EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 January 2023
EMA/CHMP/20512/2023
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on draft Paediatric Addendum on the guidelines on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease (EMA/CHMP/763438/2017)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation:

Stakeholder number	Name of organisation or individual
1.	Joint submission from the European Society of Cardiology (ESC) and Association for European Paediatric and Congenital Cardiology (AEPC) in the context of an ESC Cardiovascular Round Table (CRT) workshop**:** NOAC Research and Development for Paediatric Use, 5 June 2019 (Jointly organised by the ESC Cardiovascular Round Table (CRT) and the AEPC).
2.	Pediatric and Perinatal Scientific and Standardization Subcommittee (SSC) of the International Society on Thrombosis and Hemostasis (ISTH), Task force for paediatric anticoagulant development
3.	European Association of Hospital Pharmacists (EAHP)
4.	LEO Pharma A/S
5.	Bristol-Myers Squibb (BMS)
6.	Pfizer Limited

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Stakeholder number	Name of organisation or individual
7.	PRA Health Sciences

1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1.	The following comments reflect the results of the ESC CRT Workshop on anticoagulant research and development for paediatric use, held in Munich on 5 June 2019. Comment: 1) Do you agree on the need to conduct specific paediatric clinical trials to investigate anticoagulant therapy in children? For which disease and age group? There is a general agreement on the need to conduct specific paediatric trials in both treatment and prophylaxis settings. For aetiologies that exist only in children (e.g. premature neonates with indwelling lines), data is needed on all affected age groups. In other aetiologies, if adolescents were included in the adult pivotal trial, then subsequent paediatric trials should focus on younger age groups. We need a common understanding among clinicians, regulators, and industry of the specific requirements per age strata (sample size, endpoints, etc.). Comment 3): Due to its prevalence and significance, is the investigation of the treatment of VTE an appropriate model indication? Treatment of VTE is an appropriate model indication, however prophylaxis is deemed equally important. The question is how to conduct studies in children, particularly neonates. ESC workshop participants recommend primary focus on "at high risk" populations for VTE prophylaxis. Comment 7): What other situations, related to anticoagulation in children, do you think are prevalent and important to be investigated in clinical trials in cardiology? ESC workshop participants recommend prevention of thromboembolism in Fontan circulation / when using prosthetic cardiac valves / artificial shunts and Kawasaki disease as tangible examples. Intracardiac clots and arterial ischaemic stroke.	The experts of the ESC CRT workshop agreed on the need to conduct specific pediatric anticoagulation trials in both treatment and prophylaxis settings. They also agreed that the treatment of VTE is an appropriate model indication, but prophylaxis in "High-risk" patients is equally important. In pediatric cardiology, there are other circumstances beyond VTE in which anticoagulation (prevention of thromboembolism in Fontan circulation, prosthetic valves, artificial shunts and Kawasaki disease, intracardiac clots and arterial ischaemic stroke). However, these circumstances fall beyond the scope of the VTE pediatric addendum. Outcome: No need for changes.

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2.	The paediatric addendum is very comprehensive and well written. It highlights the specificities of paediatric thrombosis which require dedicated studies of anticoagulant drugs, but also similarities which allow some extent extrapolation from adults and between paediatric age groups. To date, the evidence on paediatric VTE and anticoagulation is low. However, the field is currently moving as the results of some DOAC trials in children will be available shortly. These will provide much more solid information on paediatric VTE, the efficacy and safety of anticoagulants, both conventional and new, and similarities to adults and between paediatric age groups. Building on that new evidence will likely influence the approaches to study future anticoagulants. Following are our comments to the 12 questions posed: 1) *Do you agree on the need to conduct specific paediatric clinical trials to investigate anticoagulant therapy in children?* All panel members agree there is a need for paediatric studies, given differences in etiology, clinical presentation, and course of paediatric VTE, and differences in PK, the haemostatic system, which may affect the response to anticoagulants between children and adults and between children of different age groups. 2) *Acknowledging that extrapolation from adults is routinely done in standard practice in children due to lack pediatric data, do you think that extrapolation from adults can be done under certain circumstances without the need for further studies? If yes, in which circumstances?* Extrapolation is considered possible by the panel in post-pubertal adolescents in whom the etiology of VTE is closer to that of adults. However, some PK/PD data would still be required to confirm appropriate doses, and some observational clinical data. Alternatively, adolescents could be included into adult trials. Adolescent data may be useful to bridge to younger age groups.	The experts of the Pediatric and Perinatal Scientific and Standardization Subcommittee (SSC) of the International Society on Thrombosis and Hemostasis (ISTH), Task force for paediatric anticoagulant development agreed on the need to conduct specific pediatric anticoagulation trials and agreed with most of the text of the pediatric addendum. With respect to additional comments to be considered for inclusion, an important type of DVT, not specifically mentioned in the guideline, is cerebral sinovenous thrombosis, which accounts for a substantial proportion of paediatric VTE. It is also important to define and measure neurological outcomes, including seizures, headaches and neurological disability, in addition to less well-defined outcomes such as neurocognitive disability and behavioural problems. This text has been included in the "secondary

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	3) Due to its prevalence and significance, is the investigation of the treatment of venous thromboembolism (VTE) an appropriate model indication? Anticoagulant treatment of acute symptomatic VTE is currently considered standard in children, and should therefore be a model indication. However, there are many unresolved questions that could be addressed as part of VTE treatment trials on new anticoagulants: To what extent does anticoagulation achieve desired outcomes, i.e. reduce of the risk of death due to thrombus extension/embolization, limit the extent of vessel damage and therefore post-thrombotic syndrome/organ damage, maintains/re-establish vascular patency for future venous access, and reduce the risk of VTE recurrence. Modalities of anticoagulation, such as the appropriate intensity and duration still need to be established. Finally, whether to treat incidentally detected asymptomatic VTE is unresolved. *4) In comparative trials of new compounds in children with VTE versus the "standard of care", is it easy to define the "standard of care" or is there variability among countries and centers?* There is not too much variability with regards to the currently used standard anticoagulants but their preferred use depends on age and clinical circumstances. Intensity of anticoagulant treatment is fairly well standardized according to guidelines but this is based on convention rather than solid evidence. There is much uncertainty, and hence, variability, regarding duration of anticoagulant treatment, particularly for CVC-related VTE. *5) In the prophylaxis setting, do you agree that the prevention of central venous catheter (CVC)-related thrombosis is a target indication to be investigated? If so, which patient profile with indwelling CVCs is most prevalent and how heterogeneous is this population?* Given the relative frequency of CVC-related VTE in children, their prevention would, if successful, have a major impact. However, whether prevention of CVC-related VTE has a positive benefit risk balance is still uncertain, and requires further proof-of-concept. There is some evidence from the recent Thrombotect trial (Haematologica 2019) showing that thromboprophylaxis reduced CVC-related thrombosis in children undergoing treatment for leukaemia, but other groups have not been studied. The majority of long-term indwelling CVCs are in children with malignancy. Other groups are children	endpoints" section. Additional proposals, about relevance of asymptomatic VTE, composition of adjudicating committees and on additional imaging methods for specific DVTs, have been considered for inclusion in the pediatric addendum. Finally, the ISTH also proposes that parallel paediatric developments of different anticoagulants should target different (sub)indications to address the various therapeutic needs and to overcome feasibility challenges. This is beyond of the paediatric addendum and seems unfeasible for the time being. Outcome: some of the ISTH comments have been implemented: a) A reference to cerebral sinovenous thrombosis has been included in sections 1, 4.1 and 4.2 of the guideline. b) Asymptomatic VTE as secondary endpoint. c) Composition of adjudicating

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	with CVCs for long-term TPN, children with cardiac disease, children in the PICU, those requiring PICCs for infection. Children with previous CVC-related VTE who require a new CVC usually receive thromboprophylaxis. Open questions relate to the timing of initiation and intensity of anticoagulation. *6) Do you think that the use of placebo is feasible in pediatric trials for prophylaxis of CVC-related thrombosis?* Placebo-controlled trials would be important to establish the proof-of-concept for prevention of CVC-related VTE in children. Given the strong thrombogenic potential of CVC, anticoagulant prophylaxis may not be sufficient to reduce the risk substantially, and may be outweighed by an increased bleeding risk. Given recent (Thrombotect) and evolving evidence (ongoing trial of Apixaban for prevention prevention of CVC-related VTE), the use of placebo may become unacceptable in the near future. Moreover, thromboprophylaxis is currently used by many centres in settings considered at high-risk of VTE (see comment 5), where it would not be acceptable to compare to placebo. *7) What other situations, related to anticoagulation in children, do you think are prevalent and important to be investigated in clinical trials of anticoagulants?* - Cerebral sino-venous thrombosis - Single ventricle, particularly Fontan circulation; - other cardiac indications (Kawasaki with coronary aneurysms, atrial fibrillation/flutter, stents, shunts, mechanical valves) - chronic inflammmatory state prone to thrombosis *8) Do you agree that the primary efficacy endpoint in a paediatric VTE trial should be as broad as possible to capture all VTE events? In this respect, do you think that the primary endpoint proposed in the EMA document (Objectively documented symptomatic and asymptomatic DVT and PE) is appropriate?* Including symptomatic and asymptomatic (recurrent) VTE as primary efficacy endpoint is considered appropriate by most members of the panel. But we want to note that the relative importance of asymptomatic events is not as clear as for symptomatic event. Asymptomatic VTE may be of significant	committees. d) Additional imaging methods for specific DVTs. d) Long-term safety endpoints.

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	size causing extensive occlusion, and may cause pulmonary embolism or paradoxical embolism (stroke). However, both short and long term outcomes have not been as clearly defined as they have been for symptomatic events. It is important to assess symptomatic and asymptomatic VTE separately as secondary endpoints, so we can learn more about their relative significance. Another important point is that screening for asymptomatic VTE is quite an effort and burden to children, and requires combination of several imaging techniques for sensitive detection of VTE in all possible locations. *9) Is asymptomatic/incident VTE normally treated in children? If not in all, in which circumstances?* Asymptomatic /incident VTE is not always treated in children. It will depend on the location of the thrombus, and whether the risk factor (CVC) is still in place. Incidental pulmonary embolism is usually treated. If the risk factor is removed, it may be appropriate to withhold treatment while doing interval imaging to monitor for thrombus extension. *10) Are there other endpoints, like improvement/deterioration in thrombus burden, that could be suitable in children for measuring the effect of anticoagulant therapy?* Change in thrombus burden could be clinically important information but whether this is a responsive parameter still has to be demonstrated for various types of paediatric VTE. Perhaps data from the ongoing pediatric studies will be informative in this respect. However, this outcome is challenging due to radiology interpretation. For cerebral sino-venous thrombosis which accounts for a substantial proportion of paediatric VTE, it is also important to define and measure neurological outcomes, including seizures, headaches and neurological disability, in addition to less well-defined outcomes such as neurocognitive disability and behavioural problems *11) The draft guideline states that the imaging techniques suitable for diagnosis of VTE in children are compression ultrasound (CUS) or venography for peripheral VTE, while central DVT and PE can be documented by magnetic resonance imaging (MRA) or computed angiography (CTA), and less*	

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	commonly by ventilation-perfusion lung scan/scintigraphy (VPLS) or catheter-directed pulmonary angiography. Are there other validated techniques to diagnose VTE that are applicable in day to day practice? In addition to those listed above: - Echocardiography for diagnosis of intra-cardiac thrombus and thrombosis of the major vessels, e.g. SVC. Abdominal ultrasound can identify portal vein and renal vein thrombosis. - For children with cardiac disease, cardiac catheterization with angiography may be used to diagnose clots in the heart, the large vessels, or shunts, particularly if catheter intervention to remove the clot are considered. The document identifies the requirement for central adjudication of imaging during clinical trials. It is important for this to be performed by radiologists who have specific paediatric experience. Moreover, clinical experts should also be part of adjudication committees since part of the adjudication relates to criterion for "symptomatic" versus asymptomatic event *12) Do you think that anticoagulated pediatric patients in your day to day clinical practice have particular safety issues to be considered as compared to adults (i.e. particularly higher incidence of certain adverse events, growth retardation, delays in neuro-motor or neurocognitive development, or different impact of the adverse effects in terms of disability/sequels?* In children with VTE, most issues like growth retardation, delays in neuro-motor or neurocognitive development, etc. are related to their co-existing diseases, and probably less to the effect of the anticoagulant. We believe that outcomes like growth retardation, or bone density or delays in neuro-motor and neurocognitive development are important in general, but not relevant in studies on short-term VTE prophylaxis or treatment. <u>Further comments</u>:	

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	Study population: Many patients with VTE have complex underlying disease, including a high risk of bleeding, comorbid organ dysfunction (kidney, liver), neuro-cognitive or neuro-motor delays, inability to take oral medications, etc. Since these children also need anticoagulant treatment, it is important that trial eligibility criteria are wide enough to ensure representative study populations, allowing to gain information on these complex patients as well. Target indication: The currently ongoing Paediatric Investigation Plans for Dabigatran, Rivaroxaban, Apixaban, Edoxaban, all target the same indication of treatment of acute VTE in all age groups (among some other indications), hence these programmes compete for the same rare patients. However, there are various subgroups of children requiring anticoagulant therapy or prevention, for many of which there exists little evidence on the benefit risk balance of anticoagulation in general, and for specific anticoagulants. On the other hand, the number of children available for studies in the various therapeutic subgroups is limited and there are practical challenges for recruitment. Therefore, the SSC recommends that parallel paediatric developments of different anticoagulants should target different (sub)indications to address the various therapeutic needs and to overcome feasibility challenges. It may be a unique challenge for a guidance document to NOT prescribe uniform model indications for new drugs. Rather, the guidance may define a core set of pharmacological data required and discuss the wide spectrum of therapeutic indications (e.g. neonatology, cardiac disease, renal disease, gastrointestinal disease; perisurgical thromboprophylaxis; etc) for which clinical efficacy and safety data could be generated, suitable for the specific properties of individual new anticoagulants.	
3.	EAHP considers that the addendum on the guidelines is well written and covers all important aspects needed for the investigation of medicinal products in children with VTE.	Outcome: no changes.
4.	LEO Pharma A/S welcomes the opportunity to comment on the Paediatric Addendum on the guidelines on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease. In general we think the document is well written and it covers the difficult	The uncertainty in the adjudication of VTE-related deaths is already addressed in the pediatric

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	issues of trials of anticoagulants in children with, or at risk of, VTE. We have noted that the document does not distinguish between the treatment of acute VTE, and treatment of Cancer Associated Thrombosis (CAT). On one hand the authors write that VTE in children is rarely primary (so more likely to be CAT, which in adults is less well treated by warfarin), on the other hand continuing SC injections of LMWH in young children, is difficult (but would need less blood tests than warfarin). In our opinion, the discussion on what the primary endpoint should be is very necessary and good. Especially important is the definition of "VTE-related death" which is normally defined as a death due to PE documented by objective imaging testing or autopsy, or a sudden death in which PE cannot be ruled out. In our experience, post mortems are rarely carried out, so many "PEs" may be assigned without evidence. Due to this, we have noticed, problems with the primary endpoint (of which fatal PE was a component) in our clinical trials. In the discussion between using "VTE related death" or "all-cause mortality" the document states *"Although both endpoints have pros and cons, it is generally recommended to include VTE-related death, rather than all-cause mortality, as a part of the primary efficacy endpoint. This choice does not prevent from including the composite of recurrent VTE plus all-cause death as a secondary endpoint."* LEO Pharma would prefer if VTE related death had to be confirmed as being a PE, either pre or post mortem, rather than just "cannot be ruled out". The numbers in any studies in children with VTE will be small, and could easily be skewed by even 1-2 cases incorrectly assigned Finally, we have noticed that bleeding complications are only mentioned separately in section 7 of the document and not listed as a secondary endpoint (which would make sense in our opinion, and which we would prefer).	addendum. The stakeholder proposes the category "sudden death in which PE cannot be ruled out" to be removed from "VTE-related deaths" because they are adjudicated "without evidence". That is not exactly true. It is a diagnosis by exclusion of other causes, which is not unusual in clinical practice. Anyway, in order to partially address the comments, the analysis of "VTE-related deaths" excluding the category "sudden death in which PE cannot be ruled out" could be recommended as secondary endpoint. With respect to mention cancer-associated thrombosis (CAT) as an specific VTE differentiated from "normal" VTE, it worth mentioning that the document is a general guidance. In the paediatric addendum is already recommended that "inclusion and exclusion criteria are well defined in order to have a predictable composition of subjects and an easily identifiable target

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		population in need for antithrombotic treatment against VTE". It is also mentioned cancer as a main risk factor. The composition of the population studied in clinical trials in children (and in adults) may impact the indication in the labelling, but this is always discussed on a case-by case basis, taking into account the populations studied in children and available data from adults. Outcome: a reference to uncertainty in the adjudication of VTE-related deaths, and whether the category "sudden death in which PE cannot be ruled out" represents an adjudication without evidence, has been included in the guideline. All other comments have not been included (see above).
5.	Recent guidelines from the American Society of Hematology (ASH 2018 VTE Guidelines: Pediatric Treatment) highlight differences in the management of VTE based on etiology and the presence of symptoms. These treatment differences (including the duration of treatment) may be even greater in the youngest pediatric patients. There are also significant differences in aetiology and clinical management of treatment of VTE versus prevention of VTE, with additional considerations for variations according to	Outcome: The ASH guideline for treatment of VTE in children was published in November 2018, after the paediatric addendum was agreed by the CHMP. It has now

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	age (i.e. infants vs adolescents). The significant variability and heterogeneity that exists in clinical practices should be reflected in clinical trial designs. We suggest the addition of an acknowledgment statement in this regard in the introduction section of the guideline.	been included by replacing the reference 4 "Chalmers EA, 2006"
6.	We would like to thank the EMA for the opportunity to comment on the Paediatric Addendum on the guidelines on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease.	Outcome: no change required.
7.	We found the document very accurate, we have only added a few comments where some more wording or additional examples were helpful.	Outcome: see proposed changes in the next section "2. Specific comments"

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Section 4, pages 4 and 5.	1	Comment 2): Acknowledging that extrapolation from adults is routinely done in standard practice in children due to lack of paediatric data, do you think that extrapolation from adults can be done under certain circumstances without the need for further studies? If yes, in which circumstances? Extrapolation can be used, particularly on mode of action, but usually some paediatric efficacy data are also needed. Extrapolation alone is not acceptable for safety data. Data on dosing, efficacy and pharmacokinetics from the adult population can only be extrapolated to children to a limited extent. Extrapolation is important to inform optimal planning of paediatric studies. Under certain circumstances, we should consider inclusion of adolescents in adult/pivotal clinical trials. Proposed change (if any):	Outcome: comments in line with the proposed text in the paediatric addendum. No changes required.
Section 6.3, page 10.	1	Comment 4): In comparative trials of new compounds in children with VTE versus the "standard of care", is it easy to define the "standard of care" or there is variability among countries and centres? The current standard of care at the respective centre might include vitamin K antagonists (different types), unfractionated heparin, or low molecular weight heparin (different types). There is variation between different centres and different countries. With some paediatric investigation plans (PIPs) on direct oral anticoagulants being completed and publication of their results pending, some direct oral anticoagulants might be introduced into standard-of-care in the near future. Regarding prevention, new, prospective trials should prioritise high-risk patients. Proposed change (if any):	Outcome: comments in line with the proposed text in the paediatric addendum. No changes required.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Section 6.3, page 10.	1	Comment 5): In the prophylaxis setting, do you agree that the prevention of central venous catheter (CVC)-related thrombosis is a target indication to be investigated? If so, which patient profile with indwelling CVCs is more prevalent in cardiology and how heterogeneous is this population in cardiology? In the prophylaxis setting, prevention of CVC-related thrombosis could be a target indication to be investigated (mostly in infants and small children). High-risk groups should be prioritised for new, prospective trials. Proposed change (if any):	Outcome: comments in line with the proposed text in the paediatric addendum. No changes required.
Section 6.3, page 10.	1	Comment 6): Do you think that the use of placebo is feasible in paediatric trials for prophylaxis of CVC-related thrombosis? Is there off-label use of anticoagulation for prevention of VTE in children with CVCs in cardiology due to very high risk of thrombosis? The objectives drive the trial design. It is feasible to use placebo, however the question of how long to treat can only be answered if you have a "no treatment" group included in the assessment. Historical control groups can potentially be used instead of placebo (randomisation) in some cases where there are high quality datasets. Proposed change (if any): The recent THROMBOTECT trial (Haematologica 2019) showed a benefit of thromboprophylaxis in the high-risk setting of children with acute lymphoblastic leukaemia and asparaginase therapy. An ongoing paediatric trial comparing a direct oral anticoagulant versus placebo in the same setting is awaited. These trials will probably influence standard of care. Thromboprophylaxis will likely not be used in all settings of children with CVC (e.g. neonates) but is variably used in higher-risk settings, e.g. cardiology patients. Thus, the feasibility of placebo-controlled thromboprophylaxis trials in children with CVC is low.	Outcome: The proposed change is not accepted. It is counterintuitive that once the benefit of thromboprophylaxis become established, then the feasibility of placebo-controlled trials will be compromised in the studied population (e.g.: high-risk patients on chemotherapy) but will still be feasible in other situations (e.g.: moderate risk patients, children not on chemotherapy, comparison of different prophylaxis durations, etc). In addition, the EMA guidelines are periodically updated. Once the results are available it should be discussed whether are of sufficient relevance to require the update of the paediatric addendum.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Section 4.1, page 5.	1	Comment 8): Do you agree that the primary efficacy endpoint in a paediatric VTE trial should be as broad as possible to capture all VTE events? In this respect, do you think that the primary endpoint proposed in the EMA document (objectively documented symptomatic and asymptomatic DVT and PE) is appropriate? The primary efficacy endpoint in a paediatric VTE trial should be as broad as possible to capture all VTE events and the proposed endpoint is deemed appropriate. However, a well-defined safety endpoint is equally important. Inclusion of quality of life tools is also important (but require validation for use in this population and thus, cannot be utilised as a component of a primary endpoint at this time). Examples of quality of life tools having potential utility in the paediatric population can be found in Table 1 of the following reference: https://onlinelibrary.wiley.com/doi/pdf/10.1017/S0012162206000673 Proposed change (if any):	The primary outcome recommended in the paediatric addendum is endorsed by the ESC. The ESC also propose quality of life to be included as secondary endpoint. The bibliographic reference provided is dated on 2006 (Davis et al. Developmental Medicine & Child Neurology 2006), and does not include any scale applicable to anticoagulated children. Therefore, it will not be included in the guideline. Alternatively, a reference by the ISTH regarding quality of life in anticoagulated children, dated in 2012 (Bruce et al. J Thromb Haemost. 2012), will be included in section 4.2 (secondary endpoints). In that review is stated that: "Both specific and generic QOL inventories may be useful when novel anticoagulants for children are evaluated. They can provide patient-reported adverse outcomes that might not be captured otherwise. However, they must be validated across different cultures and languages before implementation [16]." Outcome: a text about QoL has been included in section 4.2 "secondary endpoints".

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Section 4.1, page 5.	1	Comment 9): Is asymptomatic/incident VTE normally treated in the cardiology setting? If not all, in which circumstances? Asymptomatic and incident VTE is not always treated in the cardiology setting. It is usually a risk-based approach and centre-specific (some do/others don't) as a function of both patient age and diagnosis, and the haemodynamic consequences of thrombosis. Proposed change (if any):	Outcome: in line with the ESC comments, the following text has been included in section 4.2 "Secondary endpoints" regarding asymtomatic/incidental VTE: While incidental pulmonary embolism is usually treated, other forms of asymptomatic /incident VTE are not always treated in children [4]. Therefore, it is important to assess symptomatic and asymptomatic VTE separately as secondary endpoints, so we can learn more about their relative significance.
Sections 4.1 and 4.2, pages 5-7.	1	Comment 10): Are there other endpoints, like deterioration in thrombus burden, that could be suitable in children for measuring the effect of anticoagulant therapy? The guidelines could be re-opened to provide alternatives. It would be up to individual companies to discuss with the regulators the endpoints they would like to use and give a rationale. Deterioration in thrombus burden is not an established clinically relevant endpoint and should not be used as a primary endpoint for efficacy assessment for the time being. Proposed change (if any):	ESC comment is in line with the text of the paediatric addendum (i.e.: not recommending deterioration in thrombus burden as part of the primary endpoint in confirmatory trials). On the other hand, the possibility for the companies to propose and discuss with the regulators alternative endpoints is always opened in the context of a scientific advice procedure. There is no need to state this in the addendum. Outcome: no change required.
Section 4.1,	1	Comment 11): In the guideline, it is stated that **A)** the imaging techniques suitable for diagnosis of VTE in children are compression ultrasound (CUS) or venography for	Outcome: the corresponding text in section 4.1 of the paediatric addendum has been adapted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome

pages 6-7.		peripheral VTE, while **B)** central deep vein thrombosis (DVT) and pulmonary embolism (PE) can be documented by magnetic resonance angiography (MRA) or computed tomography angiography (CTA), and less commonly by ventilation-perfusion lung scan/scintigraphy (VPLS) or catheter-directed pulmonary angiography. **C)** Are there other validated techniques to diagnose VTE that are applicable in the day to day cardiology setting?
		
		Part A
		• The imaging techniques suitable for diagnosis of VTE in children are CUS or venography for peripheral VTE.
		  ○ If peripheral is upper and lower extremity combined, then CUS can be used. Regarding, venography: CT or MR venography can be used, while conventional venography should not be used.
		
		Part B
		• Central DVT and PE can be documented by MRA or CTA, and less commonly by VPLS or catheter-directed pulmonary angiography.
		  ○ For central DVT: use magnetic resonance venography (MRV) or computed tomography venography (CTV).
		  ○ For PE: Use CTA or VPLS. Do not use catheter-directed angiography.
		
		Part C
		• Are there other validated techniques to diagnose VTE that are applicable in day to day cardiology?
		  ○ No.
		
		Summary:
		The imaging techniques suitable for diagnosis of VTE in children are CUS for peripheral VTE, while central DVT can be documented by MR venography or CTV. PE can be documented by CTA or less commonly by VPLS. In patients with complex cardiac defects, and particularly if catheter interventions (dilatation, stenting) might be needed to re-open a thrombotic inclusion, cardiac catheterisation with conventional angiography may be an option. In day to day radiology there are currently no other validated techniques to diagnose VTE.
			according to the ESC comments.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	
Section 7, page 11.	1	Comment 12): Do you think that anticoagulated paediatric patients in your day to day clinical practice have particular safety issues to be considered in comparison with adults (i.e. particularly higher incidence of certain adverse events, growth retardation, delays in neuromotor or neurocognitive development, or different impact of the adverse effects in terms of disability/sequels)? Particular safety issues to be considered in comparison with adults: bleeding events, effect on growth in long-term treatment. Quality of life and neurocognitive development (most especially in infancy through early childhood) can be assessed via the Bayley Scale: https://www.tandfonline.com/eprint/qWhgD5mubihaEhycXzEE/full. Osteoporosis is a long-term safety issue and the paediatric data is poor. It could be important to demonstrate advantages of non-vitamin K antagonist oral anticoagulants over VKAs. Most patients have severe congenital heart defects or cancer so growth is retarded compared to a normal paediatric population. It is difficult to reach conclusions relating to long-term safety in the initial 1–2-year trials, however long-term study extensions should be considered. Proposed change (if any):	Outcome: The reference to the Bayley scale (Brito et al, 2019) has been included.
Page 7, line 208	2	Comment: We agree it is important to limit CT scans to those that are clinically indicated (e.g. no investigation at 6 weeks when the patient is being treated for 3 months regardless). However, we think it is an overstatement to say that MRA only are recommended. MRA is more expensive and much more difficult to schedule, and should only be listed as an alternative if possible to avoid CT radiation Proposed change (if any):	Outcome: the text has been modified accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Page 8, line 250	2	Comment: Proposed change (if any): -cardiac "catheterism" should be "catheterization"	Outcome: the text has been modified accordingly.
Page 8, line 255	2	Comment: We recommend to exclude the recommendation to exclude children with femoral CVC from studies. Femoral CVC play a major role in PICU or trauma patients. They may be included, maybe stratified, or studied in dedicated separate studies.	Outcome: the text has been modified accordingly.
Page 9, line 295	2	The discussion on age-specific paediatric formulations is somewhat hidden in the paragraph on PK/PD studies. Given the importance of paediatric formulation for accurate and reliable dosing, this issue would merit a separate section.	Outcome: the text has been moved the start of section 6 in order to make it more visible.
Page 9, line 327	2	Comment: Proposed change (if any): -"unspecific" should be "non-specific"	Outcome: the text has been modified accordingly.
Page 12, references	2	We suggest to add the following reference, which is the most recent evidence-based guideline for VTE treatment in children (for VTE prevention in children, reference 8, Monagle et al, Chest 2012, remains the most relevant guideline): American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. Monagle P, Cuello CA, Augustine C, Bonduel M, Brandão LR, Capman T, Chan AKC, Hanson S, Male C, Meerpohl J, Newall F, O'Brien SH, Raffini L, van Ommen H, Wiernikowski J, Williams S, Bhatt M, Riva JJ, Roldan Y, Schwab N, Mustafa RA, Vesely SK. Blood Adv. 2018 Nov 27;2(22):3292-3316.	Outcome: The ASH 2018 recommendations have now been referenced in the text, according to comments received. They were published after the draft paediatric addendum was adopted by the CHMP.

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line 244	3	Comment: typo "toinclude" Proposed change (if any):	Outcome: the text has been modified accordingly.
	4	None	
77-79	5	*The focus of this paediatric addendum is on clinical investigation of treatment and prophylaxis of VTE in neonates (first month), infants (1 month to <2 years), children (2 to <12 years) and adolescents (12 to <18 years).* Comment: The definition of age groups is not fully aligned with ICHE11 definitions. Please consider simplifying the wording (see proposal below), or align definition with ICHE11 if details are needed. Proposed change (if any): The focus of this paediatric addendum is on clinical investigation of treatment and prophylaxis of VTE in neonates, infants, children and adolescents.	Outcome: the text has been aligned with ICH E11.
207-208	5	*However, it is considered unacceptable to expose children to any radiation in a clinical trial when there is an alternative at hand. Therefore, MRA assessments only are recommended.* Comment: Regarding the use of diagnostic imaging tests we agree with the statements made from lines 195 to 205, as they are supported by clinical practice and guidelines. However,	Outcome: the text has been aligned with the comments received from the ESC and BMS.

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		lines 207 and 208 appear to be in direct contradiction to the aforementioned statements. We recommend deleting lines 207 and 208 altogether. If this statement must remain in the document, please consider the language below as a replacement for lines 207 and 208 Proposed change (if any): Every effort should be made to minimize radiation exposure to children participating in clinical trials, particularly when alternatives are practically available.	
252-255	5	*In thromboprophylaxis trials in children with indwelling CVCs, in whom the need for thromboprophylaxis is not yet well defined, the population under investigation should be restricted to patients with a CVC in the upper central venous system, while excluding peripherally placed CVCs as well as those inserted into the femoral vein.* Comment: The rationale for restricting investigation of thromboprophylaxis in children with indwelling CVCs in the upper central venous system is unclear. Regardless of the methods of insertion/placement and location, all indwelling catheters whose tips reside in the central venous system have increased thrombogenic potential, and should be eligible for study. Proposed change (if any):	Outcome: the text has been deleted after comments received from the ESC and BMS.
298-300	5	*If the product is to be administered orally, the use of a liquid formulation is preferred, as it is easy to swallow and together with the delivered liquid dosing device the formulation ensures a flexible, precise and accurate dosing. The choice for a suspension formulation may also be accepted if appropriately justified (e.g.: poor solubility of the*	Outcome: the text in the paediatric addendum is a recommendation of the PDCO and is a general recommendation. Of course, there could be situations were a tablet or other

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		active ingredient/s). Comment: The choice of a paediatric formulation needs to consider several parameters into account, including target age group, dosing flexibility need, chemical characteristics of the active substance. Liquid formulations can have stability and palatability challenges making them inappropriate in some instances. As such, we suggest not recommending specific formulations (i.e. liquid or suspension), but rather indicating that the choice of the formulation must be justified based on current guideline. Proposed change (if any):	pharmaceutical form could also be acceptable if appropriately justified. The wording has been slightly modified to account for all possible scenarios beyond liquid/suspension formulations.
41	6	Comment: There is a statement that the incidence of VTE in children is rare, but no reference is cited. Proposed change (if any): It should be stated that there is a paucity of current real world evidence providing a good estimate of VTE incidence in children. The published data regarding the incidence of VTE is limited to data sets over a decade old.	Outcome: a new updated reference 4 has been included in the introduction to support this statement (ASH 2018 Guidelines for management of venous thromboembolism).
67-70	6	Comment: We question the statement that "The majority of the recommendations for dosing in children are based on a moderate level of evidence." The most recent published guidelines for the treatment of venous thromboembolism in children, those of the American Society of Hematology (ASH) published in 2018 (https://www.ncbi.nlm.nih.gov/pubmed/30482766) describe "a very low certainty in the evidence of effects." Proposed change (if any): Suggest that the statement read, "The majority of the	Outcome: the said reference has been included in the introduction, and the level of evidence has been updated accordingly.

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		recommendations for dosing in children are based on a low level of evidence."	
71-75	6	Comment: The author's state, "The current standard of care for the treatment of VTE in children is unfractionated heparin (UFH) or low molecular weight heparin (LMWH) administered for 5-7 days followed by (at least) three months of LMWH or oral anticoagulation with a vitamin K antagonist (VKA) [10,11]." Given the author's acknowledgement that (line 52) "The typical location of VTE in neonates and infants differs from that in adults and adolescents," and that typically the VTE in these very young children is secondary to the placement of an indwelling catheter, it is difficult to imagine justifying three months of anticoagulation, if the catheter has been removed. Proposed change (if any): We would suggest that the authors review the 2018 ASH guidelines cited above, and revise the text in the proposed EMA guidelines, to highlight the observation that VTEs in children, vary with respect to aetiology. We would suggest that recommendations with respect to the duration of anticoagulation treatment must take into consideration the differences in risk and benefit that vary, with the cause of the VTE, the age of the patient, and whether or not the conditions that triggered the VTE, are still present.	Outcome: the text has been modified to acknowledge that treatment duration may depend on the underlying diseases and risk factors that triggered the VTE.
324-325	6	Comment: The author's state, "The use of half the dose in mg/m² found efficacious and safe in adults in a prophylactic indication as an initial dose and subsequent titration until the target range is achieved, is acceptable." Proposed change (if any): It is suggested to add evidence or references to the cited statement as there are no medicines approved for prevention of VTE in children.	This text has been extracted from a CHMP scientific advice about an ongoing paediatric development. No reference can be included. As the text is probably too specific for a general guideline, it has been deleted.
195-208	7	Comment:	Outcome: a brief explanation for the

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		For the diagnosis of VTE, Doppler ultrasonography, venography, computed tomography (CT) and magnetic resonance (MR) imaging can be used. As venography is invasive, painful, and difficult to access in infants and children, non invasive Doppler ultrasonography should be the first modality to diagnose DVT in children, especially for the DVT in lower extremities. MR imaging and MR angiography are recommended to confirm the diagnosis of cerebrovascular occlusion. Proposed change (if any):	recommendation of DUS versus venography in children has been included.
217-224	7	Comment: Post-thrombotic syndrome (PTS), well-known complication of pediatric DVT, is defined as edema, pain, skin pigmentation, and ulceration of the affected limb secondary to venous valvular damage initiated by DVT. PTS occurs in 20–50% of adults with DVT and up to 65% of children with DVT, causing disability in pediatric patients Proposed change (if any):	Outcome: post-thrombotic syndrome has been referenced (references 4 and 8) and its estimated prevalence in children with DVT has been added (12% to 65% in different studies).
226-235	7	Comment: INCLUDE ALSO infection/sepsis, surgery, and inherited or acquired thrombophilia, all of which act as risk factors for VTE in children and adolescents. Venous thromboembolism (VTE), especially hospital-acquired VTE, is increasingly recognized in pediatric patients. The incidence of VTE in hospitalized children has increased approximately 70% over a 6-year period and is thought to affect approximately 1 in every 200 hospitalized children (1). The rise in VTE is largely attributed to increased use of invasive support of critically ill patients, especially with the use of central venous access devices, which can lead to line-related VTE (1). Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous	Outcome: "infection/sepsis" is normally considered as comorbidity or as a complication of CVC-related thrombosis. Sometimes there is a temporal association between mastoiditis/sinusitis and cerebral sinovenous thrombosis, but broadly speaking infection/sepsis is not considered a risk factor for VTE. Surgery and thrombophilia were already included in the document. In addition, we included ".., etc" to account for additional independent risk factors for VTE that could be

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		thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics (2009) 124:1001–8.10.1542/peds.2009-0768 Proposed change (if any):	identified in the future.
384-388	7	Comment: Large epidemiologic studies of osteoporosis in pediatric patients with long-term heparin/LMWH exposure have not been conducted, but given the relationship between heparin use and osteoporosis in adults, this should likely be avoided in pediatric patients as well. Gajic-Veljanoski O, Phua CW, Shah PS, Cheung AM. Effects of long-term low-molecular-weight heparin on fractures and bone density in non-pregnant adults: a systematic review with meta-analysis. J Gen Intern Med (2016) 31(8):947–57.10.1007/s11606-016-3603-8	This paediatric addendum is not a clinical practice guideline. It is beyond the scope of this paediatric addendum to recommend against the use of LMWH in children just because the risk of osteoporosis is unknown. VKAs have also been associated to osteoporosis. Please also consider that the more recent ASH 2018 guideline panel suggests using either LMWH or VKA in pediatric patients with symptomatic DVT or PE. The paediatric addendum includes the need for further investigating osteoporosis as secondary safety endpoint, which is a reasonable approach as heparins (and VKAs) will still be used in clinical trials in children, and comparative data with novel anticoagulants regarding this endpoint are lacking. Please also refer to ESC comment: It could be important to demonstrate advantages of non-vitamin K antagonist oral anticoagulants over VKAs (regarding osteoporosis).

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			Outcome: no changes required.