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Paediatric Addendum on the guidelines on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease

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Paediatric Addendum on the guidelines on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease

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Executive summary

This is an addendum to the *Guideline on clinical investigation of medicinal products for the treatment of venous thromboembolic disease* (EMA/CHMP/41230/2015*)* [1] and the two guidelines for prophylaxis of venous thromboembolism (VTE) in surgical (EMA/CHMP/325170/2012 Rev.2) [2] and non-surgical (EMA/CPMP/EWP/6235/04 Rev. 1) [3] adult patients, and should be read in conjunction with these guidelines. This addendum includes guidance on paediatric clinical medicine development, highlighting paediatric specific issues and differences from the treatment and prophylaxis of venous thromboembolism in adults.

1. Introduction (background)

VTE is a very rare disease in children in the community (approximately 1 in 100,000 children), and infrequent in hospitalized children (approximately 6 cases per 1,000 admissions), but represents a significant management dilemma that requires therapeutic intervention [4].

The distribution of VTE events in paediatric patients is bimodal with the majority of events occurring in neonates and infants [4,5] and in adolescents [6]. In contrast to VTE in adults, VTE in children is rarely truly idiopathic in nature [7]. Approximately ≥90% of children with VTE have a serious underlying disorder [e.g.: cancer, congenital heart disease (CHD), nephrotic syndrome, etc.], a precipitation factor [central venous catheter (CVC), infection, trauma or surgery], and/or a hereditary pro-thrombotic condition. Apart from better awareness for VTE, the widely observed increase in childhood VTE is mainly due to the medical progress in the treatment and/or interventions of critically ill children. In adolescents, VTE is generally associated to the use of hormonal contraception (HC) for contraceptive and non-contraceptive indications [6]. The typical location of VTE in neonates and infants differs from that in adults and adolescents. In neonates and young children, VTE occurs more often (60%) in the upper extremity venous system (vs. only 2% in adults). This reflects the common placement of CVC (the most frequent precipitating factor of VTE in children) via the internal jugular or subclavian veins. Loss of catheter patency and loss of central venous access have important consequences in children with cancer and other serious medical conditions [7]. Non-extremity deep vein thrombosis (DVT) (e.g.: cerebral sinus vein thrombosis, renal or portal VTE) is also more frequent in children than in adults [8,9]. The location of the clots results in fewer classic VTE symptoms and also may impair the effective/precise diagnosis with standard measures [i.e. compression ultrasound (CUS) cannot be performed in these locations].

PK and PD in children may differ from that in adults. On the one hand, due to physiological differences in absorption, distribution and metabolism, children may require different proportional doses than adults according to body weight or body-mass index (BMI) to achieve the same level of anticoagulation [8]. On the other hand, hemostasis is a dynamic process that is age dependent and continues throughout life. Coagulation factors are produced by the fetal liver by 10 weeks of age. The age-dependent differences in the coagulation system are most significant in neonates and infants aged < 6 months [9]. At birth, the plasma levels of the vitamin-K-dependent coagulation proteins (factor II, VII, IX, and X) are half of the adult values and remain approximately 15% lower throughout childhood.

Anticoagulation is recommended in paediatric patients with symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE). Although there remains limited direct evidence in children, largely based upon case series and cohort studies, there is very strong indirect evidence from adults that symptomatic VTE requires treatment [4]. Further, given that the majority of VTEs occur in sick hospitalized children, in whom VTE is often life-threatening, low-quality evidence suggesting benefit justifies a strong recommendation. 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 usually followed by (at least) three months of LMWH or oral anticoagulation with a vitamin K antagonist (VKA) [4,10,11]. The duration of anticoagulation treatment must take into consideration the differences in risk and benefit that may vary with the cause of the VTE (e.g.: idiopatic versus CVC-associated VTE), the age of the patient, and whether or not the conditions that triggered the VTE are still present (e.g.: removal of the CVC line). In the absence of large randomized controlled trials, and with much of our current understanding of PK extrapolated from adult studies, ideal dosing for anticoagulation in critically ill neonates remains uncertain.

2. Scope

The focus of this paediatric addendum is on clinical investigation of treatment and prophylaxis of VTE in neonates (0 to 27 days), infants (28 days to 23 months), children (2 to 11 years) and adolescents (12 to <18 years). The need for suitable endpoints and imaging techniques adapted according to the localisation of VTE in children, specific methodological issues of clinical trials in children with VTE and the possibility to extrapolate efficacy and safety from data in adults is discussed.

3. Legal basis and relevant guidelines

This is an addendum to the Guidelines on Clinical Investigation of Medicinal Products in the treatment and prophylaxis of VTE (EMA/CHMP/41230/2015; EMA/CHMP/325170/2012 Rev.2; EMA/CPMP/EWP/6235/04 Rev. 1). It should be read in conjunction with the introduction and general principles of the Annex I to Directive 2001/83/EC as amended.

All pertinent elements outlined in the current and future EU and ICH guidelines and regulations should also be taken into account especially the following:

- ICH E11, Clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99);
- Guideline on the investigation of medicinal products in the term and preterm neonate (EMEA/267484/2007);
- Reflection paper on the use of extrapolation in the development of medicines for paediatrics. (EMA/189724/2018))
- Role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004/Corr);
- Clinical trials in small populations (CHMP/EWP/83561/2005);
- Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2);
- Ethical considerations for clinical trials on medical products conducted with the paediatric population: Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use 2008.
- Committee for Medicinal Products for Human Use ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017).

4. Efficacy evaluation

While it may not be feasible to perform studies in children of different age cohorts that are powered to provide statistically significant results for efficacy, EMA provides guidance that if there is sufficient similarity between children and adults (extrapolations of efficacy and safety data from adults (source population) to children (target population) could be used [12]. The adequacy of extrapolating clinical efficacy and safety data from adults to children, from one paediatric subgroup to another, or from one frequent VTE aetiology to a rare VTE aetiology in children, as well as the extent of this extrapolation, will depend on knowledge about the disease, understanding of the clinical pharmacology of the drug as well as the reliability of the results in the source population (i.e. adults or paediatric subgroups with available efficacy and safety results)[12]. In most cases, at least clinical pharmacology studies will be necessary to establish the dose needed in children that achieves a similar exposure and response as in adults, in order to infer efficacy and safety from adults (i.e.: inferential efficacy/safety rather than "pure" extrapolation based on plausibility alone).

Disease related aspects include the characteristics of VTE in neonates and young children (e.g. natural course of the disease, VTE localization and risk factors) should be considered when planning and conducting paediatric studies in VTE, with the purpose of adapting the design of dedicated efficacy/safety studies in children or performing an extrapolation exercise from adults. All relevant data should be systematically reviewed to identify potential differences between characteristics of the source and target populations e.g. body size, age and maturation of the haemostatic system, drug exposure (PK) and their relation to pharmacodynamic response (PD) and clinical efficacy [12]. It is also important to consider factors (e.g. maturation of organs and systems, body mass and morphology changes, immaturity in preterm neonates and long term effects) related to the susceptibility to adverse reactions, mainly bleeding events. Aspects related to the investigational treatment (e.g.: dose regimens, duration of therapy, monitoring requirements, possibility of establishing therapeutic ranges, factors influencing dose-response relationships, side effects, and the impact of general anesthesia and non-pharmacologic interventions) should also be considered.

As similarities between younger children and adults in clinical risk factors for VTE, course and response to VTE treatment are not entirely straightforward, an extrapolation of efficacy and safety data from adults only based on similar exposure and PD data is not supported, and some extent of efficacy and safety data in children are needed. Existing data of efficacy and safety in an indication already approved in adults (e.g.: treatment and secondary prevention of DVT/PE) could, however, complement the results of the paediatric studies and further support the use in children based on the totality of the data without requesting a study powered to test a formal statistical hypothesis in children. The efficacy of antithrombotic treatment or prophylaxis in paediatric VTE can be evaluated in clinical trials using combined VTE endpoints documented by objective methods. Irrespectively of the diagnostic imaging technique used for documenting the events, it is recommended that all primary events occurring during the trials are blindly adjudicated by a central Independent Adjudication Committee, whose members are experts in the field of paediatric thrombosis imaging. Moreover, clinical experts should also be part of adjudication committees, since part of the adjudication relates to criteria for "symptomatic" versus "asymptomatic" events.

4.1. Primary endpoint

The primary efficacy endpoint in treatment or prophylaxis trials in children, should be as broad as possible to capture all VTE events (i.e.: including symptomatic and asymptomatic events), in

consistency with exploratory trials in adults [1-3]. Therefore, a composite endpoint is recommended as follows:

- Objectively documented symptomatic and asymptomatic DVT and PE.
- VTE-related or all-cause death during the treatment.

Definition of primary events:

DVT and PE can be newly diagnosed (in case of primary prophylaxis, or after acute VTE if it occurs in a different localisation than the primary index VTE event) or recurrent VTE (if it occurs after acute VTE in the same localisation than the primary index VTE event).

The following definitions of primary events according to the imaging technique used are acceptable:

Suspected (newly diagnosed or recurrent) DVT may be confirmed in the presence of at least one of the following findings [10]*:

- Abnormal compression ultrasound (CUS) where compression had been normal or, if non-compressible during screening, a substantial increase in diameter of the thrombus during full compression;
- An extension of an intraluminal filling defect, or a new intraluminal filling defect or an extension of non-visualization of veins in the presence of a sudden cut-off on venography;
- An extension of an intraluminal filling defect, or a new intraluminal filling defect on computed tomography angiography (CTA) or magnetic resonance angiography (MRA).

Suspected (newly diagnosed or recurrent) PE may be confirmed in the presence of at least one of the following findings [13]:

- A (new) intraluminal filling defect in segmental or more proximal branches on CTA or MRA;
- A (new) intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels on the pulmonary angiogram;
- A high-probability result on ventilation-perfusion lung scanning (VPLS);
- Inconclusive spiral computed tomography (sCT), pulmonary angiography, or VPLS with demonstration of DVT in the lower extremity.

Diagnosis of symptomatic (newly diagnosed or recurrent) DVT or PE based solely on clinical signs and symptoms is discouraged. The number of such episodes, especially if leading to changed or renewed therapy, must, however, be noted and accommodated for in the analyses.

VTE-related or all-cause death: VTE-related death 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. VTE-related death may represent the efficacy of the experimental drug more accurately than all-cause death. However, given that in contemporary practice autopsies are rarely performed, most deaths adjudicated as VTE-related will correspond to the latter category (i.e.: conservative diagnosis due to impossibility to document fatal VTE or other causes of sudden death). All-cause death offers the advantages of being less prone to bias and to comprise also deaths that can be directly or indirectly related to anticoagulation (e.g.: fatal bleedings or deaths due to VTE after treatment has been stopped due to bleeding). However, death rates after a VTE in children may be higher than the rate of recurrent VTE depending on the underlying disease/s (e.g.: children with underlying cancer), which could result

in dilution of the drug effect, thus trending to the null hypothesis of no differences between treatments.

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. Because the category of "sudden death in which PE cannot be ruled out" is an adjudication by exclusion and not by confirmation, a secondary analysis excluding this category from VTE-related death is recommended. The composite of recurrent VTE plus all-cause death should also be included as a secondary endpoint.

Deterioration in thrombotic burden (phase II trials): In dose-finding clinical trials in the treatment of VTE in adults, deterioration in thrombotic burden (i.e.: comparison between baseline and end of treatment using imaging techniques) may be a part of the primary endpoint, as it can be considered a treatment failure (i.e.: asymptomatic recurrence). However, thrombus burden definitions available in adults [11,14] have not been validated in children, which prevents for inclusion as part of the primary endpoint in confirmatory trials. Anyway, lack of vessel patency and persistent thrombus assessed during and after treatment may be used as a composite secondary exploratory endpoint, as these events have been associated with poor long term outcomes and post-thrombotic syndrome in adults and pediatric thrombosis.

Imaging methods for assessment: The imaging technology applied is driven by the location of the venous thrombosis. Extremity venous thrombosis will in most children be documented by compression ultrasound (CUS), and less frequently by conventional venography, as it is invasive, painful and difficult to access in infants and children. Central DVT (e.g.: cerebral sinovenous thrombosis) can be documented by magnetic resonance venography (MRV) or computed tomography venography (CTV), while PE (in pulmonary arteries) can be documented by contrast enhanced magnetic resonance angiography (MRA) or computed tomography angiography (CTA), and less commonly by ventilation-perfusion lung scan/scintigraphy (VPLS) [13-15]. 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.

The available literature, though not unanimous, suggests similar sensitivity and specificity of both MRA and CTA techniques for the diagnosis of thromboembolic entities in the central venous system. Comparative studies of adequate power and design, especially in the paediatric population, are missing. MRA technique is the preferred alternative if practically available in order to minimize radiation exposure to children participating in clinical trials.

In addition to those listed above: a) Echocardiography can serve for diagnosis of intra-cardiac thrombus and thrombosis of the major vessels (e.g. superior vena cava); b) Abdominal ultrasound can identify portal vein and renal vein thrombosis; c) 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 interventions to remove the clot are considered.

Time-points for assessment:

In the treatment of acute VTE and/or extended treatment (secondary prophylaxis), time-points for assessment should include at least baseline and end of treatment, or earlier if patient experiences symptoms of recurrent VTE or new VTE. In case of trials for primary prophylaxis of CVC-associated thrombosis, VTE has to be radiographically determined if symptoms develop (expected in only 6-10%

of cases) or, if patients are asymptomatic, at 1 month from catheter placement and when catheter is removed or lost, or at 1 year, whichever is shorter.

4.2. Secondary endpoints

Main secondary efficacy endpoints of interest comprise the individual components of the composite endpoint as well as deaths, like in adults (EMA/CHMP/41230/2015; EMA/CHMP/325170/2012 Rev.2; EMA/CPMP/EWP/6235/04 Rev. 1).

While incidental PE 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.

For 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. The assessment of long-term consequences of DVT [e.g.: post-thrombotic syndrome/sequelae (PTS)], reported between12% and 65% of children after a DVT [4], or PE (e.g.: thromboembolic pulmonary hypertension) are also of interest, as they impact on quality of life (QOL) and lead to complications.

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]. It is strongly encouraged that phase III studies continue to collect PK and PD parameters from children of different ages to allow for investigation of PK/PD relationship (see also section 6.1 about clinical pharmacology studies).

5. Patient selection

The varied aetiology of paediatric VTE offers opportunities for inclusion of patients with diverse set of characteristics, but heterogeneity of the study population may be an issue. It is recommended that inclusion and exclusion criteria are well defined in order to have a predictable composition of subjects and an easily identifiable target population in need for antithrombotic treatment against VTE. Demographic characteristics to be collected should also be well defined to identify risk factors for VTE (e.g.: cancer, congenital heart disease, trauma, thrombophilic condition, etc.) as well as concomitant treatments (e.g.: thrombogenic anti-cancer medications, HC in female adolescents) that could result in different VTE rates and/or treatment effects. In children on chemotherapy, it is recommended to stratify the randomization according to expected or actual asparaginase chemotherapy, when administered, as this is considered a major prothrombotic risk factor.

An adequate representation of paediatric patients of different age ranges is necessary, unless scientifically justified (e.g.: condition not present in a specific age range, not expected benefit, identified harm, etc). In particular, it is of importance to study paediatric patients < 2 yrs due to differences in underlying aetiologies and thrombus location, as well as a not fully matured coagulation/fibrinolysis system. The challenges of including neonates into anticoagulation studies, such as concerns for central nervous system bleeding, are significant. A cautious approach could be the exclusion of neonates from the proposed study and the initiation of a study in newborns once paediatric data become available. Adolescents would be generally enrolled in dedicated paediatric efficacy/safety studies. Another potential alternatives could be to include them in adult trials or even to

extrapolate from adults if a comparable dose could be established from PK/PD data in adolescents and the cause of the VTE is comparable to causes found in adults (e.g.: VTE due to hormonal contraception).

Several conditions could be considered to be appropriate targets for studying anticoagulant primary prophylaxis, like CVC-related thrombosis, perioperative and periprocedural anticoagulation (e.g.: cardiac catheterization, cardiac surgery), immobilisation due to trauma, etc. However, given the frequency of CVC-related VTEs, a specific clinical trial is feasible and would potentially have a meaningful clinical impact [9]. The incidence of CVC-related VTEs may depend on the nature of the underlying condition, e.g. cancer, trauma, surgery, congenital heart disease. Furthermore, standard of care is likely to vary in different geographical regions, therefore data on background therapy should be provided. Further stratification for baseline VTE-risk is recommended. The same is true for the type of catheter and place of insertion. There are several mechanisms by which CVCs can cause VTEs, including thrombogenic catheter materials, irritation of the vessel wall, restriction of blood flow due to catheter size, location of insertion site, etc. As the benefit-risk of anticoagulation may differ across different primary prophylactic settings (i.e.: indwelling CVCs, surgical patients, immobilisation due to trauma, etc.), the results obtained in a specific setting are unlikely to be extrapolated to all other situations.

6. Clinical trials strategy & design

Before starting clinical trials in children, there is likely to be a necessity to develop special paediatric formulations as appropriate for different age groups, and taking into account the intended route of administration (*Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2*). 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 appropriate under certain circumstances (e.g.: poor solubility of the active ingredient/s). Other pharmaceutical forms (e.g.: tablets) may also be accepted if appropriately justified. Comparable bioavailability of the new formulation (e.g.: oral solution) versus other existing formulations of the medicinal product, children's acceptability and measuring devices are to be established. Of equal importance is to develop appropriate paediatric formulations if the product is to be administered parenterally (e.g.: lower concentrations adapted to children, graduated syringes or other administration devices adapted for paediatric use) or by other routes.

6.1. Human Pharmacology studies (Pharmacokinetic/Pharmacodynamic [PK/PD])

A difference in the PK between the adults and children (e.g.: decreased absorption, higher or lower clearance), or different PD that impacts the dosing strategies is anticipated from the evidence available with traditional anticoagulants (e.g.: warfarin, LMWHs). As a result, existing pop-PK model in adults may unreliably predict the doses needed in children. Therefore, at least one PK study in children will be needed to build a pop-PK model in children [17,18]. The challenges of including neonates into anticoagulation studies has already been addressed in section 5. The influence of intrinsic (impaired renal or hepatic function) and extrinsic factors (concomitant drugs altering haemostasis) that could be frequent and/or relevant in the studied population should also be considered.

With respect to PD, it may be first investigated in an *ex vivo* coagulation test to confirm whether the compound has no age-related effect on coagulation times or plasma anticoagulant activity markers. In case of products already approved for use in adults, an adult physiologically-based pharmacokinetic model (PBPK) may be adapted to children through a paediatric scaling approach. The model should be further qualified by comparison with the paediatric data available. Based on the PBPK approach, the dose per kg body weight and even the administration interval may differ per weight group to accommodate for physiological characteristics (e.g.: differences in Cmax, C_{min}, AUC, etc due to differences in clearance and/or absorption). Dosing based on body weight (BW) only is recommended if no relevant differences are found compared with dosing based on body surface area (BSA), and appears acceptable and a simple method to prevent dosing errors.

With respect to PK/PD relationship, suitable PD markers should be those identified in the adult populations. Depending on specific compounds, these markers may comprise coagulation times [e.g.: prothrombin time (PT), activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), diluted thrombin time (dTT), or anticoagulant activity (e.g.: anti-Xa activity)], that may be coupled with imaging surrogate endpoints (e.g.: change in thrombus burden, presence/absence of asymptomatic DVT). It is expected that the measurement of the anticoagulant activity (e.g.: anti-Xa assay for direct FXa inhibitors or any other specific assay according to the drug's mechanism of action) is based on tests already validated. As for PK, the influence of intrinsic and extrinsic factors on PD should also be considered.

6.2. Exploratory Therapeutic studies

Exploratory studies are expected to function as dose finding studies for confirmatory trials and could be placebo controlled where feasible. In addition to selecting a dosing regimen of the experimental drug that is effective and safe, these studies could also provide additional information, e.g. proof of concept, safety, comparability to adults and data to support population selection. The use of placebo could be feasible when there is clinical equipoise about starting/continuing anticoagulation versus not starting/stopping anticoagulation, either in extended prophylaxis after acute VTE, where the exact duration is unknown, or in primary prophylaxis when antithrombotic prophylaxis is not well established, or even in the treatment of asymptomatic VTE, if appropriately justified. The use of pure placebo (replacing standard of care, which includes anticoagulation) is considered unethical in the treatment of symptomatic VTE. It may be possible to derive dose information from adult studies and phase I PK studies in children using exposure response analyses and modelling, but specific dose titration studies may be required to document the safety, PK/PD in children requiring high anticoagulant doses, like those with acute VTE. In phase II trials in children with acute VTE is encouraged to follow a stepwise approach starting with adolescents and older children, followed by younger children and neonates due to safety reasons. The use of BSA rather than BW adjusted dosing may be adequate in clinical trials in children considering the fact that rapid changes in weight due to altered fluid load and/or nutritional status is frequent in this special population. Analysis of pre-specified PD biomarkers is recommended. Robust markers (e.g.: anti Xa-activity, *in vivo* thrombin generation) are preferred to less sensitive and non-specific traditional markers of coagulation. The choice will ultimately depend on the drug mechanism of action and on the PD markers identified in the adult population.

6.3. Confirmatory Therapeutic studies

It is recognised that large randomised clinical trials may not be feasible in paediatric VTE to evaluate the benefit risk of all medicinal products intended for use in this clinical condition when the difficulties

in performing clinical investigations are taken into account. Therefore, paediatric developments need to build on information on safety and efficacy of the medicinal product from the adult population. There is a need to maximise the information gathered from all other types of studies (including exploratory and PK studies conducted across groups). With the expectation that limited efficacy and safety clinical data will be available at the time of completion of the phase III trial/s, study designs should also focus on the collection of PK/PD data. Such data may also indicate the need for monitoring in this vulnerable population.

When discussing the design of confirmatory studies, it is important to distinguish between the initial treatment of VTE (usually 3-6 months), extended treatment (secondary prevention of recurrence) of VTE (once the initial treatment has finished), and primary thromboprophylaxis in high risk children, like those with indwelling CVCs.

Use of an appropriate comparator according to the best standard of care (e.g.: LMWH, vitamin K antagonists) will be generally mandatory for comparative clinical trials in the initial treatment of acute VTE in children. The use of placebo could be feasible when there is clinical equipoise about continuing versus stopping anticoagulation in extended prophylaxis after acute VTE, where the exact duration is unknown. In situations where the prophylactic use of anticoagulation is not well established in children, the use of placebo with an add-on design to the best standard of care (e.g.: nursing care of indwelling CVCs, mechanical thromboprophylaxis, early mobilisation in children developmentally able to walk, etc) in both the active and placebo group is recommended.

a) Initial treatment of VTE: It is difficult to endorse a particular sample size in the treatment of acute VTE on the basis of the information currently available. A minimum patient number per age group in the phase III program is necessary to generate efficacy and safety data, which will be generally agreed in the paediatric investigation plan (PIP). The number of children recruited is expected to be low and comparative trials in the treatment of VTE versus standard of care will normally not be focussing on formal hypothesis testing of non-inferiority or superiority due to lack of statistical power, but rather on descriptive analyses [19]. A non-inferiority approach for the combined endpoint of the proportion of children with complete thrombus resolution and/or free from recurrent VTE and VTE-related death has been used [20]. However, this composite endpoint has not been validated and the more appropriate non-inferiority margin is pending to be established. The results can be supported by efficacy and safety data from adults, provided that PK/PD studies in children have identified a proper dose in children to achieve a similar effect on PD endopoints as in adults (see also the start of section 4 about extrapolation). The sponsors are advised to consider analysis methods that capitalise on all available data, for example using statistical modelling (see *CHMP Guideline on clinical trials in small populations: CHMP/EWP/83561/2005*).

b) Secondary prevention of VTE: for secondary prevention, an extension of the study for the initial treatment of VTE (from month 3 until month 6-12) is preferred, but inclusion in a separate study may also be acceptable. Controlled data on a sufficient number of patients at high risk for recurrent VTE, should be presented. If the intended indication is chronic/indefinite use, safety data extending beyond the period of 1 year should be presented. Similar trends in the treatment effect have to be shown across different age subgroups (i.e.: infants, children and adolescents), to support an extension of the indication to the whole paediatric population (see also the start of section 4 about extrapolation).

c) Primary prevention of VTE in children at risk of VTE, including those with indwelling CVCs: Currently, there are no antithrombotic drugs approved for primary prevention of VTE in adult patients with CVCs and evidence from clinical trials is scarce and inconsistent. Clinical practice guidelines generally recommend against routine primary prevention of CVC-related VTE [21]. Therefore, extrapolation to children is not possible nowadays (see also the start of section 4 about extrapolation),

and proof of concept in children needs to be established. It is difficult to anticipate an appropriate sample size to show superiority versus placebo due to little knowledge on the expected rate of primary events, drop-out rate and the treatment effect versus placebo in this population. The study duration should closely mirror the lifetime of the catheter. On the other hand, from an analysis point of view, in the situation of individually differing observation periods, the investigation of the primary endpoint should not be solely based on incidences. The risk of developing an event will clearly depend on the individual observation period, i.e. the lifetime of the catheter. Therefore, investigation of incidences at fixed time points and also time-to-event analyses will contribute to the establishment of the treatment benefits. The exact wording of the label can only be decided after submission and assessment of the trial outcome data.

7. Evaluation of safety

Safety evaluation in paediatric VTE is expected to be generally similar to adults (i.e.: focused on major and clinically relevant non-major bleeding, as well as in related parameters, like blood tests that may indicate blood loss) [1-3].

Additional safety parameters (or endpoints) that are important in long-term anticoagulation trials in children include growth retardation, delays in neuro-motor and neurocognitive development [22] and reduced bone density. It has to bear in mind that most of these outcomes are likely to be driven by the children's underlying diseases. Short-term trials for VTE prophylaxis or treatment are unlikely to detect any effect of anticoagulation on these outcomes. Long-term extensions should be considered.

Definitions of acronyms

BSA: body surface area;

BW: body weight;

CUS: compression ultrasound;

CHD: congenital heart disease;

CTA: computed tomography angiography;

CTV: computed tomography venography;

CVC: central venous catheter;

DVT: deep vein thrombosis;

HC: hormonal contraception;

mSv: milisievert;

LMWH: low-molecular-weight heparin;

MRA: magnetic resonance angiography;

MRV: magnetic resonance venography;

PBPK: physiologically-based pharmacokinetic model;

PD: pharmacodynamics;

PE: pulmonary embolism:

PIP: paediatric investigation plan;

PK: pharmacokinetics;

QOL: quality of life;

sCT: spiral computed tomography;

UFH: unfractionated heparin;

VKA: vitamin K antagonist;

VPLS: ventilation-perfusion lung scan/scintigraphy;

VTE: venous thromboembolism.

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