29 January 2024

Submission of comments on **Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders - Revision 3**

Comments from:

Name of organisation or individual
EFPIA

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. General comments: General comments on the draft Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders

Stakeholder/Company name	General comment (if any)
EFPIA	EFPIA very much welcomes the well written revised, draft guideline, offering additional information for sponsors developing medicinal products for the treatment of epileptic disorders, especially those involving paediatric patients. To streamline the document, we are excluding editorial or typographical comments. 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".

2. Specific comments on text: Executive summary

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text

Please add more rows if needed.

3. Specific comments on text: 2.1. Introduction (background)

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text

Please add more rows if needed.

4. Specific comments on text: 2. Scope

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text

Please add more rows if needed.

5. Specific comments on text: 3 Legal basis and relevant guidelines

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text

Please add more rows if needed.

6. Specific comments on text: 4. Patient selection 4.1 Study population and selection of patients

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
158-159	EFPIA	It is recommended that examples of accepted international classification guidelines (e.g. the 2017 International League 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 and Epilepsy Syndromes **(e.g. the 2022 ILAE Classification and Definition of Epilepsy Syndromes)."**
169-170	EFPIA	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** bilateral tonic-clonic seizures ~~separately~~ **due to their rare nature.**"
183-185	EFPIA	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."

Please add more rows if needed.

7. Specific comments on text: 4. Patient selection 4.2. Selection of seizure types and epilepsy syndromes

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text

Please add more rows if needed.

8. Specific comments on text: 5. Assessment of efficacy

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
187-245	EFPIA	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.	
188	EFPIA	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."**
194-195	EFPIA	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.	The other variable ~~should~~ **could** be ~~some parameterisation using~~ the ~~actual~~ **the 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.~~
194 - 195	EFPIA	It is recommended to mention the possibility of using alternative ways to quantify non-countable seizures (e.g.	Add the following sentence to the end of the paragraph ending on line 195 "**Alternative**

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
		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.	**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."**
196	EFPIA	It is recommended to replace "variable" by "summary measure"	"The proportion of seizure-free patients is a particularly important ~~variable~~ **summary measure."**
201-210	EFPIA	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)	
219 - 220	EFPIA	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~~."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
222-225	EFPIA	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)"
244-245	EFPIA	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**."

Please add more rows if needed.

9. Specific comments on text: 6. Study design

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
260-262	EFPIA	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 endpoints.".
276 - 278	EFPIA	Please clarify whether data collected from Phase I is sufficient or whether a dedicated study are required. If additional studies are required, further information would be helpful.	
279	EFPIA	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**."
298-299	EFPIA	The text says "The purpose of this phase of the product development programme is to identify patients who may benefit from a new anti-seizure medication". However, this	"The purpose of this phase of the product development programme is to identify patients who may benefit from a new ~~anti-~~

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
		guidance also makes reference to disease modifying treatments, which may not be classified as "ASM". It is recommended to align the terminology with the scope (lines 135-136)	~~seizure medication~~ **treatment of epilepsy**, to obtain initial information on safety and suitable therapeutic dose range and dosage regimen."
314	EFPIA	Please clarify what is meant by "some" studies	
326-328	EFPIA	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).	
332	EFPIA	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"
349- 350	EFPIA	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."**
351-355	EFPIA	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

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
			modifications of ~~their~~ concomitant ASM **as intercurrent event should be described as part of the estimand."**
355-357	EFPIA	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.	
359-361	EFPIA	It would be helpful if further guidance, standards or expectations for attribution could be offered in the guideline.	
362-363	EFPIA	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 may be acceptable**".
435-437	EFPIA	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**

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
			diseases without an acknowledged standard treatment available), external controls may be used if justified."
469	EFPIA	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**"
470-477	EFPIA	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.	
471-472	EFPIA	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	"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**."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
		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 is used in order to establish and quantify evidence of efficacy. See proposed change.	
472-477	EFPIA	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."
476-477	EFPIA	"Treatment strategy" should be replaced with ""handling strategy".	"These should be handled as intercurrent events for which a ~~treatment~~ **handling** strategy should be defined and justified."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
		It would be helpful for the recipient of this guideline if the guideline could express which handling strategies are acceptable.	
531-579	EFPIA	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.**"
560-563	EFPIA	The guideline text suggest 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 a low frequency.	Replace "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

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
			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 cardiorespiratory depression) between the new product and the active comparator drug) will be assessed in an exploratory manner. "**
579	EFPIA	It is recommended to allow consideration of alternative primary endpoints (e.g. termination of refractory status epilepticus on 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	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.**"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
		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.	

Please add more rows if needed.

10. Specific comments on text: 7. Safety aspects

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
606	EFPIA	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 function in 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.**"
614 - 615	EFPIA	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.**"

Please add more rows if needed.

11. Specific comments on text: 8. Studies in special populations

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
637-639	EFPIA	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."
654-655	EFPIA	The statement is nonspecific 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…"
659-662	EFPIA	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.	
667-668	EFPIA	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."
669	EFPIA	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

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
			should be addressed by separate, applicable regulation or guideline.
672 - 673	EFPIA	It is recommended to specify that less than 100 patients may be required for rare/ultra rare DEEs or paediatric indications with a limited number of patients.	Add the following sentence to the end of the paragraph ending in line 673. "**When studying paediatric conditions that are exceptionally rare, lower numbers than 100 children may be permitted."**
676	EFPIA	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**.
696-698	EFPIA	It is recommended to remove "video/", as it might not be needed.	"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."
699-701	EFPIA	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~~.
706	EFPIA	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**

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text
			design would not significantly hinder trial recruitment.
721-722	EFPIA	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."
726-728	EFPIA	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**".
731-737	EFPIA	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-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."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text

Please add more rows if needed.

12. Specific comments on text: 9 References

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text

Please add more rows if needed.

13. Specific comments on text: Other comments

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder/Company name	Comment and rationale	Proposed guidance text

Please add more rows if needed.