COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON THE CLINICAL DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF CYSTIC FIBROSIS

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GUIDELINE ON THE CLINICAL DEVELOPMENT OF PRODUCTS FOR THE TREATMENT OF CYSTIC FIBROSIS

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EXECUTIVE SUMMARY

The aim of this guideline is to provide guidance on the clinical development of compounds for the treatment of cystic fibrosis (CF), a systemic chronically debilitating disease, mainly paediatric up to now, with a regularly increasing adult population as life expectancy improves.

Because up to now CF cannot be cured, currently the goal of therapy is to delay disease progression.

In the context of low efficacy of available treatments and high level of associated non-compliance and considerably shortened life expectancy, there is a need for new medicinal products to treat pulmonary disease and infections and exocrine pancreatic insufficiency and associated malnutrition. Both conditions affect > 90% CF patients and are the major responsible for morbidity and mortality.

Efficacy in pulmonary disease

As a rule, the goal of therapy is to maintain/restore respiratory function, as assessed by forced expiratory volume in one second (FEV1).

However, a microbiological primary endpoint at 28 days is acceptable for confirmatory trials in the treatment of early lung colonisation or of chronic infection exacerbations,

For almost all other pulmonary indications, FEV1 will be the primary endpoint:

- For prophylaxis and treatment of chronic Pseudomonas Aeruginosa (PA) infection, it is recommended to stratify the patient population at inclusion according to the severity of the pulmonary impairment based upon respiratory function tests, and to age in paediatric studies.
  An at least 6-month clinical primary endpoint assessing the respiratory function through FEV1 measurement is recommended in confirmatory trials, with a 12-month follow-up for safety. Corresponding secondary endpoints should include a microbiological endpoint documenting the potential to select resistant strains and colony density, from an efficacy as well as from a safety viewpoint.

- For slowing/stopping pulmonary disease progression, a 12-month FEV1 endpoint is recommended. Microbiological secondary endpoints such as the “number of exacerbations” are necessary to document efficacy, while enabling ruling out a negative effect on the most relevant pathogens in CF patients.

Randomised active-controlled confirmatory trials are mandatory when a reference treatment exists. When no reference treatment exists, a placebo-controlled study in mild to moderate patients on top of best supportive care is recommended.

When the claim is to improve mucociliary clearance of and treat the underlying chronic obstructive disease, currently approved mucolytic drugs should be used as an active control, in the frame of a superiority trial

The standardisation of concomitant therapy (including bronchodilators, physiotherapy and mechanical therapy) is strongly recommended.

Efficacy in exocrine pancreatic disease

Standardisation of the patient’s specific diet (on a patient per patient basis) is mandatory:

- When the claim is for a “global improvement in nutritional status”, placebo-controlled superiority confirmatory trials in the frame of add-on studies are mandatory (on top of standard therapy). The primary efficacy criterion should be clinical: target height at 12 months and normal weight at 6 months in children, weight gain or nutritional status at 6 months (changes in body weight, weight/height and lean body mass) in adults. Corresponding secondary efficacy criteria should be biological and investigate pancreatic enzymes activity (steatorrhoea and protein synthesis).

- When the claim is a pharmacological claim (e.g. for a “me too” pancreatic enzyme preparations (PEP)), active-controlled-trials are mandatory and non inferiority trials are accepted.
• A biological endpoint (steatorrhoea or protein synthesis) can be accepted as a short-term primary endpoint in confirmatory trials, preferably in the frame of cross-over design due to the high level of inter individual variability.

Efficacy in overcoming cystic fibrosis transmembrane conductance regulator (CFTR) mutation

A therapy aiming at overcoming CFTR mutation (protein of gene therapy) would be expected to translate into a clinical improvement in both pulmonary and pancreatic disease. The improvement in another organ dysfunction would be also an acceptable endpoint.

Because of the associated specificity of disease features, such trial should rely on a stratification of patients at inclusion, based on the characterisation of the class of mutation.

Further recommendations to this regard are premature.

Safety

Influence on growth and development should be systematically addressed in paediatric studies.

The emergence of resistance to an antibiotic (ATB) should always be assessed, and cross-resistance between different ATB used in the treatment of PA infection should be addressed.

Regular assessment of good aerosol technique is needed.

Also rare, a definite dose-dependent lipase-induced fibrosing colonopathy has been found in young children, which should be monitored and taken into account when establishing the initial dosing of PEP and maximal pancreatic enzyme replacement therapy (PERT).

Because the standard of care is steadily improving and life expectancy is steadily growing, revision and amendments are anticipated to be necessary within a short time frame.
1 INTRODUCTION

1.1 Definition of cystic fibrosis

CF is an autosomal recessive disorder caused by mutations in the gene encoding for the CFTR, a protein that acts as a chloride channel. The most common mutation is deletion of phenylalanine at position 508 of CFTR. The mutation has been named F508del.

The disruption of chloride and sodium transport, associated with water transport abnormalities, results in viscous secretions in different exocrine tissues, mainly the respiratory tract, pancreas, gastrointestinal tract, sweat glands and other exocrine tissues. Increased viscosity of these secretions makes them difficult to clear and patients develop progressively exocrine gland dysfunction of multiple organ systems in childhood, resulting in chronic respiratory disease as well as other pathologies including pancreatic insufficiency, obstructive hepatic and biliary abnormalities, distal intestinal obstruction syndrome, and reduced fertility (agenesis of the vas deferens in males, delayed menarche and thick cervical mucus in females).

CF is one of the most common genetic disorders among Caucasians (prevalence 2-4 in 10,000). It is a life-threatening and chronically debilitating disease markedly impairing quality of life.

1.2 Natural history of cystic fibrosis

1.2.1 Respiratory disease

The lower respiratory tract involvement is characterised by progressive bronchiectases and obstructive pulmonary disease (> 90% patients), and is the primary cause of morbidity and mortality in patients with CF (> 90% of fatalities). It thus most commonly determines outcome.

Pathogenesis

In the lower respiratory tract, the hyperviscous mucus impairs mucociliary clearance, the first line of host defence, leading to retention of particulate material and bacteria. The antibacterial properties of mucus are also decreased. As early as 4 weeks of age, CF patients begin to develop mucus plugging, bronchiectasis, neutrophilic invasion and airways inflammation.

Overtime, most patients develop chronic bacterial colonisation/infection of the airways. Bacterial colonisation occurs very early in the first few years of life. A typical persisting pathogen pattern in pulmonary tract consisting of *Staphylococcus aureus* (SA) and/or *Pseudomonas aeruginosa* (PA) strains) during routine monitoring is a hallmark of the disease. Chronic SA infection usually precedes PA infection. *Haemophilus influenzae*, *Escherichia coli* and *Klebsiella pneumoniae* also characteristically chronically colonise the airways.

Since it is rarely eradicated, PA is the main cause for chronic infection and is associated with chronic lung injury and reduced survival. The PA bacteria usually changes from a non-mucoid pattern to a mucoid type after some time of the colonisation, thereby preventing antibiotics to work efficiently. 90% of CF patients are colonised with PA, and PA infections are the cause of mortality in 80% of those patients. Mean relapse time after treatment of early colonisation is 8-12 months.

*Burkholderia cepacia* has more recently been isolated in older CF patients and its isolation from sputum has been causally associated with a rapid decline in pulmonary function progressing to death (Cepacia syndrome).

Repeated cycles of endobronchial and endobronchiolar bacterial infection and the secondary inflammation cause chronic damage to the airways. Consequences are destruction of the airways and progressive bronchiectases and obstructive pulmonary disease (> 90% patients).

Signs and symptoms

Main initial symptoms are consistent with chronic obstructive pulmonary disease (COPD): persistent cough due to thick sputum difficult to expectorate, respiratory insufficiency with altered respiratory function tests. Air trapping and hyperinflation are observed.
As the disease progresses FEV1 is reduced. It is estimated that FEV1 declines by 1.9% per year in children and adolescents.

Ultimately, chronic mucopurulent bronchiectases leads to structural abnormalities and fibrosis, and the total lung capacity and Forced Vital Capacity (FVC) decline. Acute exacerbations may occur at any time of the disease course with exacerbation of clinical symptoms (fatigue, fever, acute respiratory insufficiency, loss of appetite, weight loss) and bacterial airway overgrowth (see Section 8 for definition of exacerbation).

1.2.2 Pancreatic disease

Exocrine pancreatic insufficiency is present at birth in 40 % of patients and in up to 85 % at the end of the first year in life.

In the pancreas, abnormal mucus secretion causes obstruction and dilatation of pancreatic ducts, with associated unexplained inflammation, leading to progressive destruction of pancreatic tissue. This leads to diminished secretion of digestive enzymes, bicarbonate and water causing maldigestion and malabsorption of proteins, carbohydrates but most pronounced of fat. This picture of combined maldigestion and malabsorption is the main contributor to malnutrition in early life, which concerns 85 % of paediatric patients and continues into adult life.

Malabsorption/maldigestion-induced malnutrition

When function drops below 10% steatorrhoea develops.

Normally, the duodenum, biliary tract and pancreas secrete enough bicarbonate to buffer acidity in the duodenum and proximal jejunum. In CF patients, this bicarbonate secretion is deficient, and the duodenum and proximal jejunum remain acid. Pancreatic enzymes, especially lipase, are easily degraded by acid. Coated enzyme preparations might circumvent this degradation, but in the jejunum acidity changes and particle are dissolved, losing some efficacy over this trajectory.

Fat digestion is also dependent on bile salt micelles, and on mucosal fatty acid transport. In CF patients,

- mucosal transport is diminished for reasons still unknown.
- insufficient bile secretion in CF is responsible for insufficient biliary concentrations in the gut lumen resulting in insufficient micelle formation and thus impaired fat digestion.

Associated malabsorption/maldigestion is the main contributor of initial malnutrition.

Other causes for malnutrition

Anorexia due to chronic infection and inflammation (increased requirements) contribute significantly to malnutrition, along with malabsorption/maldigestion (supply deficiency). The prevalence of malnutrition is decreasing in paediatric patients but remains high in adults.

Malnutrition favours infections and is responsible for a decreased life-expectancy independently from respiratory function impairment. It also might contribute to impaired bone mineral status, and is aggravated by poor treatment compliance.

Endocrine pancreas damage with diabetes mellitus may follow exocrine pancreatic insufficiency (50% of patients at age 30). Progressive fibrosis of the pancreatic tissue around the islands of Langherhans results in destruction of insulin-secreting beta-cells.

The key predisposing factors are genotype, age and hepato-biliary disorders (15-20% of patients).

1.2.3 Other clinical manifestations

They include digital clubbing, sinonasal disease, meconium ileus (17% of affected newborns), obstructive biliary tract disease (15-20% of patients), agenesis of vas deference (>90% of affected men) and reduced female fertility (50%).
1.2.4 Course of the disease

Cystic fibrosis is a rare disease becoming symptomatic at paediatric age and progressing into adulthood.

CF cannot be cured for the time being, and life expectancy is considerably shortened due to the progressive respiratory damage and associated cor pulmonale. Most patients are finally listed for heart/lung transplantation. If they are transplanted the outcome is the same as for patients with other chronic lung diseases.

Up to now CF has been mainly a paediatric disease. However, due to great advances in the prophylaxis and management of chronic respiratory infection in the past 20 years, CF patients overall now reach a mean age of 30 to 40 years if all genotypes are considered, and the adult population is steadily growing. However, patients with severe phenotypes are likely to die of the disease at approximately 25 years of age.

Improved diagnostic and therapeutic approaches mainly consist of:
- Earlier diagnosis due to neonatal screening.
- Earlier Pseudomonas aeruginosa identification and use of eradication protocols during childhood; consequently, chronic Pseudomonas aeruginosa colonisation now occurs later in the course of the disease.
- Systematic optimal nutrition and replacement of pancreatic enzymes, with a subsequent decrease in malnutrition.

1.3 Management of cystic fibrosis

Cystic fibrosis is a multisystem disease, and best cared for by multidisciplinary teams including paediatricians, pneumonologists, physiotherapists, nutritionists, gastroenterologists, endocrinologists, ENT, microbiologists, social workers, psychologists. It is preferable that this global care management of patients is provided in specialised CF centres.

The management of respiratory tract symptoms combines pharmacological treatment and physiotherapy. It is to be emphasised that malnutrition, digestive problems (including hepatobiliary disorders) and diabetes contribute to the morbidity and mortality and can aggravate pulmonary complications.

Up to now, no causal therapy to correct CFTR production and function is available. The primary goal of therapy is currently supportive, and includes:
- Slowing the decline in lung function by clearing airways of mucus and by controlling respiratory infections to improve/maintain the respiratory function, thereby delaying the disease progression and increasing life expectancy.
- Maintaining nutritional status by providing pancreatic enzymes replacement therapy and high caloric food intake.

1.3.1 Current therapeutic management of pulmonary disease

- A number of inhaled and systemic ATB are used in CF patients according to EU consensus, to treat and prevent infections, mainly aminoglycosides, cephalosporins and fluoroquinolones. Colistimethate sodium is indicated in the early treatment of primary colonisation. Inhaled tobramycin has been granted a specific indication in CF. It has been demonstrated to improve pulmonary function and decrease sputum Pseudomonas colony counts. Greater clinical benefit is observed in younger patients with fewer irreversible pulmonary deficits, emphasising the need for early intervention before irreversible damage is present.
- Mucolytic therapy to improve mucociliary clearance of lower-airway secretions and treat chronic obstructive pulmonary disease. Hypersaline solutions are used to decrease mucus viscosity (osmotic mechanism). Dornase alfa (rhDNase) is the only current drug acting on mucociliary clearance specifically approved for the treatment of CF.
• Inhaled bronchodilators are used, although supported by little scientific evidence, except for β2-mimetics only.

• Anti-inflammatory therapy: no general consensus and or general recommendation is available.

For inhaled drugs, the deep pulmonary deposition relies upon nebuliser parameters (diameter of the delivered microspheres), duration of nebulisation and dosage of the inhaled solution.

Traditional inhalations of aerosols of tobramycin or colistin require an appropriate nebuliser associated with a relatively big compressor, non portable (duration of administration of 15-20 min). New portable devices (E-flow device allowing a tiny compressor) have been recently developed, reducing the duration of nebulisation to 10 minutes, with improved efficiency and better compliance. Dry powder inhalers with a light portable aerosolisation equipment are currently being developed (duration of administration of 5 min).

Management of the respiratory disease associates extensive pharmacological and physiotherapy treatments. It is burdensome and time consuming, contributing to the frequently observed non-compliance and poor quality of life.

1.3.2 Current therapeutic management of pancreatic disease

Pancreatic enzymes preparations (PEP)

PEPs are commonly used as enzyme replacement therapy and have greatly improved the nutritional status of CF patients by preventing malnutrition.

Standard treatment consists of porcine PEPs. They contain lipases, proteases and amylase, and were first marketed in the form of powder, tablets and capsules.

Recently marketed PEPs are capsules that contain enteric coated microencapsulated enzymes, either as microspheres or micro tablets with an acid-resistant film to prevent inactivation of the enzymes by gastric and upper intestinal acidity. The ratio of proteases to lipases differs between preparations.

A number of combinations of enzymes (protease, amylase and lipase) are approved as pancreas enzymes replacement therapy for the treatment of CF.

High caloric intake and nutritional supplements:

• High calorie diet (130-150% more than for healthy individuals of the same age), or enteral nutrition, if necessary.

• Nutritional supplements/calorie boosters.

• Electrolytes (NaCl preparations).

• Vitamins (especially fat soluble A, D, E, K, and B12 in specific indications).

2 SCOPE

Due to:
• the low efficacy and high burden of available treatments and the high level of associated non-compliance;
• the shortened life expectancy;
• the fact that there is currently no eradication of PA in the context of chronic colonisation;
• the impaired quality of life and
• the relatively high prevalence of the disease.

There is a need for the development of new medicinal products to treat pulmonary disease and exocrine pancreatic insufficiency. Both conditions affect > 90% of CF patients and are the major determinants of morbidity and mortality.
Therefore the aim of this guideline is to provide guidance on the clinical development and evaluation of medicinal products for the treatment and prevention of:

- Lower respiratory tract infections and destruction;
- Exocrine pancreas insufficiency, responsible for malnutrition and worsening of pulmonary status.

The specific development of gene therapy products is not covered by this guideline.

3 **LEGAL BASIS**

This guideline has to be read in conjunction with the introduction and general principles (4) and part I and II of the Annex I to Directive 2001/82/EC or 2001/83/EC as amended and in conjunction with the following guidelines:

1). Directive 2001/20/EC on the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use;

2). Regulation on Medicinal Products for Paediatric Use (EC) 1901/2006 as amended by Regulation (EC) 1902/2006;

3). Ethical Considerations for Clinical Trials Performed in Children – Recommendations of the Ad Hoc Group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use (draft);

4). (ICH E11) Clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99);

5). Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (CHMP/EWP/147013/04);

6). Reflection paper on formulations of choice in paediatric population (EMEA/196218/05)

7). Guidelines on conduct of pharmacovigilance for medicines used by the paediatric population (CHMP/PhVWP/235910/2005-rev.1);

8). Guideline on the Need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications CHMP/SWP/169215/05 (draft);

9). Note for guidance on the Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95);

10). Points to consider on Pharmacokinetics and Pharmacodynamics in the Development of Antibacterial Medicinal Products;

11). Points To Consider On Requirements For Clinical Documentation For Orally Inhaled Products (OIP) (CPMP/EWP/4151/00);

12). Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products containing Known Constituents (CPMP/EWP/239/95);

13). Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products;

14). Guideline on Clinical Trials in small populations CHMP/EWP/83561/05;

15). Regulation No (EC) 141/2000 on orphan medicinal products;

16). Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal study (CPMP/2330/99);

17). Points to Consider on Switching between Superiority and Non-inferiority;

18). Guideline on the choice of non inferiority margin (CPMP/EWP/2158/2005);

19). (ICH E9) Statistical principles for clinical trials;

20). (ICH E10) Choice of control group in clinical trials;
21). (ICH E4) Dose-response information to support drug registration;
22). (ICH E1A) Extent of population exposure to assess clinical safety for drugs(CPMP/ICH/375/95);
23). Other relevant Agency (including ICH) Guidelines.

4 PULMONARY DISEASE EFFICACY DATA

4.1 Potential claims
Because up to now CF cannot be cured, currently the goal of therapy is to improve/maintain respiratory function, therefore delaying disease progression and increasing life expectancy.

Based on recent scientific advices and orphan designations, the expected therapeutic indication claims (i.e. in section 4.1 of the SmPC), are:
- Management of broncho-pulmonary infections
Since chronic PA infection is the key factor in the development of bronchiectases and mortality, the claims may focus on:
  ▪ Treatment of early PA colonisation with or without a claim of eradication of PA;
  ▪ Treatment of chronic infection and/or exacerbations;
  ▪ Prophylaxis of chronic PA infection (this can be obtained either by ATB therapy or by improvement in mucociliary clearance).

- Prevention of progression of lung damages (fibrosis, bronchiectasis)

Nota Bene: “Improvement in mucociliary clearance” is not acceptable as a therapeutic claim, it is a pharmacological property that could translate into either “Prevention of infections” and/or “Prevention of progression of lung damage”. Consequently, a mucolytic product should have to demonstrate a long-term clinical benefit.

4.2 Patients population

4.2.1 Diagnosis of cystic fibrosis
Patients enrolled should have documented CF. Diagnosis of CF should rely on a combination of sequential approaches:

- Specific clinical features.
- Evidence of dysfunction of the CF transmembrane conductor regulator (CFTR); the latter is usually documented by elevated chloride concentration in the sweat observed in several separate tests.
- Documentation of the presence of disease-associated CFTR mutations in both alleles. Sequencing of the CFTR gene to confirm the presence of some mutations is now commercially available.
  Due to the heterogeneity of mutation pattern, a negative test does not preclude the presence of the disease.
- In case of a negative DNA test, the diagnostic strategy should be completed with the demonstration of:
  ▪ A reduced nasal epithelial chloride expression evaluated through assessment of nasal transepithelial potential difference (TEPD), or
  ▪ A reduced transepithelial electrolyte transport as assessed in rectal biopsies mounted in Ussing chambers.

4.2.2 Other Inclusion criteria
The choice of study population should reflect the claimed indication.
For pulmonary infection claims, the definition of inclusion criteria is critical, in order to separate between conditions. The Definition of the European consensus conference on CF (2000) should be used to define the accepted claims (see Section 8 for definition):

- Treatment of early colonisation;
- Treatment of chronic lung colonisation;
- Prevention of chronic lung colonisation;
- Treatment of bronchopulmonary infection;
- Prevention of chronic bronchopulmonary infection;
- Treatment of exacerbation;
- Eradication.

In clinical trials aimed at prophylaxis / treatment of chronic PA infection, it is recommended to stratify the patient population at inclusion according to the severity of the pulmonary impairment based upon Respiratory Function Tests, and, in paediatric studies, to age.

The alternative is to define an upper limit for FEV1 at inclusion along with the classical lower limit. The risk of exacerbation increases with the severity of the disease, and with age. Severity is often linked with age.

### 4.2.3 Children

CF is still mainly a paediatric disease. It concerns a small population, including infants and children, for which the relevant guidelines should be respected. However, the proportion of young adults is steadily growing, with a life expectancy of around 30 years. By way of illustration, based on the French Observatory 2007 data, 2005 out of 4775 CF patients are adults (42%).

Due to differences in disease status including bacterial colonisation and disease progression as well as possible differences in the safety profile in different age categories, efficacy and safety need to be established separately in adults and children. Age categories should be consistent with the Paediatric regulation.

Paediatric studies may be difficult to perform, particularly in very young children, because respiratory function is difficult to assess in children < 5 years. However, respiratory function tests in young children can be performed in specialised centres that are able to promote standardized methods.

### 4.2.4 PK and PD studies

Patients with CF have a different pharmacokinetic profile compared to other patient populations. Studies have shown that CF patients have increased volume of distribution and faster elimination of drugs, mainly through increased renal clearance but also due to a more rapid metabolism in the liver. This means that patients with CF usually require higher doses of medicines, which should be taken into account during clinical trials. Consequently, extrapolation from data from other patient groups is not appropriate, wherefore separate PK/PD data should be collected for each drug tested in CF patients.

### 4.2.5 PK data in bronchopulmonary infection claims

For ATB, the dosage is difficult to optimise, antibacterial activity being only one factor determining the response to treatment. Dose regimens are often deduced from the minimum inhibitory concentration (MIC) and the minimum bactericide concentration (MBC), and PK characteristics.

The point to consider on PK and PD in the development of antibacterial drugs underlines the relationships between the MIC and antibacterial activity for aminoglycosides, fluoroquinolones, beta-lactams, along with the relationships between Cmax and MIC in the selection of micro-organisms resistant to fluoroquinolones and aminoglycosides.

Therefore, there is a need to perform PK/PD investigation to document that the adequate dose has been selected with an aim to minimise the risk for resistance development.
4.2.6 PK/PD in children

For PK data in CF children, drug disposition, especially for antibiotics given orally, intravenously or by nebulisation, is a key problem as drug pharmacokinetics and pharmacodynamics are specific. Consequently, extrapolation from adult data is not appropriate and pharmacodynamic curves should be evaluated, for each drug tested in children.

4.3 Efficacy studies: possible endpoints in cystic fibrosis patients

Up to now, there is no available systemic therapy to correct CFTR production and function. Currently, primary goal of therapy is supportive, and includes slowing the decline in lung function by clearing airways of mucus and controlling respiratory infections to improve/maintain respiratory function, therefore delaying disease progression and increasing life expectancy.

Based on the pathophysiology of the disease and the intended claim, several categories of endpoints may be distinguished:

4.3.1 Clinical endpoint: assessment of respiratory function

FEV1 is the recommended primary endpoint (because the initial pulmonary defect in CF is obstructive); FEV1 is easy to measure but should be standardised to decrease variability. FEV1 has been criticised in patients with COPD, because forced expiratory manoeuvres cause airway collapse and impede adequate evaluation of lung function. Therefore, FVC (forced vital capacity) and/or FEV25/27 could be also used, as secondary endpoints, to explore the respiratory function.

- Rate of decline in FEV1 has been demonstrated to correlate with survival and to be the strongest clinical predictor of mortality, with a more marked effect in patients with pancreatic-insufficient disease. This prognostic value increases when patients grow older, with a plateau at the age of 15.
  FEV1 is repeatable and, adjusted for age and sex, has been shown to be a cofactor for mortality.
- Effect size: a clinically relevant change in FEV1 should be defined and justified \textit{a priori}, and the study should be powered accordingly.
- The frequency of FEV1 measurements depends on the protocol and has to be justified.
- The time point for the clinical endpoint should allow concluding on the long-term benefit for the patient. Therefore, a study duration of at least 6 months is recommended for the demonstration of efficacy (based on repeated measurements of FEV1), with a (pre-defined in the protocol) 12-month follow-up for safety.

Clinical endpoint in children

It is acknowledged that functional respiratory exploration is hardly feasible in children <5 years. However, respiratory function tests in young children can be performed in specialised centres able to promote standardised methods.

4.3.2 Microbiological endpoint

The microbiological endpoint should document:

- The microbiological efficacy.
- The potential to select resistant strains (including MICs of isolates, stability of resistant mutants).
- Colony density.

Time point

When the primary endpoint is microbiological, a one-month study duration is acceptable for efficacy assessment.
Recommendations for sample-taking procedure for microbiological assessment

In patients with spontaneous expectoration:

Sputum induction and culture (oropharyngeal cultures) is recommended, although this method has not been compared to the reference standard bronchoalveolar lavage (BAL). The sample may be optimised by chest physiotherapy or by using bronchodilators and/or an rhDNAse aerosol.

In the absence of spontaneous expectoration:

- Throat swab, which may be taken after coughing (cough swab), is the recommended sample-taking procedure in the absence of spontaneous expectoration. It is the only test that has been validated in comparison with BAL. It is frequently used in children, and exhibits a high specificity and sensitivity towards PA.
- Nasopharyngeal aspiration with a small catheter introduced through the nostril (feasible whatever the age). It is frequently used and well tolerated in infants. However, it has not been evaluated when compared to the reference standard.
- Induced sputum technique: expectoration is induced with nebulisation of hypertonic saline after inhalation of beta-2-mimetics. It requires monitoring of lung function. Its role has not yet been determined.

4.3.3 Biological endpoints

Inflammation or infection markers.

4.3.4 Physiological endpoints

In adults, weight changes and lean body mass change.

In children, target height and normal weight (as assessed by standard deviation scores and Z-scores).

4.3.5 Quality of life (QoL) endpoints

CF is a chronic condition associated with poor quality of life, partly due to the heavy and time consuming therapeutic management.

A quality of life (QoL) assessment is valuable in long-term studies. The time point should be at least at 3 to 6-month (shorter study duration can only assess the efficacy of the product, not its specific impact on HRQL).

The CF QoL questionnaires are fully validated in CF patients and are recommended.

A demonstration of a benefit on health-related quality of life (HRQL) should be performed apart from the demonstration of efficacy, and supplementary to it.

A claim of improvement in QoL (or lack of deterioration) would be acceptable only in section 5.1 of the SmPC.

Such a claim should be supported by studies specifically designed to demonstrate a HRQL benefit.

4.4 What should be the efficacy endpoints in bronchopulmonary infection trials?

4.4.1 Recommendations for the primary efficacy endpoint in bronchopulmonary infection claims

For claims of treatment/prevention of bronchopulmonary infections, the following should be taken into consideration:

- Even for an ATB, a specific claim in cystic fibrosis, which falls into the scope of this guideline, should demonstrate that the drug enables achieving the primary goal of treatment of the pulmonary disease, currently supportive (i.e. to improve/maintain the respiratory function, see section 4.3.1). Therefore the primary endpoint should be clinical and demonstrate the benefit of therapy on respiratory function.
Moreover, several other arguments speak against a unique microbiological primary endpoint:

- There is great difficulty to obtain microbiological samples, particularly in children.
- The sputum is not homogenous and a negative result do not correspond to eradication.
- The result depends to a large extent on the sample-taking procedure (see Section 4.3.2), the gold standard, bronchoalveolar lavage (BAL), is invasive and cannot be repeated frequently. No consensus on other methods is reached, and a negative result cannot enable to rule out the presence of germs.

Consequently:

- A microbiological primary endpoint at 28 days is acceptable for the treatment of early colonisation or of exacerbations;
- For all other claims related to bronchopulmonary infections, the recommended endpoint is a clinical one: an at least 6-month clinical primary endpoint assessing the respiratory function is recommended for prophylaxis and treatment of chronic infection. (see section 4.4.1. assessment of respiratory function).

4.4.2 Recommendations for secondary and other endpoints in bronchopulmonary infection claims confirmatory trials

- When the primary endpoint is clinical, a microbiological secondary endpoint is mandatory for ATB. Data on the potential to select resistant strains should be provided (including MICs of isolates, stability of resistant mutants), and on colony density, from an efficacy as well as from a safety viewpoint. High quality microbiology laboratories are required as standardised pathogen isolation and enrichment methods are mandatory.
- For establishing a clinical benefit for the patient in the treatment of chronic infection, the FEV1 (or equivalent) primary endpoint should be supported by other, harder and more clinically relevant endpoints such as:
  - Number and time to exacerbations.
  - % of patients with decreased exacerbations.
  - Number of hospitalisations.
  - Duration of hospitalisation.
- Weight change is supportive in long-term studies (requires at least a 6-month study duration).

4.5 What should be the efficacy endpoints in trials using a drug improving mucociliary clearance?

Two types of trials can be performed, corresponding to the two potential claims identified in section 4.1.

4.5.1 Efficacy endpoints for demonstration of slowing/stoping inflammation-induced lung damage

Primary endpoints in phase II exploratory trials

Biological markers for inflammation can be used in proof of concept studies.

Biological of pharmacological markers of inflammation are also acceptable primary endpoints in phase II exploratory trials.
Primary endpoints in confirmatory trials

The primary endpoint should be a clinical endpoint enabling the demonstration of a benefit for the patient, i.e. assessment of respiratory function (FEV1) (see section 4.3.1. assessment of respiratory function).

The time point for assessment depends on the expected progression rate of the disease and should be justified but should probably be 12 months.

Secondary endpoints in confirmatory trials

- Microbiological endpoints such as the ‘number of exacerbations’ are necessary to document efficacy.
- While enabling ruling out a negative effect on the most relevant pathogens in CF patients.
- Physiological (weight loss in adults, height/weight/lean body mass improvement in children) and biological markers (inflammation and infection markers) are needed as supportive endpoints in long term studies.

4.5.2 Efficacy endpoints with drugs improving mucociliary clearance in confirmatory trials in the “prevention of infection” claims

The primary endpoint should investigate the occurrence of infections, such as the ‘number of infections’ or ‘number of exacerbations’. It should be in all cases discussed and justified.

4.6 Design of confirmatory trials

Randomised active-controlled trials are mandatory, when a reference treatment exists.

Blinding may be difficult in studies with inhaled products, due to different associated aerosol devices and to formulations with physical and taste differences. However, every effort should be made to achieve blinding, and any deviation from this goal should be clearly justified.

When no reference treatment exists, a placebo-controlled study in mild to moderate patients on top of best supportive care is recommended (see Section 4.8).

4.7 Comparators in efficacy trials

4.7.1 Comparators in bronchopulmonary infection trials

Different ATB protocols are used for treatment of early colonisation (in children > 6yrs) or of acute exacerbations, or for systematic treatment of chronic infection, and for prophylaxis of chronic colonisation following treatment of early colonisation:

- **Treatment of early PA colonisation**: there is no international consensus, the comparator should be an active control, refer to the current consensus.
- **Prophylaxis of chronic PA infection** following treatment of early colonisation: this prophylaxis should be systematically performed; the comparator should be an active control (including tobramycin, refer to the European consensus).
- **Treatment of chronic PA infection**: the comparator should be an active control (including tobramycin and periodic IV ATB courses). When the claim is treatment of chronic infection, inhaled tobramycin should be the comparator and not a placebo.
- **Treatment of acute exacerbations of chronic PA infection**: the active control should be an IV ATB, depending on susceptibility. Dual combination therapy is currently recommended. Ciprofloxacin *per os* is not recommended as part of an effective dual therapy, but may be added to the dual therapy (triple therapy, but not currently validated).

For inhaled solutions, the nebuliser performance should be harmonised between groups.
The comparator dose regimen should take into account the PK characteristics of CF: increase in renal and non-renal clearances and/or in Vd, inhibition of the antibacterial properties of the sputum. Thus, high doses are generally necessary, often higher that the ones recommended in the SmPC of comparators with no specific CF indication. The reference doses should be those recommended in the EU Consensus conference.

4.7.2 Comparators in trials assessing efficacy of drugs improving mucociliary clearance

Pulmozyme (rhDNase) acts on mucociliary clearance and has been approved for the treatment of CF. When the claim is for mucolytic therapy (to improve mucociliary clearance of lower-airway secretions and to treat the chronic obstructive pulmonary disease), currently approved mucolytic drugs should be used as an active control, in the frame of a superiority trial.

4.8 Concomitant therapies in confirmatory trials

The standardisation of concomitant therapy (including bronchodilators, physiotherapy and mechanical therapy) is strongly recommended. This seems mandatory in case of a test drug administered on top of best supportive care. Current standard therapeutic management of CF consists of pancreatic enzymes preparations, inhaled antibiotics, rhDNase, mucolytics, bronchodilators and optimal nutrition. Due to the key role of mechanical respiratory therapies and the influence of nutritional status on respiratory infection, the multidisciplinary management needs to be standardised as far as possible, including the non pharmacological management and diet, especially because of the influence of nutritional status on lung function.

5 EXOCRIN PANcreATIC INSUFFICIENCY EFFICACY DATA

There is a need for the development of age-appropriate formulations of pancreatic enzymes preparations (PEPs) and of bile salts, including acid-resistant ones. The aim of therapy in CF patients should be to restore (in case of malnutrition) or maintain (in case of risk for malnutrition) the nutritional status (always impaired in exocrine pancreas insufficiency) by ensuring optimal digestion and absorption of nutrients. In that respect, pancreatic enzymes replacement therapy (PERT) along with standard nutritional high caloric intake nutrition (oral or tube-feeding) are standard therapy. Clinical data on addition of bile salt therapy and improvement of mucosal transport are still needed and would be of great interest for CF patients with on-going steatorrhoea despite optimal standard treatment.

5.1 Patients population / inclusion criteria

5.1.1 Diagnosis of cystic fibrosis patients with pancreatic insufficiency

The pancreatic insufficient population is well-defined, based on the evidence of two severe mutations associated with a biological test such as elastase test or steatorrhea. Measurement of the amount of the pancreatic enzyme elastase in the faeces is the diagnostic test preferred and much widely used than steatorrhea, because it is not dependent on the supplementation diet.

5.1.2 Malnutrition criteria in children

Well-accepted malnutrition criteria are defined by:

- A weight/height ratio < 90%, or by
- A height/age ratio < 95% associated with weight stagnation.

The following criteria for weight stagnation broken down by age range are recommended:
### Age range

<table>
<thead>
<tr>
<th>Age range</th>
<th>Quantitative criteria for weight stagnation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 6 months</td>
<td>Weight gain &lt; 500 g/month during ≥ 1 month</td>
</tr>
<tr>
<td>6 – 12 months</td>
<td>Weight gain &lt; 300 g/month during ≥ 2 months</td>
</tr>
<tr>
<td>12 – 36 months</td>
<td>Weight gain &lt; 150 g/month during ≥ 3 months</td>
</tr>
<tr>
<td>3 – 6 years</td>
<td>Weight stagnation during ≥ 3 months or weight loss during ≥ 2 months</td>
</tr>
<tr>
<td>6 – 18 years</td>
<td>Weight stagnation during ≥ 6 months or weight loss during ≥ 2 months</td>
</tr>
</tbody>
</table>

Height and weight changes are assessed using standard deviations scores.

#### 5.1.3 Malnutrition criteria in adults < 70 years

- Either weight losses ≥ 5% within a single month or ≥ 10% within 6 months, or
- Body mass Index ≤ 18.5 kg/m² (normal values range from 18.5 to 25 kg/m²).

#### 5.1.4 Risk for malnutrition

Nutritional status is still normal, but food intake represents < 2/3 of needs.

#### 5.2 Potential claims

**5.2.1 Pharmacological claim (e.g. for a ‘me too’ PEP)**

Up to now, PEPs have been granted indications based on demonstration of a reduced steatorrhoea in controlled trials versus reference PEPs.

When the claim is for a ‘me too’, the granted indication will be the one of the originator.

**5.2.2 Claim for global improvement in nutritional status**

A claim for a global improvement in nutritional status implies to take into account the overall exocrine pancreas insufficiency (lipase + protease + sugar enzyme activities) along with the caloric balance. It is particularly relevant with:

- A new mechanism of action (e.g. PEP improving fat and/or protein digestion and/or absorption and/or bile salt function, antacids acting on intestinal acidity)
- A new chemical entity (e.g. improvement in mucosal transport, improvement in enzymes survival).

#### 5.3 Possible efficacy endpoints and related study duration

For each patient, the fat, sugar and protease intake should be recorded to enable further efficacy assessment.

Standardisation of the patient’s specific diet (on a patient per patient basis) is mandatory: the patient’s diet should be reviewed by a dietician regularly, which will provide the most useful estimate of fat intake for a particular patient. Faecal fat excretion should be assessed as percentage of fat intake which should be at least 30 grams of fat per day to avoid fluctuations in the results.

**5.3.1 Clinical endpoints**

*Children*

In children, given that the lean body mass development lags behind from the age of 5, target height and normal weight should be the clinical endpoints. This is achieved through a regular follow-up of height and weight growth curves, in comparison with reference curves (i.e. standard deviations scores). Logistic regression analysis enables estimating the weight/height ratio and the height for age and weight for age Z-scores.
Time-point for assessment should be 6 months for weight and 12 months for height.
In order to specify the risk level and adapt the nutritional supply, the use of the Paediatric Nutritional Risk Score is recommended.

**Adults**
In adults, weight gain or nutritional status (changes in body weight, weight/height and Lean Body Mass) could be considered as the relevant primary endpoints.

The corresponding time point of assessment is 6 months.

### 5.3.2 Biological endpoints

**Steatorrhoea**
Steatorrhoea measures the efficacy of lipase administration. Meaningful beneficial effect on steatorrhoea at 72 hours may be accepted as a surrogate (mean decrease in stool fat and number of responders should be considered). The decrease in steatorrhoea should be expressed as a percentage of the fat intake.

However, although the main focus of studies is to decrease steatorrhoea based on lipase content of preparations, almost all patients persist with steatorrhoea and dose increases rarely diminish it further. This can be partly explained because steatorrhoea is also dependent on low bile acid levels in the intestinal lumen and on acidity of the duodenum/jejunum due to the lack of bicarbonate in pancreatic, biliary and mucosal secretions.

The dosing of lipase should be expressed as IU lipase per gram of fat ingested.

Most children titrate themselves with 1500-2000 IU lipase/gram of fat ingested (variation 500 – 4000 IU/g fat ingested). Dosing per kg makes no sense, because young children eat 5 grams fat/kg, older ones 2 grams fat/kg of body weight.

**Protein synthesis**
Follow-up of protein synthesis could be an acceptable biological endpoint. As a matter of fact, in CF patients, a dose-dependent (when compared to the dose of orally-administered proteins, between 1 and 5 g/kg body weight) increase in protein synthesis is observed despite increased catabolism.

It is to be underlined that the consequences of undernutrition are more severe (associated with increased (mainly infectious) morbidity and mortality) when the deficit is predominantly proteic, with associated hypo-albuminemia.

### 5.4 Study characteristics when the claim is for a ‘Global improvement in nutritional status’

#### 5.4.1 Design of confirmatory trials
Placebo-controlled superiority trials in the frame of add-on studies are mandatory (on top of standard therapy).

#### 5.4.2 Efficacy criteria in confirmatory trials
The primary efficacy criteria should be a clinical one.

Secondary efficacy criteria should include steatorrhoea and protein synthesis assessment when relevant (i.e. when the lean body mass is improved). This is particularly relevant for an antacid claiming a global improvement in nutritional status.

### 5.5 Study characteristics for a pharmacological claim (e.g. for a ‘me too’ PEP)

#### 5.5.1 Design of confirmatory trials
Double-blind active-controlled-trials are mandatory. Placebo-controlled studies are unethical and are not acceptable, unless in the frame of add-on studies on top of standard enzyme replacement therapy.
If blinding is considered impossible, careful justification will be required that the trial results are free from important bias.

Non-inferiority or superiority trials comparing 2 active drugs are both recommended.

The cross-over design provides paired analysis of data. It is particularly appropriate due to the high level of inter individual variability and to the moderate level of reliability of measurement of steatorrhoea.

5.5.2 Efficacy criteria in confirmatory trials

A biological endpoint can be accepted as a primary endpoint when the claim is pharmacological.

Apart from steatorrhoea, protein synthesis is also an acceptable primary endpoint in studies assessing efficacy of an acid neutraliser such as PPI or bile salts.

5.5.3 Non inferiority margin / Effect size

Non-inferiority margins need to be pre-defined and appropriately justified, taking assay sensitivity into consideration, and keeping in mind that only a slowing down of disease progression can be expected, if not only an absence of worsening.

Similarly, in superiority trials a margin of clinical relevance should be defined and justified.

5.6 Concomitant therapy

Optimal oral or tube-feeding complementary nutrition should be administered in malnutrition conditions or in conditions of risk for malnutrition.

This should consist primarily of high calories intake and high protein content. High doses of vitamin A-D-E-K should be added.

In children, several studies including the recent CALICO trial demonstrated the absence of benefit of a long-term use of nutritional supplements in the absence of malnutrition or risk for malnutrition as defined in sections 5.1.3 and 5.1.4, respectively.

6 OVERCOMING CFTR MUTATION

A therapy aiming at overcoming CFTR mutation (protein of gene therapy) would be expected to translate into a clinical improvement in both pulmonary and pancreatic disease.

Such trial should stratify patients at inclusion, based on the characterisation of the class of mutation, because each class of mutations is associated with specific disease features (severity, type of organ dysfunction) and a potential specific treatment approach. Based on a combination of genotype and phenotype, 5 classes of mutations have been identified.

Class I: no protein translated (stop mutation), Class II: misfolding and defect of glycosylation in the Golgi apparatus, leading to intracellular degradation and minimal dysfunctional CFTR insertion in the membrane, Classes III-IV: dysfunctional CFTR in the membrane, Class V: diminished amount of CFTR in the membrane. Usually, Classes I-II give rise to a more severe phenotype including exocrine pancreatic insufficiency, and Classes III-V to a less severe phenotype with normal pancreas function.

Pharmacodynamic “proof of concept” studies could use in vitro data from rectal biopsies due to the high density of CFTR in that anatomic area.

For confirmatory trials, any above-detailed primary endpoint accepted either for pulmonary or for pancreatic disease would be acceptable in that specific indication.

The improvement in liver (biliary secretion, impaired liver function) or intestinal functions (fat absorption) or in any CF-induced conditions can also be accepted, with stratification at inclusion according to the severity of the (CF-induced) damage.
7 SAFETY DATA

7.1 General safety considerations
Safety is difficult to assess in CF patients, because of the debilitating underlying disease and the large number of concomitant medications.

Safety assessment should rely on a 6-to-12-month follow-up, depending on the claim (i.e. the intended duration of use) and on the specific expected safety profile of the test drug; this is also applicable for treatments administered as relatively short courses of treatment (e.g. some ATB), because repeated therapeutic courses will be administered life-long in this chronic condition.

The safety data base is expected to be rather small, especially in the paediatric population; therefore, whenever data from other populations exist, they should be submitted and their relevance discussed.

Influence on growth and development should be systematically addressed in paediatric studies.

7.2 Specific pulmonary disease safety data
• Resistance to ATB:
  As CF is a life-long chronic condition and that there is no eradication of chronic PA colonisation, the emergence of resistance should always be assessed when the test drug is an ATB by in vitro characterisation of antibacterial activity, eventually on isolates from various centres geographically separated, if relevant.

  Cross-resistance between different ATB used in the treatment of PA infection should be addressed.

• Repeated courses of antibiotics over many years mean that hepatic and renal toxicity should be monitored.

• For neurotoxic ATB such as tobramycin, ototoxicity should be monitored, as well as paresthesia and vestibular disorders.

• Regular assessment of good aerosol technique is needed.

7.3 Specific pancreatic insufficiency safety data
• Signs and symptoms of malabsorption (including steatorrhoea) should also be considered as safety variables.

• Although rare, a definite dose-dependent lipase-induced fibrosing colonopathy has been found in young children, leading to the European consensus recommendation to remain below a dose of 10 000 IU lipase/kg fat ingested. This should be taken into account when establishing the initial dosing of PEPs and maximal PERT.

Anyhow, the possibility of occurrence of fibrosing colonopathy even with lower doses has not been ruled out, and the occurrence of such lesions should be thoroughly monitored.
8 DEFINITIONS AND ABBREVIATIONS

**ATB**: antibiotics

**BAL**: bronchoalveolar lavage

**Bronchopulmonary infection***:
Early colonisation combined with direct or indirect signs of infection. For *P. aeruginosa*, infection in non-expectorating patients with negative bacterial cultures can also be diagnosed on the basis of antibody detection in two successive tests.

**CF**: cystic fibrosis

**CFTR**: cystic fibrosis transmembrane conductance regulator

**CFU**: colony forming units

**Chronic lung colonisation***:
Presence of *P. aeruginosa* in the bronchial tree for at least 6 months, based on at least three positive cultures with at least one month between them without direct (inflammation, fever *etc.*.) or indirect (specific antibody response) signs of infection and tissue damage.

**Chronic bronchopulmonary infection***:
Chronic colonisation combined with direct or indirect signs of infection. For *P. aeruginosa*, chronic infection in non-expectorating patients with negative bacterial cultures can also be diagnosed on the basis of antibody detection in two successive tests.

**COPD**: chronic obstructive pulmonary disease

**Early colonisation***:
Presence of *P. aeruginosa* in the bronchial tree without direct (inflammation, fever, *etc.*.) or indirect (specific antibody response) signs of infection and tissue damage.

**Eradication***:
Eradication of an organism is the disappearance, after treatment, of an organism previously detected in a high-quality airway secretion sample.

**Exacerbation***:
The definition adopted by the jury was onset of an *acute episode* of clinical deterioration when the patient is in a stable state:
- increased cough;
- increased expectoration (volume and purulence);
- decreased tolerance to effort or physical activity;
- loss of weight or loss of appetite;
- deterioration of respiratory function ((FEV1, FVC);
- marked increase in airway bacterial load (in CFU/ml) during routine monitoring.

**FEV1**: forced expired volume in one second

**FVC**: forced vital capacity

**HRQL**: health-related quality of life

**MBC**: minimum bactericide concentration

**MIC**: minimum inhibitory concentration

**PA**: *Pseudomonas aeruginosa*

**PD**: pharmacodynamics
**PEP**: pancreatic enzyme preparations

**PERT**: pancreatic enzyme replacement therapy

**PK**: pharmacokinetics

**QoL**: quality of life

**SA**: *Staphylococcus aureus*

* Definitions from the European and French consensus conferences (see Section 9 References).
9 REFERENCES


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US FDA: regulations requiring manufacturers to assess the safety and effectiveness of drugs and biological products in paediatric patients.
