European Medicines Agency

London, 22 October 2009
Doc. Ref. EMEA/CHMP/EWP/9147/2008-corr*

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

(CHMP)

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

DRAFT AGREED BY EFFICACY WORKING PARTY	May 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	30 May 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 November 2008
AGREED BY EFFICACY WORKING PARTY	September 2009
ADOPTION BY CHMP	22 October 2009
DATE FOR COMING INTO EFFECT	30 April 2010

KEYWORDS	*Antibiotics, cystic fibrosis, exacerbations, exocrine pancreas insufficiency, metabolism, malnutrition, paediatrics, pancreatic enzymes preparations (PEP), pulmonary disease, pulmonary infection, Pseudomonas aeruginosa.*

* correction related to a change on p. 23

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The aim of this guideline is to provide guidance on the clinical development of compounds for the treatment of cystic fibrosis, a systemic chronically debilitating disease, mainly paediatric up to now, with a regularly increasing adult population as life expectancy improves (47% adults in 2006 according to ECFS, mean-aged 16-22 yrs).

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

In the context of insufficient long-term efficacy of available treatments, and high level of associated non-compliance, morbidity 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 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 PA infection, it is recommended to stratify the patients 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 treat the underlying chronic obstructive disease by improving airway clearance, either by altering the thick mucus or by enhancing mucosal hydration, currently approved mucoactive drugs should be used as an active control, in the frame of a superiority trial or a 3-arm non inferiority trial.

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

Efficacy in exocrine pancreatic disease (replacement therapy)

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' dependent on nutrient digestion and absorption, placebo-controlled superiority confirmatory trials in the frame of add-on studies are mandatory (on top of standard therapy). The primary efficacy criterion should allow demonstrating a clinical benefit: 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' PEP), active-controlled-trials are mandatory and non inferiority trials are accepted.
  A biological endpoint (steatorrhea 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 improving CFTR function

A therapy aiming at improving CFTR function (protein therapy or protein modulator) may be expected to translate into a clinical improvement in pulmonary disease. The disease improvement through assessment of another organ function would be also an acceptable endpoint.

The translation of disease improvement into improved organ function may be limited by the level of irreversible damage at the time of treatment initiation, and may be unlikely in pancreas. That is why the greatest expected benefit of such therapy would be expected in young children.

Since we have no data in that field, the primary endpoint in confirmatory trials should be clinical to evidence that the CFTR default correction actually translates into a long-lasting clinical benefit. The clinical endpoint used will be based on the target organ.

Because of the associated specificity of disease features, trials should rely on a stratification of patients at inclusion, based on the characterisation of the class of mutation. Alternatively, it may be more appropriate to conduct trials in patients with specific mutations or mutation class.

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 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).

1 INTRODUCTION

1.1 Definition of cystic fibrosis

Cystic fibrosis is an autosomal recessive disorder caused by mutations in the gene encoding for the cystic fibrosis transmembrane conductance regulator (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 (CFU/ml 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, and less commonly Escherichia coli and Klebsiella pneumoniae are also cause of infection of the lower airways in CF patients.

Infection with PA can only be eradicated in its early stages. *P. aeruginosa* is the main cause for chronic infection and is associated with chronic lung injury and reduced survival. After some time of the colonisation, the PA bacteria usually changes from a non-mucoid to a mucoid phenotype, which then progress to biofilm formation. This biofilm may then prevent many antibiotics from working effectively. 90% of CF patients are colonised with PA by the age of 18 years,, and PA infections are the cause of mortality in 80% of those patients. Mean relapse time after treatment of early colonisation is probably between12 months and 18 months.

Burkholderia cepacia complex has more recently been isolated in older CF patients; isolation of the Burkholderia *cenocepacia* species from sputum has been in some patients 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: 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, forced expiratory volume in one second (FEV1) is reduced. It is estimated that FEV1 declines by 2% 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, but are more frequent as the disease progresses; they translate into exacerbation of clinical symptoms (fatigue, 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. Intestinal absorption in itself is diminished due to CFTR dysfunction. 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.

Malabsortion/maldigestion-induced malnutrition

When exocrine pancreatic 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 acidic. On top of the already diminished pancreatic enzyme secretion, enzymes, especially lipase, are easily degraded by acid.

Enteric coated enzyme preparations are protected against gastric acid, and might circumvent this degradation, the coating being dissolved at a specific predefined intestinal PH. If this PH is not reached in time, the enzyme might only be released in the jejunum instead of the duodenum.

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. Faecal bile salt losses due to CFTR dysfunction in the ileum contribute to a diminished bile salt pool.

Associated malabsortion/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 malabsortion/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 primary damages

They include digital clubbing, sino nasal 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 lung or less frequently heart/lung transplantation. If they are transplanted the outcome is the same as for other patients with other chronic lung disease.

Up to now CF has been mainly a paediatric disease; mean age at diagnosis is around 3 yrs, with a mean 56% [45-68%] diagnosed at < 1 yr of age (ECFS, 2006).

However, due to great advances in the prophylaxis and management of chronic respiratory infection and exocrine pancreatic insufficiency in the past 20 years, CF patients overall now reach a mean 30 to 40 years of age if all genotypes are considered, and the proportion of young adult population is steadily growing; based on the European Cystic Fibrosis Society 2006 registry report data, 47% out of 9118 patients were young adults (mean 16-22 yrs), patients with severe phenotypes are likely to die of the disease at approximately 25 years of age, although some patients continue to die in childhood.

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, pulmonologists, 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, several causal therapies to correct CFTR production and function are in development, but none is yet 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**;**
- With the increasing adult disease, current major preoccupations are now including the management of diabetes, osteoporosis and renal disease.

1.3.1 Current therapeutic management of pulmonary disease

- A number of inhaled and systemic antibiotics (ATB) are used in CF patients according to EU consensus, to treat and prevent infections, mainly aminoglycosides, cephalosporins and fluoroquinolones. Inhaled colistimethate sodium plus oral ciprofloxacin is used to eradicate early PA 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.
- Therapy with mucoactive drugs (mucolytics or mucus rehydrating drugs) to improve airway mucosal 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 mucoactive drug acting on airway obstruction specifically approved for the treatment of CF.
- Inhaled bronchodilators are used, although supported by little scientific evidence.
- 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 with a vibrating membrane instead of 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 exocrine pancreatic disease

Pancreatic enzymes preparations (PEP):
PEPs are commonly used as enzyme replacement therapy and have greatly improved the nutritional status of CF patients.

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 minitablets 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 calorie intake and nutritional supplements:

- High calorie diet (130-150% of Recommended Daily Allowance for healthy volunteers), or enteral nutrition, if necessary, Patients with CF often require a greater fat intake (35-40% of calories) than that recommended for the general population (≤ 30%);
- 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 insufficient long-term efficacy, and high burden of available treatments and the high level of associated non-compliance in the treatment of pulmonary disease,
- 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 symptomatic 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;
- Novel therapies aiming at restoring normal CFTR functionalities.

The aim of this guideline is to provide specific guidance on the clinical development and evaluation of medicinal products, with a specific claim in CF patients, based on validated data:

- For the treatment and prevention of:
    1. lower respiratory tract infections and destruction,
    2. exocrine pancreas insufficiency, responsible for malnutrition and worsening of pulmonary status.
- Restoring CFTR functions.

Therefore, this guideline will take into account solely data that are specific to CF and already demonstrated.

New concepts that are not yet validated and demonstrated (new mechanisms of action, new endpoints including rate of decline or biomarkers as surrogate endpoints), are to be managed in the frame of scientific advices.

Novel therapies such as:

- Corrector, potentiator and/or corrector/potentiator combinations (protein folding);
- Ion-channel therapies (ENaC inhibitors);
- Novel anti-inflammatory therapies (anti-neutrophil compounds or non-antibiotic macrolides);
- Surfactants (anti-inflammatory/anti-infective/mucus regulatory properties.

are currently in development and related data are highly expected; specific recommendations to this respect are however:

- Either premature, because related data need to be validated and demonstrated first (which fall into the scope of Scientific Advices);
- or not in the scope of this guidance because there is no CF specificity (e.g. the development of new inhalation devices is detailed in the guidance on Orally inhaled drugs).

When relevant, reference to existing appropriate guidelines will be made.

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 2001/83 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. Guideline on the Clinical Requirements C For Orally Inhaled Products (OIP) (CPMP/EWP/4151/00 Rev. 1)
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. Annex I to Directive 2001/83/EC, as amended
24. Other relevant Agency (including ICH) Guidelines

4 PULMONARY DISEASE EFFICACY DATA

4.1 Potential claims

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

The Definition of the European consensus conference on CF (2000) should be used to define the accepted claims (see section 5 on Definitions*)*. The Definition of exacerbation is currently subject to debate and will be revised during next 2009 European Consensus Conference, and should be followed thereafter.
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 (see 5.1 Definitions):
  - Treatment of early PA colonisation with or without a claim of eradication of PA;
  - Treatment of chronic infection;
  - Treatment of exacerbations;
  - Prophylaxis of chronic PA infection (this can be obtained either by ATB therapy while treating the first early infections, or by improvement in airway mucosal clearance).
- Prevention of progression of lung damages (fibrosis, bronchiectasis)

Nota Bene: '*Improvement in airway mucosal clearance*' is not acceptable as a specific CF therapeutic claim. In CF patients, this pharmacological property would be expected to translate into either '*Prevention of infections*' and/or '*Prevention of progression of lung damage*'. Thus, to be granted a specific indication in CF, a mucoactive product or a product decreasing airway obstruction must demonstrate a long-term clinical benefit.

4.2 Patients populatio

4.2.1 Diagnosis of cystic fibrosis

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

- Specific clinical features, and
- **E**vidence 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; however, a negative test does not preclude the presence of the disease, and
- **D**ocumentation 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 inclusion criteria (see section 5 on Definitions) and differentiate between the following conditions: early colonisation, chronic lung colonisation, bronchopulmonary infection, chronic bronchopulmonary infection, exacerbation.

Those conditions are the basis for the above-defined claims (see section 4.1), depending on whether the goal of therapy is to prevent or to treat a given condition.

In clinical trials aimed at prophylaxis or 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 (refer to section 1.2.4 above). It concerns a small population, including infants and children, for which the relevant guidelines should be respected. Mean age at diagnostic is around 3 yrs, with a mean 56% [45-68%] diagnosed at < 1 yr of age (ECFS, 2006).

Due to differences in disease status including bacterial colonisation and disease progression as well as possible differences in PK characteristics and in the safety profile in different age categories, efficacy and safety need to be established separately in adults and children. Age groups should be justified based on available paediatric guidance.

Extrapolation of efficacy data from children aged > 5 years to children aged < 5 years of age is not acceptable, because of differences in the underlying condition, differences in the severity of the disease, and differences in drugs used.

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. Any other primary efficacy criterion must be previously validated before used as a basis for a demonstration of efficacy in children.

For specific guidance on issues related to clinical studies conducted in children, please refer to the relevant guidance (see section 3 Legal Basis).

4.3 PK and PD studies

Patients with CF have a different pharmacokinetic profile compared to other patients populations. Studies have shown that CF patients have increased volume of distribution, and faster elimination of some drugs, mainly through increased renal clearance but also due to a more rapid metabolism in the liver. This means that patients with CF require dose modification (usually 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,

4.3.1 PK data in bronchopulmonary infection claims

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

The primary PK/PD consideration in the development of antibacterial drugs in CF is to assess the relationship between Cmax, AUC and MIC to support appropriate dosing and dose regimen selection (refer to the PtC on PK and PD in the development of antibacterial drugs).

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.

4.3.2 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.

Nebulised ATB is a key issue in children due to difficulties in using injection and oral administration. PK/PD studies should pay particular attention to nebulised ATB and patients < 5 years of age.

4.4 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 and inflammation 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.

4.4.1 Clinical endpoint : assessment of respiratory function

FEV_1 (forced expiratory volume in one second) is the recommended primary endpoint (because the initial pulmonary defect in CF is obstructive); FEV_1 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 $FEV_{25/75}$ could be also used, as secondary endpoints, to explore the respiratory function.

- Rate of decline in FEV_1 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 *a priori*, and the study should be powered accordingly.
- The frequency of FEV_1 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 6 months is recommended for the demonstration of efficacy on respiratory function (based on repeated measurements of FEV1), with a (pre-defined in the protocol) 12-month follow-up for safety. Demonstrating the slowing of the rate of decline would require a study of longer duration, but any guidance on that issue is premature due to the lack of data.

Clinical endpoint in children

It is acknowledged that functional respiratory exploration is difficult to perform in children < 5 years. However, respiratory function tests in young children can be performed in specialised centres able to promote standardised methods. Any other efficacy criterion intended to be used as a surrogate for assessing the lung disease in CF must be previously validated before used as a basis for a demonstration of efficacy in this age group.

4.4.2 Microbiological endpoint

The microbiological endpoint should document:

- The microbiological efficacy as well as,;
- 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 bronchoalveolar lavage (BAL), considered as a reference in the last European consensus conference. 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.
- Naso-pharyngeal 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. This technique is useful for paediatrics and is successfully used for tuberculosis diagnosis in paediatrics; it is much less aggressive than gastric aspiration technique and well standardised.

4.4.3 Biological endpoints:

Inflammation or infection markers

4.4.4 Physiological endpoints

In adults, weight changes, lean body mass changes.

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

4.4.5 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 (a shorter study duration can only assess the efficacy of the product, not its specific impact on HRQL).

The CFQR-revised 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, with HRQL assessment as primary endpoint.

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

4.5.1 Recommendations for the primary efficacy criteria 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 4.4). 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 below section 4.1.2.5); the method currently considered as the reference, 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.
    - Prior ATB therapy has a substantial impact on the magnitude of the microbiological response to subsequent antibiotic therapy.

Consequently,

- A microbiological primary endpoint at a relevant time point depending on the duration of a full standard course of treatment (i.e. 28 days for currently available treatments) 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: a 6-month clinical primary endpoint assessing the respiratory function is recommended for prophylaxis and treatment of chronic infection (see section 4.4.1 for assessment of respiratory function).

4.5.2 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

  As a matter of fact, 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 number or time to exacerbations,
  - number of hospitalisations,
  - number of IV treatments,
  - duration of hospitalisation.
- Weight change is supportive in long-term studies (requires at least a 6-month study duration).

4.6 What should be the efficacy endpoints in trials using a mucoactive drug drug decreasing airway obstruction?

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

4.6.1 Efficacy endpoints for demonstration of slowing/stopping inflammation-induced lung damages

Primary endpoints in phase II exploratory trials

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

Biological or 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 4.4.1 for 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.

4.6.2 Efficacy endpoints with drugs improving decreasing airway obstruction 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.

4.7 Design of confirmatory trials

Randomised active-controlled trials are mandatory, when a reference treatment exists (refer to the ICH-E10 Guideline on the Choice of Control Group in clinical trials).

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 4.9 Concomitant therapies).

4.8 Comparators in efficacy trials

4.8.1 Comparators in bronchopulmonary infection claims

Different ATB protocols are used for treatment of early colonisation (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 (refer to the appropriate specific guidances on ATB, this issue is not specific to CF).
- *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 for the time being, refer to the European consensus).
- *Treatment of chronic PA infection*: the comparator should be an active control (including inhaled-tobramycin and periodic IV ATB courses) 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 (see reference "*Guideline On The Requirements For Clinical Documentation For Orally Inhaled Products (OIP) Including The Requirements For Demonstration Of Therapeutic Equivalence Between Two Inhaled Products For Use In The Treatment Of Asthma And Chronic Obstructive Pulmonary Disease (COPD)").*

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. When the relevant active comparator is specifically approved for CF in the population included, the approved dose regimen of this comparator for the same patient population should be used.

4.8.2 Comparators in trials assessing efficacy of drugs improving airway clearance

Pulmozyme (rhDNAse) acts on airway clearance by altering the thick mucus and has been approved for the treatment of CF.

When the claim is for a mucoactive therapy (including mucolytics and mucus hydratating drugs), to improve clearance of lower-airway secretions and treat the chronic obstructive pulmonary disease, currently approved mucoactive drugs should be used as an active control, in the frame of a superiority trial, or of a three-arm non inferiority trial (i.e. with placebo as an internal control). Any other design should be thoroughly justified.

4.9 Concomitant therapies in confirmatory trials.

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

The balance across treatment arms for the use of major supportive therapy 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, mucoactive drugs, 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, specially 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 improve (in case of malnutrition) or maintain (in case of risk for malnutrition) the nutritional status (always impaired in exocrine pancreas insufficiency) by ensuring a better digestion and absorption of nutrients.
In that respect, Pancreatic Enzymes Replacement Therapy (PERT) along with a standard nutritional high calorie 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 CF 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.

ELISA measurement of the concentration of the pancreatic enzyme elastase in the faeces (human faecal elastase ug/g stool) is a diagnostic test much preferably and much widely used than steatorrhea, because it is not dependent on the supplementation diet; it however cannot be used to monitor therapy.

5.1.2 Malnutrition criteria in children

Well-accepted malnutrition criteria are defined by

- a weight/height ratio < 90%, (the w/h ratio is weight as the % of expected weight at the given height, calculated from the 50th percentile, *i.e.* Watelow nutritional Index), or
- a height/age ratio < 95% associated with a weight stagnation.

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

Age range	Quantitative criteria for weight stagnation
0 – 6 months	Weight gain < 500 g/month during ≥ 1 month
6 – 12 months	Weight gain < 300 g/month during ≥ 2 months
12 – 36 months	Weight gain < 150 g/month during ≥ 3 months
3 – 6 years	Weight stagnation during ≥ 3 months or weight loss during ≥ 2 months
6 – 18 years	Weight stagnation during ≥ 6 months or weight loss during ≥ 2 months

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/m^2 (normal values range from 18.5 to 25 kg/m^2).

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 + amylase) 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 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 intake of fats, carbohydrates and proteins and total calorie intake should be recorded to enable further efficacy assessment.

Standardisation of the individual 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 or coefficient of fat absorption (CFA) should be assessed as percentage of fat intake which should be at least 30 grams of fat per day (up to 100 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). The reference for standard deviation scores is the WHO global database on Child Growth and Malnutrition.

Logistic regression analysis should be performed to estimate 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 72h 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 intake should be expressed as FIP unit 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). Although dosing per kg may be appropriate in adults and adolescents, it makes no sense in children, because young children eat 5 grams fat/kg , older ones 2 grams fat/kg of body weight.

Dosing references for enzymes of different origins need to be established and justified based on clinical data.

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 (see 5.3.1).

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.

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 steatorrhea.

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 steatorrhea, 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 calorie intake and high protein content. High doses of vitamin A-D-E-K are highly recommended.

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 THERAPIES AIMED AT IMPROVING CFTR FUNCTION (PROTEIN THERAPY / CFTR MODULATORS)

It is reminded that gene therapy does not fall into the scope of this guideline.

A therapy aiming at overcoming CFTR mutation (protein therapy or protein modulator) may be expected to translate into a clinical improvement in pulmonary disease, and in non pulmonary disease if relevant, and insofar as the existing damages are not irreversible.

The disease improvement through assessment of another organ function than the lung would be also an acceptable endpoint.

The translation of disease improvement into improved organ function may be limited by the level of irreversible damage at the time of treatment initiation, and may be unlikely in pancreas. That is why the greatest expected benefit of such therapy would be expected in young children.

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 cell membrane. Usually, Classes I-III give rise to a more severe phenotype including exocrine pancreatic insufficiency, and Classes IV-V to a less severe phenotype with normal pancreas function.

Trials 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. Alternatively, it may be more appropriate to conduct trials in patients with specific mutations or mutation class. Please refer to the Guideline on clinical trials in small populations (see section 3 Legal Basis).

Pharmacodynamic 'proof of concept' studies may use *in vitro* data from rectal biopsies due to the high density of CFTR in that anatomic area,

Exploratory trials may rely on pharmacodynamic endpoints, as well as on clinical endpoints used in confirmatory trials.

- Measurement of faecal bile salts losses, because CFTR modulation might improve bicarbonate intestinal secretion, nutrient absorption and bile salt losses to an unprecedented level. Bile salt testing in stools does not limit testing even in very young children, the population in whom the greatest benefit is expected from the correction of CFTR disfunction.
- Test of functional activity of CFTR used for diagnosis: nasal or rectal potential difference, sweat chloride testing.

Since we have no data in that field, the primary endpoint in confirmatory trials should be clinical to evidence that the CFTR default correction actually translates into a long-lasting clinical benefit.

The clinical endpoint used will be based on the target organ. The anticipated treatment effect on a particular organ will be affected by the mode of delivery and the point of disease progression at the time of treatment initiation.

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 a stratification at inclusion according to the severity of the (CF-induced) damage, in the absence of non reversible damages.

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 (also needed to define the ATB dose in young children). For inhaled medications, clear disinfection instructions of the device have to be provided. If the inhalation device cannot be disinfected on a regular basis (once daily, there is a high risk of contamination with Pseudomonas. Microbiologic testing of used inhalers should be included in clinical trials.

7.3 Specific pancreatic insufficiency safety data

- Although primarily efficacy variables in the context of exocrine pancreatic insufficiency, 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 with very high doses of PEP, leading to the European consensus recommendation to remain below a dose of 10 000 IU lipase/kg body weight[†]. This should be taken into account when establishing the initial dosing of PEPs and maximal PERT.

New formulations are also expected to lead to a standardisation of enzyme content; as a matter of fact, due to the loss of activity of enzyme over time, and to ensure the labelled activity at the end of shelf life, all PEPs approved and marketed in EU contain a stability overfill. To overcome potential safety problems, any PEP should be formulated to 100% of the label-claimed lipase enzyme activity.

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.

[†] corr: further to a comment received the WP has agreed to amend the dosing reference from 10 000 IU fat ingested to 10 000 IU lipase/kg body weight.

8 DEFINITIONS AND ABBREVIATIONS

ATB: antibiotics

BAL: bronchoalveolar lavage

Bronchopulmonary infection*:
Early colonisation combined with direct or indirect signs of infection. For *PA*, 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 *PA* 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 broncho-pulmonary infection*:
Chronic colonisation combined with direct or indirect signs of infection. For *PA*, 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 *PA* 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. The definition of clinical deterioration is currently subject to debate and will be revised during next 2009 European Consensus Conference, and should be followed thereafter.
Currently, the clinical deterioration is defined by the presence of at least 3 new clinical findings:
- 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); and
- A marked increase in airway bacterial load (in CFU/ml) during routine monitoring.

FEV_1: forced expired volume in one second

FVC: forced vital capacity

HRQL: health-related quality of life

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

Consensus conference: **management of patients with cystic fibrosis; pulmonary disease and infection guidelines**. Paris 2002

Consensus conference: **management of patients with cystic fibrosis; pancreas, gastroenterology, metabolism and nutrition guidelines**. *Arch Pediatr* 2003;10:382-97

Cystic Fibrosis Foundation patients registry report 2007

European cystic fibrosis society (ECFS): European cystic fibrosis registry report 2006 data

Boucher RC. **Cystic Fibrosis: a disease of vulnerability to airway surface dehydration**. *Trends Mol Med* 2007;13:231-40

Davis PB et al. Centennial review *Am J Respir Crit Care Med* 2006; 173: 475-482.

Doering & al. Clinical trials in cystic fibrosis. J Cyst Fibrosis 2007;6:85-99

Döring G, Hoiby N; **Early intervention and prevention of lung disease in cystic fibrosis**: a **European consensus.** *Journal of cystic fibrosis* 2004;3:67-91

Döring G, Conway S, Hiejerman HGM, Hodson ME, Hoiby N, Smyth A, Tow DJ; **Antibiotic therapy against Pseudomonas aeruginosa in cystic fibrosis: a European consensus**. *European respiratory journal* 2000; 16: 749-767

Elkins, Robinson & al. **A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis.** *N Engl J Med* 2006; 354:229-240

Emerson et al**Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis**. *Pediatr Pulmonol* 2002;34:91-100

Ferkol *et al*. **Cystic fibrosis pulmonary exacerbations**. *J Pediatr* 2006;148:259-64

Fitzsimmons SC, Burkhart GA *et al*. **High-dose pancreatic-enzyme supplements and Fibrosing colonopathy in children with cystic fibrosis** *N Engl J Med* 1997;336(18):1283-9

Fuchs, Borowitz *et al* **Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis**. The Pulmozyme Study Group.*N Engl J Med* 1994;331:637-642

Gee *et al*. 2005 **Associations between clinical variables and quality of life in adults with cystic fibrosis** *J Cyst Fibros* 2005;4(1):59-66

Geller DE, Rubin BK. Respiratory care and cystic fibrosis. Respir Care. 2009; 54:796-800.

Hoiby & Frederiksen, **Microbiology of cystic fibrosis** In: Hodson & Geddes, editors. Cystic fibrosis. London 2000, p 83-107

Kalnins D, Corey M *et al*. **Failure of conventional strategies to improve nutritional status in malnourished adolescents and adults with cystic fibrosis**. *J Pediatr* 2005; 147(3):399-401

Kerem E, Conway S, Elborn S, Hiejerman H; **Standards of Care for Patients with CF**: a **European consensus.** *Journal of CF* 2005;4:7-26

Koch *et al*. **Pathogenesis of cystic fibrosis**. *Lancet* 1993;341(8852):1065-9

Koch *et al*. **Presence of cystic fibrosis-related diabetes mellitus is tightly linked to poor lung function** : data from the European epidemogical registry of cystic fibrosis. *Pediatr Pulmonol* 2001;32:343-50

McKone *et al*. **CFTR genotype as a predictor of prognosis in cystic fibrosis**. *Chest*. 2006 Nov;130(5):1441-7.

O'Malley CA. Infection **Control in Cystic Fibrosis: Cohorting, Cross-Contamination, and the Respiratory Therapist**; *Respir Care*. 2009;54:641-57.Oliveira Assis AM *et al*. **Determinants of mild to moderate malnutrition in preschoolers: a hierarchical approach**. *Public Health Nutr.* 2008;11(4):387-94

Ordonez, Henig *et al*. **Inflammatory and microbiologic markers in induced sputum after intravenous antibiotics in cystic fibrosis.** *Am J Respir Crit Care Med* 2003;168:1471-1475

Poustie *et al*. for the CALICO trial collaborative Group. **Oral protein energy supplements for children with CF**

Ramsey BW. **Management of pulmonary disease in patients with cystic fibrosis**. *N Engl J Med* 1996; 335: 179-188

Ramsey, Pepe *et al*. **Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group** *N Engl J Med* 1999;340:23-30

Rosenfeld M. **Defining a pulmonary exacerbation in cystic fibrosis**. *J Pediatr* 2001;139:359-65

Saiman, Marshall *et al*. **Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial** *JAMA* 2003;290:1749-1756

Saiman *et al*. **Cystic fibrosis foundation consensus conference on infection**. *Infect Control Hosp Epidemiol* 2003;24:1-52

Sermet-Gaudelus SRNP, **Simple paediatric nutritional risk score to identify children at risk of malnutrition** *Am J Clin Nutr* 2000; 72(1): 64-70

Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Hiejerman HGM, Roberecht E, Döring G; **Nutrition in patients with cystic fibrosis : a European consensus**; *Journal of cystic fibrosis* 2002; 1: 51-75

Smyth *et al*. **Oral caloric supplement for cystic Fibrosis**. *Cochrane database of systematic reviews* 2007, issue 1

Smyth *et al*. **Fibrosing colonopathy in cystic fibrosis: results of a case control study**. *Lancet* 1995;346:1247-51

US FDA Guidance for industry: **acute bacterial exacerbation of chronic bronchitis – developing antimicrobials for treatment**

US FDA Guidance for industry: **exocrine pancreas insufficiency drugs products** – submitting NDAs

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

Veeze HJ, Sinaasappel M *et al*. **Ion transport abnormalities in rectal suction biopsies from children with cystic fibrosis**. *Gastroenterology* 1991;101(2):398-403

Walters *et al*. **Clinical monitoring of steatorrhoea in cystic fibrosis**; *Arch Dis Child* 1990;63:99-102