



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

21 July 2016  
EMA/CHMP/259918/2016  
Committee for Medicinal Products for Human Use (CHMP)

## Concept paper on the need for revision of the guideline on the clinical development of medicinal products for the treatment of cystic fibrosis (CHMP/EWP/9147/08)

|                                                     |                 |
|-----------------------------------------------------|-----------------|
| Agreed by Respiratory Drafting Group                | 29 April 2016   |
| Agreed by PDCO                                      | 17 May 2016     |
| Adopted by CHMP for release for public consultation | 21 July 2016    |
| Start of public consultation                        | 1 August 2016   |
| End of consultation (deadline for comments)         | 31 October 2016 |

The proposed guideline will replace 'Guideline on the clinical development of medicinal products for the treatment of cystic fibrosis EMA/CHMP/EWP/9147/2008-corr

Comments should be provided using this [template](#). The completed comments form should be sent to [RespiratoryDG@ema.europa.eu](mailto:RespiratoryDG@ema.europa.eu)

|          |                                                                                                                                                                                         |
|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Keywords | <b><i>Cystic fibrosis, CFTR defect, CFTR modulators, pulmonary disease, exacerbations, exocrine pancreatic insufficiency, paediatric population, biomarkers, clinical endpoints</i></b> |
|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|



## 1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the gene encoding for the CF transmembrane conductance regulator (*CFTR*), a protein that acts as a chloride channel. More than 2000 mutations in the *CFTR* gene have been identified for CF, with the deletion of phenylalanine at position 508 of *CFTR* (F508del) being the most common.

The defect of chloride and sodium transport results in viscous secretions in different exocrine tissues mainly the respiratory tract, pancreas gastrointestinal tract, sweat glands and other exocrine tissues. Increased viscosity makes secretions difficult to clear and patients develop progressively exocrine gland dysfunction of multiple organ systems in childhood, resulting in chronic respiratory disease as well as other pathologies including pancreatic insufficiency, obstructive hepatic and biliary abnormalities, distal intestinal obstruction syndrome, and reduced fertility (agenesis of the vas deferens in males, delayed menarche and thick cervical mucus in females). The lower respiratory tract involvement is characterised by progressive bronchiectases and obstructive pulmonary disease in more than 90% patients, and it is the primary cause of morbidity and mortality in patients with CF.

## 2. Problem statement

At the time when the current guideline was adopted, medicinal products were developed for either the management of the pulmonary disease or the pancreatic exocrine insufficiency associated with CF and, as a consequence, the guideline is mainly focused on these clinical situations. However, the knowledge of the genetic principles and other recent developments in the field of CF has provided huge insight into the pathophysiology of the disease. There are elements in the current guideline which are outdated based on these recent advances.

A number of *CFTR* modulators are currently either under development or have been recently authorised. This has represented a shift in the therapeutic understanding of CF treatment from the symptomatic treatment towards a disease modifying approach. The clinical trial design, choice of comparator, duration, endpoints etc. in the existing guideline may not be adequately covered for all clinical developments.

Furthermore, such new treatments offer the prospect of early intervention to prevent the progression of the disease and so clinical trials are expected to be performed progressively in younger children. However, although not all clinical outcome measures are feasible in young children, no reference is made in the current guideline to clinical endpoints that would be relevant to this young population. Further, there is no detailed discussion of the potential for extrapolation between different age groups.

The understanding of the *CFTR* mutations is critical for the design and the development of target therapies for CF. However, sufficient guidance is not provided in the current guideline. Given that the CF phenotype is highly heterogeneous, it is relevant for an adequate interpretation of efficacy and safety data that the patient populations are well characterised in terms of disease characteristics and prior CF related morbidity and concomitant medications. The progress in the management of the CF patients has improved the prognosis considerably with patients living longer. These positive effects also raise the expectations for future treatments. In addition, this makes it challenging to use historical control or published literature for inferring the benefits of new treatments.

Finally, biomarkers are only described in a very general way despite several biomarkers having been identified or are under assessment that could become useful to individualise treatment or to assess therapeutic effects. These merit more detailed discussion.

### 3. Discussion (on the problem statement)

The following items have been identified and would need to be addressed in the revised guideline:

- The current guideline (EMA/CHMP/EWP/9147/2008-corr) is outdated and would benefit from an update, simplification and restructuring according to the new template.
- The scope of the guideline needs to be widened to cover newer drug classes and mechanisms of action.
- Potential study designs, use of comparators (placebo, active), biomarkers and endpoints considering recent clinical trial experience, regulatory assessments and scientific advice procedures will be discussed. Definition of pulmonary exacerbation will be updated in line with recent scientific discussions.
- There is a need to improve quality of the baseline data to be collected for CF patients as this is essential for a robust efficacy assessment. The following items will be discussed in the guideline as part of baseline data: *CFTR*-mutations, concomitant medications, age at diagnosis, prior pulmonary disease, prior gastrointestinal disease, CF-related comorbidities.
- More than 2000 *CFTR* mutations have been identified but only very few have been characterised in terms of the defect they cause or in terms of whether they are disease-causing. Since it is virtually impossible to study all of them in clinical trials, the appropriateness of extrapolating data across different mutations within a certain class needs to be discussed in the revised guideline.
- As CF affects children since birth, early treatment is desirable and, therefore, it is particularly relevant to address specific issues related to this population. For example, most young children have well preserved lung function and normal anthropometric measurements and therefore, the clinical endpoints suitable for older children and adults would not be adequate for such young children.
- The feasibility of extrapolating between different age groups needs to be discussed in the revised guideline.

### 4. Recommendation

The Respiratory drafting group recommends revising the current guideline on CF taking into account the issues identified above.

### 5. Proposed timetable

This CP will be released in August 2016 for 3 month public consultation, ending 31 October 2016. Following this it, is planned to release the draft Guideline for 6 month public consultation in October 2017, ending in April 2018. Following the receipt of comments, the guideline will be finalised within approximately 6 months and published in 4Q 2018.

### 6. Resource requirements for preparation

The update of the guideline will involve representatives of Member States from the Respiratory drafting group and it should be discussed in their meetings. Consultation with other working parties or committees (e.g. PDCO) will be initiated as appropriate.

## 7. Impact assessment (anticipated)

The document is intended to provide guidance on clinical development programmes for the treatment of CF. In addition, it will be useful to reach a common approach for the assessment of these products and scientific advice given by European regulatory authorities.

## 8. Interested parties

Healthcare professionals, pharmaceutical industry, patient organisations, European learned societies involved in CF research, education and care.

## 9. References to literature, guidelines, etc.

- Mayer-Hamblett N, Boyle M, VanDevanter D. Advancing clinical development pathways for new CFTR modulators in cystic fibrosis. *Thorax* 2016; 71:454–461.
- De Boeck K, Wilschanski M, Castellani C, Taylor C, Cuppens H, Dodge J, et al. Cystic fibrosis: terminology and diagnostic algorithms. *Thorax* 2006; 61:627–35
- Smyth AR et al. European Cystic Fibrosis Society Standards of Care: Best Practice guidelines. *Journal of Cystic Fibrosis* 2014; 13: S23–S42.
- Bodewes F et al. Cystic fibrosis and the role of gastrointestinal outcomes measures in the new era of therapeutic CFTR modulation (Review). *Journal of Cystic Fibrosis* 2015; 14:169-177
- Guideline on the clinical development of medicinal products for the treatment of cystic fibrosis (CHMP/EWP/9147/08)  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/12/WC500017055.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500017055.pdf)
- Reflection paper on extrapolation of efficacy and safety in paediatric medicine development (EMA/199678/2016).  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2016/04/WC500204187.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/04/WC500204187.pdf)
- Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. Doc. Ref. EMEA/CHMP/EWP/147013/2004 Corrigendum.  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003066.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003066.pdf)
- ICH Topic E 11. Clinical Investigation of Medicinal Products in the Paediatric Population.
- Guideline on clinical trials in small populations (CHMP/EWP/83561/2005).  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003615.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf)
- Wagener S et al. Pulmonary function outcomes for assessing cystic fibrosis care. *J Cyst Fibros* 2015; 14 (3): 376–383
- De Simpson SJ et al. Novel end points for clinical trials in young children with cystic fibrosis. *Expert Rev Respir Med* 2013; 7(3):231-43

- 132 • De Boeck K. Guideline on the design and conduct of cystic fibrosis clinical trials: The European  
133 Cystic Fibrosis Society–Clinical Trials Network (ECFS-CTN). *Journal of Cystic Fibrosis* 2011; 10 (2):  
134 S67–S74
- 135 • Tiddens H et al. Novel Outcome Measures for Clinical Trials in Cystic Fibrosis. *Pediatric*  
136 *Pulmonology* 2015; 50:302–315