EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 October 2023
CHMP/EWP/566/98 Rev.3
Committee for medicinal products for human use (CHMP)

Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders

Draft

Discussion at the Efficacy Working Party	April 1998/September 1999
Transmission to CHMP	October 1999
Release for consultation	October 1999
Deadline for comments	April 2000
Re-submission to the EWP	September 2000
Adoption by CHMP	November 2000
Date for coming into operation	May 2001
Draft rev. 2 agree d by efficacy working party	January 2009
Adoption by CHMP for release for consultation rev. 2	January 2009
End of consultation (deadline for comments)	July 2009
Rev. 2 agreed by efficacy working party	January 2010
Adoption by CHMP rev. 2	January 2010
Date for coming into effect	August 2010
Corrigendum	July 2010
Draft agreed by Central Nervous System Working Party	June 2018
Adopted by CHMP for release for consultation	26 July 2018
Start of public consultation	17 August 2018

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End of consultation (deadline for comments)	17 February 2019
Draft agreed by Central Nervous System Working Party	September 2023
Adopted by CHMP for release for consultation	30 October 2023
Start of public consultation	10 November 2023
End of consultation (deadline for comments)	30 January 2024

This guideline replaces Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders CHMP/EWP/566/98 Rev. 2/Corr

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Keywords	***Epilepsy, seizures, anti-seizure medication (ASM)***

Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders

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Executive summary

The present document is a third revision of the existing guideline. It should be considered as general guidance on the development of medicinal products for the treatment of epileptic disorders and should be read in conjunction with other EMA and ICH guidelines, which may apply to these conditions and patient populations.

The main changes to the existing guideline include incorporation of the new classification / definitions of seizure types and epilepsies, the acceptance of add-on studies in support of a monotherapy claim on a case-by-case basis, the inclusion of new sections on neonates and status epilepticus and other changes related to paediatric developments.

This Guideline provides assistance for the development and evaluation of medicinal products for the treatment of epilepsy in adults and children. The scope of this document is restricted to treatment of seizures in epileptic disorder although there are some remarks concerning non-seizure features of epilepsy syndromes.

1. Introduction (background)

Epilepsy is a brain disorder defined by recurrence, or a high risk of recurrence, of spontaneous/unprovoked seizures. It constitutes a vast ensemble of diverse clinical conditions which differ by age of onset, type of seizures (only one or several type(s) in an individual patient), aetiological background, including genetic predisposition, prognosis and response to treatment, that entail neurobiological, cognitive, psychological and socioeconomic burden.

More than 50 million adults and children suffer from epilepsy world-wide. The two highest peaks of incidence are in children and in the elderly (above 65 years). Prevalence estimates of epilepsy in the total population vary from 4 to 8 per 1000 subjects.

Clinically recurrent seizures are the primary marker of epilepsy. The classification of seizure types has been revised in 2017 by the International League Against Epilepsy (ILAE). The classifiers are mode of onset and main behaviour descriptors such as occurrence of impairment of awareness, and of motor or non-motor signs at onset (see Annex I).

In addition to the type of seizures, the classification of epilepsies has been revised among three levels, i.e. seizure type, epilepsy type, and epilepsy syndrome. An epilepsy syndrome is defined as a characteristic cluster of clinical and EEG features, often supported by specific etiological findings (structural, genetic, metabolic, immune, and infectious) (see Annex II). Many of the epilepsies are age-dependent and are accompanied by comorbidities, e.g. motor deficits, impaired neurodevelopment, and behavioural problems.

Developmental and epileptic encephalopathies (DEEs) refer to conditions where there is developmental impairment related to both the underlying aetiology independent of epileptiform activity and the epileptic encephalopathy.

Focal onset seizures and focal epilepsies, related to a focal brain dysfunction, occur in approximately 60% of cases and may have an identified etiology (including genetic) or unknown. Generalised onset of seizures and generalized epilepsies represent approximately 30% of cases. They occur often in a genetic context. In the remaining 10%, the classification includes a “generalized and focal” category (co-existing) and an uncertain/unknown category.

The majority of paediatric epilepsies consist of age-dependent epilepsy syndromes whose manifestations are affected by ongoing brain maturation and development. Another major difference in

paediatric and adult epilepsies is that the DEEs are more commonly diagnosed in early childhood (up to 12 years of age). Consequently, an earlier initiation of the appropriate treatment may yield a better prognosis. Focal non-genetic epilepsies in childhood may also have an important impact on cognitive development if not treated early and appropriately. Some age-dependent epilepsy syndromes do not persist into adulthood (e.g. West syndrome or "self-limited" epilepsy with centrotemporal spikes).

Status epilepticus is a condition resulting from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures. Persisting neuronal damage may occur with variable outcome. Severe status epilepticus has a high mortality rate. A new diagnostic classification system of status epilepticus has been proposed by the ILAE with four axes, i.e. semiology, aetiology, electroencephalography seizures, correlated or not with clinical seizures, and age.

Anti-seizure medication (ASM) is the main treatment option of seizures. Approximately 60% of newly diagnosed patients become seizure-free on a single ASM (monotherapy). An additional 10%-20% achieve freedom of seizures with polytherapy. It follows that about 30% of patients are not satisfactorily controlled. In addition many patients suffer from significant treatment related adverse reactions.

New ASMs have been developed with the aim of improving the benefit/ risk balance of existing ASM therapy. The evaluation of a new ASMs is traditionally performed as adjunctive therapy in patients already receiving at least one concomitant ASM. Typically, in these studies 20 to 40% of patients with focal epilepsy obtain a 50% or greater reduction in the frequency of seizures, compared to 2 to 25% of patients given placebo. However, few patients become seizure-free, which is the ultimate goal of treatment. Differences exist in the efficacy and tolerability profiles of ASM depending on seizure type and epilepsy syndrome. A given compound may for instance improve one type of seizure type but worsen another.

An ASM may have different spectra of efficacy:

- In terms of seizure types, most ASMs are effective against focal seizures and focal to bilateral tonic-clonic seizures. Certain ASM show a broader spectrum of efficacy, including focal and many generalised seizure types. For others, efficacy is limited to one or two seizure types, for instance absence seizures only.
- In terms of epilepsy syndromes, it is important to know on the one hand which (and how) seizure types associated with a given syndrome are affected by a specific medication. On the other hand, a given seizure type may not show the same responsiveness in the various syndromes, particularly in age-dependent conditions. Moreover, some ASMs may exacerbate some seizure types while being efficacious in coexisting seizure types.

2. Scope

This Guideline provides assistance for the development and evaluation of medicinal products for the treatment of epilepsy in adults and children. The scope of this document is restricted to treatment of seizures in epileptic disorders although there are some remarks concerning non-seizure features of epilepsy syndromes and Developmental and Epileptic Encephalopathies (DEEs).

3. Legal basis and relevant guidelines

This Guideline has to be read in conjunction with the introduction and general principles (4) and Part I and II of the Annex I to Directive 2001/83/EC as amended. Applicants should also refer to other

relevant adopted European and ICH guidelines. In the context of this guideline the following guidelines are specifically mentioned:

- CPMP/ICH/378/95 Note for guidance on dose response information to support drug authorisation
- CPMP/EWP/560/95 Note for guidance on the investigation of interactions.
- EC 2008 "Ethical considerations for clinical trials on medicinal products conducted with the paediatric population"
- ICH Guideline E11A on paediatric extrapolation
- EMA/189724/2018 Reflection paper on the use of extrapolation in the development of medicines for paediatrics, rev 1
- EMA/CHMP/458101/2016 Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling 5 and simulation

Further is referred to the ICH/EMA guidelines on pharmaceutical development PK/PD topics, clinical trials design, special populations including the elderly and Paediatric Population

https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines

4. Patient selection

4.1. Study population and selection of patients

Patients included in the clinical trials should be classified according to the International Classification of Seizures and International Classification of Epilepsies and Epilepsy syndromes.

The seizure type, epilepsy type, epilepsy syndrome and aetiology of the subjects included in the studies should be clear. This should allow an evaluation of (lack of) differential effect of the new medicine by the seizure type, epilepsy type, epilepsy syndrome and aetiology. Moreover, the seizure types studied must be clearly recognised by the subject who records the seizures (patient, relatives, and investigator). Training programmes for a reliable seizure recording are recommended.

4.2. Selection of seizure types and epilepsy syndromes

For studies in special patient populations e.g. the paediatric population see section 8.

Usually, focal seizures in adults is the first seizure type that is evaluated in clinical development plans, since they are frequent and a substantial percentage (approximately 30%) of them are not well controlled or responding suboptimal to treatment. Efficacy needs to be evaluated for focal seizures and focal to bilateral tonic-clonic seizures separately. It is however highly desirable to explore efficacy in other epilepsy syndromes/seizure types. Efficacy in seizure types or epilepsy syndromes should be explored separately (e.g. idiopathic generalised epilepsies, focal epilepsy, West syndrome, Dravet syndrome, Lennox-Gastaut syndrome, epilepsy with myoclonic-atonic seizures). Evaluation requires analysis of the efficacy of an agent on the different seizure types present within a given condition (e.g. spasms, generalised tonic-clonic, absences, myoclonic, tonic or atonic seizures).

Inclusion of subjects can be seizure type based within a given syndrome (e.g. primary generalised tonic-clonic seizure in Juvenile Myoclonic Epilepsy) or seizure type based across different syndromes (e.g. generalised-onset tonic-clonic seizure in Idiopathic Generalised Epilepsy and Lennox Gastaut syndrome) or it can be syndrome based. In the seizure type based approach the syndromes should be carefully characterised for further evaluation (see 4.4. statistical analysis).

Global antiseizure efficacy of an agent in an epilepsy syndrome can only be claimed when efficacy has been shown for all seizure types of the syndrome or at least for the most severe and disabling seizure types of the syndrome without any aggravation of the other seizure types. Where an effect on the encephalopathic process itself in epileptic encephalopathies is claimed, efficacy should be shown for neurodevelopment, cognition, socialisation, EEG and not only on seizures.

5. Assessment of efficacy

5.1. Efficacy criteria/treatment goals

The assessment of efficacy should be based primarily upon seizure frequency / occurrence**.**

5.1.1. Add-on trials

In add-on trials, the period over which seizure frequency is measured should be pre-defined (e.g. the number o*f* seizures per 4 weeks). Two important variables should be specified in the protocol. The primary endpoint should be responders/non-responders, where responders are patients who obtained at least a certain pre-defined percentage reduction of seizure frequency (e.g., a 50% reduction is commonly used). The other variable should be some parameterisation using the actual change in seizure frequency, e.g., median percentage change in seizure frequency.

The proportion of seizure-free patients is a particularly important variable. The cumulative distribution of percent reduction in seizure from baseline over the fixed dose period should also be presented. .

The following additional endpoints should be assessed: seizure severity, treatment retention rate, functional outcomes and quality of life. These endpoints allow an assessment of the clinical benefit of the ASM for the patients.

A time to event approach (e.g. time to pre-randomisation monthly seizure count) is an acceptable approach. An advantage of this design would be that the duration of the study is reduced. However, the underlying assumption that the seizure risk within a patient is constant over time, i.e. no clustering occurs, will need to be justified. In addition, the methods used to handle missing data would need to be very carefully considered. Further, reducing the time in the study or allowing change of treatment after an event makes an assessment of maintenance of effect, tolerability to treatment and safety more difficult as the exposure will not be equal across different treatment groups. Therefore, this study design is not recommended as the sole study design in the clinical development plan as in addition, potential exacerbation of seizures (e.g.. by 25 % or more) and the appearance of new seizure types should be assessed.

Evaluation of efficacy should be based on the changes in seizure frequency between the treatment maintenance phase and the baseline period excluding the titration period (see section 6.3.2.). In principle, efficacy should first be evaluated for all seizure types. Deviation from this should be justified. Consistency of the effect per seizure type (focal, generalised, unknown onset) should be part of the secondary analyses. A meta-analysis of several add-on studies if predefined may be considered (see also section 6.3.3. Statistical analysis).

In epilepsy syndromes where different seizure types may co-exist, emphasis may be on improvement of the most debilitating seizure types while it might be accepted that concomitant seizure types might not improve or even worsen. This will be subject of the benefit-risks assessment. A prerequisite is that it should be predefined and justified in the study protocol what would be acceptable.

5.1.2. Monotherapy trials

In monotherapy trials (adults and children) in newly or recently diagnosed patients, the primary efficacy variable should be based on the probability of patients remaining seizure free for at least six months (excluding the dose titration period). The trial should have a minimum duration of one year in order to assess safety and maintenance of efficacy.

5.1.3. Add-on and monotherapy trials

Secondary efficacy variables applying to both add-on and monotherapy trials may concern:

a) Treatment retention time, measuring the combination of failed efficacy and tolerability, enables to assess the global clinical effectiveness of the drug. The exit criteria defining failed efficacy (e.g.: n^{th} seizure, addition of another ASM, need of rescue medication) should be justified by the applicant.

b) Seizure type, seizure severity, including duration of seizure, warning symptoms or not, loss of consciousness, falls, injuries, post-ictal confusional state or neurological focal deficit, etc.

c) Patient reported outcomes, scales measuring social and working capacity if validated.

d) An additional secondary endpoint may be, provided it is properly validated, a composite rating scale wherein seizure frequency, change in seizure types and adverse events are weighted and expressed in one score.

e) EEG pattern according to specific syndromes (i.e. Continuous Spike-Waves in Slow Sleep in children).

5.2. Methods to assess efficacy criteria

The counts of clinical seizures represent the main marker of the expression of epileptic diseases, and thus of the efficacy of treatments. Usually seizure counts are recorded by the patient and/or caregiver using diaries. In cases of very frequent seizures, (e.g. absences) or seizures difficult to quantify clinically it is recommended to develop more precise tools of quantification of the seizure frequency such as quantitative EEG recordings or telemetry by video-EEG and/or alternative methods, as appropriate.

6. Study design

6.1. Non-clinical data

Non-clinical data, particularly the mode(s) of action and the results on experimental models, may be helpful to build hypotheses on the agent's potential in clinical situations although available animal models do not cover the entire range of seizure types/epilepsy syndromes observed in humans.

The neurobiological mode of action of the candidate antiepileptic drug is important, since it may indicate in which seizure types and epilepsy syndromes the drug will be efficacious. It may be also predictive for the risk of certain adverse events. For instance some drugs have been specifically designed to target an established mechanism (e.g., GABA-mediated), which would help predict their safety and efficacy based on known class effects. In contrast, others may be the result of systematic screening and their mode(s) of action may need to be further identified to guide clinical development decisions. The study of the efficacy profile should be performed in a variety of experimental models, including those of focal epilepsies and generalised epilepsies. It is important to know if the drug in development displays anti-seizure activity only or if it has a disease-modifying effect as well.

In case of clinical development of antiepileptic drugs for all children, in particular for the age group below the age of 4 years, the potential neurotoxic effects of the agent in the developing rodent brain ought to be investigated, including neuropathologic and behavioural endpoints.

6.2. Pharmacology studies

6.2.1. Pharmacokinetic

The PK of the new medicinal product should be thoroughly described. Absorption, bio-availability, protein binding, and route(s) of elimination (including metabolites and enzymes involved) should be characterised. These investigations are often closely related to those concerned with interactions (see section 6.2.3 and 6.3.2). The dossier should contain sufficient data on the plasma concentration of the new product (and active metabolites) with respect to efficacy and safety. This is in order to establish the reference range of the new agent and to evaluate the clinical significance of minor changes in the plasma concentration of the agent or its active metabolites. Plasma concentrations should therefore be checked at the time of the assessments of efficacy as well as at the time of significant undesirable effects. These data are helpful in developing an exposure–response (E-R) Modelling and Simulation in support of the extrapolation of the study results.

6.2.2. Pharmacodynamics

The pharmacological effects on some neuropsychological functioning, such as cognition, memory, learning, sleep and/or reaction time, should be studied in healthy volunteers as well as in the general patient population and especially in children and elderly, to assess the neurodevelopmental impact. Studies should include a positive control arm. Neuropsychological tests known to be sensitive to sedative/CNS depressive effects should be applied.

Specific claims, e.g., psychostimulatory effects must be substantiated in controlled clinical trials especially designed for such a purpose, using both appropriate clinical and laboratory measures and including a positive control.

6.2.3. Interactions

Pharmacokinetic in vitro and in vivo interaction studies should be performed in accordance with the CHMP guideline on interactions, with special focus to the interaction between the test product and any anti-seizure product given simultaneously in clinical practice.

The effect of the new anti-seizure product on the pharmacokinetics of concomitant anti-seizure medications to be used in the pivotal clinical studies should be known (and vice versa) before such studies start.

Pharmacodynamic interactions expected to occur between the test product and any anti-seizure product which is given simultaneously with the test product in clinical practice should be studied. See also section 6.3.2.

Potential interactions with the contraceptive pill must be determined. Also, the potential pharmacodynamic interactions with alcohol and CNS active products should be investigated.

6.3. Therapeutic studies

6.3.1. Exploratory and dose finding studies

The purpose of this phase of the product development programme is to identify patients who may benefit from a new anti-seizure medication, to obtain initial information on safety and suitable therapeutic dose range and dosage regimen. These studies are also important for exploring the spectrum of efficacy of the test drug in a variety of seizure types and epilepsy syndromes. The designs of the exploratory studies should be sufficient to properly inform the decision of whether or not to proceed to confirmatory trials and, if so, the population and dose of experimental treatment to pursue.

The exploratory nature of this phase in the clinical development plan allows a variety of designs. Examples are randomised placebo-controlled parallel or cross-over studies, enrichment designs, controlled studies in patients with epilepsy subjected to a pre-surgical evaluation programme, and open add-on studies among others.

The photo-paroxysmal response on EEG or the study of effects on interictal EEG epileptic discharges may be considered a model to evaluate preliminary efficacy and a potential effective dose.

In the exploratory studies a reduction in the frequency of seizures and/or the time to event approach may constitute the primary criteria of efficacy. Changes in seizure pattern and seizure severity should also be measured. Special attention should be given to quantifying an increase in seizure frequency and the appearance of new seizure types.

Psychomotor performance should be recorded systematically in some studies, irrespective of whether or not it correlates with the anti-seizure potential of the substance.

For focal onset seizures, monotherapy in patients undergoing pre-surgical evaluation for focal epilepsy may generate some short-term efficacy data which, however, are not relevant for longer term clinical use.

The dossier should contain fixed dose-arm dose finding studies in order to justify the dosages used in confirmatory clinical trials and dose recommendation in the SmPC. The dossier should contain sufficient data on the plasma concentration of the new product (and active metabolites) and its relation to efficacy and safety.

It is custom to titrate a new ASM until an optimal effect is seen or until the maximal tolerated dose is reached or up to the maximal doses allowed. If the dosing schedule incorporates titration the additive value of increasing the dose for efficacy should be evaluated.

Natural History Study, registry studies may contribute to provide information on the disease relevant for the design of the clinical studies (inclusion, age-distribution, duration, endpoints) and supportive data for long-term safety of the drugs.

New devices can be useful tools for outcomes measurement if validated.

6.3.2. Confirmatory studies

As for trials in any disease area it is of critical importance to clearly specify the scientific question of interest that the trial seeks to address. The target of estimation, including specification of how to account for intercurrent events to reflect the scientific question of interest, will need to be pre-specified and well justified given the therapeutic situation and scientific objective under consideration. Intercurrent events of particular interest in this setting are not reaching the target dose titrated to,

discontinuation or modification of treatment received, including the use of other ASMs. Referred is to ICH E9 R1 (addendum on estimands).

Add-on studies

Traditionally, the initial evaluation process for a new ASM involves the evaluation of its efficacy in reducing the frequency of seizures or seizure burden, in patients who continue to have seizures despite therapy with an adequate regimen of appropriate drug(s).

Add-on studies however may not allow the full assessment of the anti-seizure effect of a new compound. Interferences between the concomitant anti-seizure medications and the test product are common in add-on studies for various reasons [e.g. pharmacokinetic (PK) interactions, pharmacodynamic (PD) interactions and additive toxic effects]. Therefore, it may be difficult to disentangle the relative contribution of these changes superimposed on the true drug effect. The interaction potential should be taken into account regarding both directions, concomitant treatment versus test drug and test drug versus concomitant, pre-existing ASM.

Therefore, add-on trials should be conducted preferably in the presence of up to three pre-existing ASMs, with plasma levels being kept stable within appropriate limits. Plasma monitoring of concomitant ASM s and test agent is required to exclude interference of PK interaction with the treatment effect. If it turns out that it is impossible to keep the concomitant medication constant during the maintenance period, for instance due to additive adverse events, the target of estimation and efficacy analysis plan should consider in advance how to deal with patients with and without dose modifications of their concomitant ASM. Given the add-on setting, the number of possible ASM combinations is large. An evaluation of a (potential) different effect of the test drug depending on the background ASMs is expected for both efficacy and safety. Add-on studies should be large enough to allow evaluation that the effect is consistent regardless of background ASM.

Also for safety it is often difficult to determine whether an adverse event can be attributed to the test-product, to changes in plasma concentration of the concomitant anti-seizure medications / active metabolites, a pharmacodynamic effect or to an additive toxic effect.

The pivotal add-on studies should have a randomised, double-blind, placebo-controlled parallel group study design.

The studies should include a baseline period, a titration period (when applicable), and a maintenance period. All changes in dosage of the test product and concomitant anti-seizure medications should be documented in detail.

Baseline period

Baseline seizure frequency should be sufficiently high and duration of baseline should be sufficiently long to detect decreases as well as increases in seizure frequency in the treatment phase. The spontaneous fluctuations in the frequency of epileptic seizures must be taken into account; for instance, patients in whom baseline seizure frequency differs substantially from their usual seizure frequency should not be included.

Concomitant anti-seizure medication should be optimised and stable during the baseline period. If a concomitant anti-seizure medication is stopped before the start of the trial, the washout period should be sufficient long to avoid PK/PD carry-over effects.

Titration period

In the titration period, when applicable, the dose of the test product may be increased up to the maximal tolerated doses or maximal predefined doses. The criteria of judgement of an optimal effect and intolerance should be carefully and unambiguously defined in the study protocol.

Dose adaptations of the concomitant anti-seizure products may also be necessary due to interactions. It should be pre-defined in the protocol and carefully documented preferably by monitoring plasma concentrations.

At the end of the titration period, patients should be on a stable dose, either the individually determined optimal dose or the maximal pre-defined dose.

It is recommended to study more than one dose arm in order to establish the lower end of the clinically effective dose range as well as the optimal effective dose. If titration is applicable, patients should be titrated to their target dose which is subsequently maintained during the whole maintenance period (see section 6.3.1).

In the add-on setting the determination of plasma concentrations is needed in order to verify whether the effect / adverse events observed may be attributed to the test agent or may also be explained by changes in plasma concentrations of the concomitant anti-seizure medications. This should be included in the study protocol.

Maintenance period

In the maintenance period the test and concomitant products should be kept stable whenever possible. The maintenance period should last at least 12 weeks in order to establish that efficacy is not short lasting.

Long term Efficacy/Safety

Long-term data should be generated by continuation of add-on studies or by conducting open label extension studies in order to assess absence of tolerance and/or long term alterations in the therapeutic effect over time and maintenance of safety. Data concerning potential withdrawal and / or rebound effects should be generated. Treatment retention rate is recommended as a global indicator of perceived effectiveness. A one year study duration is considered the minimum.

Conversion to monotherapy

Some add-on studies may allow conversion to monotherapy in the open-label extension phase in patients on multiple-drug treatment. Treatment retention time may be a useful outcome variable. The availability of conversion to monotherapy data, as well the lack of these data, is informative for the prescriber as it facilitates the decision to attempt secondary monotherapy or not in an individual subject. Therefore, these data or the absence thereof will be incorporated in the SmPC.

Monotherapy studies

Placebo controlled monotherapy trials in epilepsy are in general not feasible. However, placebo controlled trials in subjects where it is not clear whether an ASM should be started could be considered, especially when a benign safety and tolerability profile has been shown e.g. in the add-on setting.

Monotherapy trials traditionally have been active controlled trials of one year duration in newly or recently diagnosed patients, with the primary efficacy variable being the proportion of patients remaining seizure free throughout the duration of the randomised trial period. In practice, seizure recurrence in these trials has been low, so that the majority of the patients remain seizure free for the duration of the trial. These trials therefore often lack or have limited assay sensitivity and therefore results are difficult to interpret.

On a case by case basis, it may be justified that a monotherapy trial is not necessary to support a monotherapy indication. Factors to be taken into account would include, among others, known characteristics of the class of ASM including documented mechanism of action, results of trials in the add-on setting such as magnitude of effect, known PK/PD relationship, type of seizures wherein a product is effective and/or consistency of efficacy of the new compound when added to different classes of other ASMs.

Where the mechanism of action of a new ASM may work by augmenting the efficacy/effectiveness of another ASM and hence where the new ASM might not have substantial efficacy on its own, monotherapy trials are likely to be required if a monotherapy indication is sought. This would not necessarily always be the case when the mechanism of action is novel in case the evidence from available non-clinical and clinical data is persuasive to support that the new ASM would be efficacious on its own. In case extrapolation of efficacy from add-on to monotherapy cannot be justified, alternative studies could be considered. A randomized, standard of care controlled, open-label study of at least 1months duration evaluating treatment retention rate as the primary endpoint might be an option to provide the required clinical data. CHMP scientific advice is recommended in such situations.

Where extrapolation is not possible, monotherapy trials should be randomised, double-blind, active controlled non-inferiority trials comparing the test treatment to an acknowledged and well justified standard ASM at an optimised dose. Specific measures are necessary to ensure assay sensitivity i.e., including subjects with a high seizure frequency at baseline or extension of the duration of follow-up.

Therefore, patients should have characteristics that make them more likely than the general monotherapy population to have at least one seizure during the trial period. The following types of patients could be suitable:

- Newly or recently diagnosed patients with high baseline seizure frequency.
- Patients on monotherapy with insufficiently controlled seizures willing to convert to an alternative monotherapy in preference to adding a second ASM.
- Patients with focal onset seizures without focal to bilateral tonic-clonic seizures who accept occasional seizures on monotherapy in preference to ASM polypharmacy.

Although the type of patients described above may not be entirely representative of patients receiving monotherapy, extrapolation of efficacy to the more responsive forms is considered possible.

The most appropriate trial objectives and efficacy measures will depend on the trial population. In newly or recently diagnosed patients previously untreated with an ASM an appropriate primary efficacy endpoint would be the proportion of patients who experience a seizure during the randomised period of the trial. A non-inferiority margin should be justified a priori by the applicant.

The duration of the trial should be sufficient to achieve a sufficient proportion of patients with events (seizures) for a sensitive analysis and may be different depending on the seizure type and epilepsy syndrome. Follow-up of individual patients should be at least one year from randomisation for safety reasons and in order to verify that the proportion of patients remaining seizure-free is not below the expected rates in this population.

Plasma level monitoring may also be useful for correlating plasma concentrations to efficacy and the occurrence of adverse events and PK/PD modelling.

Monotherapy-safety

The safety in the add-on setting is not representative for the safety profile of the same product used in the monotherapy setting. Therefore, safety data under monotherapy should be generated e.g. open

label data of at least one year to collect additional safety information. In principle this may be done post-approval unless the safety profile observed in the add-on setting suggests that the benefit risk in the monotherapy setting may be different. Randomised comparative studies with retention rates as a global indicator of an overall favourable benefit-risk balance should be considered.

6.3.3. Statistical analyses

Statistical analyses should be embedded within the estimand framework. Referred is to ICH E9 R1 (addendum to estimands).

In the superiority studies the analysis of efficacy will usually be based on all randomised patients analysed as randomised, i.e., the intent to treat (ITT) principle. In the non-inferiority studies the analysis of efficacy will usually be based on all per protocol population. In both situations the analysis should be over period when patients are established on a fixed dose of either the study product or placebo/comparator i.e., the maintenance dose. Regardless of what happens to patients during the titration phase (e.g., discontinuing or otherwise modifying dose of randomised treatment, using other ASM, or discontinuing from the trial) they should not be excluded from the analysis. These should be handled as intercurrent events for which a treatment strategy should be defined and justified.

As the distribution of seizure frequencies is usually heavily skewed, careful consideration should be given to the parameterisation of the seizure frequencies and the choice of the primary analysis. Sensitivity analyses should be pre-specified to assess the influence of the modelling assumptions on the results.

The primary analysis of efficacy should be unadjusted except for factors used to stratify randomisation. Factors known to influence outcome such as aetiology, seizure type, baseline seizure frequency, seizure severity and epilepsy syndrome may be taken into account in supportive analyses. The use of concomitant anti-epileptic medicines should be summarised and the differential effect on efficacy of different ASMs used in combination with the investigational agent should be evaluated and discussed.

For the evaluation of less frequent seizure types (e.g., focal to bilateral tonic-clonic seizures) and differences in efficacy in seizures of different aetiology (epilepsy syndromes), individual studies are not expected to have adequate statistical power to establish a treatment effect. Efficacy in these seizures may be evaluated by a meta-analysis of individual studies. Such (meta) analysis is expected to be covered in a separate protocol and statistical analysis plan in advance, including a plan to investigate consistency of the effects observed across separate studies to establish the validity of the analysis.

6.3.4. Specific cases

The development of anti-seizure agents for indications in epilepsy syndromes other than focal epilepsy is encouraged. However, as trial experience is rare, in general no specific recommendation can be made. Some comments are made with respect to specific epilepsy syndromes in children, absences and status epilepticus.

Epilepsy syndromes

In specific epilepsy syndromes in children duration of the different phases of the trial, specific end-points, and small population trial designs and analysis should be discussed according to the characteristics of a given syndrome.

Compounds could be effective in age-dependent seizures/epilepsy syndromes but may be ineffective in seizure types occurring in adults. The minimal study duration should be discussed according to the specific characteristics of epilepsy syndromes as well as the outcome criteria.

Because not all of these conditions are likely to benefit from a new medicinal product, identifying those that may be candidates is a key point. Exploratory strategies are recommended to identify one of these syndromes as candidate to one randomised controlled trial with a new compound. It is recommended to enter patients in add-on studies as soon as the dose for children has been established. These studies would ideally be large studies including all types of paediatric epilepsy syndromes (whether common with adults or not), stratified by syndromes and/or age bands, they would permit to obtain initial information on population pharmacokinetics, and data on safety and efficacy. Results from such a trial should be interpreted with caution in case efficacy is not consistent across that multiple syndromes included as efficacy in any given syndrome may show particular promise by chance alone. In that case efficacy has to be confirmed by further confirmatory randomised controlled trial(s) for that particular syndrome. .

On a case-by-case basis a more focused, tailored approach may be an option if based on the understanding of the mechanism of action as well as the available non-clinical and (adult) clinical data certain epilepsies/syndromes can be identified as promising target indications. Such approach should however not jeopardise the identification of a possible benefit in other epilepsies/syndromes for which no or insufficient data exists.

For absence seizures short term randomised placebo-controlled withdrawal trials with EEG monitoring endpoints may be considered as proof of concept studies. It should be supplemented by longer randomised efficacy studies monitoring clinical and EEG freedom from absences. This preferably should be a randomised placebo control parallel group study with escape criteria. It might be complemented by a randomised withdrawal phase to establish benefits of continued treatment or a separate randomised withdrawal study. In the long-term open label safety studies maintenance of effect may be verified over time with repeat EEG monitoring.

Of note, if a product is exclusively developed for a specific condition more safety data need to be generated as compared to development plans where safety data in patients with different epileptic disorders or other conditions already exist.

Status epilepticus

Status epilepticus is an acute medical and neurological emergency that is potentially life-threatening and requires prompt diagnosis and treatment. In 2015, the ILAE proposed to define Status epilepticus as a transient condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures. Two time points are of relevance, i.e., the time point when treatment should be started and the time point when the status should be controlled in order to prevent structural damage. This differs per type of status epilepticus (e.g., tonic-clonic status epilepticus, absence status epilepticus) [78]. Trials in status epilepticus should have clear criteria for rescue treatment, including specifying time points by which treatment should be initiated depending on the seizure type.

Three situations should be considered: treatment of the acute status epilepticus, prevention of recurrence of status epilepticus and (super) refractory status epilepticus. For each condition both the trial design and study endpoints are different.

Treatment of the acute status epilepticus

Trials of new medicinal products intended for the treatment of acute status epilepticus should be performed first in the controlled setting. Depending on the nature of the new product and the available clinical and/or non-clinical data, new medicinal products intended for the treatment of acute status epilepticus may be tested either as first line treatment (in early status epilepticus) or as second line treatment after standard treatment with a benzodiazepine has failed (in established status epilepticus).

Stratification by prognostic factors is (e.g., aetiology) is recommended. Trials should be designed to show non-inferiority or superiority to an appropriate active comparator. For first line status epilepticus treatment this would be an approved benzodiazepine. For trials in second line treatment, appropriate comparators could be intravenous (fos)phenytoin or phenobarbital. Persistent seizure cessation should be the primary endpoint.

For a medicinal product intended to be used by non-medically trained caregivers, it is necessary to justify that the new product is suitable for administration by caregivers in an out of hospital setting. If the intended medicinal product is a drug-device combination, safe and effective use of the integral medicinal product by the intended user population needs to be demonstrated in line with the requirements set out in the Guideline on quality documentation for medicinal products when used with a medical device (EMA/CHMP/QWP/BWP/259165/2019). The sample size should be sufficient to conclude that both the efficacy and safety (especially in relation to cardiorespiratory depression) of the new product can be expected to be non-inferior to products that are approved for this indication (e.g. buccal or nasal midazolam).

Prevention of recurrence of status epilepticus

This refers to the situation where the status is controlled but another ASM is simultaneously given as an umbrella to prevent recurrence. Trials for new products for this purpose should have two arm designs intended to show non-inferiority or superiority to an appropriate active comparator e.g. phenytoin. Absence of recurrence of seizures after the primary treatment of status epilepticus seizures is no longer effective (i.e. there is no carryover) is the primary endpoint.

Refractory status epilepticus

Refractory status epilepticus refers to ongoing seizures without recovering of consciousness to baseline, failing to respond to first line treatment with a benzodiazepine and second line intravenous anticonvulsant treatments such as phenytoin and/or phenobarbital. Refractory status epilepticus typically requires treatment with general anaesthesia, continued for 12−24 hours after the last clinical or electrographic seizure, in order to prevent or minimise neurological damage. Treatment is intended to reverse prolonged status epilepticus and prevent (further) structural damage. Whereas initial treatment is focused on seizure cessation and silencing the brain, this is an intermediate endpoint as the ultimate goal is to prevent further neurological damage. Thus, for any new medicinal product studied in this setting, a functional outcome after weaning is recommended as the primary endpoint.

7. Safety aspects

7.1. Specific effects

As for any other medicinal product, the occurrence of liver, blood and skin disorders should be carefully monitored and documented in detail. In the case of ASM, special attention should be given to metabolic and endocrine function, and also to the following types of possible adverse events.

7.2. Long-term effects

The total clinical experience must generally include data on a large and representative group of patients (see ICH Topic E 1, Guideline on the Extent of Population Exposure to assess Clinical Safety.

7.3. Safety endpoints

7.3.1. Exacerbation of seizures

There is an increased awareness that ASM can sometimes worsen epileptic disorders and this should be taken into account in the design of clinical trials. Aggravation may consist in increased seizure frequency, often for specific seizure types (e.g. absence or myoclonic seizures), or appearance of new seizure types. Efforts should be made to identify the causal mechanism, such as inappropriate choice of the drug regarding the seizure types or the syndrome of the patient; spontaneous fluctuation of the condition; intoxication with or without over dosage; modification of concomitant therapy. In the absence of an explanation, a paradoxical reaction (which is when an ASM appears to exacerbate a type of seizure against which it is usually effective) might be considered. The potential for seizure worsening, and the seizure types and/or syndromes concerned, should be identified as early as possible in the drug development as it determines appropriate use of the product, i.e. it may have labelling consequences.

7.3.2. CNS adverse events

Special attention should be given to the occurrence or exacerbation of CNS adverse events (e. g. those involving cognition, thought processes, memory, lethargy, emotional and behavioural reactions, psychotic or depressive symptoms, suicidal behaviour/ideation, disturbances of gait, speech, coordination, or nystagmus). In children impact on cognitive function needs to be addressed in short term pharmacodynamic studies. See section 6.2.2.

Similarly, special attention should be given to the occurrence of rebound seizures and/or behavioural changes after the test product is tapered off. Data concerning potential withdrawal and / or rebound effects should be generated. If the test agent or placebo is withdrawn, withdrawal symptom and dependence should be carefully evaluated. A randomised withdrawal phase with a quick and slow taper off schedule for both placebo and active study arms in subjects who will stop treatment may be very informative.

Visual functions, including visual field defects, have to be clinically investigated. If problems in this area are to be expected, it is necessary to study systematically the visual function by using adequate ophthalmological procedures.

8. Studies in special populations

8.1. Studies in paediatric patients

8.1.1. Development of ASM in children

Efficacy in paediatric patients

Half of epilepsies begin before the age of 18 years and one fourth of these are intractable, having severe social and cognitive consequences. Epilepsy in childhood differs from epilepsy in adults especially by the occurrence of seizures in a structurally and functionally maturing and developing brain, the occurrence of seizure/epilepsy types not seen in adults and the occurrence of seizures as part of age dependent epilepsy syndromes. In addition, treatment of seizures as early as possible with respect to seizure onset is of particular importance because 'seizures beget seizures', which means that intensity, frequency and type of epileptic seizures tend to worsen over time and can lead to detrimental consequences for brain development. An epilepsy syndrome may persist or change in

characteristics over time, and other epilepsies can arise. Therefore, epilepsy may affect the normal development of children. The information about seizures and aetiology should be recorded at baseline.

In paediatric studies, the endpoints are in principle the same as for adults although other responder definitions are acceptable where justified (e.g., days without myoclonic seizures in IGEs, absence of spasms and hypsarrhythmia in the West syndrome). These and the secondary variables should allow full investigation of the distribution of change in seizure frequency after treatment.

In infants and very young children subtle seizures are more frequent and likely to be missed. In younger children from 1 month to less than 4 years, EEG or video-EEG may complete and provide evidence of seizure reduction, in particular subtle clinical seizures can be confirmed when linked with EEG, video-EEG and/or alternative methods, as appropriate. Hence video-EEG is recommended depending on the epilepsy syndrome or seizure type, in particular for use at screening/baseline, for identification and confirmation of diagnosis.

Novel approaches such as wearable devices might facilitate and improve seizures detection and recording and could be acceptable if validated.

Study design with a time to event approach with variable exposure to treatment is acceptable (see 5.1.1) and may improve the feasibility of the study.

For a claim of efficacy in the paediatric population several situations are distinguished warranting a different clinical development plan.

In focal-onset epilepsies, idiopathic generalised epilepsies, as well as absences, myoclonic and/or generalised convulsive seizures, the efficacy of ASMs may be comparable between childhood and adulthood. With a few exceptions, focal-onset epilepsies in young children may have a similar clinical presentation to focal epilepsies as in adolescents and adults. For focal-onset epilepsies, the results of efficacy trials performed in adults may be extrapolated to children and adolescents suffering only from focal-onset seizures, provided that the exposure-response (E-R) relationship in adults is established and that the dose regimen proposed in children and adolescents results in similar exposure levels as in adults in all age categories. This approach should be planned and pre-specified in a modeling and simulation study and extrapolation plan. The model should be also validated in the subsequent younger age-subset cohorts, which should be planned according to drug pharmacology (See Reflection paper on the use of extrapolation in the development of medicines for pediatrics, EMA/199678/2016, ICH E11A). The number of children should be distributed across all age subsets and sufficiently large to ensure dose determination.

For non-focal seizures, once efficacy has been shown in the older age-subsets, short term assessment of response by using diary and/or video EEG/EEG monitoring only may be sufficient as supportive of efficacy. Preferably, the observed response should be similar within predefined limits to the predicted response based on the E-R relationship established in the older age groups.

For epilepsies/seizure types which are specific to children (e.g., West syndrome, Dravet syndrome, Doose syndrome and Lennox Gastaut syndrome), efficacy should be shown based on randomised controlled trials. PK modelling and simulation may be useful for the estimation of the dose in children that leads to similar exposure as observed studies in adults with other seizure types.

In case an effect of a disease-modifying effect is claimed it should be shown that the effect on seizures translates in an improved neuro-motor development. This would require long-term comparative data. As this is a developing area of research CHMP scientific advice is recommended.

Safety in paediatric patients

Generally, from the safety point of view, preferably 100 children should be treated by the study drug and followed for at least one year. Moreover, short term and long-term studies should be designed to detect possible impact in the neurodevelopment, motor development, cognition, behaviour, growth, endocrine functions and puberty. In addition, health-related quality of life should be assessed. Assessment scales should be validated by age and by language. Some of these studies may require continuation in the post marketing period as the follow up of 2-5 years to evaluate the effectiveness not only on crisis control but also on neurodevelopment, in particular in young patients [see Guideline on clinical investigation of medicinal products in children (CPMP/EWP/462/95). Prospective disease based registries or external cohorts (per paediatric epilepsy syndrome or type) may be helpful and are encouraged.

Long term comparative observational studies in children are of great potential interest in order to disentangle the long term effects of the disease and the potential undesirable effects of the product on development depending on the mechanism of action of the product. The design of these longitudinal studies will need to take into account the influence of age and underlying disease on cognition.

8.1.2. Development of ASM in Neonates

Newborns with multichannel video-EEG-proven and/or clinical repeated seizures or who are at high risk of seizures, such as with hypoxic ischemic encephalopathy, stroke or intracranial haemorrhage or with aetiologies such as cerebral malformations and genetic causes, should be considered for inclusion in clinical studies, from a birth gestational age of 34/35 weeks to less than 28 days of post-natal age. Lower gestational ages are to be included only if the new medicine has already been investigated in term age. Trial designs should ideally include a minimum seizure burden for trial entry and randomization. Trials should favour designs that test ASMs for seizures refractory to an initial standard ASM, as soon as is practically possible after seizure onset.

A claim of reduction in seizure burden may by based on the assessment of video/electroencephalographic neonatal seizures (ENS). Multichannel continuous video-EEG is needed to exclude artefacts, to identify minor clinical seizures or electrographic (or subclinical) seizures and to evaluate the frequency, duration and total seizure burden of the seizures. The duration of EEG should be sufficient to ensure the adequate recording of seizures. At least one central reader should confirm the video-EEG recordings evaluated by the local physician, with epileptiform discharges/seizures to be distinguished from artefacts. The correlation with clinical signs or not should be investigated. Other assessment tools can be considered in addition related to Patient/Caregiver Reported Outcomes.

Aetiologies are diverse and should be carefully considered based on the anticipated mode of action and efficacy as well as PK and safety. Single aetiology trials versus trials in patients with multiple aetiologies of the seizures should be discussed considering confounders versus feasibility and generalisability. Single aetiology trials may be more appropriate for confirmatory trials. In addition, seizure severity is to be considered. Therapeutic hypothermia treatment potentially impacts drug PK, efficacy and safety, and should be balanced across treatment arms if applied.

Randomised comparative studies are recommended. Historical controls are per nature less robust. If proposed, will need to be justified, including a predefined matching by age and condition, using comparable standard of care of ASM and diagnostic tools. Registry data, preferably prospectively, can be supportive.

According to scientific recommendations, electroencephalographic neonatal seizures (ENS) are defined as lasting at least 10 seconds. The seizure burden is to be defined as a duration of activity on EEG in a

defined timespan, which could be severe (> 50% seizure activity in 30 minutes) and non-severe. The evaluation period should last for at least 24 hours and continue until the patient is seizure-free for a defined period, at least of 24 hours, unless otherwise justified. For neonates with clinical observable motor seizures at baseline, the clinical signs of the seizure should be evaluated in addition to EEG.

The primary outcome in a drug efficacy trial in neonates should be a reduction in seizure burden, the extent of which should be justified, e.g. at least 50% or 80% in seizure burden (minutes/hour) from baseline period, in defined periods according to the severity of ENS. Premature drop-outs of treatment, subjects who switch to rescue medication should be counted as non-responders. A superior efficacy in seizure reduction for the active drug should be demonstrated by a pre-defined and justified relevant difference between study drug and comparator groups, which shall also inform sample size planning.

The secondary outcomes should include the need of rescue medication and other clinical measures (feeding, vision, etc), with neuroimaging before neonatal intensive care unit discharge (structural magnetic resonance imaging with a central reader) to evidence the structure of the brain.

The minimal follow-up period within the clinical study should be 30 days after final study drug intake, to evaluate the persistence of the effect, which should include routine EEG.

Long-term assessment of central nervous system (CNS) function requires at least 24 months, including motor development. Depending on data already available this may be done post-approval. More precisely, evaluation of cognitive, behaviour and neuromotor developmental function beyond the major disabilities requires follow-up to at least pre-school age and the use of standardized age-appropriate instruments. Protocolised prospective disease-specific or at least drug registries are recommended including clinical outcome and safety assessments at 1 month, 6 months and/or 1 year of age initially and for long-term outcome, for at least up to 2-5 years.

8.2. Studies in the elderly patient

The incidence and prevalence of epilepsy increase substantially after 65 years of age. Elderly patients who have suffered from epilepsy for years should be considered differently from those who developed epilepsy recently. Efficacy and safety of ASMs in newly diagnosed elderly patients may be different from those in younger adults for the following reasons:

- Predominance of focal epilepsy with known aetiology, due to cerebrovascular accidents, neurodegenerative conditions including Alzheimer's disease or brain tumour;
- An increased susceptibility to adverse effects despite the use of drugs at standard doses, especially on cognitive functions, vigilance and cardiovascular system; respective disorders should be carefully documented at baseline in order to disentangle adverse effects from pre-existing conditions.
- PK and/or PD interactions with other concomitant products frequently used in the elderly due to comorbidities.
- Therefore it is important to determine whether or not the pharmacokinetic behaviour of the drug in elderly subjects is different from that in younger adults (see guideline ICH E7). An adequate number of elderly patients should be included in the Phase III data base. A separate analysis between elderly patients, who may have suffered from epilepsy for years and those who developed epilepsy recently due to an underlying disease (e.g. stroke) should be presented as responses may be different.

Safety, especially with regards to cognitive function and on sedation in this age group should be evaluated, and corresponding AEs be evaluated as adverse events of special interest by appropriate measures depending on the anticipated safety profile. Interactions of the test product should also be assessed, especially with frequently used products in this age group where a PK/PD interaction is expected. Depending on the data, specific efficacy and safety trials in this population may be needed. In studies complementary to data on elderly patients derived from pivotal add-on studies alternative trial designs may be considered, however, it is recommended to seek Scientific Advice when planning such trials. The results, as well the lack of these data, are informative and will need to be mentioned in the SmPC.

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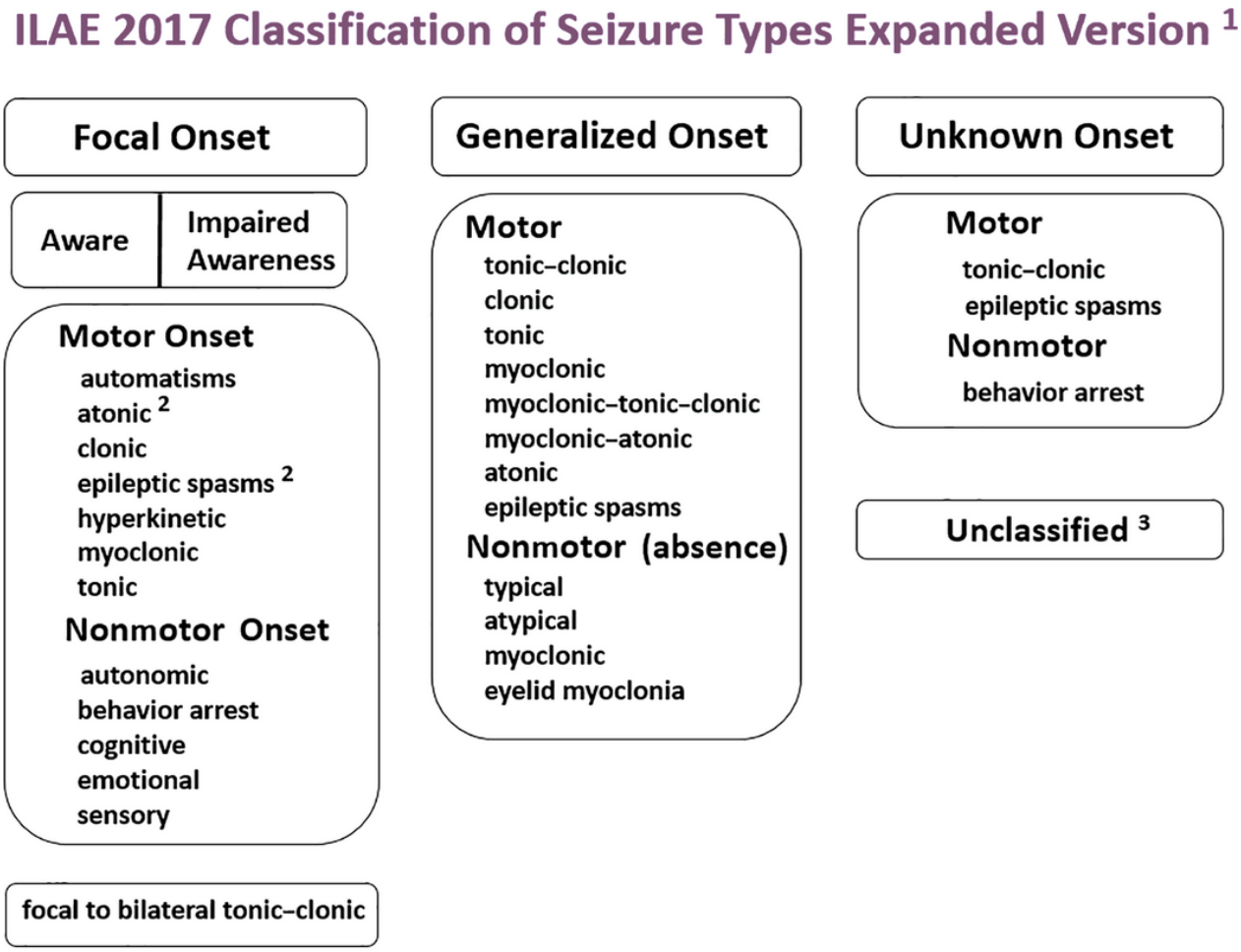
ANNEX I

Expanded ILAE 2017 operational classification of seizure types (based on Fisher et al., Epilepsia, 2017)



[1] Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms of Fisher et al.

[2] Degree of awareness usually is not specified.

[3] Due to inadequate information or inability to place in other categories.

Conversion table of old to new ILAE seizure classifying terms based on Fisher et al., Epilepsia (2017)

Old Term for Seizure The most important are in bold	New Term for Seizure [choice] (optional common descriptor)
absence	**generalized absence**
absence, atypical	generalized absence, atypical
absence, typical	generalized absence, typical
akinetic	generalized/focal/onset unknown atonic
astatic	generalized/focal/onset unknown atonic
atonic	**generalized**/focal/onset unknown **atonic**
aura	focal aware
clonic	generalized /focal/onset unknown clonic
complex partial	**focal with impaired awareness**
convulsion	[focal/generalized/onset unknown] motor [tonic-clonic, tonic, clonic], focal to bilateral tonic-clonic, tonic-clonic unknown onset
dacrystic	focal [aware or impaired awareness] emotional (dacrystic)
dialeptic	focal impaired awareness
drop attack	generalized/focal/onset unknown atonic
fencer's posture	focal [aware or impaired awareness] motor (tonic)
figure-of-4	focal [aware or impaired awareness] motor (tonic)
freeze	focal [aware or impaired awareness] arrest
frontal lobe*	focal
gelastic	focal [aware or impaired awareness] emotional (gelastic)
grand mal	**generalized tonic-clonic, focal to bilateral tonic-clonic, tonic-clonic unknown onset**
gustatory	focal [aware or impaired awareness] autonomic (gustatory)
infantile spasms	**generalized/focal/onset unknown epileptic spasms**
Jacksonian	**focal aware motor (Jacksonian)**
limbic	focal impaired awareness
major motor	generalized tonic-clonic, focal to bilateral tonic-clonic
minor motor	focal motor, generalized myoclonic
myoclonic	**generalized myoclonic**
neocortical*	focal aware
occiptal lobe*	focal
parietal lobe*	focal
partial	focal
petit mal	**generalized absence**
psychomotor	**focal with impaired awareness**
Rolandic	focal aware motor
salaam	generalized/focal/onset unknown epileptic spasms
secondarily generalized tonic-clonic	focal to bilateral tonic-clonic
simple partial	**focal aware**
supplementary motor	focal motor tonic
Sylvian	focal motor
temporal lobe*	**focal aware / with impaired awareness**
tonic	**generalized/focal/onset unknown tonic**
tonic-clonic	**generalized tonic-clonic, focal to bilateral tonic-clonic, tonic-clonic of unknown onset**
uncinate	focal [aware or with impaired awareness] sensory (olfactory)

* Anatomical classification may still be useful for some purposes, for example in evaluation for epilepsy surgery.

ANNEX II

ILAE Framework for Classification of the Epilepsies (based on Scheffer et al., Epilepsia Open, 2016)