16 February 2026
EMA/21378/2026
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the clinical investigation of medicinal products for the treatment of cystic fibrosis

Draft

Draft agreed by RIWP and IDWP	October 2025
Adopted by PDCO for release for consultation	January 2026
Adopted by CHMP for release for consultation	February 2026
Start of public consultation	01 March 2026
End of consultation (deadline for comments)	31 August 2026

This guideline replaces '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 EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	***Antibiotic, Antisense oligonucleotide, CFTR-modifier, CFTR modulator, cystic fibrosis, CF-related liver disease, CF-related diabetes, exocrine pancreas insufficiency, gene-targeting therapies, mRNA, nutritional status, paediatrics, pancreatic enzyme replacement therapy, Pseudomonas aeruginosa, pulmonary function, vector-based gene therapy***

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Tabulated list of abbreviations

Abbreviation	Term
AON	Antisense oligonucleotide
BMI	Body mass index
CF	Cystic fibrosis
CFA	Coefficient of Fat Absorption
CFLD	Cystic fibrosis related liver
CFQ-R	Cystic fibrosis questionnaire-revised
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CFU	Colony Forming Units
CT	Computed tomography
DDI	Drug drug interaction
EPI	Exocrine pancreatic insufficiency
EU	European Union
FC	Faecal calprotectin
FE-1	Faecal elastase-1
FEF	Forced Expiratory Flow
FEV1	Forced expiratory volume during one second
FVC	Forced Vital Capacity
GI	Gastrointestinal
GLI	Global Lung Function Initiative
HRQoL	Health-related quality of life
ICE	Intercurrent event
IMP	Investigational medicinal product
IRT	Immunoreactive trypsinogen
LCI	Lung clearance index
MAA	Marketing authorisation application
MAR	Missing at random
MCC	Mucociliary clearance
MNAR	Missing not at random
MRI	Magnetic resonance imaging
MUAC	Mid-upper arm circumference
PAES	Post-authorisation efficacy study
PA	*Pseudomonas aeruginosa*
PASS	Post authorisation safety study
PBPK	Physiologically based PK
PD	Pharmacodynamic
PE	Pulmonary exacerbation
PEP	Primary efficacy endpoint
PERT	Pancreatic enzyme replacement therapy
PET	Positron emission tomography
PFT	Pulmonary function test
PIP	Paediatric investigation plan
PK	Pharmacokinetic
ppFEV1	percentage of the predicted value FEV1
PPI	Proton pump inhibitor
PRO	Patient reported outcome
pwCF	People with CF
SmPC	Summary of Product Characteristics
SoC	Standard of care
SwCl	Sweat Chloride

Executive summary

This document is the first revision of the Guideline on clinical development of medicinal products for the treatment of cystic fibrosis (EMEA/CHMP/EWP/9147/2008-corr).

The main purpose of this revision is to address:

- the development of new medicinal products which mechanism of action allows restoring, at least partially, functional Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein, thus allowing the granting of a general indication of "treatment of cystic fibrosis (CF)" when the route of administration is systemic. They are referred to under the new generic term of CFTR-modifiers. The previous version was focusing on specific organ/system indications for symptomatic medicinal products.
  CFTR-modifiers encompass CFTR modulators (aiming at correcting trafficking or gate defects associated with a specific mutation of the CFTR gene) and products aiming at restoring the synthesis of functional CFTR proteins. The latter include mRNAs and gene-targeting therapies, i.e., therapies aiming at modifying the genome expression by acting on the DNA and that comprise vector-based gene therapies and antisense oligonucleotides (AONs).
  Specific issues associated with the development of CFTR-modifiers include the comparator, null hypothesis, treatment duration and the desirable endpoints for a general CF indication;

- the accumulated regulatory experience with CFTR modulators, that allows making specific recommendations on designs for confirmatory trials depending on the genotype of the target population. Whenever relevant, consideration is given to the respective weight of non-clinical and clinical data and extrapolation exercise across mutations;

- the subsequent changes in paradigm associated with the generalisation of combination therapy with CFTR modulators of complementary mechanisms of actions led to critical changes in the disease progression and features:
  - CFTR modulators combination therapy allows slowing disease progression and motivates treating people with CF (pwCF) as soon as possible. The treatment of pre-or pauci-symptomatic young children with CF is now part of routine clinical practice. The updated Guideline provides recommendations for use of the specific pharmacodynamic lung clearance index (LCI) as primary efficacy endpoint (PEP) in the paediatric population in whom the percentage of predicted value of Forced expiratory volume in one second (ppFEV1) is not a sensitive efficacy measure to detect the pulmonary disease before 12 years of age. Along the same lines, specific gastrointestinal outcomes measurements are needed to prove efficacy in patients up to 6 years of age, in whom pancreatic insufficiency may be present at an infra-clinical level with uncertain room for improvement due to the early administration of CFTR modulators combination therapy and possible recovery until 6 years of age.
  - Conducting a successful confirmatory trial for symptomatic medicinal products such as muco-active or anti-inflammatory medicinal products or bronchodilators as add-on to a CFTR modulators regimen would likely not be achievable any longer, considering the marginal added symptomatic improvement in respiratory function and the intrinsic beneficial effect on mucus production of CFTR modulators. Specific sections on these classes of medicinal products, previously with a significant place in the guideline, are no longer included in this updated version.
  - Updated recommendations are provided for the clinical development of new antibacterial medicinal products/new route of administration/new dosing regimen. Both for early eradication and for suppressive therapy of lung chronic infection, recommendations now focus on *Pseudomonas aeruginosa* (PA).

- This update also groups recommendations on products aiming at improving the nutritional status, depending on whether a specific defect is targeted (e.g., pancreatic insufficiency) or whether a general claim of improvement in growth is pursued.

1. Introduction (background)

Cystic fibrosis (CF) is a rare genetic autosomal recessive disease most often presenting from birth or in infancy. Prevalence in the European Union (EU) is difficult to ascertain as it varies significantly across countries (*Farrell 2008*), with an average prevalence > 1:10,000 (*Orphanet 2020*). The disease is caused by the presence of 2 mutations in both alleles of the gene encoding for the CF transmembrane conductance regulator (CFTR) protein, a chloride and bicarbonate ion channel expressed at the surface of epithelial cells. The resulting ion transport defect results in impaired secretion of chloride and bicarbonate and a multisystem disease affecting lungs, the pancreas, the intestinal tract, the liver, and reproductive organs.

More than 2000 mutations in the *CFTR* gene have been described (*Veit & al. 2016; CFTR2 mutations database*), not all of which being CF-causing mutations, and some being associated with wide variations in the severity of the clinical presentation, if any. The CF-causing CFTR mutations are usually divided into six functional classes reflecting their associated main impaired pathway. Class I leads to total absence of CFTR protein and is associated with the most severe phenotype. Class II and class III mutations are associated with minimal to no CFTR function and usually a more severe phenotype. Class IV, V and VI mutations maintain residual CFTR function and are usually associated with a milder phenotype.

F508del (class II) is the most common mutation world-wide; approximately 40-50% pwCF are homozygous for the F508del mutation and an additional 30-40 % carry a *F508del* mutation on one allele only, resulting in approximately 80% of pwCF being candidate to therapies targeting the most common *F508del* mutation (*Veit & al. 2016; Bell & al. 2020*).

There has been over the past years a remarkable increase in life expectancy due to improvement in the standard of care (SoC), including targeted treatment with CFTR modulators. CFTR modulators are small molecules that bind to defective CFTR proteins (hence not active for class I mutations) and partially restore their function through an activity specific of a given impaired cellular pathway and are therefore mutation specific. CFTR modulators are usually divided into correctors and potentiators. Correctors facilitate the cellular processing and trafficking of class II mutant forms of CFTR to increase the amount of functional CFTR channels at the apical cell surface. Potentiators increase the channel opening probability (channel gating activity) of class III and IV mutated CFTR channels already at the apical membrane to enhance chloride transport (*Meoli & al. 2021*).

In the EU, various CFTR modulator therapies have been approved, either as monotherapies or as combination therapies of CFTR correctors and a CFTR potentiator. Clinical trials are currently running with vector-based gene therapies, antisense oligonucleotide (AON) and mRNA under development.

2. Scope

This document replaces the Guideline on clinical development of medicinal products for the treatment of cystic fibrosis (EMA/CPMP/EWP/9147/2008-corr*) which came into effect in April 2010. Guidance is provided on the clinical development of medicinal products in view of registration in the EU with the product information specifying a CF indication.

While the previous version of the Guideline was focusing on specific organ/system indications for symptomatic medicinal products, this revision is a major update introducing recommendations for the

development of new medicinal products which mechanism of action allows restoring, at least partially, functional CFTR protein. They are referred to under the new generic term of CFTR-modifiers and encompass CFTR modulators (aiming at correcting trafficking or gate defects associated with a specific mutation of the CFTR gene) and products aiming at restoring the synthesis of functional CFTR proteins. The latter include mRNAs and gene-targeting therapies, i.e., therapies aiming at modifying the genome expression by acting on the DNA and that comprise vector-based gene therapies and AONs.

CFTR modifiers are meant to be disease modifiers and will need to be developed for administration as early as possible in pwCF. This revision introduces specific recommendations related to the development in children below 12 years of age who may be pauci-symptomatic.

Significant revisions are introduced on the development of symptomatic medicinal products due to the introduction of CFTR modulators as part of the SoC for the vast majority of pwCF (all except class I mutations):

- Specific sections on bronchodilators, muco-active or anti-inflammatory medicinal products are no longer included in this updated version. It is at present unlikely that a successful confirmatory trial can be conducted with as add-on to CFTR modulators.
- Pulmonary exacerbations (PE) have become too rare an event to be a recommended primary efficacy endpoint in the assessment of CF lung disease any longer.
- Updated recommendations are provided for the clinical development of new antibacterial medicinal products/new route of administration/new dosing regimen adapted to the evolving landscape of pulmonary infections in pwCF.

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, and all other relevant EU and ICH guidelines. These include, but are not limited to:

Pharmacokinetics / Pharmacodynamics (PK/PD)

- ICH E4 Dose response information to support drug registration (CPMP/ICH/378/95)
- Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products (EMA/CHMP/594085/2015)
- ICH M15 guideline on general principles for model-informed drug development – Step2b (EMA/CHMP/ICH/496426/2024)
- Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (EMA/CHMP/458101/2016)
- Reporting the Results of Population Pharmacokinetic Analyses (CHMP/EWP/185990/06)
- Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**).

Paediatric development

- ICH E11(R1) Guideline on clinical investigation of medicinal products in the paediatric population (EMA/CPMP/ICH/2711/1999).
- Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004),

- Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004 Corrigendum).
- Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/1897724/2018).
- ICH guideline E11A on paediatric extrapolation (EMA/CHMP/ICH/205218/2022)

Methodology and statistics

- Guideline on clinical trials in small populations (CHMP/EWP/83561/2005).
- ICHE9 (R1) Addendum on estimands and sensitivity analysis in clinical trials (EMA/CHMP/ICH/436221/2017)
- Guideline on the choice of a non-inferiority margin (CPMP/EWP/2158/99).
- Guideline on Registry-based studies (EMA/426390/2021).

ATMPs

- Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014)
- Guideline on follow-up of patients administered with gene therapy medicinal products (EMEA/CHMP/GTWP/60436/2007)
- Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products (EMEA/149995/2008)

General clinical principles

- Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017)
- ICH E1 Population exposure: the extent of population exposure to assess clinical safety (CPMP/ICH/375/95)
- Reflection paper on the regulatory guidance for the use of Health-Related Quality of Life (HRQL) measures in the evaluation of medicinal products (EMEA/CHMP/EWP/139391/2004).
- ICH E19 selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials (EMA/782210/2022)

4. Patient selection

4.1. Diagnosis of cystic fibrosis

For screening purposes of pwCF, the diagnosis of cystic fibrosis should be documented based on internationally agreed diagnostic criteria developed and published by professional bodies, i.e., sweat chloride test plus genotyping. (*Farrell & al. 2017*). Neonatal screening is widely implemented in most EU Member States.

For inclusion of pwCF in clinical trials, diagnosis should be confirmed based on clinical signs and symptoms in one or more organ systems, elevated sweat chloride ≥ 60 mmol/L and genetic diagnosis of two identified CF-causing mutations (*De Boeck & al. 2017, Castellani & al. 2018)*.

In less than 5% of pwCF, mainly with a milder phenotype, the diagnosis might be more complex i.e., sweat chloride is within the intermediate range (30-59 mmol/L) and/or patients have only one identified CF causing mutations, and such patients are classified as having either CF or a CFTR-related disease, depending on the phenotype. The development of a product in patients with CFTR-related disease is not within the scope of this Guideline.

4.2. Age of study population

Although CF remains a fatal condition, with lung disease being the major cause of morbidity and mortality, significant improvement in survival has been achieved in the past decades, with a global life expectancy over 50 years of age in 2020 (*Bell & al. 2020*). As a result, the demographic characteristics of the CF population have dramatically changed, and CF is no longer a pure paediatric disease, adults representing 50-60% of patients in countries with well-established CF care.

The prevalence of the various CF symptoms is genotype- and age-dependent. In genotypes associated with a severe phenotype, some gastrointestinal (GI) symptoms of CF can be present at birth while other symptoms, including respiratory symptoms, will develop during childhood and adulthood because of the long-standing CFTR dysfunction with associated fibrosis. Some genotypes are associated with a milder phenotype, with sometimes symptoms appearing only in adulthood.

4.3. Baseline characteristics of the study population

At baseline, the study population should always be characterised by *CFTR* genotype, sweat chloride, and lung function.

Additional baseline characteristics should:

- define the specificities of the study population that are reflective of the target population to support the pursued indication;
- allow an assessment of a medicinal product effect on outcomes specific of the medicinal product's target organ(s)/system(s), depending on its specific mechanism of action (e.g., baseline respiratory function and/or baseline pancreatic function parameters);
- allow an assessment of the subject overall health status using global measures when they are part of secondary or exploratory endpoints, e.g., anthropometric parameters, quality of life scores.

5. Assessment of efficacy

5.1. Treatment goals and associated specific CF indications

1. Medicinal products improving signs and symptoms of specific organs/functions

a) Antibacterial agents

Two possible indications relate to the carriage outside the frame of a pulmonary exacerbation:

i) Eradication of acute lung infection (to delay the establishment of chronic lung infection) and

ii) Suppressive treatment of chronic lung infection (to decrease the bacterial burden when eradication is no longer achievable).

b) Pancreatic enzyme replacement therapy (PERT)

Depending on whether either only the digestive function or the overall beneficial consequences of the correction of maldigestion are assessed, two indications may be pursued:

i) "Treatment of exocrine pancreatic insufficiency"

ii) "Improvement in nutritional status and growth"

In case other CF indications are considered, the Applicant is highly recommended to seek feedback from the CHMP through a scientific advice request.

2. CFTR-modifiers

CFTR modifiers aim at restoring the defective CFTR function. They act by either correcting the CFTR protein defect (CFTR modulators), or by restoring the synthesis of CFTR, i.e., gene-targeting therapies (including vector-based gene therapy and AONs) and mRNAs.
Depending on the mechanism of action and route of administration, related claims may be:

i) either a general indication of "Treatment of CF",

ii) or an organ-specific CF indication, depending on the route of administration (e.g., lung function for an inhaled gene therapy).

5.2. Methods to assess efficacy

5.2.1. Microbiological assessment of the lung

Sputum (spontaneously expectorated or induced) is the preferred specimen to assess the bacteriological burden through cultures. There exist protocols applicable to infants for induced sputum collection.
If sputum cannot be collected (e.g. young children), oropharyngeal swabs are acceptable as sampling method. Oropharyngeal swabs may however not fully reflect the lower airway microbiota as compared to sputum samples and may not be appropriate for culture of mycobacterial and fungal organisms (*Eyns & al. 2018; De Bel & al. 2013*).

In early colonisation, microbiological eradication is defined by at least 3 consecutive negative cultures, one at end-of-treatment followed by at least two subsequent negative cultures, starting at least 1-2 weeks post-treatment and with an at least 2–4-week interval between the following ones. The final culture used to declare eradication should not be obtained earlier than 4 weeks following end-of-treatment. Other definitions may be acceptable provided they are adequately justified.

Demonstration of sustained eradication requires a more prolonged follow-up of at least 6 to 12 months post end-of-treatment. Failure to eradicate may be the result of a recurrence of infection with the initial infecting agent (relapse) or infection with a new strain of the same bacterial species (reinfection). No single consensus definitions exist on corresponding intervals between last eradication and recurrence for respectively relapse and reinfection, and Applicants are recommended to thoroughly predefine these terms in the protocol if recurrence is part of the efficacy endpoints. Assessment of recurrence is made through regular monitoring over 6 months following end-of-treatment and is evidenced by a positive culture during this 6-month period that follows the demonstration of eradication by the ≥ 3 negative cultures at the end of the treatment period.
In chronic infection, the decrease of the bacterial burden of the lung is preferably assessed in sputum and should be expressed as Colony Forming Units (CFU).

It is recommended that a detailed laboratory manual is provided, covering and standardising i) respiratory sample collection methods, including the protocol to obtain induced sputum; ii) samples handling, storage and transport conditions; iii) laboratory handling and initial processing (e.g. specifying sputum digestion methods if used); and iv) culture methodologies, including methods for quantification and assessment of the presence of multiple sub-species, which may vary in colony characteristics. Only suitably experienced laboratories should be used.

Additional testing, such as genetic analysis to differentiate baseline from post-baseline strains, and susceptibility testing (which would be part of exploratory endpoints) should be conducted at a central laboratory on shipped primary isolates.

5.2.2. Assessment of respiratory function

5.2.2.1. Pulmonary function tests

Pulmonary function tests (PFTs) are being used for assessing the lung disease severity and progression in pwCF. Any claims of improvement in signs and symptoms related to lung disease should be supported by the results of the PFTs.

The following measurement tools can be used to investigate the effects on respiratory function:

Forced expiratory volume during one second (FEV1)

FEV1, as measured by spirometry, is the most widely used standardised outcome measure for the monitoring of respiratory function in adults with CF. FEV1 assesses principally large airways function. It is a clinically meaningful endpoint as it has been demonstrated to be correlated to exacerbation rate and repeatedly shown to be a predictor of survival.

FEV1 is usually expressed as a percentage of the predicted value (ppFEV1), i.e., standardised through correction for gender, age, height and ethnicity.

Forced Expiratory Flow between 25 to 75% (FEF25%-75%) and Forced Vital Capacity (FVC) are additional spirometry parameters meaningful to follow the respiratory function in pwCF.

However, spirometry requires active contribution from the patient and thus usually cannot be performed in children younger than 6 years of age.

Bronchodilator therapy should be temporarily withdrawn before performing spirometry. The timeframe for withholding bronchodilator therapy should be clearly pre-specified in the trial protocol, using Global Lung Function Initiative (GLI) reference equations recommended by the American Thoracic Society and European Respiratory Society unless appropriately justified *(Graham & al 2019).*

Lung clearance index (LCI)

Lungs develop from birth to puberty. Large airways grow steadily, while peripheral smaller airways and alveoli develop in a more exponential manner up to 14 years. In contrast to FEV1 that measures large airway function, LCI is PD parameter assessing primarily the function of smaller, peripheral airways. Since CF disease affects in a first instance small peripheral airways before large airways are damaged, LCI is the most sensitive tool to measure lung function in young children up to 6 years (who are asymptomatic or poorly symptomatic from a respiratory viewpoint), and in older children (usually 6-12 years) in whom CF has started deteriorating the peripheral airways but not yet sufficiently the large airways to be detected by FEV1 (refer to Section 8). Although LCI is not a validated surrogate for direct assessment of the respiratory function status, there is a clear rationale and a significant amount of supportive data to justify its use in paediatric CF trials (*Lombardi et al, 2019*), and it is accepted as primary efficacy endpoint in paediatric pivotal trials. In young children below 2 years of age, some challenges need to be considered when using LCI as an efficacy outcome measurement in clinical studies *(Lee & al 2025*).

The most frequently used metric is LCI2.5, defined as the number of lung turnovers required to washout a tracer gas (either air or pure O2), to 2.5% of the initial starting concentration. LCI5.0 is sometimes used (*Sandhu & al. 2023*).

Standardisation of the equipment, training of personnel and a standardised protocol detailing the conditions under which LCI should be performed are needed. A centralised blinded (when applicable) readout of the LCI measurements should be implemented.

5.2.2.2. Pulmonary exacerbation (PE)

PwCF may experience PE, i.e., acute worsening of respiratory symptoms. Because there is no universal definition of PE, the use of (rate of or time to first) PE as an efficacy endpoint in clinical trials requires that its definition is pre-specified in the study protocol. PE may be defined using different approaches, such as event-driven definitions (e.g. need for IV antibiotics and/or hospitalisation) and symptom-driven definitions based on predefined scoring systems. Applicants should pre-specify and justify the chosen approach in the protocol and SAP, taking into account age (e.g., children versus adult patients as the use of intravenous antibiotics in the former is less common), disease severity, background CFTR modulator use and the expected PE rate. Where event-driven definitions are used, consideration should be given to the potential influence of local practice patterns (e.g. thresholds for IV therapy or hospitalisation). Symptom-based tools should be standardised, validated where possible, and applied consistently across sites.

5.2.2.3. Thoracic imaging

Structural lung changes occur over time in pwCF and start well before the onset of pulmonary symptoms, first with small peripheral airways, then larger airways. These morphological changes may be sensitive to medicinal products aiming at restoring a level of CFTR function and slowing disease progression. Thoracic imaging techniques such as high-resolution computed tomography (CT), magnetic resonance imaging (MRI) or positron emitting tomography (PET) scan are relevant tools to assess morphological changes of the lung parenchyma over time. However, there is no established correlation between thoracic images and a clinically meaningful outcome. The decision to use a CT scan as a longitudinal assessment of the disease status should balance the expected advantage versus the anticipated life-long cumulative radiation exposure. In this chronic disease, the radiation dose per CT scan should be kept as low as possible.
It is recommended to standardise the imaging protocols in the clinical trials and to document intra-observer reliability, especially if a semi-quantitative CT scoring system is used Central reading is recommended, especially in confirmatory trials i.e., with 2 primary readers plus an adjudicator or another validated procedure ensuring a robust, unbiased assessment.

5.2.3. Assessment of exocrine pancreatic insufficiency and malabsorption

5.2.3.1. Coefficient of fat absorption/steatorrhea

Measurement of steatorrhea is the standard method to assess the extent of fat malabsorption.
The gold standard test to measure steatorrhea is the 72-hour fat balance method with the calculation of a Coefficient of Fat Absorption (CFA-72h) (*Dorsey et al. 2010*).

CFA should be expressed as a percentage of fat intakes (at least 30 and up to 100g of fat per day).

The CFA should be determined based on an individualised high-calorie and high-digestible fat diet as recommended in experts' consensus on CF nutrition (*Turck et al. 2016*). Standardisation of the individual patient's specific high digestible fat and protein diet is mandatory (on a per patient basis depending on the observed acceptability of the diet) to limit variability and allow between-arm fair comparisons in a clinical trial. Detailed diet instructions and adherence checks are expected in the

protocol and site manual. The actual amount of digestible fat and protein intake should be recorded during the course of the trial.

The CFA can be adequately performed in most centres, even though it requires high quality carefully conducted faecal fat balance studies.
In infants, toddlers and young children, CFA may be difficult to perform and requires specialised laboratories. A central laboratory is recommended.

5.2.3.2. Complete assessment of nutritional status

A complete assessment of the nutritional status is requested when improvement in nutritional status is part of trial objectives. It should be based on:

- anthropometric measures using established criteria e.g. height, weight and body mass index (BMI).
- growth parameters by gender in growing populations, expressed as Z-scores for weight, height and BMI, as well as weight for age and weight for length. For a correct interpretation of the results, simultaneous assessment of changes in dietary intakes (assessed by appetite and dietary diary), in digestion and in catabolism, as measured by resting energy expenditure or inflammatory markers is required (*Stallings & al. 2018*).
- Body composition measurements (including lean/fat mass index). The mid-upper arm circumference (MUAC) is an accurate measurement of lean body mass.
- Biochemical and haematological parameters (even if non-specific).

5.2.3.3. Exploratory biomarkers of exocrine pancreatic insufficiency (EPI)

Faecal Elastase-1 (FE-1) is an exocrine pancreatic digestive enzyme resistant to intestinal degradation (normal values >500 µg/g stool). While not validated as a surrogate for exocrine pancreatic function, FE-1 allows monitoring the efficacy of a CFTR-modifier on exocrine pancreatic function in young children with not yet irreversible impairment. The FE-1 assay to be used in the trial should be pre-specified in the protocol.

5.2.3.4. Exploratory biomarkers of intestinal and pancreatic inflammation

Blood Immunoreactive Trypsinogen (IRT) is elevated in case of pancreatic stress and can be used for monitoring early efficacy of CFTR-modifier treatment in infants not suffering yet from pancreatic insufficiency, since recurrence of pancreatic stress (pancreatic ductular congestion) precedes measurable EPI. Thus, at the time of diagnosis in the neonatal period, normalisation of elevated IRT might be the only marker to assess the efficacy of a CFTR modifier treatment.

Even though not CF specific and not validated, faecal calprotectin (FC) is an inflammatory marker that may be used in clinical trials with CFTR-modifiers. FC might be increased by CF-associated pancreatic and intestinal inflammation from early infancy onwards. In view of the lack of standardisation and variability of the test, when FC is used to assess the efficacy of an investigational medicinal product (IMP) on pancreatic and intestinal inflammation, the relative decrease in FC should be measured in a carefully age-matched placebo-controlled trial.

5.2.4. Biomarkers of CFTR function

Biomarkers related to CFTR protein activity are currently not validated surrogates for clinical efficacy.

Non-mutation-specific functional CFTR biomarkers include sweat chloride test (SwCl) and trans-nasal potential difference test to measure the presence and/or functionality of the CFTR protein at baseline

and longitudinally, and thus the pharmacodynamic effect of a CFTR-modifier. Standardisation among the various centres during the trial is recommended.

5.2.5. Assessment of Quality of life and activities of daily living

The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is the most widely used Patient Reported Outcome (PRO) for pwCF in clinical trials. It is a validated CF-specific patient-reported outcome measuring Health-Related Quality of Life (HRQoL) across several domains, including respiratory symptoms, gastro-intestinal symptoms, BMI, physical functioning and treatment burden, and has been specifically developed for use in pwCF from 6 years of age upwards.

The correlation between the severity of GI clinical symptoms and the HRQoL as measured by the CFQ-R is low, due to the restricted number of GI items in this questionnaire (*Solé & al. 2018*). It is advised to also use another validated specific GI-QoL tool.

Time off school for children and time off work for caregivers are part of the assessment of the benefit on activities of daily living and it is recommended that they are both assessed individually if not already included in a PRO chosen as secondary assessment tool. Diary-based data collection is recommended to improve reliability and allow comparability across studies.

Reference is made to the Reflection paper on regulatory guidance for the use of health-related quality of life measures in the evaluation of medicinal products (EMEA/CHMP/EWP/139391/2004).

6. Study design

6.1. Clinical pharmacology studies

Reference is made to the relevant guidelines on clinical pharmacology studies during the development of medicinal products, including the Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products (EMA/CHMP/594085/2015), Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004), and Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004 Corrigendum).

6.1.1. Pharmacokinetics and pharmacodynamics

Thorough and in-depth PK evaluation should be conducted in adults, also because paediatric extrapolation should rely on robust PK/PD characterisation in adults (refer to section 8.2).

Systemically active medicinal products

PwCF may exhibit differing plasma pharmacokinetics compared to non-CF individuals after systemic administration, especially oral bioavailability might be reduced due to the CF-induced gastrointestinal disease, poor nutrition status and low BMI. Therefore, extrapolation of PK data from other populations than pwCF is not acceptable unless justified. Consequently, even for a product already registered in (an)other indication(s) than CF, a dedicated PK study should be conducted in order to collect complete descriptive pharmacokinetic data specifically in pwCF and potentially support specific dose recommendations.

Locally active medicinal products

Even for locally acting medicinal products such as orally inhaled products and PERTs, systemic passage should be assessed for safety considerations. Systemic PK parameters should be characterised when

systemic exposure is quantifiable and relevant for safety. Absence of quantifiable exposure should be justified analytically (e.g., based on LLOQ limitations). Paradoxical bronchospasm, a potential undesirable effect of chronically inhaled therapies, should be thoroughly monitored including assessment of the time course.

In case non-clinical data show evidence that the mucociliary clearance may be affected by the inhalation therapy, and the IMP does not exert itself a beneficial effect on mucociliary clearance (MCC) (e.g. mainly inhaled antibiotics), it is desirable that clinical data on mucociliary function are collected to confirm the potential for a detrimental effect on MCC. These clinical data should come from a phase 1 trial conducted preferably in non-smoking healthy volunteers who are the most sensitive population to detect changes from baseline in mucociliary clearance, if any.

6.1.2. Drug-drug interactions (DDI)

Applicants should refer to the Guideline on the investigation of drug interactions (*CPMP/EWP/560/95/Rev.1 corr.2 **).*

The extent of systemic exposure determines the required depth of DDI evaluation, particularly for inhaled or GI-local products where systemic exposure may be low but not absent.

For products with a significant systemic passage, assessment of both PK and PD drug interactions is critical for medicinal products developed for the treatment of CF, considering the high need of pwCF for multiple concomitant therapies, some of which showing a quite complex interaction potential. Physiologically-based PK (PBPK) modelling can be used to support DDI predictions in this population when aligned with EMA Guideline on the reporting of PBPK modelling and simulation (*EMA/CHMP/458101/2016*).

PD interactions with PERTs are of special relevance since the local exposure in the GI tract and the activity of exogenous pancreatic enzymes is affected by several factors such as the gastric pH, degradation by endogenous proteases, and gastric emptying times. Therefore, local interactions in the GI tract with medicinal products affecting these parameters need to be investigated, either by dedicated studies or by mechanistic justification.

6.2. Therapeutic studies in adults and the paediatric population with clear and clinically detectable symptoms

This section focuses on studies conducted in paediatric patients (children and adolescents) and adult patients presenting with clear and clinically detectable organ dysfunction and standard outcome measures (e.g., ppFEV1, CFA) have measurable sensitivity. Additional specificities and associated recommendations related to children pauci- or presymptomatic (below 6 years of age for treatment of pancreatic disease and below 12 years of age for treatment of respiratory disease) are provided in Section 8/Special populations addressing development specificities in pre- or pauci-symptomatic children, with associated considerations on dose selection, conditions for extrapolation across ages and what amount of clinical data would need to be generated, as well as on and primary and secondary endpoints.

Depending on the mechanism of action of the test product, specific recommendations are provided in corresponding subsections named after the pursued CF-specific indication as detailed in section 5.1.

6.2.1. General comments

Shared design characteristics across pursued indications and investigational medicinal products (IMP)

Dose-finding trials

Dose-finding trials should be randomised, double-blind, parallel-group, placebo-controlled on top of SoC (see below corresponding sections 6.2.2.1; 6.2.3.1; 6.2.4.1). They should include a range of doses to assess the exposure-response relationships on a number of endpoints tailored to the proposed mechanism of action and to the pursued indication (see section 5.2).

Reference is made to ICH E4 Guideline on Dose-response information to support drug registration.

Confirmatory trials

Confirmatory should be randomised, double-blind, placebo- or active-controlled on top of SoC, parallel-group trials, unless a different design could be justified. Considering the limited population of pwCF, a single confirmatory trial could be acceptable provided that results are compelling in terms of robustness of the design and conduct of the trial, internal and external validity, clinical relevance of the findings, consistency across the various outcomes measured and data quality.

Estimand strategies for handling of intercurrent events

The Applicant should pre-plan in the protocol all anticipated intercurrent events (ICEs), and, for each ICE, define a corresponding estimand strategy and how associated missing data will be handled, using the estimand framework as detailed in ICH E9 (R1) Addendum. Final data generated under the chosen option should be in line with the indication pursued. Therefore, all chosen options should be thoroughly justified as i) corresponding to the trial objectives and treatment goals, and ii) allowing the assessment of the clinical benefit of the treatment under the conditions of use as will be specified in the SmPC.

Recommended estimand strategies for the most frequently encountered ICEs are detailed below:

In case of treatment discontinuation, a treatment policy strategy is usually preferred for continuous endpoints (e.g., change from baseline), unless otherwise thoroughly justified. All efforts should be made to retain the participants in the trial, and data should be recorded at each pre-planned visit as if the treatment had been continued. For binary endpoints (e.g., responder analysis), a composite strategy where participants having discontinued are counted as non-responders is recommended. However, it is recommended to also pre-plan a key secondary estimand that handles treatment discontinuation also with a treatment policy strategy, as for continuous endpoints, to assess the impact of a higher number of discontinuations in the placebo arm.

In case of rescue therapy, for continuous endpoints, a hypothetical strategy is preferred to estimate the effect of the treatment in the scenario that rescue medication would not have been used. For binary endpoints (e.g., where treatments are compared regarding the % participants with an increase from baseline in ppFEV1 of ≥ 5%), a composite strategy where participants rescued are counted as non-responders is recommended (see above).

Depending on i) the participants baseline characteristics, ii) the trial objectives, iii) therapeutic indication pursued and iv) the clinical practice/standard of care, alternative estimand strategies may be considered if adequately justified. In such cases, the Applicant is advised to seek feedback from the CHMP on such proposals through a scientific advice request.

Statistical analysis

The Applicant should pre-plan and pre-define in the protocol all key points of the statistical analyses that may impact the estimate of the effect size and statistical hypothesis testing, including the number and objectives of interim analyses if any.

The statistical analysis should be aligned with the estimand of interest. Analyses estimating supplementary estimands can also assist in the interpretation of trial data and may supplement benefit-risk assessment.

Efforts should be made to collect all relevant data for the primary and important other estimands (e.g. follow-up regardless of intercurrent events) to minimise the need to rely on untestable assumptions in the analysis and interpretation of the trial results.

When missing data need to be imputed following treatment discontinuation, since treatment discontinuations are likely to be due to safety issues or a perceived lack of efficacy, the missing at random (MAR) assumption for the handling of corresponding missing data is not favoured. The analysis should not (implicitly) assume that all the benefit from treatment is retained, which is not considered clinically plausible. Therefore, for the primary analysis, a statistical approach based on a suitably conservative strategy under a missing not at random (MNAR) assumption is recommended, e.g., reference-based multiple imputation with a justified assumption on the amount of benefit retained after discontinuation of treatment, if any. At least, these approaches should be part of sensitivity analyses or tipping point analyses.

Regarding the estimation of the hypothetical strategy for the ICE of rescue therapy, data after the initiation of rescue therapy should not usually be used in the efficacy analysis as observed. Instead, statistical modelling of the values that would have occurred in absence of rescue medication is recommended (e.g. considering data after the ICE as missing data with a suitably conservative imputation approach).

Assumptions underlying the analysis of the primary and key secondary analysis should be examined through pre-specified and justified sensitivity analysis (e.g. tipping point analyses) that explore a range of clinically plausible and conservative assumptions. Even in cases where a less conservative approach might be justified, planning several sensitivity analyses under more conservative assumptions/approaches is strongly recommended.

Descriptive statistics should be provided for the number of the different intercurrent events and missing data at all measurement timepoints stratified by treatment group. Additionally, within the same overview, information should be included on whether data became missing after the intercurrent event.

Long-term efficacy and safety follow-up

Although pivotal trials should be of sufficient duration to collect comparative placebo or active-controlled mid-term efficacy and safety data, long-term follow-up trials for efficacy and safety should always be planned in the development program for products intended to be administered life-long in this chronic condition. Such trials should assess long-term safety and maintenance of efficacy. For CFTR modifiers and inhaled therapies for CF, post-approval commitments to provide long term data are often required (e.g., post authorisation efficacy study (PAES)/ post authorisation safety study (PASS)/registries, see also Section 7). Yet it is of the remit of the CHMP to assess the amount of long-term data that should be available at the time of MAA for a sound benefit/risk assessment.

PwCF with co-morbidities, usually excluded from confirmatory trials, should be included in long-term trials as far as feasible, e.g., pwCF with cystic fibrosis related liver disease (including cirrhosis) and CF-related diabetes.

6.2.2. Treatment of lung infection

Contrarily to evidence collected with *Pseudomonas aeruginosa* (PA), there is currently little evidence that chronic maintenance therapy would translate into a long-term clinical benefit on lung function for

bacteria other than PA (*Castellani & al. 2018*). Regulatory experience on early eradication with non-PA CF pathogens is also too scarce to allow making recommendations organisms other than PA. Therefore, for any clinical development of an antibacterial agent against non-PA pathogens, Applicants are recommended to seek feedback from the CHMP through a scientific advice request.

6.2.2.1. Exploratory and dose-finding studies

Eradication of acute infection

The available prior PK and PD knowledge about authorised antibacterial agents should be taken into consideration to decide whether dedicated dose-finding studies are needed. PK/PD integration is usually expected to support dose selection. If a different route of administration is targeted, then PK studies should be conducted as described in section 6.1.1, keeping in mind that, for inhaled products, systemic exposure is usually limited, so that PK/PD integration might not be feasible and dedicated dose-finding studies are usually expected. The microbiological PD endpoint relevant for the pursued indication (i.e. bacterial eradication, see section 6.2.2.2.1.) should be assessed unless otherwise justified.

In case an indication of eradication of initial infection is pursued for an antibacterial agent not yet authorised, the Applicant is strongly recommended to seek feedback from the CHMP through a scientific advice request and discuss to which extent population PK(-PD) may suffice for dose-finding or if additional studies are needed.

Suppressive therapy of chronic infection

In dose-finding trials with proposed suppressive therapies, it is acknowledged that ppFEV1 may not be sensitive enough to detect between-dose differences, if any, considering the relatively small sample size and short treatment duration of such trials. Hence, the pharmacodynamic endpoint of changes in bacterial load in sputa over approximately 4 weeks of treatment may be more sensitive to disentangle 2 candidate doses. Although a defined relationship between reductions in bacterial loads in sputa (which do not inform about any effect on biofilms) and clinically relevant outcomes has not been established, it may still be reasonable to select the test regimen showing the largest reduction in bacterial loads, particularly in the absence of safety concerns and when supported by effects on lung function endpoint(s).

The effects of short-term treatment on respiratory function should be systematically assessed to provide supportive information on antimicrobial activity. If not selected as primary efficacy endpoints, lung should be measured as secondary efficacy endpoint.

Given the short-term evaluation period of a dose-finding study in this patient population, it may be feasible to use a placebo control arm, which is the preferred option. Alternative options include i) a comparison with a single licensed therapy or ii) randomisation of patients on established suppressive regimens to either continue their treatment or switch to the test regimen.

6.2.2.2. Confirmatory studies

A single randomised pivotal trial would be acceptable to support an indication for eradication of acute infection or for suppressive treatment of chronic infection (see section 6.2.1 for requirements on the quality of data collection).

6.2.2.2.1. Eradication of acute infection

Design elements

Placebo is not an acceptable comparator for ethical reasons, and the recommended design is randomised, double blind controlled with a comparator active on the target bacterial species, whether or not this comparator is granted a specific CF indication.

As there is a lack of evidence of the magnitude of the treatment effect to define an adequately justified non-inferiority margin, an appropriate aim of confirmatory studies is to show superiority versus the active comparator for eradication rates. The timepoint for assessment of the eradication rate varies depending on the bacterial species and pharmacodynamic behaviour of the medicinal product.

In the absence of an appropriate active comparator or in case demonstrating superiority is not achievable, one option could be to demonstrate on the frame of a single-arm trial that the lower bound of the 95% confidence interval of the eradication rate for the test regimen exceeds a threshold considered to be clinically meaningful, provided that there is strong prior evidence to support the chosen threshold (Report of the workshop on endpoints for cystic fibrosis clinical trials European Medicines Agency, London, 27-28 September 2012: https://www.ema.europa.eu/en/documents/report/report-workshop-endpoints-cystic-fibrosis-clinical-trials_en.pdf). In case this option is considered, the Applicant is strongly recommended to seek feedback on the acceptability of the strategy and associated threshold from the CHMP through a scientific advice request.

Choice of endpoints

The recommended primary efficacy endpoint is the microbiological eradication rate, with eradication as defined in section 5.2.1. Other definitions of eradication may be acceptable if appropriately justified, notably for target organisms other than PA.

Secondary endpoints should include time to relapse or to reinfection as defined in section 5.2.1., determined at predefined intervals after the end of antibacterial treatment. The proportion of patients (originally eradicated) who are re-infected within 1-6 months after end of treatment is of clinical interest to document the delay in progression to chronic colonisation.

6.2.2.2.2. Suppressive treatment of chronic infection

Design elements

Orally inhaled antibacterial agents with an indication of suppressive therapy of chronic lung infection with PA are approved for chronic administration every other month (4 weeks "on/off" periods). However, for new chemical entities, new formulations and/or new regimens, the dose regimen that should be used for comparators consist of cycled and continuous alternating use of several existing antibacterial agents that is considered the standard of care. It is therefore highly unlikely that a single approved antibacterial regimen may be maintained over a period of approximately 6 months to serve as a unique comparator versus the test regimen (whether the test regimen or comparator is administered cyclically or continuously). Furthermore, a trial comparing the test anti-infective regimen to a standard of care anti-infective regimen comprising various agents during the duration of the trial may raise recruitment difficulties due to the need to administer the test agent for a prolonged period covering whole cycles of the standard of care products.

One option would be the comparison of the test anti-infective medicinal product to placebo as add-on to the SoC for CF over 4 weeks (one cycle) to show superiority of the efficacy on respiratory function at end of this period. Non-inferiority versus a reference product is also a valuable option in case a reliable and adequately justified non-inferiority margin could be defined, which would however be very challenging to achieve (*Nichols & al. 2019*).

In view of the above-detailed challenges, Applicants wishing to develop new treatments for chronic infection are recommended to seek feedback from the CHMP through a scientific advice request.

Choice of endpoints

Primary efficacy endpoint

Chronic infection due to PA is expected to be present during adolescence but is rare in children under 12 years of age. In standard on-off trials with cycled administrations for suppressive therapy of PA for new antibacterial agents/new route of administration/new regimens, the primary efficacy endpoint should be clinical and reflective of the respiratory function. The absolute change from baseline to week 24 in ppFEV1 (i.e., to the end of the third off-treatment period and 28 days after the last dose of any active inhaled therapy) used to be the recommended primary efficacy endpoint. However, because of the increased clinical stability of many pwCF, ppFEV1 might be no longer sensitive enough to evidence efficacy, particularly in patients receiving CFTR modulators. Since no fully validated alternative clinically meaningful efficacy endpoint is available, in case the Applicant proposes another PEP than ppFEV1, the Applicant is strongly recommended to seek feedback from the CHMP through a scientific advice request with an adequate justification why ppFEV1 is insufficiently sensitive to change accompanied with a rationale for the proposed alternative PEP.

Secondary efficacy endpoints

Secondary endpoints should include microbiological endpoints (see section 5.2.1.), change in the respiratory domain of CFQ-R and changes in anthropometric measures as appropriate to the age range considered (see section 5.3).

Because the decrease in PEs has been shown to be associated with improved survival, secondary endpoints should also always include PEs, although they have become rare events due to the increasing stabilisation of pwCF, especially in pwCF receiving CFTR modulators. Hence, in these subjects, PE endpoints are unlikely to detect treatment effects on chronic infection and will mainly provide supportive information, unless the background disease is more advanced or the trial duration is sufficiently long and include flu and respiratory syncytial virus seasons (e.g. $\geqslant$48 – 52 weeks) (Cogen and Quon, 2024). The PEs outcome should be preferably assessed as a time-to-event endpoint (e.g. time to first PE and/or time to first PE requiring intravenous antibiotics or hospitalisation).

Measures of treatment burden/acceptability of the formulation as well as documentation of administration time per individual dose and per day should always be collected, using e.g., diaries, as additional secondary endpoints as it is critical for real-world adherence. The impact on selection of microorganisms with high MICs over time and associated specific mechanisms of resistance should be documented.

6.2.3. Improvement in nutritional status and treatment of exocrine pancreas insufficiency

Fat malabsorption is a prominent feature of the GI CF phenotype, resulting both from maldigestion and malabsorption due to exocrine pancreatic insufficiency (EPI), and from malabsorption of fatty acids due to dysfunctional CFTR. This process ultimately results in altered nutritional status, further amplified by the pulmonary/endocrine pancreatic impairment/gastrointestinal and liver disease(s). Consequently, the correction of exocrine pancreatic insufficiency with PERT improves steatorrhea but only partially the global nutritional status.

6.2.3.1. Exploratory and dose-finding studies for PERT

Although rare, clearly dose-dependent PERT-induced fibrosing colonopathies have been observed in young children receiving very high doses of PERT, which led to a European consensus recommendation to remain below a PERT daily dose of 10 000 IU lipase/kg body weight/day (*Littlewood & al. 1996*). This should be accounted for when defining the initial and maximal doses of PERT in exploratory and dose-finding studies.

For conventional porcine PERT, dose-finding trials are usually not needed, due to the important variation in individual responses to PERT. The dosage of exogenous pancreatic enzymes is therefore usually individualised, based on fat content of the diet, the level of steatorrhea, and clinical symptoms, taking into account the recommended maximal daily dose of 10 000 IU lipase/kg body weight/day as detailed above.

For non-porcine PERT, dose finding trials are required considering the limited experience with these products. The design should include an individualised dose escalation, starting with the minimal amount of lipase, as calculated based on either fat content of the diet, taking into account BMI, or preferably height and weight in growing children.

An 8-day procedure is needed to assess efficacy of an individual dose, i.e., 24-hour wash-out of the previous administered product followed by a 3-day dosing, then collection of data until the last stool marker is recovered (Recommendation from the cystic fibrosis foundation *Konstan & al, 2013*).
A double-blind randomised controlled design is recommended because of interindividual heterogeneity in responses to PERT. Both previous PERT and placebo are acceptable comparators. Placebo may be appropriate as long as the treatment duration does not exceed 8 days and a rescue protocol is planned. To minimise the number of patients on placebo, a cross-over or a parallel withdrawal design is recommended. In the latter design, pwCF are all administered the new PERT during an initial 8-day treatment sequence, then randomised to either shifting to placebo or maintaining the new PERT for an additional 8-day treatment sequence. An active-control design is recommended in young children and/or children with a severely compromised nutritional status, where pwCF are sequentially randomised to one of the two-day treatment sequence (previous PERT versus test PERT) (*Konstan & al, 2013*).

Steatorrhea (CFA) in stool content should always be the primary endpoint in dose-finding trials.
The fat content of the stool collected during the trial should reflect only the standardised high-digestible diet as detailed in section *5.2.3.1)* and not the pre-trial fat intake. For that purpose, one option is to plan a short run-in period with the usual PERT and the trial high digestible fat diet before randomisation occurs. The duration of this run-in period should allow complete evacuation of the stool content reflecting the pre-trial diet, and may last 24h to a few days, depending on the individual transit time.
As an alternative option to the run-in period, the first measurements of CFA should be delayed by 1 to 3 days, depending on the transit time for an individual patient, to ensure that CFA measurements will not integrate pre-trial diet contents.

In the growing paediatric population, a 24-week open-label extension where all patients would be administered the test PERT should follow the usually short cross-over part of the trial to assess the maintenance of the efficacy on CFA and any beneficial effect on anthropometric parameters.

The trial should be performed in centres experienced in conducting clinical trials in pwCF and/or in trials assessing PERT.

6.2.3.2. Confirmatory studies with PERT

Patient selection/target population

PwCF should have documented EPI as defined by i) either current PERT therapy and faecal elastase-1 below 50-100 µg/g stool (since CFA is corrected under PERT) or ii) in the absence of PERT supplementation, by a CFA below 70%. Patients on stable treatment with acid-suppression therapy such as proton pump inhibitors (PPIs) may be enrolled. Any concomitant CFTR modulator therapy should be at stable doses.

Exclusion criteria should relate to either safety risks (history of fibrosing colonopathy, unstable state of health, an acute illness), or to potential confounding of CFA measurement (treatment with other medications that affect intestinal motility, maldigestion or malabsorption).

Randomisation should be stratified by age class and concomitant PPIs (considering the PPIs contribution to the relief of upper GI symptoms). To limit the number of stratification factors in this rare condition, it is recommended that other important effect-modifying factors are used as covariates in the statistical analyses. They include a subgroup of seriously undernourished patients (as defined by baseline CFA and BMI), who have been shown to better respond to therapy.

Design elements

For porcine PERTs, long-standing experience document their beneficial effect on anthropometric parameters. Therefore, short-term trials as described for dose-finding in non-porcine PERT are adequate (see section 6.2.3.1).

For non-porcine PERTs, confirmatory trials should allow demonstrating their beneficial effects on nutritional status. Therefore, they should be of sufficient duration to allow assessing all nutritional status parameters, including anthropometric measures and lean/fat mass parameters (see section 5.2.3).
A double-blind randomised active-controlled parallel-group design is recommended to avoid a long placebo duration.

Non-inferiority versus a licensed PERT should be demonstrated with a thorough justification of the non-inferiority margin (*refer to the EMA Guideline on the choice of a non-inferiority margin: EMEA/CPMP/EWP/2158/99*).

No wash-out period is necessary before inclusion, provided that the treatment duration is not less than 8 weeks, to allow complete elimination of lipase from the previous treatment and rule out that any residual lipase may have a non-negligible impact on the subsequent CFA-72h collection at the end of the treatment period.

For all confirmatory PERT trials,

- The clinical trial protocol should pre-specify the maximum dose of PERT that is allowed (expressed as lipase units/kg of body weight per day) and whether and for how long dosage adjustments during the trial course are permitted to relieve clinical symptoms (in which case rules governing dosing adjustments should be thoroughly pre-defined and standardised in the protocol).
- Following the double-blind period, a 24-week open-label follow-up is recommended for assessment of longer-term safety and of the translation of the short-term efficacy into sustained long-term benefits in terms of nutritional status and gastro-intestinal symptoms this (see section 7 Safety).

Choice of endpoints

Primary efficacy endpoint

For porcine and non-porcine PERT, for a claim of improvement in EPI and no specific claim of global improvement in nutritional status, the change from baseline (see section in the coefficient of fat absorption over 72 hours (CFA-72h) should be the primary endpoint, and can be assessed following an 8-day treatment period, whatever the recommended total double-blind trial duration.

In case of a specific claim of global improvement in nutritional status, the primary endpoint should be a complete assessment of nutritional parameters (see section 5.2.3.2). Usually, nutritional parameters should be presented as a change from baseline at the end of 48-w treatment period.

Besides the primary analysis on the ITT population, it is recommended to conduct sub-group analyses in undernourished subjects, and by sex and age (if applicable).

Secondary efficacy endpoints

For porcine PERT, full assessment of the nutritional (see section 5.2.3.2) should be part of secondary endpoints only in case the improvement in nutritional status is a secondary trial objective. It is recommended that they are presented as change from baseline at the end of 48-w treatment period.

For new non-porcine PERTs, a complete assessment of nutritional status should always be part of secondary endpoints if not already the primary endpoint.

In case of a specific claim of improvement in nutritional status, a responders' analysis (e.g., percent of patients achieving the nutritional target as defined in CF nutrition guidelines) should also be provided as secondary endpoint. Other definitions of responders may be acceptable if adequately justified.

Whatever the PERT class, other secondary endpoints should always include:

i) the coefficient of nitrogen absorption,
ii) PROs-based assessment of clinical symptoms (stool frequency, consistency, flatulence, and abdominal pain) that should be recorded on a daily basis or a weekly basis (for stool frequency) throughout the randomised treatment period and
iii) Quality of life using the Cystic Fibrosis Questionnaire-Revised (CFQ-R) or any other validated PRO measurement tool.

6.2.4. Treatment of CF

CFTR-modifiers may pursue a general indication of "treatment of CF" when administered through a systemic route of administration.

6.2.4.1. Dose-finding studies

Population

For mutation-specific products such as CFTR-modulators or AONs, it is recommended that the dose-finding studies, when feasible considering the size of the target population, are conducted in the population harbouring the most frequent mutation(s) among all mutations targeted by the candidate therapy under development. Extrapolation of the optimal dose across the targeted mutations may be acceptable where supported by robust PK/PD data and consistent exposure–response relationships and should be justified in the clinical development programme.".

Endpoints

ppFEV-1 has limited dose-finding responsiveness/sensitivity to discriminating doses. Therefore, it is acceptable that the optimal dose is determined based on PK/PD analysis with a validated PD endpoint, such as the sweat chloride test, although they are not validated surrogates for efficacy.

Steatorrhea, when present, does improve with CFTR-modifiers due to the improvement in the quality of gut mucosal secretion. It is directly related to a clinical benefit and may be a relevant candidate endpoint for selection of the optimal dose to be assessed in confirmatory trials, especially in pwCF with significant room for improvement, e.g., early CFTR-modulator treatment in children.

6.2.4.2. Confirmatory trials

6.2.4.2.1. Generalities on selection of the target population

Patients should have a documented diagnosis of CF with genotyping of both mutations.

Main Inclusion criteria

It is generally recommended to include a CF patient population with relative stable disease with ppFEV1 ≤ 80-90% at the screening visit to ensure sufficient room for lung function improvement.

Main Exclusion criteria

- acute upper or lower respiratory infection with organisms associated with a rapid decline in pulmonary status or pulmonary exacerbation or change in therapy for sinopulmonary disease (including antibiotics) within usually 4 weeks before inclusion,
- abnormal laboratory values of haemoglobin and bilirubin,
- renal impairment. Yet, trials in renally-impaired pwCF are also needed in order to investigate whether dose adjustments will be needed, usually through PK assessments in a small group of pwCF,
- severe hepatic impairment.

Co-morbidities

Liver involvement is frequently reported in CF patients and associated with high morbidity. While new medicinal products restoring functional CFTR are not requested to specifically assess the efficacy on liver disease, such patients should not be excluded from confirmatory trials and monitored for safety as well as descriptively for consistency of efficacy, except for patients with advanced CF-related liver disease who should normally be excluded (see Section 7).

The same applies to CF-related diabetes that is present in overall 10% of adolescents and ≥ 25% of adults with CF in Europe, with increasing prevalence with age and high variability across countries (*Olesen & al. 2020*). While improvement of diabetes is not a target for medicinal products restoring CFTR function, such patients should not be excluded from CF trials and should be descriptively monitored.

Stratification factors

It is recommended to stratify randomisation according to the most relevant prognostic factors for the IMP. Relevant stratification factors may include age class (e.g., adolescents/adults), baseline ppFEV1, baseline SwCl, baseline status of lung chronic infection due to the presence of specific microorganisms (especially Pseudomonas aeruginosa considering its high prevalence). For this rare condition, the number of stratification factors needs to be restricted to the most relevant effect-modifying parameters. It is advised that other potential effect-modifying parameters are covariates in the statistical analyses.

6.2.4.2.2. Generalities on the choice of outcome measurements

Clinical outcome measures

CFTR-modifiers, by restoring a level of functional CFTR, are expected to have a global and ubiquitous effect on the disease signs and symptoms. A global improvement/stabilisation/slowing of disease progression should be evidenced; above-detailed respiratory and nutritional clinical outcomes are relevant in this respect (see section 5.2).

The primary endpoint should allow demonstration of efficacy in at least one organ/function that should be lung function each time it is impaired.

Respiratory function

- Most often, and each time the lung function is impaired, improvement in respiratory function is the primary objective to be achieved. Therefore, ppFEV1 will be expected to be part of the primary endpoint(s) (*see Section 8 for specific respiratory endpoints in children aged ≤ 12 years*).

  The recommended timepoint for assessment of ppFEV1 is at least 6-month to allow assessing the sustainability of an initial effect and rule out a carry-over effect in subjects already on CFTR modulators.

- Pulmonary exacerbations, although having become rare events since the generalisation of CFTR modulators and optimised antibiotic therapy, should be part of the secondary endpoints for any new medicinal product with no pre-existing significant efficacy data in another pwCF population, since their decrease has been shown to be associated with improved survival. Due to the seasonal variability, the time-point for assessment of PE should have an at least one-year duration.

- Secondary endpoints should also include repeated assessment of ppFEV1 at earlier time points than the recommended 6-month timepoint for assessment of the primary endpoint.

Gastrointestinal function

- Improvement both in exocrine pancreatic insufficiency and in global nutritional status are the recommended goals for assessment of efficacy of a CFTR-modifier on a second organ function (*see section 5.2.3 for specific recommendations on the corresponding endpoints, diet, etc.*).

- pwCF on CFTR modulators therapy are also on PERTs due to their exocrine pancreatic insufficiency. Success in withdrawing PERTs would represent a clinically relevant alternative proof of efficacy in a second organ and may be in all cases a clinically relevant secondary endpoint. Discontinuation attempts should be primarily based on the absence of residual steatorrhea, absence of GI-symptoms, and normal growth and body weight for age (*Sathe and al, 2023*).

- In case pwCF with CF-related liver disease (CFLD) are included, outcomes related to improvement in liver tests (including imaging and elastography) and liver function should be reported descriptively as secondary or exploratory endpoints without the need for formal statistical significance, at least to rule out any detrimental effect (see section 6.2.4.2.1).The clinical relevance of any effect would be assessed based on the consistency of findings across subjects and on the effect size.

- Several tests can be used to assess whether CFTR modulators may modify the progression of glucose abnormalities, however, such investigations are exploratory only. Tests that can be used include the oral glucose tolerance test or continuous glucose monitoring (see section 6.2.4.2.1).

Nutritional status and anthropomorphic parameters

Anthropomorphic parameters such as weight and BMI Z-scores, and growth parameters for still growing patients should always be at least part of secondary endpoints.

Quality of life and overall patient's status

Collection of quality-of-life data in CF clinical trials directly measures the patients derived benefit, and it is recommended that this endpoint is systematically assessed as secondary endpoint using a validated measurement tool as recommended in section 5.2.5.

Time off school for children and time off work for caregivers should also be assessed as secondary endpoint, e.g. using a diary-based PRO (see section 5.2.5).

Biomarkers

- The demonstration of efficacy should be supported by an improvement in a pharmacodynamic biomarker indicative of the disease status as secondary endpoint (e.g., sweat chloride values, see section 5.2.4), especially in case of a single pivotal trial. Results should be analysed as the absolute change from baseline in the biomarker to the end of the treatment period. A responder analysis based on pre-defined thresholds of response to treatment is recommended.

  However, until a biomarker is established as surrogate for clinical efficacy and fully validated (including sensitivity to change and minimal clinical important difference), it can only be used as a supportive secondary endpoint.

  The response on the SwCl of CFTR modulators has been shown to be discordant for some mutations. For this reason, it is advisable to include other biomarkers (see section 5.2.4) when collecting supportive data on pwCF carrying rare mutations.

6.2.4.2.3. Confirmatory trials with CFTR modulators

a) Population

The genotype of the target population defines the pursued indication and should thus be thoroughly characterised.

Modulators targeting the F508del mutation

The largest potential target population is the global F508del mutation population, whatever the homozygous or heterozygous status (80% of pwCF, see section 1. Introduction).

However, in heterozygous subjects with no Class I mutation (see Section 1. Introduction), uncertainty will remain on whether the observed efficacy is primarily due to an effect on the F508del mutation or an effect on the non-F508del mutation of the other allele; therefore, for a robust demonstration of the efficacy on the global F508del population, it is recommended to stratify the randomisation on homozygous or heterozygous status, to allow conducting specific subgroup analyses and assessing the consistency of the efficacy across both subgroups.

Modulators targeting non-F508del mutations

The study population may be selected based on the responsiveness in in vitro or ex-vivo non-clinical models depending on the mechanism of action of the tested CFTR modulator. Several ex-vivo (including organoid-based) or *in vitro* cell-based tests are being or have been developed to select candidate mutations that could be sensitive to a candidate CFTR modulator. The Applicant is strongly encouraged to validate the test intended to be used. In case the planned test is not validated, the Applicant is recommended to seek feedback from the CHMP on the acceptability of the selection strategy through a scientific advice request.

b) General design considerations

Reference is made to the Guideline on clinical trials in small populations (CHMP/EWP/83561/2005).

The currently approved CFTR modulators have different and complementary mechanisms of action on a specific CFTR channel defect (e.g., trafficking, gating etc.). Hence, the standard of care is to use in combination several CFTR modulators specific of the same mutation(s) and with complementary mechanisms of action, whenever feasible. For the development of new fixed-dose combinations of CFTR modulators, Applicants are referred to the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017). The contribution of each single agent to the overall effect should be assessed starting in phase 2 dose-finding trials.

Many pwCF harbour a mutation pattern giving them access to CFTR modulators. Hence, in this CF population, a placebo arm does not appear feasible unless as add-on to the standard of care including approved CFTR modulators for the mutation(s) considered, if available.

The double-blind treatment duration should generally be 48-52 weeks to account for seasonal variability of pulmonary exacerbations and allow assessing the maintenance of the effect on ppFEV1 and comparative assessment of safety. For an extension of indications of an already approved combination therapy which efficacy proved to be stable over time, 6-month could be accepted to collect clinically meaningful ppFEV1 data, capitalizing on data previously collected in another population. The double-blind treatment period should be followed by an additional 24-week open-label treatment period to assess the maintenance of efficacy in case the double-blind duration is less than 48 weeks.

c) Specific design elements for efficacy in pwCF carrying at least one F508del mutation

The concerned population represents roughly 80% of pwCF, and it is considered that the population is large enough to apply standard power and type-1 error control when designing the trial. This population is anticipated to be already receiving CFTR modulators combination therapy to a large extent, and this should condition the study design.

- Unless otherwise justified, a randomised double-blind superiority trial versus placebo is recommended. A placebo-controlled trial would be feasible in case both placebo and the IMP are administered as add-on to the standard of care including already approved CFTR modulator(s).

- In case the new product is aimed at replacing a CFTR modulators combination (and not at being administered as add-on to it), a placebo-controlled trial is ethically challenging.
  A superiority trial versus the SoC is an option in such cases where the test product is expected to show clinically meaningful incremental efficacy versus the CFTR modulator combination within the planned study duration.

- If clinically meaningful superior efficacy versus SoC cannot be anticipated, demonstrating non-inferior efficacy versus an approved CFTR modulators combination regimen as reference product on the PEP of ppFEV1 is an acceptable option. Patients stabilised and adequately/optimally controlled with their CFTR modulators combination would be randomised to either continue their previous treatment or switch to the IMP. The non-inferiority margin should be thoroughly justified (*Reference is made to the Guideline on the choice of a non-inferiority margin (CPMP/EWP/2158/99).*

  Sufficient knowledge on the expected effect size of the reference product should be available to ensure internal validity and indirect superiority of the IMP versus placebo. The treatment period after the randomisation should be sufficiently long to rule out any carry-over effect.

d) Specific design elements for efficacy in pwCF not harbouring any F508del mutation

When a non-F508 mutation indication is pursued, the corresponding target population is genetically very heterogenous and numerically restricted, harbouring two copies of individually rare CFTR mutations. The targeted population may comprise several very rare mutations, possibly grouped by

mutation-type. The Applicant is strongly advised to make a scientific advice request and seek feedback from the CHMP on the overall strategy as well as on the nature and extent of overall data that should be submitted.

An extrapolation plan along the following lines is recommended:

- Clinical data should always be submitted in the marketing authorisation application (MAA) dossier:
  i) whenever feasible, conducting an umbrella clinical trial in a mixed population including a number of selected (and justified) candidate mutations is recommended. Data should be presented as global and per mutation data in the form of descriptive qualitative and quantitative assessments, and the choice of the design and potential comparator should be thoroughly justified.
  ii) All available clinical data on efficacy of the medicinal product on the candidate mutations should be detailed, including literature-based, off-label use, compassionate use and registries data.
  iii) Supportive clinical evidence may come from overall data gained in the F508del population, if any and if relevant and adequately justified. Whenever feasible, it is advised to explore the relationship between exposure and biomarkers response using PK-PD modelling and simulation. Although sweat chloride and other CFTR function biomarkers are not validated surrogate endpoints and cannot replace clinical efficacy outcomes, they play an important role as pharmacodynamic markers to support extrapolation across CFTR mutations when appropriately bridged to clinical data. This will allow comparing the medicinal product performance in subjects with the rare mutations to its performance in subjects with F508del mutation. Fit-for-purpose options to collect data for the modelling exercise should be detailed and appropriately justified.
- Non-clinical (*in vitro* and/or *ex vivo*) data will have a critical weight in the benefit/risk assessment as part of the extrapolation process. When the non-clinical proof of efficacy stems from the selection of candidate mutations based on an *in vitro* and/or *ex vivo* test/organoid using the CFTR modulator(s) regimen under investigation, it is recommended to use a validated or qualified test/organoid if any, or to make a request for qualification of the candidate test by the CHMP.

6.2.4.2.4. Design elements and endpoints specificities for products modifying the genome expression

Gene-targeting therapies may be developed as either "one shot" treatment (e.g., vector-based gene therapy) or chronic treatment (e.g., mRNA; AONs).

The mechanism of action of products modifying the genome expression may or may not be mutation dependent. The pursued indication and related endpoints will depend on whether a global CF population may be targeted. The regulatory experience is limited for these products, and the Applicant is recommended to request a scientific advice to seek feedback from the CHMP on the proposed design and endpoints of confirmatory trials. The scientific advice request should take the following considerations into account when drafting the briefing book:

a) In vivo vector-based gene therapy products

General comments

For a vector-based gene therapy (e.g., AAV-based), the relevant design for this "one-shot" therapy would depend on the population enrolled, as well as on the route of administration, conditioning whether a systemic or local effect is targeted. While for systemic products a general "Treatment of CF" indication may be pursued, inhaled therapy can only pursue an indication of "treatment of CF lung

disease". Yet, both systematically or inhaled products share the same recommended design and primary efficacy endpoint.

It is recommended to assess sequentially efficacy and safety in an older CF paediatric population before enrolling the younger CF population in a trial.

The timepoint for assessment of the efficacy endpoints should also be chosen based on the time required for achievement of full expression of the transgene in the target tissues.

The development of a vector-based gene therapy should preferably be initiated in subjects not amenable to CFTR modulators (homozygous to class I mutations and not responding to or intolerant to CFTR modulators) since they offer the demonstration of efficacy versus placebo due to the absence of confounding from CFTR modulators and represent the highest unmet need.

Moreover, pwCF already on CFTR-modulators have much lower unmet need since they are already receiving a beneficial treatment. It is thus preferable to expose this population to the risks associated with a gene therapy product only once the efficacy of this product has been demonstrated in subjects not amenable to CFTR modulators.

Assessing clinical efficacy and safety in subjects already on CFTR modulators will allow determining whether gene therapy may offer an additional benefit in this population and establish the place of vector-based gene therapy in the therapeutic armamentarium for the broader CF population.

pwCF naive for CFTR-modulator

Population

Initial development in the naïve population is anticipated to concern mainly pwCF not amenable to CFTR modulators (*see General comments above*). Newly diagnosed young paediatric patients will represent a critical target to prevent disease progression once efficacy and safety have been established in the older ones.

Stratification of randomisation is recommended by baseline disease severity as well as by disease duration/age.

Design

A randomised double-blind superiority trial versus placebo on top of best supportive care is a recommended option. Subgroup analyses by disease durations are recommended to assess whether there will be a beneficial effect in older subjects with significant lung fibrosis. Formal statistical significance is not requested for this purpose. The disease duration/extent of fibrosis threshold should be justified in the protocol.

pwCF already on a CFTR-modulator

Population

Gene therapy has the potential to cure the disease, and the target population could be included regardless of their mutation.

A homogeneous population with not too much advanced disease allowing the demonstration of a stabilisation or slowing of disease progression is recommended since a ceiling effect might be anticipated beyond a given disease duration in relation to the extent of fibrosis. Efficacy results gained in pwCF not amenable to CFTR modulators may guide on the relevance of including subjects with a long disease duration (*see above*).

Design

A compelling clinically relevant effect size in terms of disease stabilisation or slowing of disease progression is expected for a favourable benefit/risk ratio, considering the known safety concerns and significant level of safety uncertainties associated with AAV-based gene therapy *(see Section 7).*

Clinical questions of interest when defining the objectives and design of a confirmatory trial in a population receiving a CFTR modulators combination therapy at baseline include the following:

i) is there an added benefit of gene therapy on top of CFTR modulators?
ii) once full expression of the transgene is reached, can CFTR modulators be successfully withdrawn?
iii) If CFTR modulators can be withdrawn, what is the size of the intrinsic benefit of gene therapy?

Answering these questions should allow documenting the therapeutic decision whether the CFTR modulator therapy should be maintained following administration of the gene therapy. The demonstration of a superior efficacy of gene therapy over CFTR modulators would strengthen the case for vector-based gene therapy, considering the higher risks associated with gene therapy when compared to CFTR modulators.

Therefore, a relevant option is a double-blind-randomised 2-arm trial of gene therapy versus placebo, both on top of standard-of-care including CFTR-modulators regimen. The CFTR-modulators treatment should be maintained at least 6 months, i.e., during the 3-4-month interval between vector-based therapy administration and full expression of the transgene in the target tissues, plus an additional 2-month for maximal effect of gene therapy on ppFEV1. At that timepoint, it is desirable to assess whether there is an added benefit of gene therapy on top of CFTR modulators using superiority testing. After assessment of this endpoint, an attempt should be made to withdraw the CFTR-modulators regimen in the gene therapy arm. A randomised withdrawal period would be relevant for this purpose. A relevant objective for this period would a between-arm comparison of time to decrease in ppFEV1. Assessment should be measured at least 6 months after withdrawal to rule out any carry-over effect, or even longer to collect data on the maintenance of efficacy. A decrease in efficacy in the arm where modulators will be withdrawn versus the arm where they are maintained would orientate the place of vector-based gene therapy in the therapeutic armamentarium.

b) mRNAs and AONs

Demonstrating superiority of mRNAs/AONs over placebo in class I mutations or over CFTR modulators is a relevant study objective.

The same study designs for demonstration of efficacy as for gene therapy may also be relevant for mRNAs. However, there is no anticipated delay in achievement of full efficacy with mRNAs.

Patients already on CFTR modulators could enter the trial without wash-out provided that the treatment duration is long enough to allow ruling out any carry over effect.

AONs are likely to be mutation-specific, and thus the designs considerations as detailed for CFTR-modulators may apply.

7. Safety aspects

The safety of an investigational product may be difficult to assess in pwCF, because of the debilitating nature of the underlying disease and the large number of concomitant medications, which reinforces the recommendation of a double-blind controlled assessment of the safety profile in confirmatory trials.

The safety data should stem from a minimal 6- to 12-month follow-up, depending on the objectives of the trial, the intended duration of use, and on the specificities of the anticipated safety profile of the IMP. This is also applicable to treatments administered as relatively short-term treatment courses

(e.g., some antibiotics), considering that these short therapeutic courses are likely to be repeated life-long in this chronic condition.

The Applicant should make efforts so that the extent of the safety database approaches as far as feasible the recommendations the *ICH E1 Population exposure: the extent of population exposures to assess clinical safety* Guideline (data should be available from at least 100 subjects receiving doses not lower than the to-be-recommended dose during at least 12 months).

7.1. Specific effects related to a specific mechanism of action or a specific formulation

7.1.1. Chronic inhalation therapy

Adverse events of special interest include aspects related to local tolerance, such as coughing and hoarseness.

Well-known adverse events specifically associated with the inhaled route of administration include paradoxical bronchospasm. Appropriate preventive and/or rescue measures may therefore be needed during clinical trials, e.g., to use a short-acting bronchodilator immediately prior to the medicinal product administration. In case of inhalation of large molecules such as proteins, immunogenicity should be adequately characterised.

7.1.2. PERTs

Signs and symptoms of malabsorption (including steatorrhea), that are efficacy variables for the treatment of exocrine pancreas insufficiency, should also be considered as safety parameters and included in the standard safety assessment along with abdominal pain and constipation (*Castellani & al. 2018*).

The risk for PERT-induced fibrosing colonopathy cannot be ruled out, even with doses < 10,000 IU/kg/day (see section 6.2.3.1); the occurrence of such lesions should be actively monitored in all PERTs trials whatever the dosing regimen.

A 24-week follow-up period following treatment cessation is recommended in all PERTs trials to allow monitoring the occurrence of uncommon serious events.

7.1.3. CFTR modulator therapy

Liver toxicity is of special interest for CFTR modulators and liver function should be specifically monitored in clinical trials. Dose reduction and stopping rules should be predefined in the protocol. Patients with suspected drug-induced liver injury, including cholangitis, should undergo intensified monitoring, preferably until resolution of the event. Causality assessment of serious clinical liver events using expert adjudication is recommended.

Underlying cystic fibrosis related liver disease (CFLD) may confound an assessment of potential liver toxicity, and patients with advanced liver disease are at risk of developing a more severe reaction in case of CFTR modulator-induced liver toxicity. Patients with advanced CFLD should be excluded from trials with new CFTR modulators, and the definition of the advanced CFLD should be pre-defined in the protocol.

Respiratory events such as haemoptysis, bronchospasms, dyspnoea and rarely pulmonary exacerbations, as well as ocular adverse effects (cataracts) have also been described and should be actively monitored until complete resolution in clinical trials with CFTR modulators.

To actively detect any potential CFTR modulators-related pancreatitis, IRT supported by amylase and lipase should be included in the standard safety evaluations.

Other adverse events that have been reported to be related to CFTR modulators include rash and neuropsychiatric disorders such as depression and insomnia; they should also be part of the standard safety assessment in clinical trials.

7.1.4. Gene-targeting therapies and mRNA

AAV-based gene therapies have been shown to cause serious undesirable effects, especially when a systemic effect is targeted, including liver toxicity, thrombotic microangiopathy and neurotoxicity. The occurrence of these events should be carefully monitored. Reference is made to the related specific existing guidelines (*Guideline on follow-up of patients administered with gene therapy medicinal products EMEA/CHMP/GTWP/60436/2007*; and *Guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products EMEA/149995/2008*).

7.2. Long-term safety

Considering the rarity of the disease, and the ultra-rarity of some disease genotypes, the size of the safety database and the level of characterisation of the safety profile might be limited at the time of approval.

Depending on the mechanism of action and of the pursued indication, the pivotal trial might not be of sufficient duration to allow capturing appropriate long-term safety. In this case, long-term safety should be assessed in the frame of open-label extension(s) initiated pre-authorisation, typically followed by post-authorisation safety monitoring e.g., through medicinal product registries and/or PASS. CF registries are a key tool for collecting multi-year safety data (e.g. hepatic, ophthalmologic, carcinogenicity concerns for gene-targeting therapies. A prospective longitudinal cohort design is recommended. For growing children, these long-term trials should include an assessment of the impact of the medicinal product on the growth and overall development.

Findings of host cell DNA integration have been reported with AAV-based gene therapies. The safety of AAV-based products should therefore be long enough to assess the occurrence of potential events associated with insertional mutagenesis, including malignancies. Safety monitoring of up to 15 years has been recommended by the CHMP at the time of approval of MAA for several AAV-based therapies.

8. Specific designs and endpoints for CFTR modifiers in children below 12 years of age

Young children are expected to be included as early as possible in clinical trials assessing the efficacy of CFTR-modifiers, be they clearly symptomatic or not, with the aim of slowing disease progression and preventing irreversible damage. In not clearly symptomatic children, the primary efficacy endpoints recommended for trials in older populations may not be sensitive enough to show a treatment effect, and specific outcome measurement tools need to be used for primary efficacy analysis.

Reference is made to the *ICH E11(R1) Guideline on clinical investigation of medicinal products in the paediatric population* as regards the general recommendation of a staggered inclusion of paediatric patients of a given age class after sufficient efficacy and safety data have been collected in the older age groups.

8.1. Specificities of dose finding

Reference is made to:

- the *Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population* (EMEA/CHMP/EWP/147013/2004 Corrigendum),
- the *Reflection paper on the use of extrapolation in the development of medicines for paediatrics - Revision 1* (EMA/1897724/2018) and to the *ICH guideline E11A on paediatric extrapolation* (EMA/CHMP/ICH/205218/2022) for recommendations on extrapolation of doses across paediatric age classes.

Efficacy on respiratory function

The PK/PD relationships established in adults also apply to children. The doses for paediatric development may be extrapolated from adult data, upon appropriately justified scaling, taking into account the mechanism of action, the potential maturation of the pharmacological target, weight, and any specificity in PK characteristics (e.g., any observed age-dependent clearance variation).

For inhaled products, dose extrapolation across ages relies on more complex considerations since inhaled therapies require device-, deposition- and lung-maturity–dependent justifications. Feedback from the CHMP through a scientific advice request is generally recommended.

Efficacy on exocrine pancreatic function

In rapidly growing children below 6 years of age, the highest dose as determined based on justified scaling from older and the dose-effect on IRT or elastase will be the optimal one to be recommended for confirmatory studies with CFTR modifiers.

8.2. Confirmatory studies

Design considerations

Whenever feasible, paediatric efficacy and safety trials should be conducted, especially for products modifying the genome expression. In young children, trial designs should incorporate pragmatic elements (e.g. flexible visit windows, centralised LCI expertise, minimised procedural burden) to ensure the generation of interpretable data.

An extrapolation strategy for efficacy on respiratory function across age classes might be an accepted option, especially for CFTR modulators and in very young children aged below 2 years in whom collecting LCI data is not feasible (see section 5.2.2.1/LCI). Reference is made to the *Reflection paper on the use of extrapolation in the development of medicines for paediatrics - Revision 1* and to the *ICH guideline E11A on paediatric extrapolation* for recommendations on extrapolation of efficacy across paediatric age classes.

The extrapolation plan should usually be based on i) established B/R in older paediatric patients and adults; ii) PK/PD collected in the paediatric population of interest; although sweat chloride and other CFTR function biomarkers are not validated surrogate endpoints and cannot replace clinical efficacy outcomes, they play an important role as pharmacodynamic markers to support extrapolation across age groups when appropriately bridged to clinical data. iii) exposure-response modelling & simulation data (efficacy and safety response in the paediatric population of interest); and iv) PAES and/or PASS to collect clinically meaningful data to confirm benefits and risks in the concerned age class.

Each specific extrapolation plan is defined on a case-by-case basis, depending on the availability and feasibility of each step as described above, e.g. the feasibility of testing several doses in the paediatric population of interest. Therefore, if an extrapolation strategy is considered by the Applicant, the

Applicant is recommended to seek feedback from the EMA on the appropriateness of the extrapolation approach, as well as on their extrapolation concept and plan.

It is reminded that, as a regulatory requirement, a Paediatric Investigation Plan (PIP) should be submitted as soon as PK data have been acquired in clinics and before phase 2 is initiated.

Endpoints

In the age subset not yet presenting with clear pulmonary symptoms, the assessment of both improvement in gastrointestinal parameters additionally to improvement in respiratory parameters may be needed to support the proof of the clinical benefit of an early initiated treatment, and is recommended for genome-modifying therapy with a systemic effect (vector-based gene therapies, mRNAs and AONs) when administered to young children in whom CFTR modulators therapy has not yet been initiated. The use of co-primary endpoints, or at least a key secondary endpoint (i.e., powering the trial on this endpoint, and controlling for type 1 error, e.g., with hierarchical testing) is recommended.

As for trials in older populations, the pharmacodynamic endpoint of SwCl should always be performed.

Respiratory endpoints

Lungs develop from birth to puberty. CF disease first affects small peripheral airways. In children up to 12 years of age, CF has not deteriorated the large airways to such an extent that it can be detected by ppFEV1.

- $LCI_{2.5}$ is the recommended primary endpoint to assess deteriorations in lung in children up to age 12 years of age in whom large airways may not be yet sufficiently deteriorated to be detected by ppFEV1 and may be performed in infants with appropriate caution (see section 5.2.2.1). However, it is recommended that data on changes in LCI are supported by ppFEV1 data from adolescents and adults.

  Absolute change from baseline in $LCI_{2.5}$ is the recommended primary efficacy endpoint. Upon appropriate justification, the absolute change from baseline in $LCI_{5.0}$ might also be accepted.

  A minimal clinically important difference of 1 has been accepted for LCI for previous Marketing Authorisations and is considered clinically meaningful based on available literature supportive data and clinical experience.

- CT scans or MRI may be part of secondary endpoints as they may show deteriorations on small airways that are not detectable by ppFEV1. Endpoints based on CT scans or MRI, are not accepted as primary efficacy endpoints as no clear correlation with changes in lung function has been evidenced.

Nutritional status and anthropomorphic parameters

Anthropomorphic parameters such as weight and BMI Z-scores, and growth parameters should always be at least part of secondary endpoints.

Gastrointestinal endpoints

As detailed above, in the population of children aged below 12 years of age, the gastrointestinal signs and symptoms are more pronounced than the pulmonary symptoms and thus a gastrointestinal outcome might be of clinical interest.

Established EPI is usually evident in the first weeks or months of life and, in the absence of treatment, infants are pancreatic insufficient by one year of age. However, under CFTR modulators therapy initiated below 6 years of age, delay in progression has been observed and EPI process is slow (*Davies & al. 2021; Davies & al. 2016; Rosenfeld 2018; Rosenfeld 2019*). Consequently, young paediatric subjects in whom CFTR modulators have been initiated below 6 years of age might have too limited clinical EPI signs and symptoms to leave sufficient room for statistically significant improvement in steatorrhea or parameters of nutritional status.

In these children, the pharmacodynamic biomarkers faecal elastase, IRT and FC may be the only tools to show early organ response to a CFTR-modifier therapy (e.g., CFTR modulator, gene therapy). These biomarkers have been assessed in trials conducted with CFTR modulators in young paediatric subjects aged < 6 years of age, and faecal elastase has been shown to be improved (*Davies & al. 2021; Davies & al. 2016; Rosenfeld 2018; Rosenfeld 2019*). Faecal elastase-1 values should be analysed as the change from baseline to the last trial visit. In addition, an analysis of responders should be provided using a cut-off value 200 µg/g stool for definition of response (*De La Iglesia & al. 2025*).
Elastase has not be shown to return to normal if CFTR-modifier therapy is initiated after 6 years of age (*Davies & al. 2021(2)*), and in this case normalisation of elevated markers of intestinal and pancreatic inflammation IRT and FC might be the only tool/marker to assess the efficacy of a CFTR modifier treatment in children with still preserved pancreatic function (*Davies & al. 2021(2)*).

Validation efforts before the use of these biomarkers in a confirmatory trial (i.e., during exploratory and/or phase 2 trials) are encouraged.

Other biomarkers may be used if appropriately validated, considering the lack of associated clinical experience.

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10. Definitions

CFTR-modifier: medicinal product which mechanism of action allows restoring, at least partially, CFTR function. They include CFTR modulators, gene-targeting therapies, and mRNAs.

CFTR modulators: small molecules aiming at correcting trafficking or gate defects associated with a specific mutation of the CFTR gene.

Gene-targeting therapies: therapies aiming at modifying the genome expression by acting on the DNA (including vector-based gene therapy, AON).