Drug development for rare pediatric epilepsies: current state and future directions

Stéphane Auvin[1,2], Andreja Avbersek[3], Thomas Bast[4,5], Catherine Chiron[1,6], Renzo Guerrini[7], Rafal M. Kaminski[3], Lieven Lagae[8], Pierandrea Muglia[3], J. Helen Cross[9]*

1. PROTECT, INSERM U1141, Université de Paris, Paris, France

2. AP-HP, Hôpital Universitaire Robert-Debré, Service de Neurologie Pédiatrique, Paris, France

3. UCB Pharma, Braine-l'Alleud, Belgium

4. The Kork Epilepsy Center, Kehl-Kork, Germany

5. Medical Faculty of the University of Freiburg, Freiburg, Germany

6. AP-HP, Hôpital Necker-Enfanst Malades, Service de Neurologie Pédiatrique, Paris, France

7. Neuroscience Department, Children's Hospital Anna Meyer-University of Florence, Florence, Italy

8. University Hospitals, University of Leuven, Department Development and Regeneration, section Paediatric Neurology, Leuven, Belgium

9. UCL NIHR BRC Great Ormond Street Institute of Child Health, London, UK

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Corresponding author:

Stéphane Auvin, MD, PhD

Service de Neurologie Pédiatrique et des Maladies Métaboliques

CHU Hôpital Robert Debré

48, Boulevard Sérurier

75935 PARIS CEDEX 19 - France

Phone: +33 1 40 03 57 24,Fax: +33 1 40 03 47 74

Email: stephane.auvin@aphp.fr

*Current address: Roche Pharma Research and Early Development (pRED), Roche Innovation Center Basel, Switzerland

Abstract Rare diseases provide a challenge in the evaluation of new therapies. However, orphan drug development is of increasing interest because of the legislation enabling facilitated support by regulatory agencies through scientific advice, and the protection of the molecules with orphan designation. In the landscape of the rare epilepsies, very few syndromes, namely Dravet syndrome, Lennox-Gastaut syndrome and West syndrome, have been subject to orphan drug development. Despite orphan designations for rare epilepsies having dramatically increased in the past 10 years, the number of approved drugs remains limited and restricted to a handful of epilepsy syndromes. In this paper, we describe the current state of orphan drug development for rare epilepsies. We identified a large number of compounds currently under investigation, but mostly in the same rare epilepsy syndromes as in the past. A rationale for further development in rare epilepsies could be based on the match between the drug mechanisms of action and the knowledge of the causative gene mutation or by evidence from animal models. In case of the absence of strong pathophysiological hypotheses, exploratory/basket clinical studies could be helpful to identify a subpopulation that may benefit from the new drug. We provide some suggestions for future improvements in orphan drug development such as promoting pediatric drug investigations, better evaluation of the incidence and the prevalence together with the natural history data, and the development of new primary outcomes.

Key points

- Very few epilepsy syndromes, namely Dravet syndrome, Lennox-Gastaut syndrome and West syndrome, have been subject to orphan drug development.
- A large number of compounds are currently under investigation, but mostly in the same rare epilepsy syndromes as in the past
- A compound could be relevant for orphan drug development based on its mechanism suggested by the knowledge of the causative gene mutation or by data obtained from animal models
- In the absence of pathophysiological hypotheses, exploratory/basket clinical studies could be helpful for identifying a target population

1. Introduction

Rare diseases provide a challenge in the evaluation of new therapies, not only because of the numbers of subjects required for sufficiently powered clinical trials, but also because of the lack of previous experience in clinical trials, clear endpoint trajectories, and required regulatory package. The heterogeneity in the clinical presentation observed in central nervous system diseases is also challenging for drug development. This is even more the case for the increasing number of rare epilepsies, leading to the question as to how we should move forward. The aim of this review is to provide an overview of current limitations and opportunities for drug development for rare pediatric-onset epilepsies.

There is no single, universally accepted definition for rare or orphan diseases. A recently published review by the Rare Disease Terminology & Definitions Used in Outcomes Research Working Group revealed 296 definitions used by 1109 agencies or organizations. While some definitions rely exclusively on the prevalence of a disease, others consider additional factors, such as severity or existence of adequate treatments. The terminology related to definitions has important implications, for example in the context of regulatory approvals of new medications . The United States (US) was the first country to introduce a set of commercial incentives for drug development for diseases affecting small populations with the Orphan Drug Act in 1983 [2]. Similarly, the European regulation 141/2000 covers development of products for rare diseases in the European Union (EU) [3]. The Food and drug Administration (FDA) Office of Orphan Products Development provides orphan status to drugs ‘intended for the safe and effective treatment, diagnosis, and prevention of rare diseases/disorders that affect fewer than 200,000 people in the US’ [2], or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug [4]. These criteria are sufficient to obtain orphan designation by the FDA. In the EU, a disease is considered rare if the prevalence is less

than five per 10,000 of the EU population [3], and for the European regulatory agency (EMA) to grant orphan status, the low prevalence of the disease needs to be associated with a clear unmet need. The status can also be granted if 'it is unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development' [4]. An 'orphan' disease is the label given to a disease that does not receive a lot of attention in the research world. It could also be a disease for which there is no specific treatment. Patients can therefore feel 'orphaned' in the world of healthcare. Although no legal definition of 'ultra-orphan' diseases has been established, this sub-category has been used by the National Institute for Health, in the US and the National Institute for Health and Care Excellence (NICE) in the UK for diseases with a prevalence of less than one in 50,000 of the population [5].

Legislation enabling advantageous regulation and pricing has been an important driver of increased interest in orphan diseases [6]. For any particular company, orphan drug development benefits are to have a priority review voucher in the US and need a limited sale force that could be helpful for small companies, start-up and biotech. Orphan designation is a way to obtain marketing authorization after completing phase II trials. However, these are not the only factors contributing to the significant increase in drug development programs for orphan diseases, in particular, for rare epilepsies. Some epilepsy syndromes are easily identifiable because of better definition and progress in the knowledge with regard to early identification. Advances in genetics and molecular biology, as well the ability of social media to allow patient groups to organize and connect with millions of people worldwide inexpensively, have also been some contributing factors promoting orphan drug development [7, 8]. The ability to include homogenous populations in clinical studies, combined with a clear link with the disease mechanism increases the probability of regulatory success [9]. Finally, the classic paradigm of antiepileptic drug (AED) development focused on focal onset seizures has been almost completely exhausted by the approval and marketing of many new compounds in recent years.

Combined with the patent expiration for blockbuster drugs, this has provided a motivation for pharma industry to explore other epilepsy syndromes. An additional advantage is that no established standard of care drugs needs to be included in the trial design, except in the EU where an established standard of care is/can be required for a comparative design. However, in most of rare epilepsies, the high level of pharmacoresistance might mitigate the need of comparative data.

Traditional drug development in epilepsy has resulted in the availability of more than 40 AEDs, focused mainly on epilepsy with focal onset seizures, allowing a large possibility of choice for such patients. However, since most approvals have been based on placebo-controlled randomized trials, there is a general lack of comparator data from head-to-head trials and it is not possible to ascertain which AEDs are more efficacious than others [10]. A significant decrease in seizure frequency does not prove that a compound is more effective than any other drug just as it does not prove that this compound is more appropriate for a particular epilepsy syndrome. The prescribers have to choose an AED at an individual level based on the pharmacological and side effect profile. Considering the multitude of approved AEDs without differentiating features, payers have started, particularly in the EU to request comparative data. This is usually provided through indirect comparison or network meta-analysis methodology, an approach which is often unable to capture unmeasured confounding factors and population heterogeneity [11]. An example of such an issue was the withdrawal of perampanel from the German market between 2013 and 2017 [4]. Considering the lack of animal models with good predictive value for clinical superiority together with truly innovative and/or more specific mechanism of actions, pharmaceutical industry seems to have a decreased interest in developing new AEDs for partial onset seizures in adults.

Meanwhile the number of orphan designations has increased over recent years [12]. In 2016, a cross-sectional analysis evaluated the impact of orphan drug designation in the US and

in Europe [12]. Although the number of orphan drug designations has dramatically increased over time, the number of approved drugs is four-fold less than the number of orphan drug designations in the same period of time. It is therefore obvious that the number of orphan designations cannot be used as the only criterion to evaluate the success of the orphan drug regulations. Indeed, the orphan designation is not part of the drug approval process. Since it is essential for a company to ensure the drug is eligible for commercial incentives, applying for orphan designation may sometimes be a strategy for data protection or to access scientific advice by the regulatory agencies. There have been more orphan designations in the US than in the EU [12], and this is partly because of some differences in drug development and regulatory pathways in both regions as exemplified by the approval of vigabatrin or clobazam [12]. Both drugs have been approved several years ago in EU but went through orphan drug development recently in the US.

In the study of rare epilepsies, Dravet syndrome (DS) has been used as a model for orphan drug development following on from those for Lennox–Gastaut syndrome (LGS) [13, 14]. The electroclinical features of DS as well as the outcome are relatively homogeneous, facilitating development. Moreover, 70–80% of the patients exhibit a de novo mutation of the *SCN1A* gene [15]. This has led to a well-defined and homogeneous population with convulsive seizures that are reliably countable. Several drugs have undergone evaluation through randomized controlled trials (RCTs) for DS. Stiripentol and cannabidiol (Epidiolex) received an orphan approval while fenfluramine pivotal studies have been completed with positive results [16-18]. With the increase in approvals, this will lead to a possible saturation of the market with an issue for the pricing and possibly the request from the regulatory agencies to demonstrate superiority to the previously approved drugs. Considering the large number of AEDs for common epilepsies approved, and the larger unmet medical need for rare pediatric epilepsy syndromes, it is crucial to now consider the opportunity for drug development in rare epilepsies other than LGS and DS.

In June 2017, a group of European Pediatric Epilepsy experts met in Brussels to discuss the current state and directions of drug development in the rare epilepsies. The goals of the meeting were to consider the ongoing clinical trials, identify gaps and unmet needs, limiting factors for drug development, as well as to provide suggestions for improvements for the future. The summary of this meeting is outlined in the present manuscript.

2. Current orphan drugs in rare epilepsies

Both the orphan drug regulation and the evolution of the drug development market has led to a rising interest in orphan drug development [6, 12]. With more products available, the payers have started pushing back and searching for ways to reduce the costs. Companies may be discouraged by a large number of competitors in certain diseases, competing for small populations for clinical trials. The most attractive orphan diseases are those where effective treatment may also apply to another disease with a larger population, and consequently expansion is possible.

In recent years, this growing interest has led to different pediatric orphan epilepsy designations and drug approvals (TABLE 1). Orphan designation provides a special status to a drug because it will be developed for an orphan disease. This status gives access to protocol assistance (EMA), market exclusivity (EMA), tax credits (FDA) and fee reductions (EMA, FDA) [19, 20]. The designation, however, does not guarantee that a drug will be approved. Orphan drug approval will be dependent of the data collected during drug development. Over the 10-year period from January 1, 2008 to December 31, 2017, the FDA granted 53 orphan designations for epilepsy drugs of which 30 (70%) were for pediatric orphan epilepsy

indications. The remainder were mostly for status epilepticus or acute repetitive seizures. Most of the 30 pediatric orphan epilepsy indications were for an orphan epilepsy syndrome with already previous successful drug development (DS, LGS and infantile spasms (IS)). Finally, the number of FDA-approved orphan epilepsy drugs in the same period was only three (rufinamide and clobazam for the treatment of LGS, and vigabatrin for IS). Of note, these were drugs already in use for focal seizures. Only cannabidiol (Epidiolex) is an FDA-approved orphan drug with approval for a specific seizure type. Meanwhile, the EMA granted seven orphan designations that were also for the same orphan pediatric epilepsy syndromes mentioned above. There has been only one approval for an orphan drug for pediatric epilepsy in the past 10 years by the EMA, which is for cannabidiol (Epidiolex). Everolimus has been approved for epilepsy in Tuberous Sclerosis Complex (TSC) while the orphan designation has been given for treatment of subependymal giant-cell astrocytoma [21]. Cerliponase alfa, a recombinant form of human tripeptidyl-peptidase 1, has been approved with an orphan status as enzyme replacement for neuronal ceroid lipofuscinosis type 2, a neurodegenerative disease that is one cause of progressive myoclonic epilepsy [22].

Despite the above described observations, drug development for the rare epilepsies is definitively an active field. TABLES 2 and 3 report the current landscape of orphan drug development. This analysis shows a non-homogeneous distribution of the drugs currently under development for rare epilepsies. Indeed, four rare epilepsies accumulate most of the studied compounds that we have been identified – namely DS, LGS, West syndrome (IS) and epilepsy in TSC – whereas some others do not have any drug currently under investigation. Moreover, progressive myoclonic epilepsies are a group of uncommon clinically and genetically heterogeneous disorders characterized by myoclonic seizures, other seizure types, and progressive neurological deterioration. Recently, biological insights in this group of conditions have provided the possibility of meaningful treatment as recently illustrated by the development and the approval of cerliponase alpha [23]. We describe below the factors that are limiting drug

development.

3. Unmet needs in pediatric epilepsies

The majority of the rare epilepsy syndromes have no approved drugs for treatment. Based on the discussion of the workshop using the International League Against Epilepsy (ILAE) Commission on Classification and Terminology list of syndromes and the list of syndromes by etiology (https://www.epilepsydiagnosis.org/index.html), we have generated a list of epilepsies with unmet needs (TABLE 4).

In addition to this limited list, we highlighted that a significant number of patients in clinical practice cannot be classified in any of the existing categories even when they have been appropriately evaluated and investigated by an expert center [24-26]. This subgroup is characterized by developmental delay, pharmacoresistance, the lack of identified cause despite adequate imaging and genetic investigations, with poor long-term outcomes. There is a clear need for drug development for this population, however, since these patients do not meet the criteria for a specific syndrome, they often prove ineligible for participation in clinical trials. We suggest extending our understanding of what constitutes an orphan pediatric epilepsy population considering this population with unmet needs as a separate, definite entity, despite the lack of syndromic or etiologic categorization. Within this population, we could then consider grouping patients based on one seizure type such as, for example, tonic seizures. Further delineation of this population including epidemiologic data would be of interest for trial regulatory discussion.

There are also unmet needs in the epilepsy syndromes with already approved drugs, and not only because a significant proportion of patients remain inadequately controlled. Drug

approvals for all rare epilepsies have been based on countable seizures. An evaluation of other seizure types experienced by the patients or a more holistic evaluation of the treatment (including behavior, cognition, long-term development, quality of life, adverse events) would be of interest. Some investigators are developing composite scores that could be used for this purpose [27]. Improving long-term developmental outcomes remains a very important and insufficiently addressed aspect in all these syndromes. However, returning to the epilepsy syndromes with approved drugs, there are specific unmet needs in each syndrome. For DS, there is no study that has explored the efficacy of the drug in the early stages of the disease, i.e. before the age of 2 years, when status epilepticus is frequent. For LGS, the usual designs for RCTs rely on drop-attack seizure count (mix of tonic and atonic seizures) as the outcome. Even though this has led to the approval of several drugs (lamotrigine, felbamate, topiramate, rufinamide, clobazam), the clinical picture of a patient with LGS is broader than the drop seizures [28]. These patients experience other types of seizures including generalized tonic-clonic seizures, atypical absences and tonic seizures at night. In West syndrome, approved first-line treatments are associated with significant response rates. However, the treatment options for the pharmacoresistant population are very limited and as yet there have been no successful clinical trials leading to drug approval after the first-line treatment. Finally, the epilepsy community would need a paradigm shift towards the development of disease modifying medicines capable of altering the course of the underlying rare diseases rather than simply modifying epileptic symptoms with currently available antiseizure drugs.

4. Limiting factors for drug development

4.1 Limiting factors in pediatrics

There are several limiting factors for orphan drug development in pediatric onset epilepsies. Some of these are related to the investigations in a pediatric population, while others are more

specific to the rare epilepsies. Drug development in the pediatric population is more challenging than in adults. This is because of a mix of identified factors such as [29, 30]:

- Unique ethical challenges
- Special protection provided to children in clinical studies
- Parents' unwillingness to enroll their children in clinical studies (exposure to an investigational drug or time spent for the trial procedures)
- Reluctance of parents to participate when the design includes a placebo, especially when a drug may be obtained by prescription
- Concern by physicians of the use of placebo
- Special vulnerability at this age (growth, puberty, behavior, learning process, cognition)
- Relatively small populations when compared with the adult population
- Lack of trained pediatric investigators
- Decades of off-label use of drugs for pediatric ages leading to clinical use before investigation.

In the large group of epilepsies with focal-onset seizures, some of these limitations might change with the use of extrapolation of the data from adults, which should reduce the number and complexity of pediatric trials necessary to achieve pediatric labeling, although supportive pediatric data would still require that age-related pharmacokinetic, safety, growth/puberty impact, behavior and cognitive impact are explored. In the pediatric epilepsy field, the regulatory bodies have accepted the extrapolation of the efficacy of an AED down to 4 years based on adult data [31-33]. More recently, accumulating data suggesting the possibility extrapolating the efficacy down to 2 years of age led to a FDA agreement for this lower age [34-36]. The extrapolation of the efficacy for children would lead to simpler clinical trials assessing safety and pharmacokinetics. The time and the money made available by using extrapolation of the efficacy for focal-onset seizure could become an opportunity to direct the efforts towards orphan

drug development.

4.2 Placebo effect in pediatric epilepsy

The placebo effect in the pediatric population has been identified as a methodological challenge in the assessment of epilepsy with focal onset seizures. Using a meta-analysis, a consistent two-fold higher placebo effect has been shown in the pediatric population compared with the adult population resulting in lower difference of 50% responder rate for active AED over placebo [37]. Including five RCTs conducted in children, this study found that 19%±2.3 were responders in the placebo arm, while in adults this was 9.9%±4.6. Some authors suggested that this placebo response could be an age dependent phenomenon [38, 39]. Other authors have shown that some seizure reduction might be because of the natural course of the disease itself [40]. Regardless of the causes, this effect should be taken into consideration in the design of RCTs in children, although certain severe and rare epileptic syndromes have lower placebo response rate (TABLE 5).

The data from the RCT investigating drugs in DS and in LGS syndrome do not show a high placebo response (TABLE 5). In these syndromes, it is unclear if the placebo response is similar in children and adults due to the fact that the available trials have been conducted either in the pediatric population only, or in both pediatric and adult populations. This placebo effect should be taken into consideration for the calculation of the requested number of patients for future trials planning, particularly if there is no previous trial.

4.3 Limiting factors in rare epilepsies

Some factors are more specific to the rare condition itself. In the US, when a marketing application is submitted to the Office of Orphan Product Development (OOPD), an orphan drug designation request must have been submitted previously [20]. For the FDA the request should

contain information on the disease and its prevalence, the drug and its rationale for use, and it should also include some estimation and justifications of non-recovery of cost (i.e. cost related to the orphan development that would not be recovered), if applicable [7, 41]. For the EMA, an orphan drug approval can be granted for a life-threatening or chronically debilitating disease with a prevalence of less than five in 10,000 and for which the EU marketing of the drug would not generate sufficient returns to justify the investment required for development. This should be considered when no satisfactory treatment exists, or if there is a treatment, the drug that is developed should provide a significant benefit (TABLE 6).

4.4 Unknown incidence and prevalence of the diseases. Except for DS, there are very few true incidence studies about rare epilepsies. The same applies for prevalence. In many cases, the prevalence is extrapolated from the incidence [42]. However, it seems that this approach is inadequate because the calculated prevalence differs from the real prevalence [42]. It would be of interest to promote good epidemiological studies for the prevalence of rare pediatric epilepsies. Rigorous epidemiological data are important for evaluating whether the number of patients that would be required for a clinical trial actually exists taking into an account that only a fraction of the patients may enter into a study according to the inclusion criteria. This population could be narrowed down to a dedicated age range for inclusion in view of the age limited expression of some epilepsies or based on the homogeneity of the electroclinical phenotype at a specific age. Similarly, some patients may have a lower seizure frequency than required during the screening period related to an already available effective treatment. The epidemiological data evaluated with the factors limiting the includable patients would also give some insights regarding the number of centers that would need to be opened and the duration of recruitment required. Finally, an accurate prevalence estimation would also have a clear impact on the strategic choice for a company to start drug development for one given syndrome or another. It would be an important point for pricing negotiation after approval.

4.5 Diagnosis criteria for the pediatric epilepsy syndromes. The pediatric epilepsy syndromes, including the rarest, are now well identified. The successive ILAE classifications or the ILAE terminology modification have constantly updated these concepts [43, 44]. However, there are currently no validated or accepted diagnostic criteria for all pediatric epilepsy syndromes. This is currently a work in progress by the ILAE nosology Task Force. The availability of clear and validated diagnostic criteria will be helpful for inclusion criteria as well as for prescreening evaluation of a targeted population.

The absence of defined diagnostic criteria might result in some heterogeneity of the included patients challenging the quality and results of a clinical trial. Attempts to improve the quality in the diagnosis of included patients have been undertaken in recent clinical trials. A validation of the diagnosis by central reviewers (e.g. the epilepsy consortium [45]) has been utilized to optimize reliability in the diagnosis. This has been undertaken in trials in idiopathic generalized epilepsies, LGS and DS [16, 46, 47].

There is probably a need for several levels of diagnosis. If the diagnostic criteria describe the full picture of a well-established epilepsy syndrome, it may not be possible to develop a drug that will be used early in the course of the disease. Some syndromes such as LGS need time from the first seizure to develop all types of seizures and all electroencephalographic criteria. It would be useful to evaluate whether some operational diagnostic criteria would permit the inclusion of patients in clinical trials in earlier stages of their disease. Unfortunately, however, this might introduce some heterogeneity to the studied population; post-hoc analysis of more homogeneous subgroups might partially rebalance this bias.

4.6 Lack of robust data on natural history of rare pediatric epilepsy syndromes. Accumulating knowledge on rare epilepsies has provided clinicians with a good overview of the outcomes for a significant proportion of these conditions. However, for some of them, robust

data with standardized evaluation are missing. Longitudinal, prospective, multicenter well-phenotyped cohorts would be of interest. The clinical evaluation should include seizure characteristics as well as behavior, cognition and other neurological symptoms.

This could be an opportunity to build groups of historical controls and to minimize placebo use. Historical controls have been used for the evaluation of AED monotherapy in adult patients with focal onset seizures [48-51].

This is a requirement, in particular, if we wish to develop new treatment strategies or new primary outcomes. In order to develop first- or second-line treatments, it will be required to be aware of the usual rate of those who are seizure-free or responders >50% after the usual standard of care. If a primary outcome other than seizure response is to be considered, data would also be needed on the cognition, behavior, or any symptoms that we want to target by a treatment.

For some epilepsy syndromes, we know that the outcome can be highly variable from one patient to another. The treatment response prediction could then become a real challenge. For example, in epilepsy with myoclonic atonic seizures it appears that approximately half of the patients are easily controlled [52, 53]. For a clinical trial in this syndrome, it would then be important to know when a patient can be considered to be most likely in one group or the other, and what predictors may help to identify a patient likely to be pharmacoresistant during early evaluation, or for evaluation of disease-modifying effect.

5. Developing new orphan drugs

There are several ways to initiate the exploration of a drug for a rare epilepsy (FIG. 1). These methods are not unique and a combination of several approaches could be helpful. For some rare epilepsies, a drug could be relevant based on its mechanism of action suggested by the

knowledge of the causative gene mutation or by data obtained from animal models. In the absence of pathophysiological hypotheses, exploratory/basket clinical studies could be helpful for identifying a target population. The efficacy of stiripentol in DS was first suspected in such a study [54] before the confirmation of the effect with two RCTs [55].

5.1 Either MoA- or gene-driven

A drug development could be initiated based on the neurobiology of a rare epilepsy syndrome. The landscape of gene discovery in the rare epilepsies is rapidly expanding [56], and drives both rational drug discovery and phenotypic screening efforts.

Genetic models, of mammalian and non-mammalian (e.g. zebrafish) type, are now used increasingly for drug discovery, and in particular for monogenic epilepsies. Some of these models (e.g. Dravet zebrafish scn1Lab mutant) enabled wide drug screening efforts and appear to have good predictive value (e.g. fenfluramine) [57-59]. In vitro models have also been developed (e.g. human iPS-derived neuronal cultures) that could be used to understand the underlying mechanisms of gene mutation and perform preclinical drug evaluation [60].

Gene sequencing and cloning from patient material have allowed rapid expression and identification of dysfunctional proteins (e.g. ion channels) using in vivo or in vitro model systems, which can enable precision in medical treatments in patients (TABLE 7). However, the initial preclinical findings do not always fully translate to the clinic, as recently reported with the lack of efficacy of quinidine in children with KCNT1 mutations [61, 62]. In contrast, preclinical discoveries in genetic models of TSC provided strong support for clinical studies with mTOR inhibitors [63, 64], which have now proven clinical efficacy for this syndrome [65]. The use of genetically modified mice might also be useful for screening drugs that are not necessarily directly linked with the disease-causing mutation. For example, it has been shown that in the TSC mouse model a GluN2C antagonist [66] and anti-inflammatory drugs (IL-1b and CXCL10 inhibitor) reduce seizures during a specific time window of brain development [67]. These

hypotheses have not yet been evaluated at the clinical level. Interestingly, additional support for drug discovery efforts comes directly from patient organizations funding drug screening research (e.g. TS Alliance in the US) [68]. The preclinical evaluation could also be based on the use of an appropriate animal model not derived from genetic findings , such as in various models of West syndrome [69]. However, the lack of well-described predominant mutation for some rare epilepsies complicate development of robust and predictive animal models. For example, there are no models for LGS, for epilepsy with myoclonic-atonic seizure, or for epileptic encephalopathy with continuous spikes and waves during sleep (EE-CSWS) [70, 69].

The neurobiology of neurotransmission during brain development could also be used to identify new treatment modalities. There are several developmental brain changes (presynaptic and post synaptic) that lead to a decrease or inefficiency of the GABAergic pathways during early brain development. The most prominent example is the fact that GABA exerts a paradoxical depolarizing action during early development. The paradoxical GABAergic excitatory action results from a change in chloride transporter expression. There is a preponderance of neuronal chloride importers during early development, such as the chloride transporter, sodium-potassium-chloride co-transporter 1 (NKCC1), over chloride exporters, such as the potassium-chloride co-transporter 2 (KCC2). This results in a relatively elevated intracellular chloride level and changes in chloride reversal potential [71, 72]. When $GABA_A$ receptors are activated, chloride flow is outwards, causing neuronal depolarization [71-76]. During brain development, there is a gradual increase in the KCC2 cotransporter which lowers intracellular chloride level resulting in a facilitation of hyperpolarizing GABA effect in more mature neurons [72]. These findings have led to the evaluation of bumetanide, an inhibitor of NKCC1, for neonatal seizures. However, an initial trial resulted in a safety issue in the treated newborns, without clear seizure improvement [77]. The data from a second trial are now pending [78], [79].

5.2 Exploratory clinical studies

Exploratory studies have been used successfully to identify potential orphan drug candidates [54, 80, 81]. Such an approach represents a unique way of exploring candidates for orphan drug development, in particular, when there is no gene or identified underlying mechanisms [82]. An initial well-conducted phase 1 study would be required before any exploratory study. There are several ways to conduct exploratory studies. The first consists of including a diverse cohort of patients with pharmacoresistant epilepsy to perform a stratification analysis after drug treatment that could lead to the identification of a particular syndrome or subgroup of responders. The second would be to include patients with pharmacoresistant developmental and/or epileptic encephalopathies of unknown origin with several seizure types. Looking at drug development in children with focal onset seizures, the patients are not selected on the underlying etiology but on one common seizure type. Therefore, for the same epilepsy syndrome, i.e. epilepsy with focal onset seizures, there are many underlying etiologies such as malformations of cortical development and the acquired structural abnormalities in those with a normal MRI. The same approach might be considered in other epilepsies. This kind of design could be helpful in identifying the efficacy of a drug on a particular seizure type rather than the efficacy in a given syndrome. We could then consider selection of patients based on seizure types more frequently observed in rare epilepsies such as tonic seizures, myoclonic-atonic seizures or myoclonic seizures.

These two proposals for conducting exploratory studies are complementary. A large exploratory study would avoid missing the efficacy of a drug potentially useful in any rare epilepsy. In addition, exploratory studies provide us with the opportunity to collect data (pharmacokinetic, safety) important in drug development. This would enable the risk of seizure worsening to be explored, such as that observed with carbamazepine in childhood absence epilepsy, and with lamotrigine in children with DS [83]. It could also be of interest to evaluate the maintenance of the effect in the longer term during extension studies. Finally, at a later stage of

development there could be the opportunity to collect data on cognition, behavior and quality of life.

The use of large exploratory studies in drug development does not exclude the possibility of conducting a smaller exploratory study in a selected rare epilepsy syndrome. During the meeting, the experts suggested that two particular groups of patients would be interesting for such study: patients with cyclin-dependent kinase-like 5 gene (CDKL5) disorder and those with epilepsy following perinatal hypoxic-ischemic encephalopathy. The CDKL5 patients might represent a group with unmet needs which could be helpful in identifying a candidate drug. Mutations in the X-linked CDKL5 gene cause an early-onset epileptic encephalopathy with severe neurological impairment. CDKL5 mutations are much more frequently found in females [84]. Clinical features are seizures starting before the first 4 months of life, poor development of motor, cognitive and speech abilities and, often, hand stereotypes. While half of the children with CDKL5 mutations older than 3 years of age may experience seizure remission, others continue to experience intractable spasms, and multifocal and myoclonic seizures [85-87]. The common genetic cause could then be considered as the factor delineating a homogeneous population for assessment. Among patients with pharmacoresistant epilepsy, this clinical picture is homogeneous with a low responder rate at 3 months of treatment [88]. In a recent multicenter retrospective study, the usual responder rate (defined by a decrease of ≥50% of seizure frequency) was approximately 20% at 3 months, regardless of the type of AED (except in the three patients treated with felbamate) suggesting that a drug providing a better responder rate after 3 months would deserve a full investigation [88].

In essence, exploratory studies may offer a good opportunity for identifying potential orphan drug candidates, but are also useful for collecting early data and for enabling clinical experiences that may prove invaluable in the later stages of clinical development. This path might also be useful in exploring drugs currently in clinical development or on the market.

6. Primary outcomes

Most clinical trials of AEDs have used seizure frequency reduction as the primary outcome, based on a seizure type that is reliably countable and disabling. The median reduction of seizure frequency compared with baseline and the percentage of treatment responders (i.e. those with a decrease of ≥50% of the seizure frequency) are the typical criteria for assessment of antiseizure properties of investigated drugs. Although there is a need to develop new drug trials for evaluating antiepileptogenesis or disease-modifying effects, and this is being increasingly discussed, this has not yet come about because of numerous challenges [89].

The current approach for evaluating a change in seizure frequency is to rely on countable identifiable seizures. It is based, for example, on motor convulsive seizures in DS and on drop seizures (i.e. both tonic and atonic seizure) in LGS. In IS, the investigation of the drug when used as first line is usually based on the proportion of spasm-free patients. It is more reliable to differentiate patients by defining the presence or absence of spasms than to have a reliable count of the epileptic spasms themselves. Most of the time, the observation by parents/caregivers is inadequate to reliably assess seizure occurrence. Video-electroencephalogram (video-EEG) recording may therefore be required to ensure subtle epileptic spasms are not present. For IS, a consensus has defined a suitable primary outcome as the absence of epileptic spasms within 14 days of the initiation of treatment and this absence persisting for 28 consecutive days or more [90]. It is also based on the fact that only the disappearance of the epileptic spasms might modify the outcome. The approach of combining parental/caregiver observation with video-EEG recording has also been used in other common pediatric epilepsy syndromes such as childhood absence epilepsy [91].

Even if the use of reliable countable seizure types for the primary outcome has been successful in some syndromes, the seizure burden in some orphan pediatric epilepsy syndromes is not only based on easily countable seizures. Some seizure types, such as myoclonic seizures, atypical absence seizures or any seizure without a recognizable motor involvement that could be easily missed, are difficult to reliably count by parents and caregivers. The usual way to evaluate these seizure types would be to use prolonged video-EEG recording, but this increases the difficulties in conducting such trials. Moreover, there is no study validating the duration of such recordings that would reflect the seizure frequency or that would be sufficient to discriminate any significant change in the seizure frequency. Innovative methods might provide some tools to reliably record this type of seizure (e.g. easily portable devices or smart clothing for easy EEG recording).

A novel way to evaluate the change in the seizure frequency could also be considered. The use of time to events might become a way to measure the change in seizure occurrence. The use of time to event can reduce the time exposure to placebo if used in case on infrequent events such as generalized tonic-clonic seizures in the idiopathic generalized epilepsies [92]. These methods could also be used with a time to Nth seizure. An adaptative design of the study based on the seizure frequency during baseline allow evaluation of the compound in time to Nth event during the maintenance period [93]. This type of design would allow the inclusion of a larger group of patients with a wider spectrum of seizure frequency at baseline.

Furthermore, the use of only one type of seizure as the primary outcome limits the evaluation of a drug on other seizure types that could be observed in a single epilepsy syndrome. The evaluation of a drug for LGS has been based only on the effect on drop seizures. This does not reflect the real seizure burden as patients also exhibit other seizure types such as epileptic spasms, generalized tonic-clonic seizures, or atypical absence seizures.

It would be interesting to evaluate the reliability of alternative primary outcomes such as the number of seizure free days [94].

While EEG analysis is relatively reliable in the case of hypsarrhythmia for West syndrome and electrical status epilepticus in slow-wave sleep, the EEG pattern for the EE-CSWS, it is currently not justified to consider EEG analysis as a primary endpoint of other pediatric epilepsy syndromes. Alternatively, it could be included as a secondary endpoint.

As mentioned, composite scores may also be useful but there are some methodological challenges in using this type of score as a primary outcome in a clinical trial. We have no knowledge as to whether such measures can be used for repetitive assessments, if there is any evolution with the natural history, if there is a fluctuation of the score based on the change of the health status of a patient, or if there is any change in environmental factors that could modify such a score. Finally, even with a robust and predictive composite score, we have no information regarding the number of patients required for inclusion in a trial based on these parameters.

7. Conclusion

Even with an increasing interest in the development of orphan drugs for rare epilepsies, most of the current investigations remain focused on the same syndromes. We described here some factors that may limit the development of new drugs for treatment of the rare epilepsies. TABLE

8 provides an overview of the factors limiting orphan drug development by epilepsy syndrome. To promote and accelerate the development of drugs with new indications for rare epilepsies, support should be given to these missing elements. Epidemiological studies should be promoted to better evaluate both the incidence and the prevalence of the rare epilepsies. Resources should be dedicated to develop reliable preclinical models as well as validation of new primary outcome measures that could be used for regulatory trials. Finally, multiple explorations of a drug should be encouraged in order to avoid missing potential efficacy for a rare epilepsy syndrome.

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Compliance with Ethical Standards

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Conflicts of interest

Stéphane Auvin has served as consultant or received honoraria for lectures from Advicenne Pharma, Biocodex, Eisai, GW Pharma, Novartis, Nutricia, Shire, UCB Pharma, Ultragenyx, Zogenix. He has been investigator for clinical trials for Advicenne Pharma, Eisai, UCB Pharma and Zogenix.

Andreja Avbersek and Pierandrea Muglia are full time employees of UCB Pharma.

Rafal Kaminski was an employee of UCB Pharma during the time this analysis was completed.

Thomas Bast has participated as a clinical investigator or DMC member for Eisai, Marinus, Novartis, Nutricia and UCB Pharma. He has been a member of advisory boards and/or speaker for BIAL, Biocodex, Eisai, Desitin Arzneimittel GmbH, GW Pharmaceuticals, Shire, UCB Pharma and Zogenix.

Catherine Chiron has been member of advisory boards and/or speaker for BIAL, Biocodex, UCB Pharma and Zogenix.

J. Helen Cross has participated as a clinical investigator for GW Pharma, Marinus Pharmaceuticals, Vitaflo and Zogenyx. She has been a member of advisory boards and speaker for Eisai, GW Pharma, Nutricia and Zogenix. All renumeration has been made to her department.

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Figures

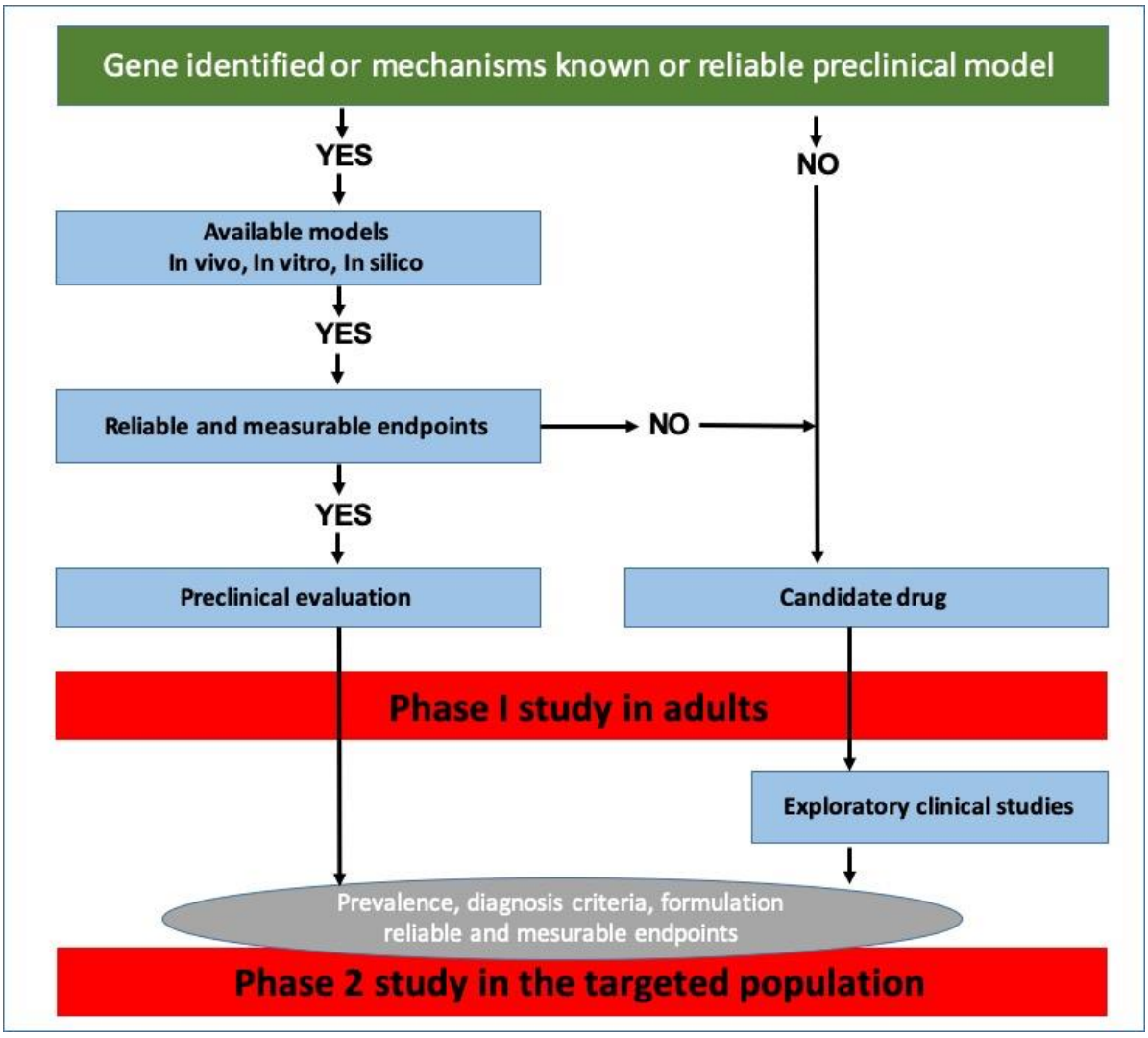

FIG. 1. Flowchart for rare epilepsy drug development according to the knowledge on the underlying mechanisms and the availability of preclinical models. The phase 1 clinical trial is a mandatory step before any introduction in the pediatric population. If there is sufficient evidence (preclinical data or exploratory clinical studies) and successful phase 1 trials, a phase 2 trial could be considered if some criteria are met. Phase 3 trials would then be required most of the time.

Tables

TABLE 1 **Designations and approvals of drugs for epilepsy disorders from January 1, 2008 to December 31, 2017**

	FDA	**EMA**
Number of orphan designations for epilepsy disorders (January 1, 2008 to December 31, 2017)	53	7
Number of individual compounds granted an orphan designation	30	4
Number of designations for pediatric orphan epilepsies	37 (70%) 27/37 (73%) for DS, IS, or LGS	7 (100%) 7/7 (100%) for DS, IS, or LGS
Number of drug approvals for epilepsy disorders (January 1, 2008 to December 31, 2017)	3 (none of them were novel AEDs)	0

AED, antiepileptic drug; DS, Dravet syndrome; EMA, European Medicines Agency; FDA, Food and Drug Administration; IS, infantile spasms; LGS, Lennox–Gastaut syndrome.

TABLE 2 | **Drug development landscape in orphan pediatric epilepsies**

Syndrome	Discovery / Preclinical	Phase 1	Phase 2	Phase 2/3 pivotal	Marketed
ADNFLE	NA	NA	NA	NA	NA
Dravet syndrome	CUR-1916 EPX-101, 102, 103 Gladstone – undisclosed mechanism Splice modulating oligomers (SMO)	EPX-100 (clemizole)	Ataluren (PTC124) TAK-935 (OV935)	Fenfluramine (ZX008) Ganaxolone	Epidiolex® (cannabidiol, CBD) Diacomit® (stiripentol) Depakote® (valproate)
EE (multiple types)	NA	CanniMed®	TAK-935 (OV935) Ataluren (PTC124; CDKL5 deficiency)	NA	NA
EE-CSWS	NA	NA	Valium® (diazepam)	Diamox® (acetazolamide) Ganaxolone	NA
EIEE	XEN901 (EIEE13)	NA	NA	NA	NA
EME	NA	NA	NA	NA	NA
EOEE	NA	NA	NA	NA	NA
Epilepsy with myoclonic-atonic seizures	NA	NA	NA	NA	NA
Epilepsy with myoclonic absences	NA	NA	NA	NA	NA
FIRES	NA	NA	NA	NA	NA
Focal cortical dysplasia	NA	NA	Afinitor® (everolimus)		NA

Infantile spasms (West syndrome)	NA	CPP-115	NA	Epidiolex® (cannabidiol, CBD) Synthetic cannabidiol (add-on to vigabatrin)	Acthar® (corticotropin) Kigabeq® (vigabatrin) Sabril® (vigabatrin) Synacthen® (tetracosactide)
Landau–Kleffner syndrome	NA	NA	Valium® (diazepam)	Diamox® (acetazolamide)	NA
LGS	Clobazam transdermal patch (AQS1302)	NA	Ganaxolone	Fycompa® (perampanel) Fenfluramine (ZX008)	Banzel® (rufinamide) Epidiolex® (cannabidiol, CBD) Felbatol® (felbamate) Lamictal® (lamotrigine)
Rasmussen syndrome	NA	NA	NA	NA	NA
Resistant seizures in TSC	NA	NA	TAK-935 (OV935)	Epidiolex® (cannabidiol, CBD)	Vigabatrin (Sanofi-Aventis) Votubia® (everolimus)

ADNFLE, autosomic dominant nocturnal frontal lobe epilepsy; EE, epileptic encephalopathy; EE-CSWS, epileptic encephalopathy with continuous spike-and-wave during sleep; EIEE, early

infantile epileptic encephalopathy; EME, early myoclonic encephalopathy; EOEE, early onset epileptic encephalopathy; FIRES, febrile infection-related epilepsy syndrome; LGS, Lennox–Gastaut syndrome; NA, not applicable; TSC, tuberous sclerosis complex.

Sources: Publicly available information including publications, company websites, press releases, and clinical trial registries: **https://clinicaltrials.gov, https://www.clinicaltrialsregister.eu/ctr-search/search**

TABLE 3 | **Mechanism of action of drugs currently in development for orphan pediatric epilepsies**

Drug	MOA	Developer	Comments
ALREADY APPROVED DRUGS			
Afinitor	mTOR inhibitor	Yonsei University (phase 3; FCD type II) New York University School of Medicine (phase 2; FCD)	NA
Banzel® (rufinamide)	Sodium channel antagonist	Eisai	NA NA
Depacote® (valproate)	GABA uptake inhibitor	AbbVie	NA
Diacomit® (stiripentol)	Positive allosteric modulator of $GABA_A$ receptors	Biocodex	EMA orphan drug designation for Dravet syndrome
Diamox® (acetazolamide) for EE-CSWS and Landau–Kleffner syndrome	GABA receptor agonist	Mayo Clinic	NA
Epidiolex® (cannabidiol, CBD)	Cannabinoid receptor antagonist	GW Pharmaceuticals	NA
Felbatol® (felbamate)	NMDA antagonist, $GABA_A$ modulator	AESCA, Essex Chemie, Merck	NA
Fycompa® (perampanel)	AMPA receptor antagonist	Eisai	NA
Kigabeq® (vigabatrin)	GABA-aminotransferase inhibitor	Orphelia Pharma	Reformulation (soluble tablet)
Lamictal® (lamotrigine)	Sodium channel antagonist	GSK	NA
Sabril® (vigabatrin)	GABA-aminotransferase inhibitor	Sanofi / Lundbeck	Orphan drug designation for infantile spasms
Synacthen® (tetracosactide)	Corticotropin receptor agonist	Novartis	NA
Valium® (diazepam) for EE-CSWS and	Carbonic anhydrase inhibitor	Mayo Clinic	NA

Landau–Kleffner syndrome			
Vigabatrin (Sanofi-Aventis)	GABA-aminotransferase inhibitor	Sanofi, Alfresa Pharma, Lundbeck	NA
Votubia® (everolimus)	mTOR inhibitor	Novartis	NA
INVESTIGATED DRUGS			
Acthar® (corticotropin)	Corticotropin receptor agonist	Mallinckrodt	Orphan drug designation for infantile spasms
Ataluren (PTC124)	Modulation of ribosomal function	PTC Therapeutics	NA
Cannimed® (medical cannabis oil)	Cannabidiol	University of Saskatchewan	NA
Clobazam transdermal patch (AQS1302)	$GABA_A$ receptor agonist	Aequus Pharmaceuticals	NA
CPP-115	GABA-aminotransferase inhibitor	Catalyst Pharmaceuticals	Orphan drug designation for infantile spasms (FDA and EMA for West syndrome)
CUR-1916	Antisense RNA inhibitor	OPKO Health	EMA orphan drug designation
EPX-100 (clemizole)	Serotonin (5HT) receptor modulator	Epygenix Therapeutics	FDA orphan drug designation
EPX-101, 102, 103	Serotonin (5HT) receptor modulators	Epygenix Therapeutics	NA
Fenfluramine (ZX008)	Serotonin receptor agonist; sigma-1 receptor agonist	Zogenix	Dravet: FDA and EMA orphan drug designation, fast track and breakthrough therapy
Ganaxolone	$GABA_A$ receptor agonist	Marinus Pharmaceuticals	NA
Gladstone – undisclosed mechanism	NA	Gladstone Institutes / BioMotiv; Cure Network Dolby Acceleration Partners	NA
Splice modulating oligomers (SMO)	Direct modulation of RNA splicing	LifeSplice	NIH funding
TAK-935 (OV935)	Cholesterol 24-hydroxylase inhibitor; NMDA receptor modulator	Takeda / Ovid Therapeutics	FDA orphan designation for Dravet syndrome and LGS

XEN901	Nav1.6 voltage-gated sodium channel inhibitor	Xenon Pharmaceuticals, Inc.	NA

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EE-CSWS, epileptic encephalopathy with continuous spikes and waves during sleep; EMA, European Medicines Agency; FCD, focal cortical dysplasia; FDA, Food and Drug Administration; GABA, gamma-aminobutyric acid; IS, infantile spasms; LGS, Lennox–Gastaut syndrome; MOA, mechanism of action; mTOR, mechanistic target of rapamycin; NA : not available ; NIH, National Institutes of Health; NMDA, N-methyl-D-aspartate.

TABLE 4 **List of epilepsy syndromes classified by age range or epilepsy due to genetic, metabolic or inflammatory causes with unmet needs for treatment**

	ORPHAN CONDITION? **Orphan EU <50/100,000**	**ORPHAN CONDITION?** **Ultra-orphan <2/100,000**	**Self-limited?**	**Approved drug?**
NEONATAL/INFANTILE epilepsy syndromes				
Self-limited neonatal seizures and self-limited familial neonatal epilepsy	YES	Presumed ultra-orphan	Self-limited	NO
Self-limited familial and non-familial infantile epilepsy	YES	Presumed ultra-orphan	Self-limited	NO
Early myoclonic encephalopathy	YES	Presumed ultra-orphan	NO	NO
Ohtahara syndrome	YES	Presumed ultra-orphan	NO	NO
West syndrome (infantile spasms)	YES	Presumed orphan	NO	VGB, steroid
Dravet syndrome	YES	NO	NO	STP, CBD

Myoclonic epilepsy in infancy	YES	Presumed ultra-orphan	Self-limited	NO
Epilepsy of infancy with migrating focal seizures	YES	Presumed ultra-orphan	NO	NO
CHILDHOOD				
Epilepsy with myoclonic-atonic seizures	YES	Presumed orphan	NO	NO
Epilepsy with eyelid myoclonias	YES	Presumed orphan	NO	NO
Lennox–Gastaut syndrome	YES	NO	NO	CBD, CLB FBM, LTG, TPM, RUF
Epilepsy with myoclonic absences	YES	Presumed ultra-orphan	NO	NO
Epileptic encephalopathy with continuous spike-and-wave during sleep	YES	Presumed ultra-orphan	NO	NO
Landau–Kleffner syndrome	YES	Presumed ultra-orphan	NO	NO
Autosomal dominant frontal lobe epilepsy	YES	Presumed ultra-orphan	NO	Drugs approved for FOS

ADOLESCENCE/ADULTHOOD				
Autosomal dominant epilepsy with auditory features	YES	Presumed ultra-orphan	NO	Drugs approved for FOS
VARIABLE AGE				
Epilepsy due to CDKL5	YES	Presumed ultra-orphan	NO	NO
Epilepsy due to TSC	YES	NO	NO	Everolimus
Epilepsy due to GLUT1-DS	YES	Presumed ultra-orphan	NO	NO but use of ketogenic diets
Epilepsy due to FCD	YES	NO	NO	NO
FIRES	YES	Presumed ultra-orphan	NO	NO
Progressive myoclonus epilepsies	YES Presumed ultra-orphan		NO	CLN2: cerliponase alpha
Rassmussen syndrome	YES Presumed ultra-orphan		NO	

CBD, cannabidiol; CLB, clobazam; FBM, felbamate; FOS, focal onset seizure; LTG, lamotrigine; RUF, rufinamide; STP, stiripentol; TPM, topiramate; VGB, vigabatrin.

TABLE 5 | **Available randomized controlled trials in Dravet syndrome and in Lennox–Gastaut syndrome with placebo and drug responses**

Syndrome	Drug	Age	Primary endpoint (time)	Placebo	Drug
Dravet[14]	Stiripentol	3–20 y	Responder ≥50% 2M	n=20 5%	n=21 71%
Dravet[55]	Stiripentol	3–20 y	Responder ≥50% 2M	n=11 9%	n=12 66%
Dravet[16]	Cannabidiol 20 mg/kg	2–18 y	% seizure change 14W	n=59 –13.3% (–91.5 230)	n=61 –38.9% (–100 337)
Dravet[17]	Fenfluramine 0.2 mg/kg/d 0.8 mg/kg/d	2–18 y	Median % convulsive seizure reduction 14W	n=40 17.4%	n=39 (0.2 mg/kg) 33.7% n=40 (0.8 mg/kg) 72.4%
Dravet[18]	Fenfluramine 0.5 mg/kg/d	2–18 y	Median % convulsive seizure reduction 14W In addition to valproate +clobazam +stiripentol	n=44 1.2%	n=43 62.7%
LGS[95]	Lamotrigine	3–25 y	Median % drop seizure reduction 16W	n=90 9%	n=79 34%

LGS[13]	Felbamate	4–36 y	Median % drop seizure reduction 70D	n=36 9%	n=37 34%
LGS[96]	Topiramate	1–30 y	Median % drop seizure reduction 11W	n= 50 –5.1%	n=46 14.8%
LGS[97]	Clobazam	2–60 y	Median % drop seizure reduction 12W	n=59 12.1%	n=59 68.3%
LGS[98]	Rufinamide	4–30 y	Median % drop seizure reduction 12W	n=64 –1%	n=74 42.5%
LGS[99]	Cannabidiol	2–55 y	Median % drop seizure reduction 14W	n=85 21.8%	n=86 43.9%
LGS[46]	Cannabidiol	2–55 y	Median % drop seizure reduction 14W	n=76 17.2%	n=76 (20 mg/kg) 41.9% n=73 (10 mg/kg) 37.2%

D, day; LGS, Lennox–Gastaut syndrome; M, month; W, week; y, year.

TABLE 6 **Identified limiting factors for the development of orphan drug for rare epilepsies without any approved drug to date**

Limiting factors	**Interest for drug development**
Unknown incidence/prevalence	Data requested for orphan designation
	Feasibility of recruitment in a trial
	Decision of the investment for a sponsor
	Pricing discussions after approval
Diagnostic criteria	Data requested for orphan designation
	Definition of inclusion criteria
	Use of diagnosis validation by committee for inclusion in a trial
	Homogeneity of the studied population
	Avoid off-label use after approval
Natural history	Calculation of requested patients for a phase 3 trial
	Develop first or second-line treatment
	Consider new primary outcome (behavior/cognition…)

TABLE 7 **Overview of drug suggested to be used a precision medicine for some genetic-related epilepsy**

Gene	**Syndromes**	**Candidate drugs**	**Available preclinical data**	**Available clinical data**
GATOR1 Cx *DEPDC5,* *NPRL2,* *NPRL3*	Familial or sporadic epilepsy with FOS+/- MCD +/- cognitive impairement FCD	mTOR inhibitors	rapamycin in Zebrafish [100]	NA
GRIN1	EDE Bilateral polymicrogyria	Memantine	In vitro [101]	NA
GRIN2A	EE-CSWS Epilepsy-aphasia	Memantine	In vitro [102]	One patient [103]
GRIN2B	EDE	Radiprodil	In vitro [79]	NA
KCNT1	MPSE ADNFLE	Quinidine	In vitro [104, 62, 105]	Varied effect including a phase 2 study [62, 106, 105, 107]

KCNQ2	BFNE EDE	Retigabine Attenuation of M-Current	In vitro [108, 109] In vivo [110]	Sodium channel blocker [111, 112]
SCN2A	EDE MPSE	Sodium channel blocker	Sodium channel blockers [113] CaMKII [114]	Sodium channel blockers [115, 112] (response according to age of onset) [115]
SCN8A	EDE	Sodium channel blocker	In vitro candidate screening [116] Mice model treated by a sodium channel blocker [117]	Case series of four patients treated with phenytoin [118]
TSC1, TSC2	WS FOS	mTOR inhibitors rapamycin	Mice models treated by rapamycin [63, 64, 119, 120]	Phase 2 and phase 3 RCT for everolimus [65, 121]

everolimus

ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; BFNE, benign familial neonatal seizure; CaMKII, calcium/calmodulin protein kinase II; Cx, complex; EDE, epileptic and developmental encephalopathy; EE-CSWS, epileptic encephalopathy with continuous spike and wave in sleep; FCD, focal cortical dysplasia; FOS, focal onset seizure; NA, not available; MCD, malformation of cortical development; MPSE, migrating partial seizure epilepsy; mTOR: mammalian target of rapamycin; RCT, randomized controlled trial; WS: West syndrome.

TABLE 8 | **Summary of limiting factors for an orphan drug development of various epilepsy syndromes.**

	Epidemiology	**Preclinical models**	**Predictability of the models**	**Diagnostic criteria used by central reviewers for trials**	**Previous Phase 2 or phase 3 RCT**	**Defined SOC**	**Available Drug**	**Natural history**
Early myoclonic encephalopathy	Unknown	+/-	Unknown	No	No	No	No	No
Ohtahara syndrome	Unknown	+/-	Unknown	No	No	No	No	No
Infantile spasms	Not clearly established	+	Unknown	Not yet used but easy to be done	Yes	Yes	Yes	Yes
Dravet syndrome	Known	+	Possible	Yes	Yes	Yes	Yes	Yes
Epilepsy in tuberous sclerosis	Known	+	Possible	Not yet used but easy to be done	Yes	No	Yes	Yes

Focal cortical dysplasia	Unknown	+	Unknown	No	No	No	No	Yes
Epilepsy with myoclonic atonic seizure	Unknown	0	NA	Not yet used but easy to be done	No	No	No	No
Lennox–Gastaut syndrome	Not clearly established	0	NA	Yes	Yes	Yes	Yes	Yes
Landau–Kleffner syndrome	Unknown	0	NA	No	No	No	No	No
EE-CSWS	Unknown	0	NA	No	No	No	No	No
Epilepsy with myoclonic absences	Unknown	0	NA	No	No	No	No	No
Myoclonic encephalopathy	Unknown	0	NAa	No	No	No	No	No

in non-progressive disorders								
Progressive myoclonic epilepsies	Unknown	+-	Possible	No	No	No	No	No
FIRES	Unknown	0	NA	No	No	No	No	Yes (not fully established)
Rasmussen syndrome	Unknown	0	NA	No	No	No	No	No

EE-CSWS, epileptic encephalopathy with continuous spike-and-wave during sleep; FIRES, febrile infection-related epilepsy syndrome; RCT, randomized controlled trial; SOC, standard of care.