4 December 2023
EMA/467818/2023
Human Medicines Division

Consolidated 3-year work plan for the Cardiovascular Working Party (CVSWP)

Chairperson: Alar Irs

Vice chair: Patrick Vrijlandt

Work plan period: July 2022 – December 2024 (review priorities 2024)

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

Table of contents

1. Strategic goals

Despite important medical advances over the last few decades, cardiovascular diseases remain a leading cause of death globally and the number one cause of death in the EU. Each year, there are more than 6 million of new cases and over 1.8 million cardiovascular disease related deaths in the EU. All these costs the EU economy over €210 billion a year (according to the European Heart Network statistics).

The Cardiovascular Working Party (CVS WP) aims at playing a role in the prevention and reduction of cardiovascular diseases, diabetes and obesity through supporting the development of new medicinal products in these fields.

Short-term goals

- To release the final *Paediatric addendum to CHMP guidelines on the clinical investigations of medicinal products for the prevention and treatment of thromboembolic disease (EMA/CHMP/20507/2023).*

  A number of EMA guidelines related to clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolism (VTE) are already available, but recommendations are applicable only to adults. In contrast to adults, VTE in children is a rare event, but represents a significant management dilemma that requires therapeutic intervention. A paediatric addendum (PA) to the guidelines on clinical investigation of medicinal products for the treatment and prophylaxis of VTE was considered necessary to discuss and make methodological recommendations adapted to children. The final PA was adopted by the CHMP on 26 January 2023:

  Need for a paediatric addendum of the guideline on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease - Scientific guideline | European Medicines Agency (europa.eu)

- To release the final *Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 2)*

  The Draft Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 2) was published in 2018 for external consultation. It has been decided to consider in the final version of the Guideline (in addition to implementing external comments) if the data requirements with respect to confirmatory studies for certain claims in the wording of the therapeutic indication would benefit from revisions. A Reflection Paper describing this issue was published in May 2022 for 3 months public consultation. The final Guideline was adopted by the CHMP on 22 June 2023:

  https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-prevention-diabetes-mellitus-scientific#current-version---effective-from-01/01/2024-section

- To provide specialised input in cardiovascular, diabetes and obesity fields on request of the CHMP.
- To follow up on initial discussions regarding workshops on innovative approaches in cardiovascular development such as cardiovascular registries, unmet medical need and surrogate endpoints in the CV field.

Long-term goals

- To draft new or to update existing Guidelines in diabetes/obesity and cardiovascular fields:

(1) To release the *Draft Guideline updating the Note on clinical investigation of medicinal products for the treatment of peripheral arterial occlusive disease (CPMP/EWP/714/98 rev.1)* for public consultation.

In the field of peripheral arterial disease (PAD) the CVS WP will aim to ensure that the EMA updated Guideline encompasses all arterial diseases other than coronary arteries and the aorta. So far, the main focus of pharmacotherapy has been on the lower extremity artery disease (LEAD) and this is also reflected in the scope of the current CHMP Note for Guidance. In line with recent clinical guidelines (ESC 21 2017 Guidelines on the Diagnosis and Treatment of PAD) it is proposed to broaden the focus to also discuss interventions in the context of other peripheral arterial diseases, including the carotid and vertebral, upper extremities, mesenteric and renal arteries. Clinical classifications to describe the symptomatic severity of the disease will be further discussed. Endpoints to establish efficacy in different settings will be revised to add clarity, to reflect the value of preventing major adverse limb events when pharmacological therapy is used in conjunction with other treatment modalities, to discuss the acceptable ways of establishing symptomatic benefit or to base the efficacy demonstration on complete ulcer healing or other local endpoints. The concept of estimands will be briefly contextualised in the field of PAD trials. Issues specific to ATMP development for PAD will be covered as there have been recent development programmes in the field of ATMP (cell therapy) which target vasculogenesis, angiogenesis, arteriogenesis and immunomodulation and may possibly aim at limb salvage in addition to symptomatic benefit.

(2) To release the *Concept Paper on the need to revise Paediatric addendum to CHMP Guidelines on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (CHMP/EWP/213972/10)* for public consultation.

An EMA/FDA workshop was organised on 12 June 2017 to discuss the requirements for the development of medicines for pulmonary arterial hypertension (PAH) that address the high unmet medical needs in children. The objectives were to analyse the problems related to the conduct of clinical trials in children with PAH, to refine endpoints and study design, to address the challenges identified, to set priorities for future research, to provide medicine developers with more guidance specific to global product development taking into account current limitations in the development, to investigate potential compatible agreements between regulators and to identify remaining points to be addressed in the next steps. In this context the revision of the Paediatric Addendum for PAH is proposed.

(3) To release the *Concept Paper on the need to revise Paediatric addendum on weight control in children (EMEA/CHMP/EWP/517497/2007)* for public consultation.

In view of the fact that significant time passed since the PA was developed and that the field is active the revision of the PA is proposed. It is planned that the discussion in the updated PA will cover a run-in period and its adequate length, the inclusion criteria to match the end users population, the type of control needed for trials, the recommended primary and secondary endpoints. Safety section and the characteristics of the follow up period will be revised as well.

(4) To release the *Concept Paper on the need to develop the Reflection Paper for evaluation of cardiovascular safety of oncology medicinal products* for public consultation.

In view of growing interest and awareness regarding cardio-oncology field as well as increased number of patients surviving cancer, there is a need for use of harmonized definitions in collection of cardiovascular (CV) toxicity endpoints. Many studies have assessed CV toxicities in patients undergoing various types of cancer therapies; however, direct comparisons have proven difficult due to lack of uniformity in CV toxicity endpoints. CV toxicity sometimes only becomes evident after a large cumulative dose of a drug/metabolite has accumulated in the heart, or it is so rare

that a safety signal requires thousands of patients exposed. In such cases, it will be difficult to delineate the CV safety profile of the new compound for rare events before authorization, and these uncertainties should be managed under the RMP. However, some CV events may be apparent in the short term and/or manifest with common frequency shortly after specific treatments. Therefore, there is a room for improvement in reporting and assessing CV safety outcomes in oncology trials.

- To (co-) organise a workshop on innovative approaches in cardiovascular (CVS) development such as CVS registries and a workshop on unmet medical needs in CVS field.
- To expand connections and links to academic and clinical experts specialising in the CVS/diabetes/obesity fields and to extend collaboration with learned societies in these fields.
- To continue providing specialised input in CVS, diabetes and obesity fields on request of the CHMP or other EMA Committees.
- To review the need for publishing new guidelines/position papers in CVS, diabetes and obesity fields based on SA/PA and qualification procedures and also based on pipeline forecasts in this field.
- To ensure that the innovative methods of outcome measurement are adequately described in guidelines in the field of CVS, diabetes and obesity (including gene-therapy, artificial intelligence based methods and novel methods to measure outcome in rare diseases) to increase patient-centricity.
- To establish the European Specialised Expert Community (ESEC) in cardiovascular/diabetes/obesity field including communication and training strategies.
- To further develop the collaboration with international regulators.

2. Tactical goals: activities/projects to deliver the strategic goals

2.1. Guideline activities

Guideline activities will be performed by one or two Rapporteurs that report back to the CVSWP on a regular basis.

New EU Guidelines:

Paediatric addendum to CHMP guidelines on the clinical investigations of medicinal products for the prevention and treatment of thromboembolic disease (EMA/CHMP/20507/2023)

- Concept paper was released for public consultation in Q42017;
- Draft Addendum was released for public consultation finishing 30 June 2019;
- Final Addendum was adopted by the CHMP on 23 January 2023.

Concept Paper on the need to develop the Reflection Paper for evaluation of cardiovascular safety of oncology medicinal products

- Concept paper to be released for public consultation in 2Q2024;
- To be developed in collaboration with Oncology WP.

Revision of existing EU Guidelines:

Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 2)

- Public consultation of the concept paper ended in 31 Oct 2016;
- Draft guideline was released for public consultation finishing 30 June 2019;
- Reflection paper on data required in confirmatory studies of medicinal products for the treatment of type 2 diabetes was released on 20 May 2022 for a 3 month consultation;
- Final Guideline was adopted by the CHMP on 22 June 2023.

Paediatric addendum to CHMP Guidelines on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (CHMP/EWP/213972/10)

- Concept paper was released for public consultation until 30 September 2023;
- Draft PA to be released in Q4 2024;
- To be developed in collaboration with PDCO.

Note on clinical investigation of medicinal products for the treatment of peripheral arterial occlusive disease (CPMP/EWP/714/98 rev.1)

- Concept paper released for public consultation until 30 June 2019;
- First draft to be released in 2Q2024.

Paediatric addendum on weight control in children (EMEA/CHMP/EWP/517497/2007)

- Concept paper to be released for public consultation in 2Q2024;
- To be developed in collaboration with PDCO.

2.2. Training activities

- The CVSWP will ensure collaboration with EuNTC considering assessor training when new guidelines in CVS/diabetes/obesity fields are released.
- To develop in collaboration with EuNTC and deliver training on *Paediatric addendum to CHMP guidelines on the clinical investigations of medicinal products for the prevention and treatment of thromboembolic disease (EMA/CHMP/20507/2023).*
- To continue the cooperation with the ESC and other learned societies in the field is an opportunity for the members of the WP to increase their knowledge of the work done by Academia and Industry in CVS, diabetes and obesity fields (e.g. participation in CVS Round tables of the ESC).

2.3. Communication and Stakeholder activities:

- Contribution to IMI calls and projects
- Contribution to the ICH Guidelines

- Collaboration with other regulatory authorities in particular: FDA, HC and PMDA (on average 3 TC/year with FDA and HC to exchange experience cardiovascular, diabetes and obesity fields)
- Interaction with interested parties e.g., learned societies (e.g. European Society of Cardiology [ESC], European Association for the Study of Diabetes [EASD], Association for European Paediatric and Congenital Cardiology [AEPC]) under the supervision of the CHMP (e.g. CVS WP involvement in workshops organised by the CVS Round Table of the ESC)

2.4. Multidisciplinary collaboration

- Real World Evidence/Real World Data (RWE/RWD):
  - Discuss the currents strengths and limitations of RWE/RWD
  - Analyse the requirements for use of RWE/RWD to be used in regulatory decision-making in cardiovascular, obesity and diabetes.
  - Co-organisation of a dedicated workshop on CVS registries
- New methodologies to measure and define clinical endpoints (including gene-therapy, artificial intelligence based methods and novel methods to measure outcome in rare diseases):
  - reflection on the need to update guidelines or propose reflection papers in CVS/diabetes and obesity fields
  - contribution to a workshop organised by the ESC regarding Unmet Medical Needs
- Contribution to the *draft* Reflection paper on regulatory requirements for the 4 development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH). (EMA/CHMP/299976/2018)

Leading Group: Gastroenterology Drafting Group

- Contribution to the *draft Guideline on multiplicity issues in clinical trials (EMA/CHMP/44762/2017)*

Leading Group: Methodology Working Party (MWP)

- On request of the CHMP providing responses to queries in the field of CVS/diabetes and obesity.

3. Operational goals: medicinal product-specific activities

The CVSWP will provide product-related support upon request from Committees, CMDh and SAWP.

Priorities for 2024

4. Guidelines

4.1. EU Guidelines

Action: Lead

Paediatric addendum to CHMP Guidelines on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (CHMP/EWP/213972/10)

Target date
- Concept paper was released for public consultation until 30 September 2023;
- Draft Addendum to be released for public consultation in 4Q2024.

Comments Developed in collaboration with Paediatric Committee (PDCO)

Action: Lead

Note on clinical investigation of medicinal products for the treatment of peripheral arterial occlusive disease (CPMP/EWP/714/98 rev.1)

Target date
- Concept paper released for public consultation until 30 June 2019.
- Draft guideline to be released for public consultation 2Q2024

Comments N/A

Action: Lead

Paediatric addendum on weight control in children (EMEA/CHMP/EWP/517497/2007)

Target date Concept paper to be released for public consultation in 2Q2024.

Comments To be developed in collaboration with PDCO.

Action: Lead

Reflection paper for evaluation of cardiovascular safety of oncology medicinal products.

Target date
- Concept paper to be released for public consultation 2Q2024

Comments To be developed in collaboration with Oncology WP.

5. Training for the network and knowledge building

- Contribute to assessor trainings organised by EU network Training Centre (EU NTC).
- Maintain awareness of issues arising in order to identify the need for review and update of Guidelines and development of additional guidance documents.

6. Contribution to dialogue and engagement with stakeholders and external parties

6.1. Workshops

- Participate in the European Society of Cardiology (ESC) CVS Round Table (CRT) Workshops on the topics relevant for the WP.
- Follow up on the workshop on "Unmet medical needs" co-organised with CRT of the ESC that took place on 21 and 22 November 2023.

6.2. Collaboration with Interested parties and other stakeholders

- Consultation with external stakeholders with regards to Guidelines under development.
- Engagement and interactions with learned societies (e.g. European Society of Cardiology (ESC), Association for European Paediatric and Congenital Cardiology (AEPC), European Association for the Study of Diabetes [EASD]) and other expert communities in the field of CVS, diabetes and obesity.
- Contribution to the establishment and leadership for activities of European Specialised Expert Community (ESEC) - Cardiovascular Diseases in line with the mandate adopted by the CHMP.

7. European collaborations

None

8. International activities

Regular teleconferences with regulators FDA, HC, PMDA, TGA to exchange experience in CVS, diabetes and obesity fields