)	N.R.	YES (positive; data from the literature)
Canakinumab	Marmoset monkeys; mice	4–26 wks	N.R.	N.R.	YES (negative)
Carglumic acid	Rats	2–18 wks	YES (positive)	YES (negative)	YES (not conclusive)
Celecoxib	Rats; dogs	24–52 wks	YES (negative)	YES (not conclusive)	YES (positive)
Cladribine	Mice	4 wks	YES (positive)	N.R.	YES (positive)
Clofarabine	Mice; rats; dogs	Not indicated	YES (positive)	Not indicated	YES (positive)
Dasatinib	Rat; Cynomolgus monkeys	4–36 wks	YES (positive)	Not indicated	YES (negative)
Deferasirox	Rats; marmosets	2–39 wks	YES (− in vitro; +/− in vivo)	YES (negative)	YES (negative)
Dexrazoxane	Rats; rabbits; mice; dogs; swines	1–22 wks	YES (positive)	Not indicated	Not indicated
Eculizumab	Mice	4–26 wks	N.R.	Not indicated	YES (negative)
Eltrombopag	Dogs; mouse; rats	1–52 wks	YES (not conclusive)	YES (positive)	YES (positive)
Everolimus	Minipigs; mice; rats; monkeys	4–52 wks	YES (negative)	N.R.	YES (positive)
Galsulfase	Cynomolgus monkeys	1–27 wks	N.R.	N.R.	A full package of reproductive toxicity studies has not been conducted. Post- authrization commitments have been agreed for further reproductive toxicity studies with toxicokinetics and clinical monitoring of pregnant women
Histamine dihydrochloride	Dogs; rabbits; rats	24–48 wks	YES (negative)	N.R.	YES (positive)
Hydroxycarbamide	Rats; dogs; monkeys	1–12 wks	N.R.	Not indicated	YES (positive)
Ibuprofen	N.R.	N.R.	YES (negative)	YES (negative)	YES (negative)
Icatibant	Dogs; mice; rats	15–24 wks	YES (negative)	N.R.	YES (negative)
Idursulfase	Cynomolgus monkeys	26 wks	N.R.	N. R.	YES (negative)
Iloprost	Rats; dogs	24–52 wks	YES (negative)	YES (negative)	YES (positive)
Imatinib	Monkeys	39 wks	YES (+ in vitro and − in vivo)	ongoing	YES (positive)
Laronidase	Dogs; monkeys	8–26 wks	N.R.	Not indicated	YES (not conclusive)
Lenalidomide	Rats; monkeys	26–52 wks	YES (negative)	N.R.	YES (positive) additional investigations requested
Mecasermin	Rats; dogs	4–26 wks	YES (negative)	YES (positive)	YES (negative)
Mifamurtide	Dogs; mice; rabbits; rats	6–24 wks	YES (negative)	N.A. (to be administered in conjunction with combination chemotherapy known to cause second malignancy in a portion of pts.)	N.A. (to be administered in conjunction with combination chemotherapy reported to cause effects on fertility, as well as fetal death and/or congenital anomalies)
Miglustat	Rats; monkeys	4–52 wks	YES (negative)	YES (negative)	YES (positive)

Table 3 (continued)

Drug	Repeated dose toxicology	Exposure duration	Genotoxicity	Carcinogenicity	Reproduction toxicity
Mitotane	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated
Nelarabine	Mice; Cynomolgus monkeys	5–30 days	YES (positive)	Not indicated	YES (positive)
Nilotinib	Mice; rats; dogs; monkeys	26–39 wks	YES (negative)	Not indicated	YES (negative)
Nitisinone	Mouse; rats; rabbits; dogs; Rhesus monkeys	12–48 wks	YES (+ in vitro; − in vivo)	Not indicated	YES (positive)
Ofatumumab	Cynomologus monkey	4 days–28 wks	N.R.	Not indicated	Not indicated
Pegvisomant	Rats; monkeys	24 wks	YES (negative)	Not indicated	YES (negative)
Plerixafor	Dogs; rats	1–4 wks	YES (negative)	N.R.	YES (not conclusive)
Porfimer[a]	Rats; dogs	13 wks	YES (positive)	Not indicated	YES (negative)
Rilonacept	Mice; monkeys	6–26 wks	N.R.	N.R.	YES (negative)
Romiplostim	Marmoset monkeys; mice	4–26 wks	N.R.	N.R.	YES (negative)
Rufinamide	Mouse; rats; Beagle dogs; Cynomolgus monkeys; wild-caught baboons	4–52 wks	YES (negative)	YES (positive)	YES (negative)
Sapropterin dihydrochloride	Marmoset monkeys; mice; Guinea pig; rabbit; rats	13–104 wks	YES (negative; the in vitro positive results are possibly related to the auto-oxydation of Sapropterin, generating reactive oxygen species such as hydrogen peroxide)	YES (negative; higher incidence of benign phaeochromocytomas of adrenal medulla in the rat)	YES (negative)
Sildenafil citrate	Mice; rats; Beagle dogs	12–48 wks	YES (negative)	YES (negative)	YES (negative; but lack of data)
Sitaxentan sodium	Mice; rats; dogs	3 days–39 wks	YES (negative)	YES (positive)	YES (negative)
Sodium oxybate	Rats; dogs	12–48 wks	YES (negative)	YES (negative)	YES (negative)
Sorafenib tosylate	Mice; rat; Beagle dogs	12–48 wks	YES (+ in vitro; +/− in vivo)	Not indicated	YES (positive)
Stiripentol	Mouse; rats; Cynomolgus monkeys	4-26 wks	YES (negative)	YES (positive)	YES (negative)
Sunitinib malate	Rats; monkeys	4–12 wks	YES (negative)	Not indicated	YES (positive)
Temsirolimus	Mice; rats; monkeys	12–36 wks	YES (negative)	N.R. (too short life expectancy of pts.)	YES (positive)
Thalidomide	Dogs; mice; rats	2–52 wks	YES (negative)	YES (negative)	YES (positive)
Thiotepa	Dogs; mouse; rats	5–14 days	YES (positive)	YES (positive)	YES (positive)
Trabectidin	Mice; rats; dogs; Cynomolgus monkeys	1–3 wks	YES (positive)	Not indicated	YES (data not shown)
Velaglucerase alfa	Rabbits; rats; Rhesus monkeys	12–24 wks	N.R.	N.R.	YES (negative except for a slightly reduction of fertility and fecundity in male rats at the highest dose tested [17 mg/kg, twice weekly])
Ziconotide acetate	Rats; monkeys; dogs	2–24 wks	YES (negative)	YES (inconclusive)	Not teratogenic; embryolethality observed
Zinc acetate	Rats	53 wks	YES (not conclusive)	YES (not conclusive)	YES (negative)

N.R. Not Requested

[a] WITHDRAWN on the 7th of May 2012

sapropterin, which were investigated in about 150 patients out of at least 50,000 potential European cases of chronic immune thrombocytopenic purpura, hereditary angioedema, and hyperphenylalaninemia, and for velaglucerase tested in 35 of the 15,000 potential European cases of type 1 Gaucher disease.

As stated for the OMPs licensed in 2000–2007 [7], the primary end-points were surrogate for drugs authorized in 2008–2010 too. Biochemical parameters (eltrombopag, romiplostim, sapropterin, velaglucerase), scores (amifampridine, icatibant, rilonacept), improvement in walking (ambrisentan), and tumour responses or progression-free survival (all but two anticancer drugs) were adopted, whose clinical importance is questionable.

The clinical trials supporting the marketing authorization applications lasted less than 1 year for 27 out of 63 approved OMPs (42.9 %), 1–2 years for 16 products (25.4 %), and more than 2 years for only ten drugs (15.9 %); for 11 OMPs, the information was not available. Therefore, several OMPs were studied for only short periods in relation to the natural history of the target disease. This holds true not only for algasidase-alpha and beta, pegvisomant, anagrelide and sodium oxybate, and drugs active in pulmonary arterial hypertension or epilepsy, all authorized in 2000–2007 [7], but also for some OMPs licensed between 2008 and 2010, including rilonacept and canakinumab in cryopyrin-associated periodic syndrome, histamine dihydrochloride

for maintainance therapy in acute myeloid leukemia, romiplostim and eltrombopag in chronic immune thrombocytopenic purpura, and velaglucerase alpha in type 1 Gaucher disease (Table 4, see web extra).

Are OMPs only for orphan indications?

The 63 OMPs approved in EU have 73 indications, covering 46 diseases. This is because some have multiple indications, but mainly because many were developed for the same disease, e.g. five for pulmonary hypertension, three for chronic myeloid leukemia, and two for Gaucher's disease. By law [2], these "duplicates" should not be allowed onto the market unless proved "not similar to" and more effective or safer than OMPs for the same indications.

In other cases, pharmaceutical companies purposely seek a licence for a niche indication, e.g. an expressly identified subgroup of patients. As was pointed out in the EMA European Public Assessment Reports [5], once the product is authorized as an OMP, they then try to broaden its use to a larger setting. This applies, for instance, to some anticancer drugs, which make up a significant proportion of the approved OMPs: 22 anticancer OMPs (13 for hematological cancers) have been authorized overall (34.9 %). These include histamine hydrochloride as maintenance therapy for adult patients with acute myeloid leukemia in first remission concomitantly treated with interleukin-2; sorafenib and sunitinib in advanced or metastatic renal cell carcinoma; trabectidin in advanced soft tissue sarcoma and relapsed platinum-sensitive ovarian cancer. Non-antineoplastic OMPs with questionable selective indications include, for instance, pegvisomant intended for resistant acromegaly and aztreonam lysine for chronic pulmonary infections due to *Pseudomonas aeruginosa*, which was selectively studied in patients with cystic fibrosis. Everolimus took the opposite route: first approved for the prophylaxis of organ rejection, it is now also intended for an orphan indication: advanced renal cell carcinoma progressing on after VEGF-targeted therapy.

Another questionable approach is to use slightly modified versions of old products that are already licensed for common diseases or are used off-label to treat a rare disease. The former is the case, for instance, with the anti-inflammatory drug ibuprofen, subsequently proposed as treatment for patent ductus arteriosus, or hydroxycarbamide (the antineoplastic hydroxyurea), and more recently also indicated for pain relief in the sickle cell syndrome [5]. The latter is the case with amifampridine in the treatment of Lambert Eaton myasthenic syndrome [14] and caffeine citrate for primary apnea of premature newborns.

Final remarks

Orphan drug legislation in the United States and Europe is intended to encourage drug companies to develop drugs whose development costs would not otherwise be economic due to the small number of target patients. In the 25 years since the introduction of the US legislation, the FDA has approved 250 drugs for roughly 200 diseases, corresponding to 363 products (15.8 %) of the 2,299 designated [15]. In the decade following adoption of the EU regulation, the EMA approved 63 OMPs for 46 diseases. The higher absolute figures and rate of approvals in US may result from the longer-lasting experience, since the Orphan Drug Act was adopted in 1983. Despite the improved trend in EU approvals, which has paralleled the US authorizations [16, 17], nearly all the currently estimated 7,000 rare diseases, with approximately 250 new diseases described annually, [18] still await treatments. Only a few of these orphans have been tackled, and then not necessarily cured or even effectively treated.

It is a cause for concern that the efficacy and safety profiles of orphan drugs are so lacking. There may have been some small improvements over time in the methods for developing OMPs: toxicology studies in rodents and non-rodents, dose-finding studies and randomized clinical trials have been done for more drugs. However, the number of patients studied, the use of placebo as control, the type of outcome measure and the length of follow-up have often been inadequate. So was the adoption of non-inferiority designs, since the market exclusivity rule [2] implies that no similar competitive product is to be placed on the market unless it proves clinically superior to licensed OMPs. It is conceivable that the information from short-term, small-number trials addressing surrogate endpoints cannot prevent regulatory bodies from approving treatments for orphan conditions. However, this is only acceptable as an interim attitude. The regulatory authorities should take the opportunities of the conditional approval granted to OMPs to foster independent research on the open methodological issues as specific post-marketing obligations.

Many drug companies seem merely to aim their efforts at extending the indications for drugs that are already available rather than developing new treatments. This reflects a marketing strategy that is not necessarily in the best interests of patients or National Health Services (NHS), but is, of course, favorable to the drug companies: the conditions of the marketing authorization

Table 4 Clinical development of Orphan Medicinal Product (OMP) approved in EU

Active principle	Trade name	Indication	Prevalence[d]	Protocol assistance	Dose finding	Type of trial
5-aminolevulinic acid hydrochloride	Gliolan	Visualisation of malignant tissue during surgery for malignant glioma [World Health Organisation (WHO) grade III and IV].	1.0	YES	YES	Open label randomized controlled trial (RCT)
Agalsidase alpha	Replagal	Fabry Disease: long-term replace therapy	0.027	YES	YES	RCT
Agalsidase beta	Fabrazyme	Fabry Disease: long-term replace therapy	0.027	YES	YES	RCT
Aglucosidase alfa	Myozyme	Pompe disease (acid α-glucosidase deficiency): long-term replace therapy	0.137	NO	NO	1 = Phase II/III uncontrolled study; 2 = Phase II uncontrolleed study
Ambrisentan	Volibris	Pulmonary arterial hypertension (PAH) classified as WHO functional class II and III	0.02	YES	YES	RCT
Amifampridine	Firdapse (Zenas)	Symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.	0.1	NO	NO	1 = Prospective, double blind, cross-over study; 2 = Prospective, double blind study
Anagrelide	Xagrid	Reduction of elevated platelet counts in at risk essential thrombocythaemia (ET)	3.0	YES	YES	Open label; non-randomized; uncontrolled
Arsenic Trioxide	Trisenox	Relapsed/refractory acute promyelocytic leukaemia (APL)	0.8	NO	NO	Uncontrolled Phase II
Azacitidine	Vidaza	For the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with: 1. intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS); 2. chronic myelomonocytic leukaemia (CMML) with 10–29 % marrow blasts without myeloproliferative disorde; 3. acute myeloid leukaemia (AML) with 20–30 % blasts and multi-lineage dysplasia, according to WHO classification.	2.3	NO	YES	RCT, open-label
Aztreonam lysine	Cayston	Suppresive therapy of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged ≥18 years.	1.3	YES	YES	1 = RCT (open label); 2 = RCT
Betaine hydrochloride	Cystadane	Homocystinuria	0.165	NO	NO	Case reports[a]
Bosentan	Tracleer	Pulmonary arterial hypertension (PAH) classified as WHO functional class II–III	0.95	YES	NO	RCT
Busulfan	Busilvex	Conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult and paediatric patients	0.7	YES	NO	Uncontrolled Phase II
Caffeine citrate	Nymusa (Peyona)	Primary apnoea of premature newborns	0.5–1.2	NO	NO	RCT
Canakinumab	Ilaris	Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 4 years and older with body weight above 15 kg	0.05	YES	YES	3-part study: Parts I and III uncontrolled; Part II controlled
Carglumic acid	Carbaglu	Treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency.	0.001	NO	NO	Retrospective study
Celecoxib	Onsenal	Reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance	1.0	NO	NO	RCT
Cladribine	Litak	Nairy Cell Leukemia	3.65	NO	NO	Uncontrolled Phase II (+ literature analysis)
Clofarabine	Evoltra	Acute lymphoblastic leukaemia (ALL) in paediatric patients	0.4	NO	YES	Phase II, non-randomized, open-label, single-arm
Dasatinib	Sprycel	1. Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML);	CML = 0.9 ALL = 0.71	YES	YES	Phase II open-label

Table 4 (continued)

Active principle	Trade name	Indication	Prevalence[d]	Protocol assistance	Dose finding	Type of trial
		2. Ph + acute lymphoblastic leukaemia (ALL); 3. lymphoid blast CML				
Deferasirox	Exjade	Chronic iron overload due to: 1. frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) in patients≥6 years with beta thalassaemia major; 2. blood transfusions when deferoxamine is contraindicated or inadequate	2.7	YES	YES	1 = Phase III RCT, active-controlled, open-label; 2 = Phase II open-label trial
Dexrazoxane	Savene	Anthracycline extravasation	0.03	NO	NO	Open-label, single-arm studies, using an external control from the literature
Eculizumab	Soliris	Paroxymal nocturnal haemoglobinuria (PNH) in patients with history of transfusions	0.001	YES	NO	1 = Phase III RCT; 2 = Phase III open-label study
Eltrombopag	Revolade	Adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments	1.0–4.0	YES	YES	RCT
Everolimus	Afinitor	Advanced renal cell carcinoma progressed on or after treatment with VEGF-targeted therapy.	3.48	YES	YES	RCT
Galsulfase	Naglazyme	Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysac-charidosis VI (MPS VI; N-acetylgalactosamine 4-sulfatase deficiency; Maroteaux-Lamy syndrome)	0.024	NO	YES	1 = Phase III RCT; 2 = Phase II open-label study
Histamine dihydrochloride	Ceplene	Maintainance therapy for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2 (IL-2).	0.7	NO	YES	Phase III, open-label, uncontrolled
Hydroxycarbamide	Siklos	Prevention of recurrent painful vaso-occlusive crises, including acute chest syndrome in paediatric and adult patients suffering from symptomatic sickle cell syndrome	0.5	YES	NO	1 = paediatric population literature analysis 2 = adults RCT
Ibuprofen	Pedea	Haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age.	2.13	YES	YES	RCT; controlled (+ metanalysis)
Icatibant	Firazyr	Symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency).	3.0	YES	YES	RCT
Idursulfase	Elaprase	Long-term treatment of Hunter syndrome (Mucopolysaccharidosis II, MPS II).	0.02	YES	YES	1 = Phase II/III RCT 2 = Phase I/II open-label extension study
Iloprost	Ventavis	Primary pulmonary hypertension, classified as NYHA functional class III	2.2	YES	NO	RCT
Imatinib	Glivec	1. Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myelogenous leukaemia (CML); 2. Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph + ALL); 3. myelodysplastic/myelo-proliferative diseases (MDS/MPD); 4. advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL); 5. Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST); 6. unresectable dermatofibro-sarcoma protuberans (DFSP)	CML = 0.9 ALL = 0.65 MDS/MPD = 2.3 HES =0.15 GIST = 0.3 DFSP = 0.1	YES	YES	Uncontrolled Phase II

Table 4 (continued)

Active principle	Trade name	Indication	Prevalence[d]	Protocol assistance	Dose finding	Type of trial
Laronidase	Aldurazyme	Mucopolysaccharidosis MPS-1: long-term replace therapy	0.025	YES	NO	RCT
Lenalidomide	Revlimid	Multiple myeloma	1.3	YES	YES	1/2 = RCT
Mecasermin	Increlex	Long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 deficiency (Primary IGFD).	2.0	NO	YES	1 = Phase III RCT 2 = Phase III open-label 3 = open-label study
Mifamurtide	Mepact	Indicated in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection.	0.5	YES	YES	RCT
Miglustat	Zavesca	1. Mild to moderate type 1 Gaucher disease; 2. Niemann-Pick type C disease	0.6	YES	NO	Uncontrolled Phase II
Mitotane	Lysodren	Advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma.	0.1	YES	NO	Literature analysis
Nelarabine	Atriance	1. T-cell acute lymphoblastic leukaemia (T-ALL) 2. T-cell lymphoblastic lymphoma (T-LBL)	1.1	YES	YES	Two Phase II open-label, non-comparative studies
Nilotinib	Tasigna	1. Newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) 2. Chronic phase and accelerated phase Philadelphia chromosome positive CML	0.24	YES	YES	Uncontrolled, unblinded, non-randomised Phase IA/II study
Nitisinone	Orfadin	Hereditary tyrosinemia type 1 (HT-1)	0.1	NO	NO	Open-label, single-arm studies (based on the compassionate use)
Ofatumumab	Arzerra	Chronic lymphocytic leukaemia (CLL) refractory to fludarabine and alemtuzumab	3.5	NO	YES	Phase II, open-label, single arm
Pegvisomant	Somavert	Resistant acromegaly	0.6	YES	NO	RCT
Plerixafor	Mozobil	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	0.6	YES	YES	RCT
Porfimer sodium	Photobarr	Ablation of high-grade dysplasia (HGD) in patients with Barrett's Oesophagus (BO)	3.6	YES	NO	RCT
Rilonacept	Arcalyst (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.	0.5	NO	YES	RCT
Romiplostim	Nplate	Adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments	1.0	YES	YES	RCT
Rufinamide	Inovelon	Lennox Gastaut syndrome in patients≥4 years	0.1–0.2	N.A.	YES	RCT
Sapropterin dihydrochloride	Kuvan	Treatment of hyperphenylalaninaemia (HPA) in: 1. adult and paediatric patients≥4 years of age with phenylketonuria (PKU); 2. in adult and paediatric patients with tetrahydrobiopterin (BH4) deficiency	1.7	YES	YES	RCT
Sildenafil citrate	Revatio		1.0	NO	NO	RCT

Table 4 (continued)

Active principle	Trade name	Indication	Prevalence[d]	Protocol assistance	Dose finding	Type of trial
		Pulmonary arterial hypertension WHO functional class II–III (adult and paediatric patients aged 1 year to 17 years old)				
Sitaxentan sodium	Thelin	Pulmonary arterial hypertension (PAH) classified as WHO functional class III	2.0	NO	YES	RCT
Sodium oxybate	Xyrem	Narcolepsy with cataplexy in adult patients.	5.0	NO	NO	RCT
Sorafenib tosylate	Nexavar	1. Hepatocellular carcinoma; 2. Advanced renal cell carcinoma	1. = 0.1 2. = 3.0	YES	YES	RCT
Stiripemtol	Diacomit	Refractory generalized tonic-clonic seizures in severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) when seizures are not adequately controlled with clobazam and valproate.	0.4	NO	NO	RCT
Sunitinib malate	Sutent	1. Gastrointestinal stromal tumour (GIST); 2. Metastatic renal cell carcinoma (MRCC); 3. Pancreatic neuroendocrine tumours (pNET)	GIST = 0.3 MRCC = 3 pNET = 1.2	N.A.	YES	**GIST**: RCT; **MRCC**: single-arm, open-label
Temsirolimus	Torisel	First-line treatment of patients with advanced renal cell carcinoma	3.5	YES	YES	Phase II, randomised, blinded, dose-comparing, parallel-group
Thalidomide	Thalidomide Celgene	Untreated multiple myeloma, aged >/= 65 years or ineligible for high dose chemotherapy	1.2	YES	Literature analysis	RCT, open-label
Thiotepa	Tepadina	1. 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	0.5	NO	NO	Literature analysis
Trabectidin	Yondelis	1. Advanced soft tissue sarcoma; 2. Relapsed platinum-sensitive ovarian cancer	1. = 0.6 2. = N.A.	NO	YES	Randomised open-label study
Velaglucerase alfa	Vpriv	Type 1 Gaucher disease: long-term enzyme replacement therapy	0.3	NA	YES	non-inferiority RCT
Ziconotide acetate	Prialt	Severe, chronic pain in patients who require intrathecal (IT) analgesia.	1.55	NO	YES	RCT
Zinc acetate dihydrate	Wilzin	Wilson's disease	0.6	NO	YES	Open label; non-randomized; uncontrolled

Active principle	Control	End-point	N Patients studied	Duration	Designation date	Ma date	Notes	Δ months
5-aminolevulinic acid hydrochloride	WHITE LIGHT	Percentage of patients without definite residual contrast-enhancing tumour seen on early (within 72 hours after surgery) postoperative MRI; progression-free survival at the 6-month visit after surgery	350	21 mo	11/13/2002	9/7/2007		58
Agalsidase alpha	PLACEBO	Reduction of pain; Reduction of GB3 (NS); Reduction of cardiac mass; Improvement of renal function	41	18 wks; 24wks; 18wks; 18 mo	8/8/2000	04/05/2001[b]		9
Agalsidase beta	PLACEBO	Reduction of GL-3	56	20 wks	8/8/2000	04/05/2001[b]		9

Table 4 (continued)

Active principle	Control	End-point	N Patients studied	Duration	Designation date	Ma date	Notes	Δ months
Aglucosidase alfa	NONE	1 = Percentage of patients alive and free of invasive ventilator support (endotracheal tube) at 12 months of age, when compared to a comparable historical untreated cohort derived from the Natural History study; 2 = survival	1 = 18; 2 = 21	1 = 52 wks; 2 = 52 + 52 weeks	2/14/2001	3/29/2006	1 supportive study (extension)	61
Ambrisentan	PLACEBO	Change from baseline (defined as the mean 6MWD of the last two 6MWTs prior to randomisation) in 6 MWD evaluated after 12 weeks	394	N.A.	4/11/2005	4/21/2008	1. The reported number of randomised patients refers to two pivotal trial (no separate data are available); 2. 6MWD: 6-minute walk distance; 3. 6MWT: 6-minute walk test	36
Amifampridine	PLACEBO	1 = not clearly defined in the publication; 2 = QMG score	1 = 12; 2 = 26	N.A.	12/18/2002	23/12/2009[b]	1 = pivotal efficacy data based on published studies; 2 = QMG: Quantitative Myasthenia Gravis	39
Anagrelide	NONE	Platelet count<600×109/l or reduction>50 % from baseline and maintenance of the reduction for at least 4 w (= CR)	1446	4–5 yrs	12/29/2000	16/11/2004 [b]		47
Arsenic Trioxide	NONE	Complete response; overall survival	52	15 mo	10/18/2000	05/03/2002[b]		17
Azacitidine	Conventional Care Regimens	Overall Survival (time from randomisation to death from any cause)	358	44 mo	2/6/2002	12/17/2008		82
Aztreonam lysine	PLACEBO	1. Time to need for i.v. or inhaled anti-PA antibiotics other than trial drug with documented symptom(s) predictive of pulmonary exacerbation; 2. Change from day 0 (baseline) to Day 28 in clinical symptoms as assessed by the respiratory domain of the CFQ-R	1 = 211 2 = 164	1 = 18 mo 2 = 22 mo	6/21/2004	9/21/2009	1 = Anti-PA antibiotics: antibiotics against *Pseudomonas aeruginosa* infection; 2 = CFQ-R: Cystic Fibrosis Questionnaire—Revised	19
Betaine hydrochloride	NONE	Plasma homocysteine	140	N.A.	7/9/2001	2/15/2007		67
Bosentan	PLACEBO	Walk exercise	32	15 wks	2/14/2001	15/05/2002[b]		15
Busulfan	NONE	Same effect of i.v. as with oral busulfan	104	2.5 yrs	12/29/2000	7/9/2003		31
Caffeine citrate	PLACEBO	50 % or greater reduction in apnoea episodes form baseline and elimination of apnoea	85	N.A.	2/17/2003	7/2/2009	Pivotal efficacy data based on a published study	79
Canakinumab	PLACEBO (Part II)	Proportion of patients with disease flare in Part II (defined as those who experienced a protocol-defined clinical relapse, or discontinued from Part II for any reason)	35	46 wks	3/20/2007	23/10/2009[b]		31
Carglumic acid	NONE	Decrease of ammonia level	20[a]	3.1 yrs	10/18/2000	24/01/2003[b]		27
Celecoxib	PLACEBO	Decrease of colorectal polyps	970	6 mo	11/20/2001	10/17/2003		23

Table 4 (continued)

Active principle	Control	End-point	N Patients studied	Duration	Designation date	Ma date	Notes	Δ months
Cladribine	NONE	Complete + partial responses	120	N.A.		4/14/2004		31
Clofarabine	NONE	Complete remission (CR); complete remission without platelet recovery (CRp), partial remision (PR)	61	N.A. (every 2–6 wks, max. 12 cycles)	2/5/2002	5/29/2006		51
Dasatinib	NONE	1–5 = haematological and cytogenetic response rate	1 = 424 2 = 166 3 = 197 4 = 124 5 = 101	N.A.; mean follow-up = 6 mo	12/23/2005	11/20/2006		11
Deferasirox	1 = Deferoxamine; 2 = NONE	Liver iron content	1 = 586; 2 = 184	1/2 = 1 yrs	3/13/2002	8/28/2006		53
Dexrazoxane	NONE	1/2 = proportion of patients undergoing surgical intervention	1 = 23; 2 = 57	1 = 2 yrs; 2 = 3 yrs	9/19/2001	7/28/2006		58
Eculizumab	1 = PLACEBO	1 = co-primary endpoints: haemoglobin stabilization and number of packed red blood cell (PRBC) units transfused; 2. haemolysis as mesured by LDH (lactate dehydrogenase) area under the concentration curve (AUC)	1 = 75; 2 = 97	1 = 26 wks; 2 = 52 wks	10/17/2003	6/20/2007		44
Eltrombopag	PLACEBO	Shift from a baseline platelet count of < 30,000/μL to ≥ 50,000/μL after up to 42 days of dosing with study medication	114	12 mo	8/3/2007	3/11/2010		31
Everolimus	PLACEBO	Progression Free Survival	416	15 mo	6/5/2007	8/3/2009		24
Galsulfase	1 = PLACEBO; 2 = NONE	1 = 12-Minute Walk test; 2 = 12-Minute Walk test; Stair Climb test; Urinary GAG levels; Shoulder ROM	1 = 39; 2 = 10	1/2 = 24 wks	2/14/2001	1/24/2006		44
Histamine dihydrochloride	NO TREATMENT	Time elapsed form the date of randomisation to the date of relapse of AML or death from any cause	320	18 mo	4/11/2005	07/10/2008[b]	AML: Acute Myeloid Leukaemia	76
Hydroxycarbamide	1 = NONE 2 = PLACEBO	1 = hospitalisation due to pain episodes;number and length of hospital admission; pain episodes; 2 = mortality	1 = 378 2 = 299	1 = 6 mo-7 yrs 2 = not clearly reported	7/9/2003	6/29/2007		47
Ibuprofen	PLACEBO	Proportion of patients requiring surgical ligation of PDA after prophylactic vs. after curative administration of i.v. ibuprofen	131	36 wks	2/14/2001	7/29/2004		59
Icatibant	1 = TRANEMIC AC. 2 = PLACEBO	Time to onset of symptom relief of the first attack using VAS	1 = 77; 2 = 64	N.A.	2/17/2003	7/11/2008	VAS: Visual Assessing Scale	43
Idursulfase	1 = PLACEBO	1 = sum of the ranks of the change from baseline to week 53 in the total distance walked in the 6-minute walking test	1 = 96 2 = 12	1 = 12 mo 2 = 6 mo	11/12/2001	08/01/2007[b]		47

Table 4 (continued)

Active principle	Control	End-point	N Patients studied	Duration	Designation date	Ma date	Notes	Δ months
		(6MWT) and in % predicted forced vital capacity						
Iloprost	PLACEBO	Improvement walk; Improvement of 1 NYHA class	203	12 wks	12/29/2000	16/9/2003[b]		41
Imatinib	NONE	CML = Hematological and cytogenetic response; GIST = Tumor response	CML = 1225; GIST = 147	254 days; 24 wks	2/14/2001	27/08/2001[b]		61
Laronidase	PLACEBO	Reduction of urinary GAG; Reduction of hepatosplenomegaly; Increase Forced Vital CapacityWalk excercise (NS)	45	3 yrs; 104 wks; 26 wks; 26 wks	2/14/2001	10/06/2003[b]		57
Lenalidomide	1/2 = PLACEBO	1/2 = time to progression (TTP)	1 = 353 2 = 351	1/2 = 12 mo	12/12/2003	6/14/2007		42
Mecasermin	1 = PLACEBO	1/2/3 = linear growth rate	1 = 8 2 = 23 3 = 8	1 = 15 mo 2 = 24 mo 3 = 24 mo	8/26/2005	8/3/2007		24
Mifamurtide	Chemotherapy	Disease-free Survival	585	36 wks	6/21/2004	3/6/2009		21
Miglustat	NONE	Reduction of linea and spleen volume	28	2 yrs	10/18/2000	20/11/2002[b]		6
Mitotane	NONE	Survival; remission time; tumour size reduction	500	various time period	6/12/2002	4/28/2004		28
Nelarabine	NONE	1 = Complete and partial responses (paediatric); 2 = Complete and partial responses (adults)	1 = 70 paediatric patients (≤ 21 ys); 2 = 39 adults (≥ 16 ys)	1/2 = 1 yr	6/16/2005	22/08/2007[b]		42
Nilotinib	NONE	Major (complete + partial) cytogenetic response (MCyR)	132	12 mo	5/22/2006	11/19/2007		17
Nitisinone	NONE	Survival, survival without transplantation, death due to liver failure, transplantation due to liver failure and hepatocellular carcinoma	207	6.5 yrs	12/29/2000	21/02/2005[b]	Efficacy based on the results of the interim analysis of an ongoing study	32
Ofatumumab	NONE	Response Rate measured over a 24 week period	154	23 mo	11/7/2008	4/19/2010		24
Pegvisomant	PLACEBO	Decrease IGF-1	112	12 wks	2/14/2001	11/13/2002		57
Plerixafor	PLACEBO	1 = Proportion of patients acheiving the following target number on CD34+ cells: ≥ 5×106 CD34+ cells/kg within 4 days of apheresis; 2 = Proportion of patients achiving the following target number on CD34+ cells: ≥ 6×106 CD34+ cells/kg within 2 or less days of apheresis	1 = 298; 2 = 302	N.A.	10/24/2004	7/31/2009		25
Porfimer sodium	OMEPRAZOLE	Complete responses	208	6 mo	3/6/2002	3/25/2004	The KSS is derived from the assessment of five key symptoms (rash, feeling of fever/chills, join pain,	72

Table 4 (continued)

Active principle	Control	End-point	N Patients studied	Duration	Designation date	Ma date	Notes	Δ months
							fatigue and eye redness/pain) recorded daily by patients on the daily health assessment form (DHAF)	
Rilonacept	PLACEBO	Mean change form baseline in the mean key symptom score (KSS)	47	24 wks	7/10/2007	23/10/2009[b]		45
Romiplostim	PLACEBO	Incidence of durable response (achieving≥6 weekly platelet responses (platelet count≥50×109/L) during the last 8 weeks of treatment with no rescue medication administered at any time during the treatment period)	1 = 63; 2 = 62	36 wks	5/27/2005	2/4/2009	10 supportive study (3 extensions)	22
Rufinamide	PLACEBO	**Combined endpoint**: **A**. the percent reduction in total seizure frequency per 28 days in double-blind phase relative to the baseline phase was significantly greater ($p<0.025$; two-sided) for rufinamide than placebo; **B**. both of the following end point were met: - the percent reduction in tonic-atonic seizure frequency per 28 days in the double-blind phase relative to the baseline phase was significantly greater 8$p<0.025$, two-sided) for rufinamide than placebo; - the seizure severity rating from the Global Evaluation of the patient's condition was significantly greater ($p<0.025$, two sided) for rufinamide than placebo	139	84 days	10/9/2004	1/16/2007		54
Sapropterin dihydrochloride	PLACEBO	Reduction in blood phenylalanine levels	1 = 89; 2 = 90	N.A.	6/8/2004	12/2/2008	1 supportive study (extension)	26
Sildenafil citrate	PLACEBO	total distance walked in 6 minutes	278	12 wks	12/12/2003	28/10/2005[b]		18
Sitaxentan sodium	1 = PLACEBO; 2 = PLACEBO (for descriptive comparison, an open-label bosentan arm was included); 3° = placebo	1 = change in percent of predicted peak VO2 from baseline to week 12 as measured during cycle ergometry; 2/3 = change from baseline in 6-minute walk distance at week 18	1 = 178; 2 = 240; 3 = 98	1/2 = 12 wks 3 = 18 wks	10/21/2004	8/10/2006	4 open-label supportive studies	50
Sodium oxybate	1/2 = PLACEBO	1/2 = total number of cataplexy attacks	1 = 136; 2 = 55	1 = 2 and 4 wks; 2 = 2 wks	3/10/2005	7/19/2006	supportive study (discontinuation Phase II RCT)	21
Sorafenib tosylate	PLACEBO	Overall survival	769	1 = 29 mo	7/29/2004	7/19/2006	4 supporting studies	2

Table 4 (continued)

Active principle	Control	End-point	N Patients studied	Duration	Designation date	Ma date	Notes	Δ months
Stiripemtol	1/2 = PLACEBO	1/2 = Number of responders: subjects with>50 % reduction in the number of seizures during the treatment peiod (2 months)	1 = 41; 2 = 24	3 mo	12/5/2001	04/12/2007[c]	2 open-label supportive studies	27
Sunitinib malate	**GIST**: PLACEBO **MRCC**: NONE	**GIST**: Time to Tumour Progression (TTP) **MRCC**: Complete and Partial Response (ORR)	**GIST**: 312 **MRCC**: 106	**GIST**: 2 yrs **MRCC**: 11 mo	2/3/2003	13/10/2005[c]		22
Temsirolimus	NONE	Complete and partial responses	111	8 wks	4/6/2006	11/19/2007		79
Thalidomide	Chemotherapy	Overall Survival (time from randomisation to death from any cause)	447	65 mo	11/20/2001	4/16/2008	1 = Autologous HPCT in adult patients with haematological diseases; 2 = Autologous HPCT in adult patients with solid tumours; 3 = Allogenic HPCT in adult patients with haematological diseases; 4 = Autologous HPCT in paediatric patients with solid tumours; 5 = Allogenic HPCT in paediatricpatientswith haematological diseases	38
Thiotepa	Chemotherapy	Disease-free Survival, Overall Survival, Relapse	1 = 826; 2 = 3,675; 3 = 1,771; 4 = 476; 5 = 426	Various time period	1/29/2007	3/15/2010		2
Trabectidin	Different schedule	Time to progression (TTP)	260	24 mo	5/30/2001	9/17/2007		76
Velaglucerase alfa	IMIGLUCERASE	Change in hemoglobin concentration from baseline to week 41	35	16 mo	6/9/2010	8/26/2010	2 supportive studies (the first two studies were prolonged into a long-term open-label study)	22
Ziconotide acetate	PLACEBO	1 -3 = percent change in Visual Analogue Scale of Pain Intensity (VASPI)	1 = 112 2 = 257 3 = 220	1/2 = 5–6 days; 3 = 3 wks	7/9/2001	21/02/2005[b]		16
Zinc acetate dihydrate	NONE	Effects on copper metabolism [24 h copper excretion and non-coeruloplasmin plasma copper (NCPC); effect on speech and neurological function measured on integer scale; effect on liver function tests liver enzymes, bilirubin, albumin)]	148	3.2 yrs in symptomatic adults; 3.n in pre-symptomatic adults	31/072001	10/13/2004		39

[a] Reports retrieved from literature

[b] MA under exceptional circumstances

[c] conditional MA

[d] Prevalence is per 10,000 patients in the European Union

and price agreed with regulatory authorities are those acknowledged for OMPs, but revenues are often as high as or even higher than any generic treatment for common diseases. [14, 19]

There is a need to reflect on these findings and consider whether the present system should be changed. A specific European fund might possibly bridge the persistent gap between designations and approvals by supporting the preclinical and clinical steps along the road from discovery to the medicinal product. The EMA should require better evidence of the clinical efficacy of OMPs before they are allowed onto the market, and should consider the possibility of withdrawing the orphan status and the relative incentives when new, broader indications are approved for OMPs. The threshold for orphan status should be lowered to concentrate the efforts on really rare diseases, also considering the expansion of the EU to 27 member states [20]. NHS reimbursement schemes should only allow OMPs with affordable cost-effectiveness and renegotiate the prices when new indications are authorized.

Probably, in the light of the experience gained so far, it is time to review the current rules and find better ways of fostering the development of effective and sustainable treatments for patients with orphan diseases.

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