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 changes1-3. 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. 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, endpoints 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.).

**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 [Orfadíñ], glyceroxyl phenylbutyrate

**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.
| 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 |
|------------------|--------------|-----------------------|--------------------|-------------------------------------------------|-----------------------------------|-------------------------|-----------------------------|-----------|---------------------------|
| Fabrazymeb (2001) | Agalsidase beta | Fabry disease         | No                 | 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                        |
| Replagalb (2001)  | Agalsidase alfa   | Fabry disease         | No                 | 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 | No                        |
| Zavescab (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                        |
| Aldurazymeb (2003) | Laronidase     | MPS I                 | No                 | n/a                                             | n/a                               | n/a                     | No, but justified           | Yes; children | No                        |
| Carbaglu (2003)   | Carglumic acid | NAGS deficiency       | Yes                | n/a                                             | n/a                               | n/a                     | Yes; children               | Yes; children | No                        |
| Carbaglu (2011)   | Carglumic acid | Organic acidurias     | Yes                | n/a                                             | n/a                               | n/a                     | Yes; children               | Yes; children | 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 |
| Orfadinb (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 |
| Zavescab (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)
| Drug (Year) | Generic Name | Disease | MPS | Health Volunteers | Dose in Phase 1-2 Studies | Dose in Phase 3 Studies | Studies in Special Populations | Dose Changes Postmarketing | Dose SmPC | End Points |
|-------------|--------------|---------|-----|------------------|--------------------------|------------------------|-----------------------------|-----------------------------|-----------|-----------|
| Naglazyme® (2006) | Galsulfase | Pompe disease | MPS 6 | No² | 6-MWT, FVC, height, weight, grip strength, pinch strength, urinary GAGs, hepatomegaly, bone mineral density, visual acuity, cardiac function, sleep apnea. | CHAQ/HAQ | NR | 0.2 and 1 mg/kg | 1 mg/kg weekly | No | No |
| Myozyme (2006) | Alglucosidase alfa | Pompe disease | No² | No | 20 and 40 mg/kg | 20 mg/kg | No | 20 mg/kg EOW | No | No |
| Elaprase® (2007) | Idursulfase | MPS 2 | NR | NR | Liver and spleen volumes, pulmonary function, urinary GAGs, safety | GAGs, safety | n/a | 0.15, 0.5, or 1.5 mg/kg or pbo | 0.5 mg/kg | No |
| Cystadane (2007) | Betaine anhydrous | Homocystinuria | Yes | Yes | Safety, tolerability, blood Phe levels | GABA, urinary volumes | n/a | 5, 10 or 20 mg/kg | 10 and 20 mg/kg | No |
| Kuvan® (2008) | Sapropterin | PKU | Yes | Yes | Safety, tolerability, blood Phe levels | GABA, urinary volumes | n/a | 10 and 20 mg/kg | 20 mg/kg | No |
| Vpriv® (2010) | Velaglucerase alfa | Gaucher disease type 1 | GABA, pulmonary function, bone marrow | No² | 15, 30, and 60 U/kg | 60 U/kg | EOW | No | No | No |

(Continued)
| Drug (Year) | Generic Name | Disease | Studies in Special Populations | Dose in Phase 3 Studies | Doses Tested in Phase 1–2 Studies | Dose SmPC | Dose Changes Postmarketing |
|------------|--------------|---------|-------------------------------|-------------------------|----------------------------------|-----------|--------------------------|
| Revestive (2012) | Teduglutide | Short bowel syndrome | Yes | | 0.03, 0.10, 0.15, 0.10 or 0.15, 0.10 mg/[kg·d] and 0.10 mg/[kg·d] | 0.05 mg/[kg·d] | No |
| Orphacolb (2013) | Cholic acid | Errors in bile acid synthesis | Yes | | n/a | 5 to 15 mg/[kg·d] | n/a |
| Procysbi (2013) | Mercaptamine | Cystinosis | Yes | | 75 mg procysbi vs 150 mg cystagon | Dose equal to approximately 70% of their usual dose of cystagon | No, but justified |
| Kolbam (2014) | Cholic acid | Errors in bile acid synthesis | Yes | | n/a | 10–15 mg/[kg·d] | n/a |
| Vimizim (2014) | Elosulfase alfa | MPS 4a | No | | 0.1, 1, or 2 mg/[kg·wk] | 2 mg/[kg·wk] | No |
| Cerdelga (2015) | Eliglustat | Gaucher disease type 1 | Yes | | n/a | Yes;elderly | 84 mg (100 mg eliglustat tartrate) OD in CYP2D6 PMs; 84 mg BID in CYP2D6 IMs and EMs |
| Kanuma (2015) | Sebelipase alfa | LAL deficiency | No | | 0.35, 1, and 3 mg/kg | 1 mg/kg EOW | Yes; patients with renal/hepatic impairment |
| Ravicti (2015) | Glycerol phenylbutyrate | Urea cycle disorders | Yes | | n/a | 4.5 mL/[m²·d] to 11.2 mL/[m²·d] | No |
| Strensiqb (2015) | Asfotase alfa | Hypophosphatasia | No | | n/a | 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 |
| 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 |
|----------------|----------------------|-------------------------------|--------------------|-------------------------------------------------|-----------------------------------|------------------------|-----------------------------|------------|--------------------------|
| Ocalivac (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 (2017) | Chenodeoxycholic acid | CTX                           | No                 | n/a                                             | n/a                               | n/a                    | No                          | 750 mg/d, increased to max 1000 mg/d; Infants (1 mo–18 y) | 5 mg/kg/d in 3 divided doses | No          |
| Brineura (2017) | Cerliponase alfa     | NCL                           | No                 | n/a                                             | n/a                               | n/a                    | No, but justified 300 mg EOW | 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 xanthomatis; 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.

*ERTs are not tested in healthy subjects due to the risk of immunogenicity.

*Marketing authorization under exceptional circumstances.

*Conditional marketing authorization.
[Ravicti], and betaine anhydrous [Cystadane]), dosing based on plasma levels (eliglustat [Cerdelga]), and dosing based on modeling exercise (asfosfata 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 (asfosfata 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, 2007⁵              |
|                       |                                              | 0.5 mg/kg EOW, 0.3 mg/kg EOW  | Ghali et al, 2012⁶               |
|                       |                                              | (due to shortage)             |                                 |
|                       |                                              | 0.3–0.5 mg/kg (due to shortage)|                                 |
| Fabry                 | Replagal (0.2 mg/kg EOW)                     | 0.3 mg/kg                     |                                 |
|                       |                                              | 0.1, 0.2, or 0.4 mg/kg weekly;|                                 |
|                       |                                              | 0.2 mg/kg EOW, 0.4 mg/kg EOW  |                                 |
|                       |                                              | 0.2 mg/kg weekly              |                                 |
|                       |                                              |                               |                                 |
| Gaucher               | Zavesca (100 mg TID)                         | None                          |                                 |
| MPS I                 | Aldurazyme (100 U/kg EOW = 0.58 mg/kg)       | 1.2 mg/kg EOW                 |                                 |
| NAGS deficiency       | Start: Carbaglu (100 mg/[kg·d] up to 250 mg/kg if necessary, then 10–100 mg/[kg·d]) |                               |                                 |
| 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) |                                 |
| Hereditary tyrosinemia type I | Orfasin (1 mg/[kg·d] divided into 2 doses) | Single daily dose              |                                 |
| 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]                 |                                 |
| MPS 2                 | Elaprase (0.5 mg/[kg·wk])                    | 20 mg/[kg·wk] or 40 mg/kg EOW |                                 |
| 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]) | None                          |                                 |
| 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 |                                 |
| 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[m²·d])                       | None                          |                                 |
| Errors in bile acid synthesis | Kolbam (10–15 mg/[kg·d])                 | None                          |                                 |
| MPS 4s                | Vimizim (2 mg/[kg·wk])                      | None                          |                                 |
| Gaucher               | Cerdelga (84 mg BID) (100 mg eliglustrat tartrate) | 50 mg BID or 100 mg BID       |                                 |
| LAL deficiency        | Kanuma (<6 mo: 1 mg/[kg·wk]; >6 mo: 1 mg/kg EOW) | Infants <6 mo: 0.35 mg/kg EOW with intrapatient dose escalation up to 5 mg/[kg·wk] |                                 |
| Urea cycle disorders  | Ravicti (4.5 mL/[m²·d]) to 11.2 mL/[m²·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
| Drug (Year) | Generic Name | Disease | Healthy Volunteers | End Points | Doses Tested in Phase 1–2 Studies<sup>a</sup> | Dose in Phase 3 Studies | Studies in Special Populations | Dose SmPC | Dose Changes Postmarketing |
|------------|--------------|---------|-------------------|------------|---------------------------------|------------------------|-------------------------------|-----------|----------------------------|
| Glivec<sup>b</sup> (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 | 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. | 800 mg/d | No | Yes; elderly, patients with renal/hepatic impairment | No |
| Nexavar (2006) | Sorafenib | 1. RCC | Yes | Tolerability, safety, PK, PD, MTD, tumor response, survival | 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 |
| Sutent<sup>c</sup> (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 | 400 mg BID | 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 renal/hepatic impairment | 400 mg BID | 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<sup>2</sup> Q3W | 1.5 mg/m<sup>2</sup> | No | 1.5 mg/m<sup>2</sup> 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<sup>2</sup> twice weekly for 12 weeks; 2 mg/m<sup>2</sup> twice weekly for 12 weeks and then once weekly for 12 weeks; 2 mg/m<sup>2</sup> followed by dose titration based on monocytosis activation | 2 mg/m<sup>2</sup> | Yes; patients with renal/hepatic impairment | 2 mg/m<sup>2</sup> Q2W for 12 weeks, followed by QW for 24 weeks for a total of 48 infusions in 36 weeks. | No |
| Yondelis<sup>b</sup> (2009) | Trabectedin | 2. Ovarian cancer | No | PK, safety, ORR | 0.4–1.65 mg/m<sup>2</sup> Q3W, 0.58 mg/m<sup>2</sup> on days 1, 8, and 15 of a 28-day cycle, or 1.3 mg/m<sup>2</sup> on day 1 of a 21-day cycle | 1.1 mg/m<sup>2</sup> | No | 1.1 mg/m<sup>2</sup> Q3W | No |

(Continued)
| Drug (Year) | Generic Name | Disease | Yes/No | End Points | Doses Tested in Phase 1–2 Studies | Dose in Phase 3 Studies | Studies in Special Populations | Dose SmPC | Dose Changes Postmarketing |
|------------|--------------|---------|--------|------------|-----------------------------------|------------------------|-----------------------------|-----------|--------------------------|
| Cometrix (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 400 mg BID and subsequently at 100 mg BID, 200 mg BID, or 400 mg BID | 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, PK | 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 | 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 (2015) | Dinutuximab | Neuroblastoma | Yes | Safety, toxicity, PK, clinical response | 10 to 200 mg/m² | 25 mg/m² | No | 17.5 mg/[m²·d] on days 4–7 (courses 1, 3, and 5) and on days 8–11 (courses 2 and 4) | No |
| Lartruvo (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/m² Q3W, 80, 90, and 100 mg/m² Q2W | 80 mg/m² (if homozygous for UGT1A1*28 allele: 60 mg/m² increased to 80 mg/m² if necessary) | No | 80 mg/m² Q2W | No |

(Continued)
Table 4. Continued

| Drug (Year) | Generic Name | Disease | Healthy Volunteers End Points | Dose Tested in Phase 1–2 Studiesa | Dose in Phase 3 Studies | Dose Changes Postmarketing Studies in Special Populations | Dose SmPC |
|-------------|--------------|---------|--------------------------------|----------------------------------|------------------------|--------------------------------------------------------|-----------|
| Isqetteb (2017) Dinutuximab beta | Neuroblastoma | No primary: toxicity, pain; efficacy. Secondary: tumor measurement, immunogenicity | 7, 10, 15, 20, 30 mg/m²·d | 100 mg/m² per cycle (= 10 mg/m²·d) | No or justified | No, but justified | 5 daily infusions of 20 mg/m² (first 5 days of each course or 10 mg/m²·d loading; first 10 days of each course) |

BID indicates twice daily; C, conditional; CBR, clinical benefit rate; DCR, disease control rate; DLT, dose-limiting toxicity; E, exceptional; EOD, every other day; EOY, every other year; EOW, every other week; Q2W, every 2 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.

aSchedule a/b means treatment for a consecutive weeks, followed by a b-week rest period.

bMarketing authorization under exceptional circumstances.
cConditional marketing authorization.
dWithdrawn 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. 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. 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. 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.

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. 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 1). 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, and the
Table 5. Dose-Finding Studies Postmarketing (Oncology)

| Drug        | Disease (Registered Dose) | Studied Doses Postmarketing | References                  |
|-------------|---------------------------|-----------------------------|------------------------------|
| Glivec     | GIST (400 mg/d)           | None                        | Kerkhofs et al, 2013²⁴      |
| Lysodren   | Adrenal cortex neoplasms (2–3 g/d) | Low-dose regimen (1–3 g/d vs high-dose regimen (1.5–6 g/d) | Gore et al, 2017²⁵           |
| Glivec     | DFSP (800 mg/day)         | None                        | Kerkhofs et al, 2013²⁴      |
| Nexavar    | RCC (400 mg BID)          | None                        | Kerkhofs et al, 2013²⁴      |
| Sutent     | GIST (50 mg QD on schedule 4/2) | Morning or evening dosing 37.5 mg/d | Gore et al, 2017²⁵           |
| 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, 2017²⁷           |
| Nexavar    | HCC (400 mg BID)          | 600 mg BID in patients with radiologic disease progression | Rimassa et al, 2013²⁸        |
| Torisel    | RCC (25 mg QW)            | 20 mg/m² QW for tolerability assessment; the remaining received 25 mg QW (East Asian patients) | Sun et al, 2012²⁹            |
| Yondelis   | STS (1.5 mg/m² Q3W)       | None                        | n/a                         |
| Afinitor   | RCC (10 mg OD)            | None                        | n/a                         |
| Mepact     | Osteosarcoma (2 mg/m² 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/m² Q3W) | None                      | n/a                         |
| Cometrix   | 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, 2017³⁰ |
| Nexavar    | Thyroid cancer (400 mg BID) | 200–450 mg BID             | Mateo et al, 2016³¹         |
| Lenvima    | Thyroid cancer (24 mg OD)  | 200 mg BID (Chinese patients) | Chen et al, 2011³²          |
| Unituxin   | Neuroblastoma (17.5 mg/m² 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/m² Q2W) | None                      | n/a                         |
| Isqette    | Neuroblastoma (5 daily infusions of 20 mg/m² or continuous 10 mg/m² 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{42–44} Tyrosine kinase inhibitors, such as imatinib, sunitinib, and sorafenib, might also benefit from therapeutic drug monitoring.\textsuperscript{38,45,46} It should, however, first be shown in prospective studies that therapeutic drug monitoring will actually lead to an improved clinical outcome.\textsuperscript{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.\textsuperscript{38,41} However, not all toxicities are correlated with treatment response, and prospective studies of dose individualization based on toxicity are lacking.\textsuperscript{41} Another approach for dose individualization is to adjust the dose based on the achievement of therapeutic goals, such as in Gaucher disease.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{46} 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.\textsuperscript{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.\textsuperscript{49,50} For example, reducing the registered dose could result in reduced revenues for the pharmaceutical industry.\textsuperscript{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.\textsuperscript{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. 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. 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
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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.