MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD

agencia española de
medicamentos y
productos sanitarios

Difficulties encountered - regulatory perspective: focus on endpoints used in clinical trials

Marketing authorisation

Concha Prieto
CHMP Member
Agencia Española de Medicamentos y Productos Sanitarios

Limitations for the development of medicinal products in cystic fibrosis

- *Rare disease:* limited number of available patients for clinical trials

- *Improvement in standard of care:* results in delay of progression

- *Lung involvement begins early life*: different methods of measurement can be needed depending on age

- *Different goals of therapies* due to the systemic nature of the disease, e.g., management of bronchopulmonary infections, of exocrine pancreatic insufficiency etc. More recently drugs targeting the mutant CFTR protein.

Outcome measures in clinical trials

* *Clinical endpoints*: characteristic or variable that reflects how the patient feels, functions or survives

* *Surrogate endpoints*: a laboratory measurement or physical sign that substitutes for a clinically meaningful endpoint

* *Biomarkers*: characteristic objectively measured and evaluated as an indicator of normal or pathogenic process or pharmacological response

EMA guideline (EMEA/CHMP/EWP/9147/2008-corr*) – recommended endpoints for lung disease

Assessment of respiratory function:

- FEV_1: Primary endpoint
- FVC (forced vital capacity) and/or $FEV_{25/75}$

Microbiological endpoints:

- Microbiological efficacy, potential to select resistant strains, colony density

Physiological endpoints:

- Lean body mass and weight changes in adults
- Target height and normal weight (SD and z scores) in children

Quality of life: CFQ-R

	TOBI PODHALER®	CAYSTON®	COLOBREATHE®	BRONCHITOL®	KALYDECO®
CLINICAL ENDPOINTS		**TIME TO NEED FOR INHALED ANTI-PA ANTIBIOTICS : PRIMARY ENDPOINT** (study 005)	Use of concomitant medication	Antibiotic use	
	PRO (TSQM)	**PRO (CFQ-R) RIMARY ENDPOINT** (study 007)	PRO (CFQ-R)	PRO (CFQ-R)	PRO (CFQ-R)
	P.exacerbation (PE)	-----	Time to first PE	PE	Time to first PE
	Hospitalizations	Hospitalizations		Hospitalizations	
		Weight and BMI	Weight and BMI		Weight
		Change in symptoms and severity			
SURROGATE ENDPOINTS	**FEV1: PRIMARY ENDPOINT** (as relative change in % predicted)	FEV1 (as mean change in percent predicted)	**FEV1: PRIMARY ENDPOINT** (as mean change in % predicted)	**FEV1: PRIMARY ENDPOINT** (as absolute change over 26 weeks)	**FEV1: PRIMARY ENDPOINT** (as absolute change in % predicted)
	FVC, FEF_{25-75}	FVC, FEF_{25-75}	FVC, FEF_{25-75}	FVC, FEF_{25-75}	FVC, FEF_{25-75}
BIOMARKERS	PA sputum density Susceptibility of PA	PA sputum density MICs for PA and B cepaciae	Sputum density Susceptibility of PA		Sweat chloride (absolute change) Nasal potential difference

CLINICAL ENDPOINTS

* Survival

* Pulmonary exacerbations

* IV antibiotherapy

* Hospitalisations

* Weight and height

* Patient-reported outcomes/Quality of life

Pulmonary exacerbations

- **There is no standard definition: signs + symptoms + use of IV antibiotics.**
  - Protocol defined/investigator defined
  - Use of IV antibiotics and children
- **The standard 24-week length of comparative treatment (for *P. aeruginosa* chronic infection) too short**
- **Rare event in children**
- **Cross-study comparisons difficult; need to take into account the time each patient contributes to the follow-up and that PE may be a repetitive event.**
  - Time to first PE vs.
  - Incidence (Rate ratio; Relative risk)
- **Effect of severity of the pulmonary disease/seasonal factors.**

	DEFINITION OF PULMONARY EXACERBATION **Either 1) use of IV antibiotics; or 2) new or changed antibiotic therapy (intravenous , inhaled, or oral) for at least 4 of the following:**
TOBI PODHALER®	Change in sputum production (volume, colour, consistency), dyspnoea, new or increased haemoptysis, malaise fatigue or lethargy, fever >38 degrees Celsius, anorexia or weight loss, sinus pain or tenderness, change in sinus discharge, FVC or FEV1 decreased by >10% from previous recorded value, radiographic signs indicative of pulmonary infection, increased cough, changes in physical examination of the chest
CAYSTON®	Documented symptom(s) predictive of pulmonary exacerbation (such as decreased exercise tolerance, increased cough, increased sputum/chest congestion, decreased appetite)
COLOBREATHE®	Change in appearance of sputum b) increased productive cough, dyspnoea or respiratory rate c) progressive physical findings on chest auscultation d) new infiltrates on chest X-ray e) lassitude and decreased exercise tolerance f) fever (≥38°C) g) deterioration of 10% in highest FEV1 score in the last 6 months h) decreased appetite i) emergence of new pathogen in sputum.
BRONCHITOL®	Change in sputum production (volume, colour, consistency), dyspnoea, new or increased haemoptysis, malaise, fatigue or lethargy, fever, anorexia or weight loss, sinus pain or tenderness, change in sinus discharge, a decrease in FVC or FEV1 of 10% or more from the previous recorded value, radiographic signs indicative of pulmonary infection, increased cough, or changes in physical examination of the chest.
KALYDECO®	Change in sputum, new or increased hemoptysis, increased cough, increased dyspnea, malaise, fatigue, or lethargy, temperature above 38° C (equivalent to 100.4° F), anorexia or weight loss, sinus pain or tenderness, change in sinus discharge, change in physical examination of the chest, decrease in pulmonary function by 10%, radiographic changes indicative of pulmonary infection.

Definition of PE (Bilton D et al. 2011)

An exacerbation will be defined as the need for additional antibiotic treatment as indicated by a recent change in at least two of the following:

- Change in sputum volume or colour
- Increased cough
- Increased malaise, fatigue or lethargy
- Anorexia or weight loss
- Decrease in pulmonary function by 10% or more /radiographic changes
- Increased dyspnoea

Conclusions on PE

- Event rate preferable to time to an event (both can be analysed). Basic information is the number of patients who had a PE and the number of PE per patient.
- Characterisation of the population for the presence of chronic PA lung infection.
- PE collected as efficacy endpoint and reported also as adverse events.

Weight and height

- Height and weight positively correlate with survival
- Indicators of effectiveness of treatment

- **Limitations**

  - useful only in long-term CTs

  - height applicable only to younger populations

  - confounding effects on growth (e.g. exocrine pancreatic disease, diabetes mellitus)

  - assessment of nutritional status based mainly (but not only) on weight, height and weight-for-stature anthropometric measurements and associated reference standards.

CHMP guideline (EMEA/CHMP/EWP/9147/2008-corr*)

- ….multidisciplinary management needs to be standardised as far as possible, including the non pharmacological management and diet.
- Biomarkers ("biological endpoints"):
  - Steatorrhoea (mean decrease in stool fat expressed as a percentage of the fat intake or coefficient of fat intake)
  - Protein synthesis
  - Faecal elastase (cannot be used to monitor therapy)
  - Faecal bile salt excretion (absorption of bile acids by the ileum which is CFTR dependent)
- Clinical endpoints:
  - Children: target height at 12 months and normal weight at 6 months
  - Adults: weight gain or nutritional status at 6 months (changes in body weight, weight/height and lean body mass)
- Malnutrition criteria in children:
  - 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. Waterlow nutritional Index), or
  - a height/age ratio < 95% associated with a weight stagnation.

CHMP question

For children, length gain is also important. Given that height was measured at month 12 the Applicant is asked to discuss this data. A logistic regression analysis should be made to estimate the weight/height ratio and the height for age (EMEA/CHMP/EWP/9147/2008).

Company's answer

In patients less than 20 years old:

- Change in height: as absolute change and as height-for-age z-score.
- Height-for-age ratio: using the Waterlow nutritional index
- Weight/height ratio: assessed as percent ideal body weight (%IBW, normal weight is defined as %IBW 90–10%).

Conclusions on weight/height

- Which are the most appropriate indices to assess (in clinical trials) the nutritional status of CF patients, in particular children from birth to 6 yo?
- Is percent ideal body weight (%IBW) acceptable? Or BMI-for-age?
- Which reference standards for weight and height should be used?
  - National (e.g. Carrascosa A. et al. 2008)
  - CDC growth charts
  - WHO growth charts (children from birth to 5 yo)
- Height should be assessed
  - Acute malnutrition ("wasting" or low weight for height)
  - Chronic malnutrition ("stunting" or low height for age)

PRO: CFQ-Revised

- Multidomain CF-specific PRO measure; respiratory domain.
- The minimal clinically important difference (MCID), or the value that shows detectable improvement or decline, has been shown to be 4 points on a scale of 0 to 100 for the respiratory symptoms scale.
- Adolescent/adult version, parent/caregiver version, and the child versions (a version for 6 to 11 years of age and a version for 12 and 13 years of age)
- Validated tool and available multiple languages

Limitations

- can only be used with children older than 6 years
- the 2-week recall period, i.e. evaluates symptoms over the previous 2 weeks
- designed for patients in a stable state

Can PRO be used as primary endpoint?

- Respiratory domain used in one of the registration trials of aztreonam lysine (Retsch-Bogar et al. 2009)
- Still the granted indication "…indicated for the suppressive therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa…*"
- Likely because two pivotal trials including clinical/surrogate outcomes.

Conclusions on PRO

- It may be appropriate as primary endpoint **BUT**

  - Blinding of the trial seems essential
  - Subgroup analysis by age (children, adolescents and adults) and by disease severity
  - Consistency with clinical/surrogate outcomes needed.
  - Implications for the labelling (e.g. only for symptomatic treatment)?.

SURROGATE ENDPOINTS

- **Pulmonary function (FEV_1):**
  - Established predictor of survival.
  - Validated instrument.
  - Widely used as a primary endpoint
- Infant pulmonary function
- Imaging (chest x-ray, chest CT)

FEV_1

- Spirometry performed according to the internationally-recognized American Thoracic Society/European Respiratory Society Guidelines.
- Assessed as percent predicted FEV1 if children and adolescents are enrolled.
- Prior use of bronchodilators and appropriate time-windows.
- Equations of reference:
  - Knudson/Wang/Hankinson
  - CF-specific reference equations (e.g. Boelle PY et al., 2012)
- Timing of assessment usually at week 24-26 after start of treatment. On/off cycles for inhaled antibiotics.

Conclusions on FEV1

- Use limited by low sensitivity and high variability of spirometry, combined with improved prognosis and milder clinical course in CF (e.g. large sample sizes and long study duration required to demonstrate significance) (Montgomery 2012)
- Absolute change from baseline in FEV1% predicted (rather than relative change)
- Clinical relevance of the treatment effect on FEV1 (variability of the measure)
- Margin of non-inferiority based on the difference of tobramycin inhaled solution (TIS) vs. placebo (Ramsey 1999). However, the more recent trial of aztreonam lysine vs. TIS was unable to show the same increase of 10% in the tobramycin arm.

Alternatives to FEV1 as surrogate outcome parameter in clinical trials needed in:

- children below 4 to 6 years old
- mild lung disease

Define the role of the Lung Clearance Index* as alternative surrogate measure of lung function

*Lung Clearance index (LCI) is defined as the number of times the lung volume has to be ‘‘turned over’’ (TO) to clear the lungs from an inert tracer gas (or nitrogen). In a healthy person, this takes about 5 to 7 ‘‘turn-overs’’. In the presence of ventilation inhomogeneity, LCI increases, i.e. the number of TO before the inert marker gas has been cleared from the lungs, increases (Fuchs SI et al. 2011)

BIOMARKERS

* Eradication,
* Colony density,
* Inflammatory markers,
* CFTR functional measures (nasal potential difference, sweat chloride)

Overall, add plausibility to the proposed mechanism of action, mainly if consistent with clinical/surrogate outcomes.

For some of them limitations are the lack of standardised techniques of measurement and variability which makes interpretation of results difficult, etc.

Long-term data collection

- 24-week randomised treatment followed (usually) by 24-week of uncontrolled treatment (placebo patients switched to the active).
- Uncontrolled extension studies of 48 to 96 weeks of duration
- Registries (preferable those already set up by academia); need to know what type of information is collected in the registry.
  - Analytical studies rather than merely observational if specific safety concerns have been identified.
- Ad-hoc studies (in case specific and outstanding safety concern identified)

THANKS FOR YOUR ATTENTION