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Overview of comments received on " Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders

(CHMP/EWP/566/98 Rev.3)

Name of organisation or individual	Line from(line nr. or 0 for general comment)	Line to(line nr. or 0 for general comment)2	Comment and rationale(to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)	Outcome (To be completed by the Agency)
Dravet Syndrome Foundation	0	0	The document's overall structure is well-organized		Acknowlegded.
Dravet Syndrome Foundation	0	0	Consider summarizing and emphasizing the key points for quick comprehension		Taken aboard in the executive summary where appropriate.
Dravet Syndrome Foundation	0	0	Regarding the use of the word seizure: Not all epileptic crisis are seizures, Isuggest changing the word seizure to epileptic crisis, when relevant.		The guideline deals with seizure control mainly not only epileptic crisis
Dravet Syndrome Foundation	0	0	Legal Basis and Relevant Guidelines:Clarify if there are any recent updates or changes in the legal basis and guidelines that may impact the clinical investigation of medicinal products for epileptic disorders.		Not applicable.
Dravet Syndrome Foundation	0	0	Assessment of Efficacy: Acknowledge the inclusion of different trial types (add-on trials, monotherapy trials) and recommend providing more details on specific efficacy criteria and treatment goals for clarity.		Taken into account where appropriate. Referred is to the specific comments.
Dravet Syndrome Foundation	0	0	Study Design: Emphasize the significance of non-clinical data, pharmacology studies, and their role in shaping the study design. Suggest providing additional information or examples for each type of study design mentioned to assist readers in understanding their application.		Acknowlegded and taken into account.
EFPIA	0	0	EFPIA very much welcomes the well written revised, draft guideline,offering additional information for sponsors developing medicinal productsfor the treatment of epileptic disorders, especially those involving paediatric patients. To streamline the document, we are excluding editorial ortypographical comments. On top of the detailed comments provided below, we would particularly liketo emphasise the following: Since the document now mentions Developmental and Epileptic Encephalopathy (DEEs) and expanded the recommendations for paediatric development, it is recommended to use more flexible language which may apply to development programs in rare / ultra-rare diseases that may be paediatric-only by nature (e.g. some DEEs), where the unmet medical needis still high, without well-established standard of care, and no available adult data. We recommend including provisions in this guideline for the acceptance of lower number on patients, real world evidence, external controls and basket trials where appropriate and justified. It would be helpful if the language in the guideline could be harmonised where possible, e.g. to replace “target of estimation” with “estimand”. On top of the detailed comments provided below, we would particularly like to emphasise the following: Since the document now mentions Developmental and Epileptic Encephalopathy (DEEs) and expanded the recommendations for paediatric development, it is recommended to use more flexible language which may apply to development programs in rare / ultra-rare diseases that may be paediatric-only by nature (e.g. some DEEs), where the unmet medical need is still high, without well-established standard of care, and no available adult data. We recommend including provisions in this guideline for the acceptance of lower number on patients, real world evidence, external controls and basket trials where appropriate and justified. It would be helpful if the language in the guideline could be harmonised where possible, e.g. to replace “target of estimation” with “estimand”.		Acknowlegded and taken into account where appropriate. Referred is to the specific comments.
Lundbeck	0	0	Lundbeck appreciates the EMA’s ongoing efforts to provide sponsors with more clarity on existing guidelines, whilst reflecting current scientific knowledge and practice in research.We appreciate the opportunity to comment and look forward to a continued dialogue with the Agency and other stakeholders on these important matters.		Acknowlegded and appreciated.

Institute for Quality and Efficiency in Health Care (IQWiG)	0	0	Thank you for giving us the opportunity to comment on the new draft guideline (third revision).We appreciate that in the current draft, some changes address our comments from 2019:• Inclusion of seizure severity, treatment retention rate, functional outcomes and quality of life (at least as additional outcomes). However, crucial aspects are still not addressed in the current version:• Lack of active comparators in add-on trials• Lack of appropriate study duration. Most importantly our aim of primarily requiring active comparator trials is not addressed at all in the new draft guideline. For HTA, an appropriate comparison to estimate the benefit in relation to the respective standard therapy is indispensable. Therefore, studies based on the principles described in the guideline will usually be unsuitable for HTA. We already mentioned in our previous comments (2019) that IQWiG has evaluated several new antiepileptic drugs approved for combination treatment. A common experience from these evaluations is that the pivotal studies for this indication are consistently inappropriate to support treatment decisions in patients with epilepsy. This is due in particular to artificial restrictions in the comparison group, even though therapeutic options are still available for the patients included. In addition, the studies are usually short and not focused on collecting data on patient-reported outcomes (quality of life and functional outcomes). Since then we have evaluated several new drugs. Unfortunately, nothing has changed during the past 5 years. The studies are still unsuitable for HTA and for informing treatment decisions (Hamer et al.: Position paper of a German interdisciplinary round table on future designs of trials on adjunctive treatment with antiseizure drugs; https://doi. org/10.1016/j.seizure.2020.03.004) on new antiepileptic drugs.This way the important common goal of achieving study designs and protocols that address the requirements of both regulators AND HTA is counteracted. This also precludes the use of the current type of studies in the upcoming EU-HTA process. At least the inclusion of a third study arm with an active comparator would be required, if, according to EMA, pivotal add-on studies will in future still be placebo-controlled.		RD DB **PC** add-on studies are mandatory for showing efficacy of a potential ASM. The reason is that these studies have a high placebo effect and that placebo effect is not predictable. In absence of placebo one cannot decide if a response seen reflects the efficacy of the new ASD or reflects placebo response. In technical terms, the active controlled study without placebo would have no assay sensitivity. It is acknowledged that the comparator group may have to continue their previous therapy plus placebo, although this previous therapy has been not successful. Several points here 1) No treatment in refractory seizures is successful if success is defined as freedom of seizure 2) The add-on setting not per definition implies that subjects did not benefit from previous ASM i.e., without the treatment a subject would have been worse 3) What the active comparator should be is difficult to define as there a numerous combination of concomitant ASMs . 4) Even if a subject is responder on the new combination of ASMs sooner or later seizure control will be insufficient and there will be a seaerch for a new combination that (temporarely) is more sufficient. This is inherent on the refractory epilepsy population. Further for non-inferiorty a non-inferiority margin needs to be defined, which however is not possible due to the lack of assay sensitivity / unpredictable placebo response
International League Against Epilepsy	0	0	We strongly suggest to use ILAE terminology on seizure and epilepsy - We published a commen in Epilepsia on this - Auvin S, Arzimanoglou A, Brambilla I, French J, Knupp KG, Lagae L, Perucca E, Trinka E, Dlugos D. Call for the use of the ILAE terminology for seizures and epilepsies by health care professionals and regulatory agencies to benefit patients and caregivers. Epilepsia. 2023 Dec 17. doi: 10.1111/epi. 17868. Epub ahead of print. PMID: 38105624. We strongly suggest to use ILAE terminology on medication see Perucca E, French JA, Aljandeel G, Balestrini S, Braga P, Burneo JG, Felli AC, Cross JH, Galanopoulou AS, Jain S, Jiang Y, Kälviäinen R, Lim SH, Meador KJ,Mogal Z, Nabbout R, Sofia F, Somerville E, Sperling MR, Triki C, Trinka E, Walker MC, Wiebe S, Wilmshurst JM, Wirrell E, Yacubian EM, Kapur J. Which terms should be used to describe medications used in the treatment of seizure disorders? An ILAE position paper. Epilepsia. 2024 Jan 27. doi: 10.1111/epi.17877. Epub ahead of print. PMID:38279786. In several places, the draft guidelines speak about 'neuro-motordevelopment', we suggest to use 'cognitive and behavior development/outcome'. Motor is a small part of the development		This has been implemented
EpiCARE	0	0	When it comes to selection of patients with epilepsies to be included in clinical trials it is also important to emphasize that, starting 2017, the epilepsy community in Europe created a European Reference Network (ERN) dedicated to rare and complex epilepsies (ERN EpiCARE), cofunded by the EU. In 2024 the ERN EpiCARE is composed by 50 reference medical teams, accredited for their expertise by both the national health authorities and the EY, present in 24 EU countries. Today EpiCARE medical teams dispose of a common Registry, in which all patients with rare or complex epilepsies are listed per syndromic diagnosis and their individual follow-up data collected and validated by experts in the field. It is expected that within the next 3 years all patients with rare and complex epilepsies will be included by their respective medical teams. A major advance that will enormously facilitate both epidemiological and natural history studies as well as early identification of subgroups of patients eligible for both “basket” and syndrome-targeting clinical trials. ERN EpiCARE also has official collaborations with epilepsy centres in Europe outside the EU, for example in the UK and in Switzerland. In parallel, EpiCARE contributed, together with the scientific society ILAE (International League Against Epilepsy) and the patient advocate’sassociation IBE (International Bureau for Epilepsy), to the creation of a European Consortium for Epilepsy Trials (ECET), involving already more than 60 centres with expertise in clinical trials and working in partnership with the USA based Epilepsy Consortium, chaired by J. French.ECET offers today expertise for optimal design of clinical trials, corresponding to state-of-the-art knowledge even for very rare forms of epilepsy, reliable feasibility data etc.		Acknowlegded.
Dravet Syndrome Foundation	72		change brain for neurological		Agreed and implemented
EFPIA	158	159	It is recommended that examples of accepted international classification guidelines (e.g. the 2017 InternationalLeague Against Epilepsy (ILAE) Classification of the Epilepsies and ILAE Classification and Definition of Epilepsy Syndromes) be mentioned here.	"Patients included in the clinical trials should be classified according to ~~the~~ **accepted** International Classifications of Seizures **(e.g. the 2017 International League Against Epilepsy (ILAE)** Classification of the Epilepsies andEpilepsy Syndromes **(e.g. the 2022 ILAE Classification and Definition of Epilepsy Syndromes)**."	Not accepted. If classifcation or organisation change in the future this may not apply anymore. The classifications are mentioned in annex 1 and 2.
EFPIA	169	170	It is recommended to reflect in the guideline that bilateral tonic-clonic seizures are rare and very challenging to perform fully powered studies for them.	“Efficacy needs to be evaluated for focal seizures; ~~and focal to~~ **however subgroup analyses would be sufficient for** bilateraltonic-clonic seizures ~~separately~~ **due to their rare nature**.”	The proposed change not supported. The current wording states that efficacy needs to be evaluated for tonic-clonic seizures separately, without specifying how this should be performed. This neutral wording should be retained as this section does not relate to what kind of evidence would be sufficient for these seizure types. Moreover, here is dealt with in line 485-490.

International League Against Epilepsy	178		an exemple propose to study 'GTCS in IGE and LGS'. These syndromes are 2 differents in nature, in evolution and in comorbidities that it doesn't not make sense to combine them in a single trial	remove the example that propose to study GTCS in IGE and LGS	Not fully agreed. If the study objective is seizuretype based i.e. evaluating efficacy in GTCS , and efficacy in GTCS is observed independent of the syndrome this would support a prevention of GTCS indication. As stated in line 176-177 evaluation can be seizure type based within a given syndrome or seizure type based **across** different syndromes.
Lundbeck	180		The reference (4.4. statistical analysis) does not exist in this draft guideline. It is assumed that the reference should be for 6.3.4. Specific cases instead, which is a section that contains information about the characterization of syndromes.	"carefully characterised for further evaluation (see 6.3.4. Specific cases)"	The text has been updated to include the correct section ("6.3.3 Statistical analyses")
EFPIA	183	185	It is proposed to add "sleep pattern" to the list of potential key outcomes.	"Where an effect on the encephalopathic process itself in epileptic encephalopathies is claimed, efficacy should be shown for neurodevelopment, cognition, socialisation, EEG **and/or sleep pattern**, and not only on seizures."	Not accepted. The principle is stated here. How to this is worked out in detail at an behavioural signs and symptom level is up to an individual clinical development plan. This in order to prevent endless arbritrary discssion which conbination of items are useful and which not.
International League Against Epilepsy	183		2 major changes are required in thefollowing sentence 'Where an effect on the encephalopathic process itself in epileptic encephalopathies is claimed, efficacy should be shown for neurodevelopment, cognition, socialization, EEG and not only on seizures.'	1: EEG could not be considered as a primary endpoint for encephalopathic processes. There is no data on that.	Accepted and adapted by leaving out EEG.
EFPIA	187	245	It would be helpful for the readers if information related to estimands could be repeated either as an additional separate subsection of section 5 or 5.1, if too many differences between indications. The summaries of estimand related considerations could address the following points: endpoint description, intercurrent event list along with respective handling recommended/possible handling strategies and population level summary.		Acknowledged. However, it is deliberately abstained from specific comments. The estimand frame work is considered rather study protocol specific and should be dealt with there. Given the rather different study options in epilepsy a one fits all recommendation is not possible apart from the fact that this would kill flexibility. The general principles are pointed out in lines 331-337 and these should be applied and worked out for a specific study protocol.
EFPIA	188		It is suggested to add considerations of seizure severity as treatment outcomes.	Add to line 188: "**Seizure severity, shorter duration, post-ictal symptoms, return to baseline functioning, falls, other injury, tongue biting, enuresis. post ictal headache or tiredness may also be considered**"	Here is dealt with in 5.1.3, line 227- 237 : S*econdary efficacy variables applying to both add-on and monotherapy trials may concern ….*
Lundbeck	188		Kindly clarify whether seizure frequency and occurrence can be used interchangeably and thus they share the same definition.		The terms share the same definition.
Lundbeck	191	194	Kindly consider using a more open language in the guideline such as "the primary endpoint should be based on seizure frequency".		The proposal is not supported. The primary endpoint for a conventional epilepsy study should remain the responder rate. Exceptions for a different primary endpoint, such as change in seizure frequency in orphan epilepsies, are clarified in the other sections of the guideline.
EFPIA	194	195	It is recommended to harmonise and clarify the wording. Our interpretation is that the intention is to use the percent change from baseline in seizure frequency as (continuous) endpoint and to summarise this by using the median per treatment group. If this is correct, we suggest updating the text as per the proposed wording. It is recommended to mention the possibility of using alternative ways to quantify non-countable seizures (e.g.infantile spasms), which cannot be accurately characterized by a pre-defined percentage reduction of seizure frequency. In such circumstances, measurement of other variables (e.g. seizure free days entered in a diary) will be needed to more accurately capture the occurrence of seizure types that can be subtle and easily underestimated.	The other variable ~~should~~ **could** be ~~some parameterisation using~~ the ~~actual~~ t**he percentage** change **from baseline period** in seizure frequency, ~~e.g.~~, **this variable could be summarised using the** median **per treatment group** ~~percentage change in seizure frequency~~. Add the following sentence to the end of the paragraph ending on line 195 "**Alternative variables to a pre-defined percentage reduction of seizure frequency (e.g. seizure free days entered in a diary) can be considered as the primary endpoint for certain seizure types (e.g. infantile spasms) if those seizure types are difficult to reliably count and present a significant burden to patients.**"	The proposal is not supported. The combination of endpoints for primary and key secondary (or vice versa) remains the responder rate and the actual change in seizure frequency. By replacing should with could, this opens up the option to use other endpoints as key, which is not supported. The median percentage change in seizure frequency is used as an example, but is not absolute in terms of what the other most important endpoint should be. This is because, as correctly noted by the EFPIA, there are other endpoints that may be more suitable in specified epilepsy syndromes. Highlighting this through the addition of another phrase is not supported, as the subsequent paragraphs discuss different types of variabels such as seizure freedom leading to repitition. Finally, the guideline provides general recommendations for epilepsy trials and thus it is not always necessary to describe every exception to the situation.
Lundbeck	194	195	The individual percentage change from baseline is in general sensitive to baseline value variability and imbalance in baseline values between treatment groups, and also connected to an increase in risk for non normally distributed outcome data. Thus, instead of using percentage change as an endpoint, it is instead suggested e.g. to use the absolute change from baseline, based on original or transformed data, as an endpoint, with a possibility to then report the median percentage change as a population-level summary measure of such an endpoint.		The absolute change from baseline does not allow a useful interpretation of the effect. Considered a subject with 30 seizures at baseline as compared to a subject with 120 seizure at baseline (Note: these are realistic scenario's). Percentage change is baseline independent and takes the variability in baseline seizure into account. As the percentage change is highly skewed the median percentage change is mention as an example hoe to deal with skewness. Alternative options dealing with non-normality a may be considered that why it is given as an example. However, in our experience also log transformations apply in studies remain highly skewed. The above als implies that the absolute is sensitive to outliers.

Lundbeck	194	200	Kindly clarify what the role of the variables other than the primary endpoint should have in connection to e.g. claims made by the sponsor.		The variables would support the primary endpoint. With respect to potential claims this is a matter of review. Focus would be on primary endpoint and the most relevant endpoints to inform the prescriber what to expect. Secondary endpoints not necessarily need to be mentioned despite being defined a priori and results being highly statistically significant. Secondary endpoints that are highly correlated to the primary endpoint provide less supportive evidence in fact the same results are presented in different ways (e.g 50% responders vs 75% responders . Hence claims based on secondary endpoints depends on the justification, its relevance and the observed results.
EFPIA	196		It is recommended to replace "variable" by "summary measure"	"The proportion of seizure-free patients is aparticularly important ~~variable~~ **summary measure**."	Agreed . Adapted accordingly
Lundbeck	196	197	Kindly clarify these paragraphs as it does not constitute any endpoint, but just a statement on how to present the "other variable" mentioned on line 194-195, i.e. the percentage change in seizure frequency from baseline. The idea behind the suggested presentation seems to indicate using a non-parametric approach for the statistical analysis of the percentage change in seizure frequency from baseline, as also the term "median" on line 195 might be a sign of.		It is confirmed. The interpretation indeed is that it does not constitute an endpoint but how to present the "other variable".
Dravet Syndrome Foundation	198	199	Please specify how every aspect is evaluated: e.g. quality of life of patient? Of caregiver? of the whole family? which scales are used? etc…		This depends on the context of the study to be worked out in the study protocol here the general princple is reflected.
Dravet Syndrome Foundation	198		severity: how about duration? I think not considering epileptic crisis duration could lead to biased conclusions. How is severity defined?		See above. The guidance provides general recommendations with respect to designs and endpoints as the field changes over time, thus specific recommendations could no longer be up to date. Therefore, further specifying how seizure severity should be measured will not be implemented. The proposal to include seizure duration as an endpoint has been included.
Dravet Syndrome Foundation	198	199	Please specify how every aspect is evaluated: e.g. quality of life of patient? Of caregiver? of the whole family? which scales are used? etc…		See remark above.
Dravet Syndrome Foundation	198		How is severity defined? How about duration? I think not considering epileptic crisis duration could lead to biased conclusions.		See previous comment on seizure severity in line 198
Lundbeck	198		It is proposed to exchange "rate" (treatment retention rate) with "yes/no" as endpoints are on an individual level, the term rate would indicate a population-level summary rather than an endpoint	"The following additional endpoints should be assessed: seizure severity, treatment retention rate, treatment retention (yes/no)"	The proposal is not supported. While it is acknowledged that the retention rate is more population based outcome, the information this percentage provides is important as it provides a crude measurement of maintanenance of effect in long term open label studies. Therefore, the retention rate is maintained.
EFPIA	201	210	The text says "A time to event approach (e.g. time to pre-randomisation monthly seizure count) is an acceptable approach". However, it is not clear what "time to event" means in this context. Consider adding clarification and examples about what would be the event in this design (for example, time to first seizure, time to worsening)		See above. It is time to n^{th} seizure wherehere n is the number of seizures observed during baseline.
Lundbeck	201	202	Kindly clarify how this time-to-event approach as returning to the same number of seizures as at baseline should be interpreted as no improvement does not seem to be appropriate. As the guidance text is written, it is understood that the intention instead is to study the time it takes to reach a certain reduction in seizure frequency (e.g. 50%), and when that event has taken place, the study either ends for that patient or the patient enters an open-label treatment period, i.e. patients can have different length of followup time in the double-blind period.		The interpretation is not correct. Patients who enter the maintenance period exit the trial if the cumulative number of seizures (of seizure types of interest) reaches the number of seizures observed during their baseline. Hence the event is defined as number of days to the "nth" seizure, where n is the number of seizures observed during baseline. The advantage of this event definition is that baseline difference is seizure is accounted for i.e. the number of seizures is specific to each patient. Reference is made to: *Johnson ME, McClung C, Bozorg AM. Analyses of seizure responses supportive of a novel trial design to assess efficacy of antiepileptic drugs in infants and young children with epilepsy: Post hoc analyses of pediatric levetiracetam and lacosamide trials. Epilepsia Open. 2021;6:359–368. https://doi.org/10.1002/epi4.12482* *Auvin S, French J, Dlugos D, et al. Novel study design to assess the efficacy and tolerability of antiseizure medications for focal-onset seizures in infants and young children: A consensus document from the regulatory task force and the pediatric commission of the International League against Epilepsy (ILAE), in collaboration with the Pediatric Epilepsy Research Consortium (PERC). Epilepsia Open. 2019;4:537–543. https ://doi.org/10.1002/epi4.12356*

Dravet Syndrome Foundation	218		How are the most debilitating seizure types defined? And what aspects are considered in the word "debilitanting". The whole quality of life? Neurological effects of epileptic crisis?Post-ictal state?		The message is that where different seizure types co-exist, an effect on the more serious seizure types at the cost of no or even a worsening in another seizure type might be acceptable. This is benefit/risk assessment. The term debilitating has been replaced by most serious
Dravet Syndrome Foundation	218		How are the most debilitating seizure types defined?And what aspects are considered in the word "debilitanting". The whole quality of life? Neurological effects of epileptic crisis?Post-ictal state?		See previous comment
Dravet Syndrome Foundation	219		Benefit-risk assessment modalities should be defined here.		The benefit-risk assessment is for the review process at MAA. It depends on the observed results. results. It cannot be assessed in advance. However, the review process might be facilitated if what would be considered acceptable can be defined and justified in advance so the justification is not exclusively data driven i.e., exclusively based on the observed results.
EFPIA	219	220	As written, it is unclear what should be predefined in the clinical trial protocol. Any differing effects of a treatment on various seizure types in an epilepsy syndrome can only be evaluated as part of the overall benefit/risk assessment after study data is collected. However, the primary target of an ASM under investigation (e.g., the most debilitating / clinically important seizure type of an epilepsy syndrome) can be justified a priori.	"A prerequisite is that ~~it~~ **the seizure type(s) relevant to the primary endpoint(s)** should be predefined and justified in the study protocol ~~what would be acceptable~~."	Not accepted. See answer above. If the most serious seizure type is defined as the primary enpoint it still should be clear this is not at the cost of the other seizure types to an extend that it is no longer acceptable.
EFPIA	222	225	It is mentioned that "(…) 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)" but probability is a statistical concept from modelling not a clinical definition associated to an endpoint. Therefore, it is suggested to replace 'probability' with "proportion"	"In monotherapy trials (adults and children) in newly or recently diagnosed patients, the primary efficacy variable should be based on the ~~probability~~ **proportion** of patients remaining seizure free for at least six months (excluding the dose titration period)"	Accepted and adapted.
Lundbeck	233		It is proposed to include examples of PROs and scales		See answer below.
Lundbeck	234	236	It is proposed to include examples of such scales		These endpoints are often mentioned as a wish, as seizure frequencies based endpoint do not take into account perceived seizure burden and disadvantages of the medication. No recommendations can be given by lack of good examples for PRO and/or composites rating scales. That is why the phrase "… if validated." is used. However, if so, these could be acceptable as secondary endpoint. That is why they are mentioned here. The development of these assessment instruments is encouraged.
International League Against Epilepsy	237		In EE-SWAS, the EEG pattern is not the primary endpoint, the cognitive impairement is. This should be manipulate carrefully	remove EEG alone as an endpoint	Not accepted. This endpoint is mentioned in the list of secondary efficacy variables acceptable for both trials.
EFPIA	244	245	It is recommended to mention the possibility of using alternative ways to quantify non-countable seizures (e.g.seizure free days entered in a diary) beyond quantitative EEG recordings or telemetry by video-EEG. Quantitative EEG recordings or telemetry by video-EEG will not be practical for longer term monitoring of efficacy (beyond a few days) and may present additional challenges in non cooperative patients (e.g. those with developmental and epileptic encephalopathies).	Add the following sentence to the end of the paragraph ending on line 245 "**Alternative methods could include the measurement of seizure free days in patient diaries, particularly for those seizure types that do not occur frequently enough to accurately measure on prolonged EEG recordings, for patients who cannot fully cooperate with prolonged EEG monitoring, or when information on long term efficacy is needed.**"	The remark and lines referred to do not align. However, no objection to add.
EFPIA	260	262	The text says "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". However, depending on the route of administration (e.g. intrathecal), such assessments may not be feasible in juvenile rodents. Consider providing flexibility regarding the species for such assessments, see proposed wording.	"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 **(or, when such assessment is not practically feasible, in the developing non rodent brain (e.g., NHP) at the lowest age ethically feasible)** ought to be investigated, including neuropathologic and behavioural end points.".	Adapted as follows: 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 **or non-rodent brain (when applicable)** ought to be investigated, including neuropathologic and behavioural endpoints.
Dravet Syndrome Foundation	261		There is a lack of neurotoxicity assays on higher animal models in my opinion		No consequences for the text.
Dravet Syndrome Foundation	271	272	I think specifying the model/CT phase could be more explanatory.		It is not possible to be specific as it depends on the context. The message is if PK is measured simulatiously with efficcay asessement and in case of undesirable effect occurs this also may be helpful if a E-R modeling is intended. No consequences for the texst.

Dravet Syndrome Foundation	276	277	it could be useful to add some examples of validated scales and methods to evaluate these aspects		Referred is to the known neuropsychological test batteries.
EFPIA	276	278	Please clarify whether data collected from Phase I is sufficient or whether a dedicated study is required. If additional studies are required, further information would behelpful.		Calrified and adapted: **These dedicated randomised controlled studies should include a negative (placebo) and a positive control arm.**
EFPIA	279		It is recommended to replace "positive" with "active" control arm, as per standard terminology and to allow for alternative approaches in special situations, such as external controls.	"Studies should include a**n** ~~positive~~ **active** control arm. **Although in some circumstances this might not be feasible, in which case alternative approaches such as external controls should be considered.**"	Not accepted "positive control" refers to a compound for which is known that it impacts neuropsychological functioning (e.g. a reduced attention) . Active control could refer to any other ASM irrespective whether this ASM does/ does not affect neuropsychological functioning. Positive control ase use by the stakeholder refers to a compound not neccessarily to it mpacts on neuropsychological function. These are PD studies where subjects are subjected to neuropsychological tests battery to evaluate the potential impact of and ASM on neuropsychological functioning. Studies should be RCT either with a parallel group study design or cross-over design. It is hard to see how external control could serve as control.
EFPIA	298	299	The text says "The purpose of this phaseof the product development programme is 444 298-299 EFPIA to identify patients who may benefit from anew anti-seizure medication". However, this guidance also makes reference to disease modifying treatments, which maynot be classified as "ASM". It isrecommended to align the terminology withthe scope (lines 135-136)	"The purpose of this phase of the product development programme is to identify patients who may benefit from a new ~~antiseizure medication~~ **treatment of epilepsy**, to obtain initial information on safety andsuitable therapeutic dose range and dosage regimen."	Agreed and adapted
EFPIA	314		Please clarify what is meant by "some" studies		Some is included to indicate that that it is not necessary to sample these data in all studies. No consequences for the text.
EFPIA	326	328	It is recommended to explain in more details how natural history study and registry studies can support long-term safety (or clarify if this refers to other types of study such as post-marketing safety studies).		No recommendation can be given as there are limited data to base recommendations upon. Long term safety indeed is important the post-marketing setting. Adapted as follows: Natural History Study, registry studies may contribute to provide information on the disease relevant **features** for the design of the clinical studies (e.g. inclusion, age-distribution, duration, endpoints) and supportive data for long-term safety of the drugs post-approval. **Scientific advice is recommended.**
EFPIA	332		Please clarify if "target of estimation" is refering to "estimand"? If so, it is recommended to harmonise the wording and update accordingly	replace "target of estimation" with"estimand"	Agreed and adapted
Institute for Quality and Efficiency in Health Care (IQWiG)	338	366	As already pointed out in 2019 active comparators are important also in add-ontrials. The current type of add-on studies should no longer be recommended (currently, patients in the comparator grouphave to continue their previous therapy plus placebo, although this previous therapy has been unsuccessful). The section on add-on studies should therefore be revised with the aim of primarily requiring active comparator trials. As an active comparison, either a change to a defined combination therapy or "Physician's choice" (with selection of the therapy before randomization) should be recommended.	• Please delete "double-blind" and "placebo-controlled" in the following sentence. The pivotal add-on studies should have a randomised, double-blind, placebo-controlled parallel group study design • Please add a new section on add-on studies. In this section it should be mentioned that studies with an active comparator are required. Please clarify that this could either be done by an add-on design comparing the new anti epileptic drug with another add-on-drug or by comparing it with the "best medical treatment" as defined before randomisation. • If, according to EMA, pivotal add-on studies should still be placebo-controlled, please describe that at least a third study arm with an appropriate active comparator is required.	RD DB PC add-on studies are mandatory for showing efficacy of a potential ASM. The reason is that these studies have a high placebo effect and that placebo effect is not predictable. In absence of placebo one cannot decide if a response seen reflects the efficacy of the new ASD or reflects placebo response. In technical terms, the active controlled study without placebo would have no assay sensitivity. It is acknowledged that the comparator group may have to continue their previous therapy plus placebo, although this previous therapy has been not successful. Several points here 1) No treatment in refractory seizures is successful if success is defined as freedom of seizure 2) The add-on setting not per definition implies that subjects did not benefit from previous ASM i.e., without the treatment a subject would have been worse 3) What the active comparator should be is difficult to define as there a numerous combination of concomitant ASMs . 4) Even if a subject is responder on the new combination of ASMs sooner or later seizure control will be insufficient and there will be a seaerch for a new combination that (temporarely) is more sufficient. This is inherent on the refractory epilepsy population. Further for non-inferiorty a non-inferiority margin needs to be defined, which however is not possible due to the lack of assay sensitivity / unpredictable placebo response
Dravet Syndrome Foundation	342	345	Should the effect of the product on the pharmacokinetics of concomitant ASMs be known (and vice versa) before the study starts?		Preferably but not strict necessarily. On the one hand a weighted evidence approach could be considered i.e. based on the known PK/PD of the new compound (non-clinic/clinical) and known PK/PD of the existing ASMs . So based on strong indication of potential PK/DP on should studies this preferable should be (dis)confirmed in advanced. On the other hand interaction can also be subject of the study itself. No consequences for the text.
Dravet Syndrome Foundation	349		Please specify in which model/ CT phase		The question is not understood.

EFPIA	349	350	It is recommended to specify that certain circumstances (i.e. extremely refractory/intractable DEEs) may necessitate that higher numbers of pre-existing AEDs than 3 should be considered in inclusion/exclusion criteria.	Please add the following sentence at the end of paragraph ending with line no. 350 "**Under certain circumstances (i.e. extremely refractory/intractable DEEs), it may be appropriate to specify that higher numbers of pre-existing AEDs than three should be considered in inclusion/exclusion criteria.**"	Not accepted. The guideline covers principles. The principle here is that the smaller the number of concomitant AEs the more we are confident that the effect observed can be attributed to the test agent in the combination of ASM received. The guideline should be scarce in mentioning rare exceptions. There will be always exceptions that do not fit. Moreover, it is captured by …preferable in the presence of upto …. . Note the guideline is not cookbook with recipes wherefrom cannot be deviated based on arguments.
EFPIA	351	355	It would be helpful if the sentence and relationship to estimands could be clarified.	"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~~ **intended handling of** dose modifications of their concomitant ASM **as intercurrent event should be described as part of the estimand**."	Agreed more clear. Adapted accordingly with a slight modification to indicate this need to be predefined .
EFPIA	355	357	Please clarify whether it is meant that different estimands need to be tried out for each efficacy and safety analysis (eg as supportive analysis) or whether applied estimands (primary) might differ between efficacy and safety? Clarification could be further supported with examples of preferred/commonly used estimands.		What is excepted is a senstivity analysis in order to exclude effect modification by different background AMD profiles
EFPIA	359	361	It would be helpful if further guidance, standards or expectations for attribution could be offered in the guideline.		See remark above. The same holds for safety.
EFPIA	362	363	It is proposed to include flexibility for acceptance of external controls when appropriate (such as for certain rare diseases), in alignment with the EMA "Guideline on Clinical Trials in Small Populations" and other international guidance documents.	"**In general**, the pivotal add-on studies should have a randomised, double-blind, placebo-controlled parallel group study design. **Under exceptional circumstances (e.g. certain rare diseases), external controls and baseline control designs maybe acceptable**".	Not accepted. As stated above the guideline covers principles. The guideline should be scarce in mentioning rare exceptions as the they tend to promote to a general rule. The general principle can be deviated from based on arguments. Further it is question when in 'certain' rare diseases an external control can be reliable be defined as in general is there is substantial heterogeneity. Note an n of 1 study design (multiple crossover study in one subjcts with 1-2 placebo treatment periods) in a number of subjects with the rare conditon may be acceptable as proof of efficacy. Covered in the 8.8.1
Institute for Quality and Efficiency in Health Care (IQWiG)	393		As already pointed out in 2019 epilepsy is a chronic disease with attacks which may occur irregularly over periods of months and years. The study period should, therefore, be long enough to generate clinically meaningful results. This is usually the case with study periods of at least 12 months. During this period, adaptation of AEDs should be possible, as it is in clinical practice. Otherwise, the results of regulatory trials will be much less applicable to clinical practice.	•Please delete: "In the maintenance period the test and concomitant products should be kept stable whenever possible". The maintenance period should last at least 12 months (not weeks) in order to show longer-term efficacy. Please add: In addition, during this period AEDs should be adapted according to individual efficacy and tolerability and according to the SPC of the AEDs.	The issue raised is not understood. The maintenance period refers to the maintenance period of the RD DB PC add-on study, This stud design is for showing short term efficacy and a duration of 12 weeks is considered sufficient for this. Long term efficacy is dealt with in the next paragraph.
Lundbeck	398	399	Kindly clarify what is meant by continuation of add-on studies in relative to open label extension trials		By continuation of add-on studies continuation RD DB PC add-on setting is meant expanding the duration of add-on trial
Dravet Syndrome Foundation	402		Is it mandatory/legally binding?		It is considered rather unlikely that in absence of long term exposures data, for both efficacy and safety data a benefit/risk assessment can be made. Therefore these data will be needed. This also holds for rare conditions but here we may be more lenient with respect to the number of subjects and whether these data can be generated pre or post approval, depending on the observed safety profile .
International League Against Epilepsy	403		cf. J French presentation	We have concerns about using rigorous blinded head-to-head monotherapy studies in initial monotherapy due to lack of clinical relevance	The concerns whether such trial may not be easy to conduct is acknowledged. The argument with respect to clinical relevance is not shared. If in this setting efficacy versus placebo is show this would be a pivotal to allow a monotherapy indication.
International League Against Epilepsy	403		cf. J French presentation	We do not believe that placebo controlled monotherapy studies are acceptable for epilepsy.	Acknowledged but a position statement that can be challenged. See line 410-413.
International League Against Epilepsy	403		cf. J French presentation	We are extremely happy that extrapolation of efficacy from the add-on to the monotherapy situation is now being considered, and we strongly endorse this.	Acknowledged
Lundbeck	415	416	It is proposed to update the guidance text as it seems the proportion of patients remaining seizure free throughout the duration of the randomized trial period is rather a population-level summary than an endpoint.	whether the patient remains seizure free throughout the duration of the randomised trial period (yes/no)	The point made is not agreed.

EFPIA	435	437	It is suggested to add flexibility for use of external controls in certain rare diseases where there may not be a recognized standard of care to serve as an adequate active control and where a placebo control would be ethically challenging.	"Where extrapolation is not possible **and there is an adequate standard of care available**, 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. **In exceptional cases (e.g. certain rare diseases without an acknowledged standard treatment available), external controls may be used if justified.**"	Not accepted. As stated previously the guideline covers principles. The guideline should be scarce in mentioning rare exceptions as the they tend to promote to a general rule. The general principle can be deviated from based on arguments. Again it is questioned when in 'certain' rare diseases an external control can be reliable be defined as in general is there is substantial heterogeneity.
EFPIA	469		It is recommended to include the full title of the addendum with the first reference.	Replace "Referred is to ICH E9 R1 (addendum to estimands)" with "Referred is to ICH E9 (R1) **addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials**"	Accepted and adopted.
Lundbeck	469		Suggestion for a minor editorial adjustment	(addendum on estimands)	See above
EFPIA	470	477	It is recommended to clarify that some contents of this paragraph would not hold for a rescue medication application, eg. the ITT set will probably not be based on all randomised patients, because technically, not all randomised patients will have an event (a seizure) which requires emergency treatment, there will be no titration phase etc.		The point made is not clear. Rescue-medciation shold be dealt with as an intercurrent event with a corresponding strategy.
EFPIA	471	472	ICH E9(R1) states that the analysis of the Per Protocol Set might not add additional insights. Rather than, it might be recommended to construct estimands that better address the objective usually associated with the analysis of the PPS. In essence, one could extract those criteria of the PPS which are likely to affect the interpretation or existence of the measurements and include those as intercurrent events in the definition of the primary estimand (eg. start of prohibited ASM, violation of particular entry criteria during treatment). Based on these guideline requirements, it is suggested to rephrase this sentence into more neutral language and avoid the mentioning of the per protocol population. In this context, it might be important to distinguish between trials designed to detect whether differences exist between treatments containing the same or similar active substance (e.g. comparison of a biosimilar to a reference treatment) and trials where a non-inferiority or equivalence hypothesis isused in order to establish and quantify evidence of efficacy. See proposed change.	"In the non-inferiority studies the analysis of efficacy ~~will usually be based on all per protocol population~~ **needs to be streamlined to target a treatment effect that prioritises sensitivity to detect differences between treatments**."	Agreed and adapted.
Lundbeck	471	471	A statistical section where estimands are brought up is very welcomed. However, it is noted that the proposed aspects on non inferiority studies in this guidelines differs from the principles as laid out in ICH E9 R1addendum. Ie, any statistical analysis should be done with a focus on answering a scientific question of interest and the per protocol population subgroup cannot constitute a patient population of specific clinical interest. Instead, the basis for analysis should in general be the Full Analysis Set where intercurrent events,which could take place either in the titration phase or the maintenance phase, arecarefully considered in an appropriate way in relation to the non-inferiority setting.		See next comment
EFPIA	472	477	The text is dedicated to the clinical description rather than to the statistical analysis description, e.g.: the first sentence is part of the endpoint definition; the end of second sentence and 3rd sentence covers definition of intercurrent events and its handlings. It is therefore recommended to move the text into Section 6.3.2.	Move lines 472-477 to section 6.3.2 "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."	Not accepted. The main message here is that subjects of the titration phase should not be excluded for the main analysis which should be over hould be over period when patients are established on the fixed dose.
EFPIA	476	477	"Treatment strategy" should be replaced with "handling strategy". It would be helpful for the recipient of this guideline if the guideline cold express which handling strategies are acceptable.	"These should be handled as intercurrent events for which a ~~treatment~~ **handling** strategy should be defined and justified."	As rightly interpreted the tretament policy is the strategy that is preferred one, unless otherwise justified .
Lundbeck	478	479	It seems that the sponsor has a choice on primary analysis. However, this does not relate to what is said on lines 191-194, where for example it is stated that the primary endpoint should constitute are sponder definition. It is suggested updating the text on lines 191-197 to be aligned with text in section 6.3.3 Statistical analyses. This would include also connecting 6.3.3 text with eg the idea o fpresentation of cumulative distribution seizure frequency data in lines 196-197 more clearly.		The interpretation of the stakeholder is not shared. The message is that if seizure frequencies are analysed then……. . It leaves in the middle where this concerns seizure frequency as primary or secondary endpoint. This is made more clear
Lundbeck	482		Please clarify whether this paragraph only relate to when the endpoint is binary and alogistic regression model is planned, or if it a general statement covering also e.g. continuous endpoints. As it is now, the rationale is not clear for why in the primary analysis it should not be allowed to adjust for e.g. baseline seizure frequency, and other relevant covariates not constituting randomization stratification factors. Instead, adjusting for eg the baseline value of an endpoint is in general increasing statistical power and precision of the estimates obtained from such a statistica lmodel		The paragraph is intended as a general statement independent from whether the endpoint is binary or continuous.

International League Against Epilepsy	522		Absences could be observed in very variable epilepsy type	Absence seizure: primary endpoint should be EEG How to capture absence seizure depend of the epilepsy syndromes Study protocol (design – standard of care) depend on the included syndrome(s) Childhood Absence epilepsy Juvenile Absence epilepsy Other syndrome	Not clear what specific text changes are proposed. The difficulty of monitoring EEG freedom of absence especially if the absences are part of epileptic syndrome are acknowledged. Changed in: It should be supplemented by longer randomised efficacy studies monitoring clinical and/or EEG freedom from absences.]
EFPIA	531	579	While status epilepticus remains the seizure type with the highest co-morbidity and mortality, other seizures emergencies exist that may warrant treatment before they reach status epilepticus or as they cause significant and avoidable loss of quality of life and risk of injury and neuronal loss.Therefore, it is recommended to add other seizure emergencies, mainly seizure clusters, acute repetitive seizures, crescendo seizures and prolonged seizures (c.f., Pellock JM. Overview:definitions and classifications of seizure emergencies. J Child Neurol. 2007 May;22(5 Suppl):9S-13S.)	Add paragraph after line 562: "**Other seizure emergencies: There are other seizure emergencies which may require treatment including prolonged seizures that do not qualify as status epilepticus or acute repetitive seizures, which also may be known as cluster, crescendo, multiple-recurrent, serial, or sequential seizures (Pellock,2007). Trials in such seizure emergencies would largely follow the principles laid out for the treatment of acute status epilepticus. Primary endpoints may include prevention of seizure recurrence and time to end of seizure episode.**"	Acknowledged and agreed. Adapted accordingly.
EFPIA	560	563	The guideline text suggests that the study should be powered not only for efficacy but also a safety endpoint. This would significantly increase the sample size and render the study infeasible, particularly because safety events typically appear in alow frequency.	Replace "The sample size should be sufficient to conclude that both the efficacy and safety (especially in relation to cardio respiratory 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)." with " **The sample size should be sufficient to conclude that the efficacy 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). Comparability of the safety profile (especially in relation to cardio respiratory depression) between the new product and the active comparator drug) will be assessed in an exploratory manner.** "	The interpretation of the stakeholder that the text suggests that the study should be powered for efficacy and safety endpoint is not shared. The message is that the sample size should be sufficient to allow assessment that a product is safety also with respect to cardiorespiratory depression. Nevertheless adapted to avoid this kind of over interpretations
Lundbeck	569		It is proposed to add examples of functional outcomes		In absence of data on the psychometric properties of functional scales in refractory SE (i.e. GOS or mRS have been explored) it is difficukt to give a a specific recommndation.
EFPIA	579		It is recommended to allow consideration of alternative primary endpoints (e.g. termination of refractory status epilepticuson EEG), with functional outcome being a secondary endpoint. As EMA outlines in the section on the "Treatment of the acute status epilepticus" (starting on line 544), persistent seizure cessation can be the appropriate primary endpoint for trials of new medicinal products aimed at treating status epilepticus. In addition, the ultimate goal of treatment of status epilepticus (regardless of whether it is acute or refractory) is to prevent further neurological damage (i.e. improve functional outcome). Given functional outcome is ultimately derived from successful treatment of status epilepticus, when justified for both acute and refractory status epilepticus, sponsors should be permitted to use seizure termination per EEG as a primary endpoint rather than functional outcomes. This is particularly true in circumstances where the functional status of patients prior to the onset of refractory status epilepticus (and transfer to the tertiary centre conducting the trial) may not be thoroughly characterized. Choosing functional outcome as the primary endpoint may additionally make it more unlikely for subjects with reduced baseline functioning (e.g. those with developmental and epileptic encephalopathies) to be included in such trials. In such subjects, differences in functional status following successful versus less successful (i.e. less timely) treatment of refractory status epilepticus may be less apparent than in those subjects with normal baseline functional statuses. This would ultimately be a disservice to subjects with reduced baseline functioning who (given the underlying aetiology resulting in reduced functioning) may be more at risk for acute and refractory status epilepticus.	Add the sentence to the paragraph ending with line no 579 "**Alternative primary endpoints to functional outcomes (e.g. cessation of status epilepticus on EEG) can be considered if justified. In such circumstances, a functional outcome can still be considered for a secondary endpoint.**"	Not agreed . As stated the ultimate goal is to prevent further neurological damage although seizure cessation and silencing the brain is neccessary towards that.
Lundbeck	584	615	It is suggested to update the headers and subsequent sub-headers in terms of numbering as well as placement for section7	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 which might be considered as secondary endpoints related to safety 7.1.1. Exacerbation of seizures7.1.2: CNS adverse events7.2: Long term effects	A rationale for this proposal is lacking.
EFPIA	606		Comment and rationale It is recommended to specify that assessing cognition often requires large sample sizes as well as longer term trials (given the potential of patients to adapt to CNS medications). Therefore, the alternative of assessing cognitive functionin longer term trials (e.g. phase 3 studies) should be allowed when justified.	Add to line 606: "**Alternatively, assessing cognitive function in longer term trials (e.g. phase 3 studies) should be allowed when justified.**"	It is assumed that the PD studies referred ro in section 6,2,2 may also be incorprated in the Phase iII study . Adapted accordingly.
EFPIA	614	615	Ophthalmological procedures are often difficult to conduct in uncollaborative patients with severe DEEs.	Add the following sentence to the end of line 615: "**Exceptions may be considered in certain patient populations (e.g. DEEs) where patients may be largely uncooperative with ophthalmological procedures and where the risk-benefit of treatment still remains favourable.**"	Not accepted. As stated previously the guideline covers principles. The guideline should be scarce in mentioning rare exceptions as the they tend to promote to a general rule.
International League Against Epilepsy	634		Study for FOS for 1 Month to 2 Years of age	here is the text for possible stuy design: Auvin S, French J, Dlugos D, Knupp KG,Perucca E, Arzimanoglou A, Whalen E,Shellhaas RA. Novel study design to assess the efficacy and tolerability of antiseizure medications for focal-onset seizures in infants and young children: A consensus document from the regulatory task force and the pediatric commission of the International League against Epilepsy (ILAE), in collaboration with the Pediatric Epilepsy Research Consortium (PERC). Epilepsia Open. 2019 Sep4;4(4):537-543. doi: 10.1002/epi4.12356.PMID: 31819909; PMCID: PMC6885693.	Added to the reference list

International League Against Epilepsy	634		The RCT on GCTSz in IGE down to 12 insure that the pediatric population is adequately studied. It would be unlikely feasible to study GTCSz in IGE only in a pediatric population. Then for the rare patients with GTCSz in IGE, we suggest extrapolation of efficacy (see 2022 ILAE classification on IGE Hirsch et al. Epilepsia for the age rage down to 6Y)	For generalized tonic clonic seizure of idiopathic generalized epilepsy, we suggest extrapolation of efficacy down from 12Y to6Y. We also suggest that first RCT to demonstrate efficacy on GTCSz in IGE include adolescents down to 12Y (strongly suggestion)	Point taken. However whether for GCTS-IGE extrapolation is or is not acceptable so far cannot be decided at face value. Moreover it is covered by line 658-662 "For non-focal seizures **(e.g. GCTS in IGE),** 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. Observed response should be similar within predefined limits to the predicted response based on the E-R relationship established in the older age groups." GCTS in IGE is added as example.
EFPIA	637	639	Video-EEG is perceived as a high burden to the participant and the study site. Interpretation of the data collected is largely varying between investigators, and in case a central reader is added leads to significant discrepancies between local and central reading.	"Hence video-EEG ~~is~~ **may be** recommended depending on the epilepsy syndrome or seizure type, in particular for use at screening/baseline, for identification and confirmation of diagnosis."	Not agreed already covered by *is recommended*
EFPIA	654	655	The statement is non specific on how the model should be validated. Clarification that the validation will be done by collecting plasma samples would be helpful.	The model should also be validated **by the collection and inclusion of additional plasma samples** in the subsequent younger age-subset cohorts, which should be planned according to drug pharmacology…"	Not agreed/ It is not excluded that beyond plasma samples PD (pre/post seizure frequency) is neededdpending on the MOA , type of product. Clarfied in the tekst.
EFPIA	659	662	The prior paragraph refers to the adult population for efficacy, while here it is the older age-subset. Please clarify if the reference here should be the adult population for efficacy as well.		The statement older age subset is deliberately used here in order to cover epileptic syndromes, seizure type profiles that are no longer relevan when adult, i.e the LGS changes in pattern in towards adult age.
EFPIA	667	668	Please simplify the language	"In case ~~an effect of a~~ disease-modifying effect is claimed, it should be shown that the effect on seizures translates **to** ~~in an~~ improved neuro-motor development."	Adapted
International League Against Epilepsy	667		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.	Disease modification could also be seen on seizure/epilepsy non only on cognition. Change term 'neuro-motor': cognitive and behavior	Adapted
SME - Dracaena Consulting	667	669	This brief paragraph is the only reference in the guideline to what a disease modifying agent might look like for epileptic disorders. The general understanding in the medical field is that for a treatment to be considered disease-modifying, it must act on the underlying pathophysiology of a disease AND this must translate into clinical outcomes. Ideally a disease modifying effect should be separable from a symptomatic effect. However, by not mentioning the need for a disease-modifying agent to act on the disease pathophysiology, the current wording in the draft guidance revision in lines 667-669 fails to make a difference between a symptomatic agent that might have an effect on more than one outcome, for example on seizure frequency and cognitive scales, and an agent that specifically addresses an underlying disease process and results in those changes. We believe it is important for regulators to make this distinction in the revision 3 of the guidance, and therefore recommend this paragraph to be modified. Another option is to borrow a line from the"Guideline on the clinical investigation of medicines for the treatment of Alzheimer'sdisease" from 2018 (CPMP/EWP/553/95Rev.2) which opens the section 8.3.2 on disease modifying treatments by saying that "A medicinal product can be considered to be disease modifying when the pharmacologic treatment delays the underlying pathological orpathophysiological disease processes."	.	Adapted
EFPIA	669		We are confronted with limitations when requesting Scientific Advice for programs that are paediatric only (which is the case of some DEEs), probably because of different remits between CHMP and PDCO (which does not provide scientific advice outside the context of a PIP).	No suggested update to the guidance since we would appreciate the opportunity of receiving scientific advice from the CHMP for projects that are designed to address paediatric conditions. However, this gap should be addressed by separate, applicable regulation or guideline.	The gap is recognised and acknowlegded. See line 687-694 added. *Developmental and epileptic encephalopathies (DEEs) encompass a rather heterogenous group of epilepsy syndromes with a wide range of aetiologies and seizure type profiles. Multiple DEEs may be investigated in a single study. It is considered unlikely that the response to a specific ASM is similar in all DEE subgroups. Evidence should be provided that the efficacy of an ASM is consistent across the specific DEE subgroups included in the study. Criteria for consistency of efficacy should be defined a priori, for example a minimal important difference threshold (relative or absolute separation from placebo). Alternatively, for ultra rare specific DEE subgroups an n-of-1 study design (i.e. multiple crossover study within the same suubject with 1-2 placebo periods) in a limited number of subjects might be acceptable in support of efficacy.*
EFPIA	672	673	It is recommended to specify that less than 100 patients may be required for rare/ultrarare DEEs or paediatric indications with a limited number of patients.	Add the following sentence to the end ofthe paragraph ending in line 673. "**When studying paediatric conditions that are exceptionally rare, lower numbers than 100 children may be permitted.**"	Preferred is to state the default. Excpetion are always possible if justified. That exceptions are possible is already covered by starting with *Generally, …..* However, a paragraph is added to take somme concern away i.e., *In absence of long term exposure data, for both efficacy and safety a benefit/risk assessment may be difficult. Whereas for rare conditions the number of subjects required in the dossier may be lower if justified, long-term exposure data is still required. Whether these data are sufficient or further safety data are needed in terms of number of subjects and duration of exposure post marketing, will depend on the observed safety profile pre-marketing.*

EFPIA	676		Assessment scales are often not available in all languages within a global study.	Assessment scales ~~should be~~ validated by age and language **should be used where available**.	Not accepted , if not validated it is unclear what is assessed and what a score means.
International League Against Epilepsy	686	737	IV formulation should be a requirement if the study aiming to study acute symptomatic seizure (80-85% of the neonatal seizure)	IV formulation only because this is the treatment of the acute symptomatic seizure. In that case it is an emergency treatment that needs an adequate PK. Most of the new born are critically ill with acute enteropathy:- Issue for drug absorption- Further risk for necroziting enterocolitis See: 1: Pressler RM, Abend NS, Auvin S, Boylan G, Brigo F, Cilio MR, De Vries LS, Elia M, Espeche A, Hahn CD, Inder T, Jette N, Kakooza-Mwesige A, Mader S, Mizrahi EM, Moshé SL, Nagarajan L, Noyman I, Nunes ML, Samia P, Shany E, Shellhaas RA, Subota A, Triki CC,Tsuchida T, Vinayan KP, Wilmshurst JM, Yozawitz EG, Hartmann H. Treatment of seizures in the neonate: Guidelines and consensus-based recommendations-Special report from the ILAE Task Force on Neonatal Seizures. Epilepsia. 2023 Oct;64(10):2550-2570. doi: 10.1111/epi.17745.Epub 2023 Sep 1. PMID: 37655702.2: Carapancea E, Cilio MR. A novel approach to seizures in neonates. Eur JPaediatr Neurol. 2023 Sep;46:89-97. doi: 10.1016/j.ejpn.2023.07.006. Epub 2023Jul 27. PMID: 37544258.	It is acknowlegded that an IV formulation is the best route of administration in this case. The tekst is adapted but we can neither require it nor would not accept an ASM foe neonates because the route of administartion is not IV. Adaptation: Preferably an ASM for neonates should allow a IV route of administration.
International League Against Epilepsy	695		Video EEG assement is not an option	A claim of reduction in seizure burden must by based on the assessment of video/electroencephalographic neonatal seizures	The texst as proposed is the same as text already in the document.
EFPIA	696	698	It is recommended to remove "video/", as it might not be needed.	"Multi channel 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."	Adapted
EFPIA	699	701	Use of central reader for inclusion of neonates in a clinical study has been proven to be extremely difficult from the operational and from the timing perspective. The time window to start treatment after diagnosis is very short and can occur anytime (24/7).	~~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.~~	
International League Against Epilepsy	699		Live central reader could be an issue for feasibiliity	if central reader is mentionned the statement should not be strong	Not accepted a central reader is considered more objective
EFPIA	706		A confirmatory study in neonates having diverse aetiologies is already very challenging to conduct. While the scientific rationale is sound, it will reduce the number of available study participants even further, potentially rendering a study unfeasible.	"Single aetiology trials may be more appropriate for confirmatory trials **if warranted by the proposed mechanism of action of treatment and if such a design would not significantly hinder trial recruitment**	Partly accepted adapted accordingly i.e: "Single aetiology trials may be more appropriate for confirmatory trials i**f warranted by the proposed mechanism of action.** That recruitment for a specific condition is not possible cannot be solved by recruiting am additional but different population by relaxing in- and exclusion criteria. It still would not allow firm conclusions of efficacy in that specific condition.
International League Against Epilepsy	714		Sentence is incorrect, it is not all EEG activity but all seizure activity on EEG	The seizure burden is to be defined as a duration of seizure activity on EEG in a defined timespan	Adapted
International League Against Epilepsy	715		minor comments to be contistent with JSoul et al Recommendation for the design of therapeutic trials in neonatal seizures Pediatr Res 2018 - more fexibility to promote feasibility	The evaluation period should last for at least 12-24 hours and continue until the patient is seizure-free for a defined period, at least of 12-24 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.	No objection adapted
	719		The primaty endpoint cannot be seizure reponder but rate of seizure free - we are in an acute symptomatic setting	use rate of seizure free (not responder)	For discussion but tend to agree. Text proposal included.
EFPIA	721	722	It is recommended to include some language to provide the option to distinguish the reasons for discontinuation,eg. consider treatment discontinuation due to adverse events or due to lack of efficacy.	"Premature drop-outs ~~of treatment, subjects who~~ **due to lack of efficacy and/or** switch to rescue medication should be counted as non-responders."	Not accepted, drop-out to treatment during the trial indicates treatment failure for whatever reason unless further justified this is clearly not the case i.e. if a sibject is seizure free and treatment is no longer warranted. Even in case of consent withdrawn as reason for premature drop-out to treatment has underlying reasons.
EFPIA	726	728	It is recommended to add "when applicable" to the section describing the obtainment of neuroimaging before neonatal intensive care unit discharge. Depending on the aetiology resulting in neonatal seizures, it may not be necessary to obtain imaging, particularly an MRI (e.g. in neonates with known metabolic causes of seizures) prior to discharge and may pose a significant burden to the neonate to obtain.	"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 **when applicable**".	Agreed the absence of this facility, to serve pure research purposes, should not unnecessary hamper studies in neonatal seizures.

International League Against Epilepsy	730		minor comments to be consistent with JSoul et al Recommendation for the design of therapeutic trials in neonatal seizures Pediatr Res 2018 - more fexibility to promote feasibility and dont use 'motor development' but cognitive and behavior development'	L730: Long-term assessment of central nervous system (CNS) function requires at least 18-24 months, including motor development.	See prevous answer
EFPIA	731	737	It is recommended to delete "at least" in the sentence "Protocolised prospective disease-specific or at least drug registries are recommended..." on line 735. It is exceptionally difficult to have neonates treated at tertiary centers for neonatal seizures (who are referred from surrounding centers) return to those centers for clinical outcome and safety assessments multiple times up to the age of 5 years. Rather, drug registries will likely be the predominant (if not only) way that sponsors will be able to obtain this long term efficacy and safety information.	"Protocolised prospective disease-specificor ~~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 2-5years."	Not accepted. Disease specific regsitres are preffered abobe drug-specific registres. Moreover, the statement as written dowmm allows room for both options.