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Dose-Finding Studies Among Orphan Drugs Approved in the EU: A Retrospective Analysis

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Abstract

In the development process for new drugs, dose-finding studies are of major importance. Absence of these studies may lead to failed phase 3 trials and delayed marketing authorization. In our study we investigated to what extent dose-finding studies are performed in the case of orphan drugs for metabolic and oncologic indications. We identified all orphan drugs that were authorized until August 1, 2017. European Public Assessment Reports were used to extract the final dose used in the summary of product characteristics, involvement of healthy volunteers, study type, end points used, number of patients, number of doses, studies in special populations, and dose used for phase 3 studies. Each drug was checked for major objections and dose changes postmarketing. We included 49 orphan drugs, of which 28 were indicated for metabolic disorders and 21 for oncologic indications. Dose-finding studies were performed in 32 orphan drugs, and studies in healthy volunteers in 26. The absence of dose-finding studies was mostly due to the rarity of the disease. In this case the dose was determined based on factors such as animal studies or clinical experience. Dose-related major objections were raised for 9 orphan drugs. Postmarketing dose-finding studies were conducted in 18 orphan drugs, but dose changes were applied in only 2 drugs. In conclusion, dose-finding studies in the case of metabolic and oncologic orphan drugs were conducted in the development programs of two thirds of orphan drugs. Dose-finding studies performed postmarketing suggest that registered doses are not always optimal. It is thus important to perform more robust dose-finding studies both pre- and postmarketing.

Keywords

orphan diseases, orphan drugs, dose finding

Establishing the right dose is of major importance during the drug development process, and to do so, robust dose-finding studies are needed. Remarkably, scientifically robust dose selection is not required by US or EU law, and phase 2 studies are often abbreviated and simplified.[1] Because drug development is known to be costly and time consuming, the rationale for accelerated drug development and less robust studies may thus seem plausible. However, this may cause dose selection of new drugs to be based on expert opinions rather than on scientific studies. Several studies have shown that poor dose selection may lead to failed phase 3 trials, delayed or denied marketing authorization, and postmarketing dose changes.[1–3] It also results in dose-response characteristics that are poorly understood.

It is generally perceived that development of medicinal products for the treatment of rare diseases ("orphan drugs") does not meet the expectations of society: although more than 7000 orphan diseases exist (some of which are extremely rare), there are only 142 orphan drugs approved in the EU to date. A disease is called "orphan" if it is a life-threatening or seriously debilitating disorder affecting less than 5 in 10,000 people in the EU. There are several reasons for the difficulties of orphan drug development, such as the limited number of patients, disease heterogeneity, insufficient knowledge of the pathophysiology, and lack of appropriate pharmacodynamic measures. In addition, the high unmet medical need of many rare diseases may contribute to the pressure for fast registration of new orphan drugs. Therefore, the problem of poor dose selection may be more prevalent in orphan drug dossiers as compared to nonorphan drugs. However, to our knowledge, neither the extent to which dose-finding studies have been conducted for orphan drugs and nonorphan drugs nor the quality of these studies has

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ever been investigated. Because defining the most appropriate dose is very relevant for the effective and safe use of medicines, we considered this to be a significant regulatory science question. Consequently, our study aimed to answer the following questions: (1) To what extent are dose-finding studies performed as part of the registration dossiers of orphan drugs? In this respect, is the posology as recommended in the label based on data from dose-finding studies or otherwise well justified? (2) What are the major difficulties in defining the right dose in orphan drugs, and how have these been addressed for the orphan drugs that have reached the EU market? In our study, we focused only on orphan drugs authorized for metabolic and oncology indications.

Methods

We used the Community Register of Orphan Medicinal Products for Human Use of the European Commission to identify all orphan drugs that were authorized for the treatment of metabolic and oncologic diseases until August 1, 2017.[4] Drugs were categorized according to the Anatomical Therapeutic Chemical classification system, and drugs with Anatomical Therapeutic Chemical code A (Alimentary Tract and Metabolism) and L (Antineoplastic and Immunomodulating) were included. Of the latter category, only drugs for solid tumors were included. Orphan drugs discontinued from the community register, either at the end of the 10-year period of market exclusivity or at request of the marketing authorization holder, were also included. Compounds that were designated for orphan status but that had not yet receive EU marketing authorization were excluded.

European Public Assessment Reports, which are available on the website of the European Medicines Agency (EMA), were used to extract data on dose-finding studies. The extent to which dose-finding studies were performed was evaluated by identifying the route of administration, involvement of healthy volunteers, study type, end points used, number of patients, number of doses tested, studies in special populations, dose used for phase 3 studies, and final dose used in the summary of product characteristics. Furthermore, each orphan drug was checked for dose- and schedule-related changes after marketing authorization in EMA's "variations" forms. Also, the day-80 and day-210 assessment reports, which are part of the registration dossier, were searched for major objections (see Table 1). Additionally, a literature search for orphan drugs was conducted in PubMed to verify whether dose-finding studies were performed in the postmarketing period. Search terms included the name of the orphan drug (brand and generic), the disease name, "dose," and "dosing." The search was limited to clinical trials, and the results were screened by 1 reviewer (Y.S.).

Table 1. Major Objections

Questions raised by the EMA on evaluating a new drug are addressed to the applicant in the form of a major objection or "other concern."[47] In order to get a marketing authorization, all major objections need to be satisfactorily resolved by the applicant.[47] The ARs were screened for major objections referring to the dose. A dose- or schedule-related major objection may include an unestablished optimal dosing regimen, the unexplored impact of (non)fasted state or of ethnicity on dosing, unjustified dose proposals, or inconsistency of extrapolation from pharmacokinetic dose-finding evidence to the final proposed dose.[47]

AR, indicates assessment report; EMA, European Medicines Agency.

Results

We included 49 orphan drugs in our study, of which 28 were for metabolic diseases and 21 for solid tumors.

Alimentary Tract and Metabolism

Twenty-six orphan drugs were authorized in the Alimentary Tract and Metabolism group (Table 2). Two orphan drugs (carglumic acid [Carbaglu] and miglustat [Zavesca]) were authorized for 2 different disease indications, adding up to a total of 28 orphan drugs. Ten orphan drugs were withdrawn from the community register of orphan drugs at the end of the 10-year period of market exclusivity.

Studies in healthy volunteers were conducted in 14/28 orphan drugs (50%) before they were administered to patients. In 10/28 orphan drugs (36%, all enzyme replacement therapies), no studies in healthy volunteers were conducted, presumably because healthy subjects do not lack the enzyme and hence no meaningful pharmacodynamic effects are expected. For 3/28 orphan drugs (11%), the absence of studies in healthy volunteers was not justified (ie, no explicit explanation about their absence was provided in the European Public Assessment Report), and for 1/28 orphan drug (3%) it was not reported.

Dose-finding studies were performed in 15/28 orphan drugs (54%). In the other 13/28 orphan drugs (46%), no dose-finding studies were performed before marketing was authorized. The main reason for the absence of dose-finding studies seemed to be the prevalence and rarity of the diseases, although this was not always specifically stated by the marketing authorization holder. The determination of the dose in the absence of formal dose-finding studies was as follows: dose regimen based on data from studies in a human cell line (miglustat [Zavesca]), dose based on animal studies (laronidase [Aldurazyme]), dose based on clinical experience/well-established use (carglumic acid [Carbaglu], cholic acid [Orphacol], cholic acid [Kolbam], nitisinone [Orfadin], glycerol phenylbutyrate

Table 2. Characteristics of Dose-Finding Studies in Drugs for Metabolic Diseases

Drug (Year)	Generic Name	Disease	Healthy Volunteers	End Points	Doses Tested in Phase 1–2 Studies	Dose in Phase 3 Studies	Studies in Special Populations	Dose SmPC	Dose Changes Postmarketing
Fabrazyme[b] (2001)	Agalsidase beta	Fabry disease	No[a]	Plasma GL-3 levels	EOW: 0.3, 1.0 or 3.0 mg/kg. EOD: 1.0 or 3.0 mg/kg	1 mg/kg EOW	No	1 mg/kg EOW	No
Replagal[b] (2001)	Agalsidase alfa	Fabry disease	No[a]	Liver GL-3 content and α-Gal A activity, plasma + urine GL-3 levels	0.007, 0.014, 0.028, 0.056, 0.110 mg/kg	0.2 mg/kg	No	0.2 mg/kg EOW	No
Zavesca[b] (2002)	Miglustat	Gaucher disease	No	Organ volume, biochemical parameters	100 mg TID (In another study, 50 mg TID was used.)	100 mg TID	Not reported	Adults: 100 mg TID	No
Aldurazyme[b] (2003)	Laronidase	MPS I	No[a]	n/a	n/a	n/a	No, but justified	100 U/kg EOW	No
Carbaglu[b] (2003)	Carglumic acid	NAGS deficiency	Yes	n/a	n/a	n/a	Yes; children	Start: 100 mg/[kg·d], up to 250 mg/kg if necessary. Maintenance dose 10–100 mg/[kg·d].	No
Carbaglu[b] (2011)	Carglumic acid	Organic acidurias	Yes	n/a	n/a	n/a	Yes; children	Start: 100 mg/[kg·d], up to 250 mg/kg if necessary. Then individually adjusted.	No
Wilzin (2004)	Zinc	Wilson disease	Yes	Copper balance (the daily dietary intake of copper minus its daily excretion)	25 mg OD, 25 mg BID, 25 mg TID, 25 QID, 25 mg 6 times/d, 37.5 mg BID, 50 mg OD, 50 mg BID, 50 mg TID, 50 mg 5 times/d, 75 mg OD	50 mg TID	Yes; children, elderly. Patients with renal/hepatic impairment	Adults (>16 y): 50 mg TID with a maximum dose of 50 mg 5 times daily; 1–6 y: 25 mg BID; 6–16 y: 25 mg TID	No
Orfadin[b] (2005)	Nitisinone	Hereditary tyrosinemia type I	Yes	Urinary-SA, Plasma-SA, PBG-synthase, urinary 5-ALA, α-fetoprotein, liver function, tyrosine	0.1 to 0.6 mg/kg	0.6 mg/kg	No	1 mg/[kg·d] (divided in 2 doses)	Yes
Zavesca[b] (2006)	Miglustat	Niemann-Pick C	No	n/a	n/a	n/a	No, but justified	>12 y: 200 mg TID. <12 y: based on body surface area	n/a

(*Continued*)

Table 2. Continued

Drug (Year)	Generic Name	Disease	Healthy Volunteers	End Points	Doses Tested in Phase 1–2 Studies	Dose in Phase 3 Studies	Studies in Special Populations	Dose SmPC	Dose Changes Postmarketing
Naglazyme[b] (2006)	Galsulfase	MPS 6	No[a]	6-MWT, FVC and FEV1, height, weight, JROM, grip strength, pinch gauge, urinary GAGs, hepatomegaly, bone mineral density, visual acuity, cardiac function, sleep apnea, CHAQ/HAQ	0.2 and 1 mg/kg	1 mg/kg	No	1 mg/kg weekly	No
Myozyme (2006)	Alglucosidase alfa	Pompe disease	No[a]	Primary: % patients alive and free of invasive ventilator support at 12 months of age. Secondary: cardiomyopathy (LVMI), weight, length, and head circumference.	20 and 40 mg/kg EOW	20 mg/kg	No	20 mg/kg EOW	No
Elaprase[b] (2007)	Idursulfase	MPS 2	NR	Liver and spleen volumes, pulmonary function, urinary GAGs, safety	0.15, 0.5, or 1.5 mg/kg or pbo	0.5 mg/kg	No	0.5 mg/[kg·wk]	No
Cystadane (2007)	Betaine anhydrous	Homocystinuria	Yes	n/a	n/a	n/a	No	100 mg/[kg·d] given in 2 doses daily	No
Kuvan (2008)	Sapropterin	PKU	Yes	Safety, tolerability, blood Phe levels	5, 10 or 20 mg/[kg·d]	10 and 20 mg/kg	No	Start: 10 mg/[kg·d], adjusted between 5 and 20 mg/[kg·d]	No
Vpriv (2010)	Velaglucerase alfa	Gaucher disease type 1	No[a]	Hgb, platelet counts, liver and spleen volume, chitotriosidase, CCL18, pulmonary function, bone density, bone marrow	15, 30, and 60 U/kg	60 U/kg	No	60 U/kg EOW	No

(*Continued*)

Table 2. Continued

Drug (Year)	Generic Name	Disease	Healthy Volunteers	End Points	Doses Tested in Phase 1–2 Studies	Dose in Phase 3 Studies	Studies in Special Populations	Dose SmPC	Dose Changes Postmarketing
Revestive (2012)	Teduglutide	Short bowel syndrome	Yes	Gastrointestinal absorption, structural changes in intestinal mucosa	0.03, 0.10, 0.15, 0.10 or 0.15, 0.10 mg/[kg·d]	0.05 mg/[kg·d] and 0.10 mg/[kg·d]	Yes; children, patients with renal/hepatic impairment	0.05 mg/[kg·d]	No
Orphacol[b] (2013)	Cholic acid	Errors in bile acid synthesis	Yes	n/a	n/a	n/a	No	5 to 15 mg/[kg·d]	n/a
Procysbi (2013)	Mercaptamine	Cystinosis	Yes	WBC cysteine levels, safety and tolerability	75 mg procysbi vs 150 mg cystagon	Dose equal to approximately 70% of their usual dose of cystagon	No, but justified	Maintenance dose 1.3 g/[m^2·d], in 2 divided doses	No
Kolbam[b] (2014)	Cholic acid	Errors in bile acid synthesis	Yes	n/a	n/a	n/a	No	10–15 mg/[kg·d]	n/a
Vimizim (2014)	Elosulfase alfa	MPS 4a	No[a]	6-MWT, 3-MSCT, FVC, urine KS, HAQ	0.1, 1, or 2 mg/[kg·wk]	2 mg/[kg·wk]	No	2 mg/[kg·wk]	No
Cerdelga (2015)	Eliglustat	Gaucher disease type 1	Yes	n/a	n/a	n/a	Yes; elderly	84 mg (100 mg eliglustat tartrate) OD in CYP2D6 PMs; 84 mg BID in CYP2D6 IMs and EMs	No
Kanuma (2015)	Sebelipase alfa	LAL deficiency	No[a]	Safety, tolerability, PK, PD, survival at 12 months of age	0.35, 1, and 3 mg/kg	1 mg/kg EOW	Yes; patients with renal/hepatic impairment	<6 mo: 1 mg/[kg·wk]; >6 mo: 1 mg/kg EOW	No
Ravicti (2015)	Glycerol phenylbutyrate	Urea cycle disorders	Yes	n/a	n/a	n/a	Yes; patients with hepatic impairment	4.5 mL/[m^2·d] to 11.2 mL/[m^2·d]	No
Strensiq[b] (2015)	Asfotase alfa	Hypophosphatasia[b]	No	n/a	n/a	n/a	No	2 mg/kg 3 times per week or 1 mg/kg 6 times per week	No
Galafold (2016)	Migalastat	Fabry disease	Yes	α-Gal A activity in leukocytes, PBMCs, kidney, and skin. GL-3 in urine, kidney, plasma, and skin	BID: 25, 100, 250 mg. OD: 50 mg. EOD: 50, 150, 250 mg. 3 days on–4 days off: 250, 500 mg	150 mg EOD	Yes; patients with renal impairment	123 mg EOD	No

(*Continued*)

Table 2. Continued

Drug (Year)	Generic Name	Disease	Healthy Volunteers	End Points	Doses Tested in Phase 1–2 Studies	Dose in Phase 3 Studies	Studies in Special Populations	Dose SmPC	Dose Changes Postmarketing
Ocaliva[c] (2016)	Obeticholic acid	Biliary liver cirrhosis	Yes	Primary: % change in serum ALP from baseline	10, 25, and 50 mg or pbo	5 and 10 mg	Yes; elderly, patients with renal/hepatic impairment	5 mg OD, increased to 10 mg OD	No
Chenodeoxycholic acid[b] (2017)	Chenodeoxycholic acid	CTX	No	n/a	n/a	n/a	No	Adults: 750 mg/d, increased to max 1000 mg/d. Infants (1 mo–18 y) 5 mg/[kg·d] in 3 divided doses	No
Brineura[b] (2017)	Cerliponase alfa	NCL	No	n/a	n/a	n/a	No, but justified	300 mg EOW	No

3-MSCT indicates 3-minute stair climb test; 5-ALA, 5-aminolevulinic acid; 6-MWT, 6-minute walk test; α-Gal A, α-galactosidase A; ALP, alkaline phosphatase; BID, twice daily; C, conditional; CCL18, CC chemokine ligand 18; CHAQ, Childhood Health Assessment Questionnaire; CTX, cerebrotendinous canthomatosis; CYP2D6, cytochrome P450 2D6; EM, extensive metabolizers; EOD, every other day; EOW, every other week; ERT, enzyme replacement therapy; F, full; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GAG, glycosaminoglycan; GL-3, globotriaosylceramide; HAQ, health assessment questionnaire; Hgb, hemoglobin; IM, intermediate metabolizers; JROM, joint range of motion; KS, keratan sulfate; LAL, lysosomal acid lipase; LVMI, left ventricular mass index; MPS, mucopolysaccharidosis; n/a, not applicable; NAGS, N-acetylglutamate synthetase; NCL, neuronal ceroid-lipofuscinoses; NR, not reported; OD, once daily; PBG, porphobilinogen; PBMC, peripheral blood mononuclear cell; pbo, placebo; PD, pharmacodynamics; Phe, phenylalanine; PK, pharmacokinetics; PKU, phenylketonuria; PM, poor metabolizers; QID, 4 times daily; SA, succinylacetone; SmPC, summary of product characteristics; TID, 3 times daily; U, units; WBC, white blood cell.

[a]ERTs are not tested in healthy subjects due to the risk of immunogenicity.

[b]Marketing authorization under exceptional circumstances.

[c]Conditional marketing authorization.

[Ravicti], and betaine anhydrous [Cystadane]), dosing based on plasma levels (eliglustat [Cerdelga]), and dosing based on modeling exercise (asfotase alfa [Strensiq]) (see Online Appendix 1). In the majority of orphan drugs for which dose-finding studies were lacking, studies in healthy volunteers were present. The mean number of doses tested in the studies was 4. Whether dose-finding studies were performed did not seem to be related to the year of marketing authorization. Studies in special populations (eg, children, elderly, patients with hepatic or renal impairment) were performed in 9/28 orphan drugs (32%). The absence of studies in special populations was justified in 4/28 orphan drugs (14%); in the other 15/28 orphan drugs (54%) it was not.

Dose-related major objections were raised at day 80 of the procedure for 6/28 orphan drugs (21%), which were resolved later in the procedure. Major objections included (1) the absence of studies in healthy volunteers, (2) the lack of pharmacokinetic data in early childhood, (3) the effects of antibody formation on safety and efficacy, (4) justification of the dose in the absence of dose-finding studies, (5) the absence of pharmacokinetic (PK) parameters in patients with concomitant proton pump inhibitors, and (6) justification of a certain dose instead of a lower dose. The major objections were addressed by the marketing authorization holders by providing PK data, showing that the effect of antibodies did not significantly impact PK parameters, adequately justifying the dose based on case reports, demonstrating that concomitant use of proton pump inhibitors did not influence the characteristics of the drug, and demonstrating the benefit of a lower dose. For 1 major objection, it remained unclear how the situation was resolved. Also, the registered dose of 1 orphan drug did not correspond with the doses that were tested in the dose-finding studies. The choice of that dose was partially supported by the putative liver-uptake fraction of the total administered dose.

Postmarketing dose-finding studies were found for 10 orphan drugs (Table 3), but postmarketing dose changes were applied in only 1/28 orphan drug (4%, Orfadin). The authorized dose of this orphan drug was based on clinical experience in 5 patients. However, after marketing authorization, the recommended dose of 0.6 mg/kg appeared to be too low. Hence, the dose has been changed to 1 mg/kg postmarketing. A formal obligation for the conduct of additional postmarketing dose-finding studies existed for 1 orphan drug (asfotase alfa [Strensiq]). The results of this study are not yet published.

Oncology: Solid Tumors

Sixteen orphan drugs were authorized for the treatment of solid tumors (Table 4). One orphan drug (sorafenib [Nexavar]) was authorized for the treatment of 3 different diseases and 3 orphan drugs (imatinib [Glivec], sunitinib [Sutent], and trabectedin [Yondelis]) were authorized for the treatment of 2 different solid tumors, making a total of 21 orphan drugs. Two orphan drugs were withdrawn from the community register of orphan drugs at the end of the 10-year period of market exclusivity and 6 on request of the sponsor. One orphan drug (dinutuximab [Unituxin]) was withdrawn from use in the EU after marketing authorization on request of the marketing authorization holder. The reason was not dose related but was attributed to short- and intermediate-term inability to supply the drug.[23]

In 12/21 orphan drugs (57%), studies in healthy volunteers were performed. Of the 9/21 orphan drugs (43%) that were not tested in healthy volunteers, ethical dilemmas were the reason in 1 orphan drug. For the other 8 drugs, no justification was given in the European Public Assessment Report.

Dose-finding studies were conducted in 17/21 orphan drugs (81%), with a mean of 4 different tested doses. The reasons for not conducting dose-finding studies in the other 4 orphan drugs included clinical experience/well-established use (mitotane [Lysodren]), dose based on therapeutic effect in other indications (imatinib [Glivec] for dermatofibrosarcoma protuberans) (Online Appendix 2). No clear reason for the absence of dose-finding studies was found for imatinib (Glivec; gastrointestinal stromal tumor) and sunitinib (Sutent; renal cell carcinoma). For 2 of the oncological orphan drugs (sorafenib [Nexavar] and sunitinib [Sutent]), the dose defined in the dossier for 1 indication was also used for the other indications for which the drug was later authorized. For the other 2 oncological orphan drugs with multiple indications (imatinib [Glivec] and trabectedin [Yondelis]), the dose per indication differs. In the majority of orphan drugs for which dose-finding studies were lacking, studies for healthy volunteers were present. Studies in special populations were conducted in 10/21 orphan drugs (48%). The absence of such studies was justified in 2 orphan drugs (10%), but in the other 9 orphan drugs (42%), it was not.

Dose-related major objections were raised at day 80 of the procedure for 3/21 orphan drugs (14%). Major objections included (1) absence of data of a PK/pharmacodynamic study, (2) lack of preclinical data on dosing, and (3) lack of data on the use of lower doses. The major objections were then satisfactorily addressed by the marketing authorization holders by providing the missing study data, conducting safety studies in patients, and presenting practical implications for studying lower doses.

Although postmarketing dose-finding studies were found for 8 orphan drugs (Table 5), postmarketing

Table 3. Dose-Finding Postmarketing Studies (Alimentary Tract and Metabolism)

Disease	Drug (Registered Dose)	Studied Doses Postmarketing	References
Fabry	Fabrazyme (1 mg/kg EOW)	0.2 mg/kg EOW	Vedder et al, 2007[5]
		0.5 mg/kg EOW, 0.3 mg/kg EOW (due to shortage)	Ghali et al, 2012[6]
		0.3–0.5 mg/kg (due to shortage)	Lenders et al, 2016[7] Weidemann et al, 2014[8]
		0.3 mg/kg	Lubanda et al, 2009[9]
Fabry	Replagal (0.2 mg/kg EOW)	0.1, 0.2, or 0.4 mg/kg weekly; 0.2 mg/kg EOW, 0.4 mg/kg EOW	Clarke et al, 2007[10]
		0.2 mg/kg weekly	Schiffmann et al, 2015[11]
Gaucher	Zavesca (100 mg TID)	None	
MPS I	Aldurazyme (100 U/kg EOW = 0.58 mg/kg)	1.2 mg/kg EOW	Horovitz et al, 2016[12]
NAGS deficiency	Start: Carbaglu (100 mg/[kg·d] up to 250 mg/kg if necessary, then 10-100 mg/[kg·d])	None	
Organic acidurias	Start: Carbaglu (100 mg/[kg·d] up to 250 mg/kg if necessary, then individually adjusted.)	None	
Wilson disease	Wilzin (50 mg TID)	50 mg BID (in pregnant woman)	Masciullo et al, 2011[13]
Hereditary tyrosinemia type I	Orfadin (1 mg/[kg·d] divided into 2 doses)	Single daily dose	Schlune et al, 2012[14]
		0.55 to 0.65 mg/[kg·d]	El-Karaksy et al, 2010[15]
		0.55 mg/[kg·d]	D'Eufemia et al, 2011[16]
Niemann-Pick C	Zavesca (200 mg TID)	None	
MPS 6	Naglazyme (1 mg/[kg·wk])	None	
Pompe	Myozyme (20 mg/kg EOW)	40 mg/[kg·wk]	Van Gelder et al, 2016[17]
		20 mg/[kg·wk] or 40 mg/kg EOW	Case et al, 2015[18]
MPS 2	Elaprase (0.5 mg/[kg·wk])	None	
Homocystinuria	Cystadane (100 mg/[kg·d] given in 2 doses daily)	None	
PKU	Kuvan (start: 10 mg/[kg·d], adjusted to 5–20 mg/[kg·d])	Pediatric patients: 5 or 20 mg/[kg·d]	Qi et al, 2015[19]
Gaucher	Vpriv (60 U/kg EOW)	Starting dose: 60 U/kg per infusion EOW. Between 15 and 18 mo of cumulative treatment, patients were eligible for stepwise dose reduction to 30 U/kg per EOW based on achievement of at least 2 of 4 therapeutic goals	Elstein et al, 2011[20]
Short bowel syndrome	Revestive (0.05 mg/[kg·d])	None	
Errors in bile acid synthesis	Orphacol (5 to 15 mg/[kg·d])	None	
Cystinosis	Procysbi (1.3 g[m^2·d])	None	
Errors in bile acid synthesis	Kolbam (10–15 mg/[kg·d])	None	
MPS 4a	Vimizim (2 mg/[kg·wk])	None	
Gaucher	Cerdelga (84 mg BID) (100 mg eliglustat tartrate)	50 mg BID or 100 mg BID	Charrow et al, 2018[21]
LAL deficiency	Kanuma (<6 mo: 1 mg/[kg·wk]; >6 mo: 1 mg/kg EOW)	Infants <6 mo: 0.35 mg/[kg·wk] with intrapatient dose escalation up to 5 mg/[kg·wk]	Jones et al, 2017[22]
Urea cycle disorders	Ravicti (4.5 mL/[m^2·d] to 11.2 mL/[m^2·d])	None	
Hypophosphatasia	Strensiq (2 mg/kg 3 times per week or 1 mg/kg 6 times per week)	None	
Fabry	Galafold (123 mg EOD)	None	

BID, twice a day; EOD, every other day; EOW, every other week; LAL, lysosomal acid lipase; MPS, mucopolysaccharidosis; NAGS, N-acetylglutamate synthetase; PKU, phenylketonuria; TID, 3 times daily; U, units.

dose changes were implemented in only 1 orphan drug (everolimus [Afinitor]). However, this only applied to patients with mild, moderate, or severe hepatic impairment, for which lower daily doses were recommended.

Discussion

Our study shows that dose-finding studies for orphan drugs are performed in only two thirds of the cases: 35% of the drugs that were authorized in EU lacked

Table 4. Characteristics of Dose-Finding Studies in Oncologic Drugs

Drug (Year)	Generic Name	Disease	Healthy Volunteers	End Points	Doses Tested in Phase 1–2 Studies[a]	Dose in Phase 3 Studies	Studies in Special Populations	Dose SmPC	Dose Changes Postmarketing
Glivec[b] (2002)	Imatinib	1. GIST	yes	Primary: ORR	400 or 600 mg (escalated to 800 mg if necessary)	400 mg/d	No	Adults: 400 mg/d	No
Lysodren (2004)	Mitotane	Adrenal cortex neoplasms	No	n/a	2 g to 19 g/d	n/a	No	2-3 g/d and increased until lysodren plasma levels reach 14–20 mg/L	No
Glivec (2006)	Imatinib	2. DFSP	Yes	n/a	n/a	800 mg/d	No	Adults: 800 mg/d	No
Nexavar (2006)	Sorafenib	1. RCC	Yes	Tolerability, safety, PK, PD, MTD, tumor response, survival	BID: 50, 100, 200, 300, 400, 600, and 800 mg. OD: 50 mg, 200 mg. EOD: 50 mg. Schedules: 1/3, 3/1, 4/1. Once weekly to continuous dosing.	400 mg BID	Yes; elderly, patients with renal/hepatic impairment	400 mg BID	No
Sutent[c] (2006)	Sunitinib	1. GIST	Yes	ORR, TTP, PFS, PROMs, PK, PD	Schedule 2/2 at 25, 50, and 75 mg QD. Schedule 2/1 at 50 mg QD. Schedule 4/2 at 50 mg QD.	50 mg QD on schedule 4/2	No	50 mg QD on schedule 4/2	No
Sutent (2006)	Sunitinib	2. RCC	Yes	n/a	50 mg QD on schedule 4/2	50 mg QD on schedule 4/2	Yes; patients with hepatic impairment	50 mg QD on schedule 4/2	No
Nexavar (2007)	Sorafenib	2. HCC	Yes	PK, safety, tolerability	200 mg BID or 400 mg BID	400 mg BID	Yes; elderly, patients with renal/hepatic impairment	400 mg BID	No
Torisel (2007)	Temsirolimus	RCC	Yes	OS, PFS, ORR, and clinical benefit rate	Phase 1: 5-25 mg Phase 2: 25, 75, or 250 mg	25 mg QW (or 15 mg in combination with IFN)	Yes; elderly, children, patients with renal/hepatic impairment	25 mg QW	No
Yondelis (2007)	Trabectedin	1. STS	No	PK, efficacy, safety	0.4–1.3 mg/m^2 Q3W 1.5 mg/m^2	1.5 mg/m^2	No	1.5 mg/m^2 Q3W	No
Afinitor (2009)	Everolimus	RCC	Yes	PD, ORR, PFS	Weekly doses of 5, 10, 20, 30, 50, and 70 mg and daily doses of 5 and 10 mg	10 mg/day	Yes; patients with renal/hepatic impairment	10 mg OD	Yes
Mepact (2009)	Mifamurtide	Osteosarcoma	Yes	Safety, PFS, DFS, tolerability, histologic response, immunomodulatory effects, and efficacy	2 mg/m^2 twice weekly for 12 weeks, 2 mg/m^2 twice weekly for 12 weeks and then once weekly for 12 weeks, 2 mg/m^2 followed by dose titration based on monocyte activation	2 mg/m^2	Yes; patients with renal/hepatic impairment	2 mg/m^2 Q2W for 12 weeks, followed by QW for 24 weeks for a total of 48 infusions in 36 weeks.	No
Yondelis[b] (2009)	Trabectedin	2. Ovarian cancer	No	PK, safety. ORR	0.4-1.65 mg/m^2 Q3W, 0.58 mg/m^2 on days 1, 8, and 15 of a 28-day cycle, or 1.3 mg/m^2 on day 1 of a 21-day cycle	1.1 mg/m^2	No	1.1 mg/m^2 Q3W	No

(*Continued*)

Table 4. Continued

Drug (Year)	Generic Name	Disease	Healthy Volunteers	End Points	Doses Tested in Phase 1–2 Studies[a]	Dose in Phase 3 Studies	Studies in Special Populations	Dose SmPC	Dose Changes Postmarketing
Cometriq[c] (2014)	Cabozantinib	Thyroid cancer	Yes	Primary: safety and PK. Secondary: ORR	0.08-11.52 mg/kg intermittent 5 and 9 schedule 175 and 265 mg QD (powder in bottle) 125, 175, and 250 mg QD (capsule)	140 mg (corresponding to about 175 mg as L-malate salt weight)	Yes; patients with hepatic impairment	140 mg QD	No
Cyramza (2014)	Ramucirumab	Gastric cancer	No	Safety, MTD	2, 4, 6, 8, 10, 13, and 16 mg/kg Q2W: 6, 8, and 10 mg/kg Q3W: 10, 15, and 20 mg/kg	8 mg/kg Q2W and 10 mg/kg Q3W	Yes; elderly	8 mg/kg Q2W	No
Lynparza (2014)	Olaparib	Ovarian cancer	Not reported	Primary: ORR, PFS. Secondary: CBR, duration of response, PFS	400 mg BID and subsequently at 100 mg BID, 200 mg BID, or 400 mg BID	400 mg BID	No	400 mg BID	No
Nexavar (2014)	Sorafenib	3. Thyroid cancer	Yes	See nexavar RCC	See nexavar RCC	400 mg BID	Yes; elderly, patients with renal/hepatic impairment	400 mg BID	No
Lenvima (2015)	Lenvatinib	Thyroid cancer	Yes	Not reported	0.2–32 mg QD, 20 and 24 mg QD, 0.5-20 mg BID, 0.1–3.2 mg BID in a 7 days on/7 days off schedule, 3.2–12 mg BID with continuous daily dosing	24 mg QD	Yes; patients with renal/hepatic impairment	24 mg QD	No
Unituxin[d] (2015)	Dinutuximab	Neuroblastoma	Yes	Safety, toxicity, PK, clinical response	10 to 200 mg/m^2	25 mg/m^2	No	17.5 mg/[m^2·d] on days 4–7 (courses 1, 3, and 5) and on days 8–11 (courses 2 and 4)	No
Lartruvo[c] (2016)	Olaratumab	Sarcoma	No	Primary: Safety, MTD, ORR, PFS, PK. Secondary: PK, PD, ORR, OS, safety, immunogenicity	4, 8, 16 mg/kg QW, 4/2 schedule. 15, 20 mg/kg Q2W, 2/2 schedule. 10, 15 or 20 mg/kg Q2W	15 mg/kg Q3W	No, but justified	15 mg/kg on days 1 and 8 of each 3-wk cycle	No
Onivyde (2016)	Irinotecan hydrochloride trihydrate	Pancreatic cancer	No	Primary: toxicity, DLT, MTD, safety, PK, dose intensity. Secondary: ORR, duration of response, TTR, TTP, DCR	60, 80, 100, 120, 180 mg/m^2 Q3W. 80, 90, and 100 mg/m^2 Q2W	80 mg/m^2 (if homozygous for *UGT1A1*28* allele: 60 mg/m^2 increased to 80 mg/m^2 if necessary).	No	80 mg/m^2 Q2W	No

(*Continued*)

Table 4. Continued

Drug (Year)	Generic Name	Disease	Healthy Volunteers	End Points	Doses Tested in Phase 1–2 Studies[a]	Dose in Phase 3 Studies	Studies in Special Populations	Dose SmPC	Dose Changes Postmarketing
Isqette[b] (2017)	Dinutuximab beta	Neuroblastoma	No	Primary: toxicity, pain, efficacy. Secondary: tumor measurement, immunogenicity	7, 10, 15, 20, 30 mg/[m^2·d]	100 mg/m^2 per cycle (= 10 mg/[m^2·d])	No, but justified	5 daily infusions of 20 mg/m^2 (first 5 days of each course) or continuous 10 mg/m^2 infusion (first 10 days of each course)	No

BID indicates twice daily; C, conditional; CBR, clinical benefit rate; DCR, disease control rate; DFSP, dermatofibrosarcoma protuberans; DLT, dose-limiting toxicity; E, exceptional; EOD, every other day; EOW, every other week; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; IFN, interferon; MTD, maximum tolerated dose; n/a, not applicable; NR, not reported; QD, once daily; QW, every week; Q2W, every 2 weeks; Q3W, every 3 weeks; OD, once daily; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; PROM, patient-reported outcome measure; RCC, renal cell carcinoma; SmPC, summary of product characteristics; TTP, time to progression; TTR, time to tumor response.

[a]Schedule *a*/*b* means treatment for *a* consecutive weeks, followed by a *b*-week rest period.

[b]Marketing authorization under exceptional circumstances.

[c]Conditional marketing authorization.

[d]Withdrawn from use in the European Union.

formal dose-finding studies. Difficulties in defining the right dose seem to be mainly attributable to the rarity of most diseases. Whether or not dose-finding studies in nonorphan drugs are performed more often is unclear. Yet, the absence of dose-finding studies in orphan drugs may be particularly problematic due to the other methodological shortcomings in clinical studies and the relatively high prices.

Only 26/49 of the orphan drugs (53%) were tested in healthy volunteers before marketing authorization. Twenty-three drug dossiers did not include studies in healthy volunteers, the absence of which was justified in 11/23 drug dossiers (48%). The 12 orphan drugs in which no formal justification for the absence of studies in healthy volunteers was found in the dossier were mainly indicated for the treatment of solid tumors. In general, first-in-human studies in patients may be preferable when drugs are cytotoxic, have a steep toxicity dose-response curve, or in the case of life-threatening diseases. Also, the expression of the pharmacological target may be different (or absent) in healthy volunteers compared to patients, which challenges the extrapolation to cancer patients.[33] The question is whether these reasons outweigh the advantages of studies in healthy volunteers, including the exploration of bioavailability, the reduction of patient exposure to low or ineffective drug doses, and the rapid study accrual.[34] Although an EMA guideline on first-in-human clinical trials mentions factors to consider in the decision to conduct a study in healthy volunteers or patients, the decision on whether or not to test a new drug in healthy volunteers is for the company developing the drug and the ethics committees.[35] Because healthy volunteer studies are easy to recruit for and can provide key pharmacokinetic information in a timely manner, these should be considered whenever ethical. The latter may be supportive in the development program and accelerate studies in cancer patients.[36]

Because drug doses are rarely formally optimized in phase 3 studies, selecting the right dose based on robust phase 1 and 2 dose-finding studies is paramount.[3] One may, however, wonder whether the poor conduct of dose-finding studies is problematic, given the fact that this did not lead to many postmarketing dose changes. Our literature search demonstrated that postmarketing dose-finding studies have been performed for some enzyme replacement therapies (eg, for Fabry disease, Pompe disease, mucopolysaccharidosis I).[5,9,10,12,17,18] Higher doses than the registered dose were studied (eg, due to a lack of effectiveness) as well as lower doses (eg, due to shortage). Also, different administration schemes were tested to improve dosing convenience. Likewise, in the field of oncology, postmarketing dose-finding studies are not uncommon,[25,27,30,31] and the

Table 5. Dose-Finding Studies Postmarketing (Oncology)

Drug	Disease (Registered Dose)	Studied Doses Postmarketing	References
Glivec	GIST (400 mg/d)	None	
Lysodren	Adrenal cortex neoplasms (2–3 g/d)	Low-dose regimen (1–3 g/d) vs high-dose regimen (1.5–6 g/d)	Kerkhofs et al, 2013[24]
Glivec	DFSP (800 mg/day)	None	
Nexavar	RCC (400 mg BID)	400 mg BID, escalated to 600 and 800 mg BID	Gore et al, 2017[25]
Sutent	GIST (50 mg QD on schedule 4/2)	Morning or evening dosing 37.5 mg/d	George et al, 2009[26]
Sutent	RCC (50 mg QD on schedule 4/2)	The same daily dose 5 consecutive days per week for 5 weeks and then the same daily dose on days 1, 3, and 5 in the sixth week; consecutive 6-week cycles	Buti et al, 2017[27]
Nexavar	HCC (400 mg BID)	600 mg BID in patients with radiologic disease progression	Rimassa et al, 2013[28]
Torisel	RCC (25 mg QW)	20 mg/m^2 QW for tolerability assessment; the remaining received 25 mg QW (East Asian patients)	Sun et al, 2012[29]
Yondelis	STS (1.5 mg/m^2 Q3W)	None	n/a
Afinitor	RCC (10 mg OD)	None	n/a
Mepact	Osteosarcoma (2 mg/m^2 Q2W for 12 weeks, followed by QW for 24 weeks for a total of 48 infusions in 36 weeks)	None	n/a
Yondelis	Ovarian cancer (1.1 mg/m^2 Q3W)	None	n/a
Cometriq	Thyroid cancer (140 mg OD)	None	n/a
Cyramza	Gastric cancer (8 mg/kg Q2W)	None	n/a
Lynparza	Ovarian cancer (400 mg BID)	300 mg BID	Pujade-Lauraine et al, 2017[30]
		200–450 mg BID	Mateo et al, 2016[31]
Nexavar	Thyroid cancer (400 mg BID)	200 mg BID (Chinese patients)	Chen et al, 2011[32]
Lenvima	Thyroid cancer (24 mg QD)	None	n/a
Unituxin	Neuroblastoma (17.5 mg/[m^2·d] on days 4–7 [courses 1, 3, and 5] and on days 8–11 [courses 2 and 4])	None	n/a
Lartruvo	Sarcoma (15 mg/kg on days 1 and 8 of each 3-wk cycle)	None	n/a
Onivyde	Pancreatic cancer (80 mg/m^2 Q2W)	None	n/a
Isqette	Neuroblastoma (5 daily infusions of 20 mg/m^2 or continuous 10 mg/m^2 infusion)	None	n/a

BID indicates twice daily; DFSP, dermatofibrosarcoma protuberans; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; n/a, not applicable; OD, once daily; QD, once daily; QW, every week; Q2W, every 2 weeks; Q3W, every 3 weeks; RCC, renal cell carcinoma; STS, soft tissue sarcoma.

reasons for this may be more often related to toxicity rather than to effectiveness. Postmarketing dose changes could to a certain extent reflect the quality of drug development, regulatory review, and postmarketing surveillance.[37] Remarkably, however, postmarketing studies have rarely led to an adjustment of the registered dose. The reasons for this may be multiple: (1) Postmarketing pharmacovigilance generally focuses on safety and the benefit/risk ratio—if the benefit/risk ratio remains positive, it is unlikely that a dose change will be implemented; (2) the regulators may not be informed about the results of such studies if these are not a postmarketing commitment (mentioned at the time of marketing authorization); (3) it could also be the case that the quality of the postmarketing studies is not sufficient to implement changes (eg, small sample size, inconclusive results). Therefore, if there are doubts about the dose at the time of registration, regulators may decide whether follow-up studies on the dose in larger populations are necessary. Such postmarketing studies could be included in the postmarketing obligations and ideally should focus not only on safety but also on effectiveness. The results of postmarketing dose-finding studies need to be reported to the regulators in a more systematic fashion, to allow for an informed decision on whether official dose changes are desirable.

The lack of dose-finding studies may be of varying importance depending on the orphan indication. In general, given the different expression of oncogenes in each different tumor type, it may be questionable if 1 dose will fit all. It is known, for example, that imatinib exposure varies 3-fold in healthy subjects and over 4-fold in patients with chronic myeloid leukemia.[38,39]

Yet still the drug is administered in a fixed dose. Also, cytotoxic chemotherapy is often dosed based on body surface area, although body size does not essentially reduce interpatient variability.[38,40] Hence, adjusting the dose for each individual patient is gaining popularity. Potential approaches for dose individualization include toxicity-adjusted dosing or therapeutic drug monitoring.[41] Therapeutic drug monitoring is based on plasma drug concentrations and has been proven useful to guide dose adjustment in antibiotics, anticonvulsants, and anti-HIV treatment.[42–44] Tyrosine kinase inhibitors, such as imatinib, sunitinib, and sorafenib, might also benefit from therapeutic drug monitoring.[38,45,46] It should, however, first be shown in prospective studies that therapeutic drug monitoring will actually lead to an improved clinical outcome.[41] Toxicity-adjusted dosing relies on the theory that toxicity can be used as an indicator of drug bioavailability, with low toxicity implying low drug exposure (and possibly impaired anticancer effect) and high toxicity implying high exposure.[38,41] However, not all toxicities are correlated with treatment response, and prospective studies of dose individualization based on toxicity are lacking.[41] Another approach for dose individualization is to adjust the dose based on the achievement of therapeutic goals, such as in Gaucher disease.[20] Because Gaucher, as are many other inherited metabolic diseases, is a disease with a highly heterogeneous course, it seems logical that 1 dose does not fit all. It may therefore be worthwhile to start treatment with a low (minimally effective) dose and adjust it according to the response.[47]

Other Studies

Our findings were confirmed by a report from the EMA stating that phase 2 studies are often abbreviated and simplified in order to move as quickly as possible to phase 3 studies.[1] Although our study is the first to evaluate the presence of dose-finding studies in orphan drugs in the EU, our results seem to match the results of another study, showing that failure to determine the right dose was a major reason for denial of marketing authorization: in 15.9% of the new drug applications, uncertainty existed about the optimal drug dose.[3] However, because this study included only US Food and Drug Administration–approved drugs and did not investigate orphan drugs specifically, it might not be a perfect parallel to our study.

Our study concluded that in 9/49 orphan drugs (18%), dose-related major objections were addressed. Interestingly, a recent study on dosing recommendations for medicinal products authorized in the EU found that in 10% of the medicinal products, dose- and/or schedule-related major objections were raised during assessment.[48] This study was, however, based on a larger number of dossiers, included both orphan drugs and nonorphan drugs and spanned a shorter time frame (2010-2015), as compared to our study (2000-2017). It is therefore difficult to compare this study with the current study and to conclude whether major objections are raised more frequently in orphan drug procedures than in nonorphan drugs. The study also showed that postmarketing dose changes were implemented in about 10% of all the drugs evaluated by the EMA between 2010 and 2015.[48] Reasons for postmarketing dose changes included drug-drug interactions, improved patient convenience, and adjustment of dose in special populations.

Economic Perspectives

Although dose-finding studies are known to be costly, proceeding with phase 3 studies with an incorrect dose may eventually lead to higher expenses when unsuccessful trials need to be repeated. Also, postmarketing dose changes can have a substantial economic impact.[49,50] For example, reducing the registered dose could result in reduced revenues for the pharmaceutical industry.[49] Dose increases would also impact price because negotiated pricing arrangements may limit willingness for reimbursement of higher prices. Both situations might make the pharmaceutical industry reluctant to conduct postmarketing dose-finding studies. Given the rising costs of orphan drugs, physicians and payers are likely to be more motivated to gather evidence that can justify dose changes.

Limitations

In general, information on dose-finding studies in the public domain is scarce; the European Public Assessment Reports tend to focus more on phase 3 studies, with less information provided on the dose-finding studies. For the purpose of this study, we had access to the day-80 and day-210 assessment reports, in which the required information could be found and summarized. As a general recommendation, it may be useful if reliable information on dose finding is made publicly available. This access will also contribute to applying checklists that measure the quality of reporting of studies, such as the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[51] This checklist can be used for observational, case-control, and cohort studies. There is, however, a lack of formal guidelines that evaluate the content or quality of phase 1 and 2 studies. We were therefore not able to make a reliable judgment on the quality of the dose-finding studies. Another limitation of our study is that the results of our literature search were prone to publication bias because studies with negative results are published less frequently. A list of postmarketing dose-finding studies is provided in Tables 3 and 5, but it is possible that this list is not exhaustive.

Ways Forward

In our study we focused on orphan drugs for metabolism disorders and oncology. It would, however, be of value to broaden the sample to all orphan drugs that were authorized by the EMA. This may provide an overview of the presence or lack of dose-finding studies throughout all orphan drugs registered in the EU.

With the sample we have analyzed so far, it can be concluded that 1 of the reasons for not performing dose-finding studies in rare disease is in some cases related to the rarity of the disease. An interesting question for a future study would be to evaluate whether the presence or quality of dose-finding studies correlates with the effectiveness of the drug postmarketing.

Finally, although guidelines on the development of medicinal products for specific diseases exist and include a section on requirements for dose-finding studies, there is a lack of formal guidelines that evaluate the content or quality of dose-finding studies. This is unfortunate because it has been shown that the quality of reporting and publication of phase 3 studies has been improved since quality assurance guidelines for randomized controlled trials were endorsed.[52] It is therefore highly recommended that guidelines be developed that enable clinicians and researchers to assess the quality of (dose-finding) phase 1 and 2 studies. A first step toward this has been taken by Zohar et al, who presented a quality assessment checklist for phase 1 oncology trials.[53] In addition to developing assessment checklists for dose-finding studies, regulatory authorities are stimulated to formulate clear rules about the requirements for dose-finding studies. This may provide a stronger incentive for drug manufacturers to conduct those studies. In the process of protocol assistance, regulatory authorities may underline the importance of dose-finding studies and thereby stimulate their initiation. As a consequence, fewer major objections might be raised, and delays or denials of marketing authorization will probably be decreased. In addition, if, at the time of authorization, uncertainty remains about the correct dose, the drug manufacturers should be obliged to conduct additional dose-finding studies in the postmarketing phase. Last but not least, investigator-initiated postmarketing dosing studies should be made known by companies, and their results need to be reviewed by the regulators for their potential impact on the summary of product characteristics.

Conclusion

Our study shows that dose-finding studies are performed in two thirds, and studies in healthy volunteers in half, of the dossiers of authorized orphan drugs (for metabolic diseases and solid tumors). Dose-finding studies that have been performed postmarketing suggest that registered doses are not always considered optimal. Despite this, doses are generally not changed postmarketing, whereas dose-finding studies both pre- and postmarketing are considered important to provide the necessary information. Therefore, guidance for such studies in the premarketing period, as well as obligations in the postmarketing period, should be developed. Such measures may increase the generation of more robust data to support finding the correct dose for treatment of patients with rare diseases. This is of importance both from a health care and economical perspective.

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Authors' Contributions

C.H., V.S., C.G., H.L., and Y.S. contributed to the study design. Y.S. was responsible for collecting research data, carried out the literature search, and drafted the manuscript. Data interpretation was performed by Y.S. and supervised by V.S. C.H., H.L., C.G., and V.S. critically reviewed the manuscript. All authors read and approved the final manuscript.

Competing Interests

The authors declare no conflicts of interest that are directly related to the content of this article. C.E.M.H. is involved in premarketing studies with Genzyme, Protalix, and Idorsia. Financial arrangements are made through AMC Research BV. No fees, travel support, or grants are obtained from the pharmaceutical industry. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of, or reflecting the position of, the EMA or 1 of its committees, working parties, or any of the national agencies.

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Data Sharing

Data are available from the lead author on request.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.