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Experience with CF in Scientific Advice

Workshop on endpoints for cystic fibrosis clinical trials

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Outline

- SAWP
- Extrapolation of efficacy to CFTR mutations not studied in pivotal trials
- Eradication and Microbiology
- Generics / hybrids / biosimilars / me too
- 28d on / off cycles
- Qualification of novel methodologies

Drug Development Overview

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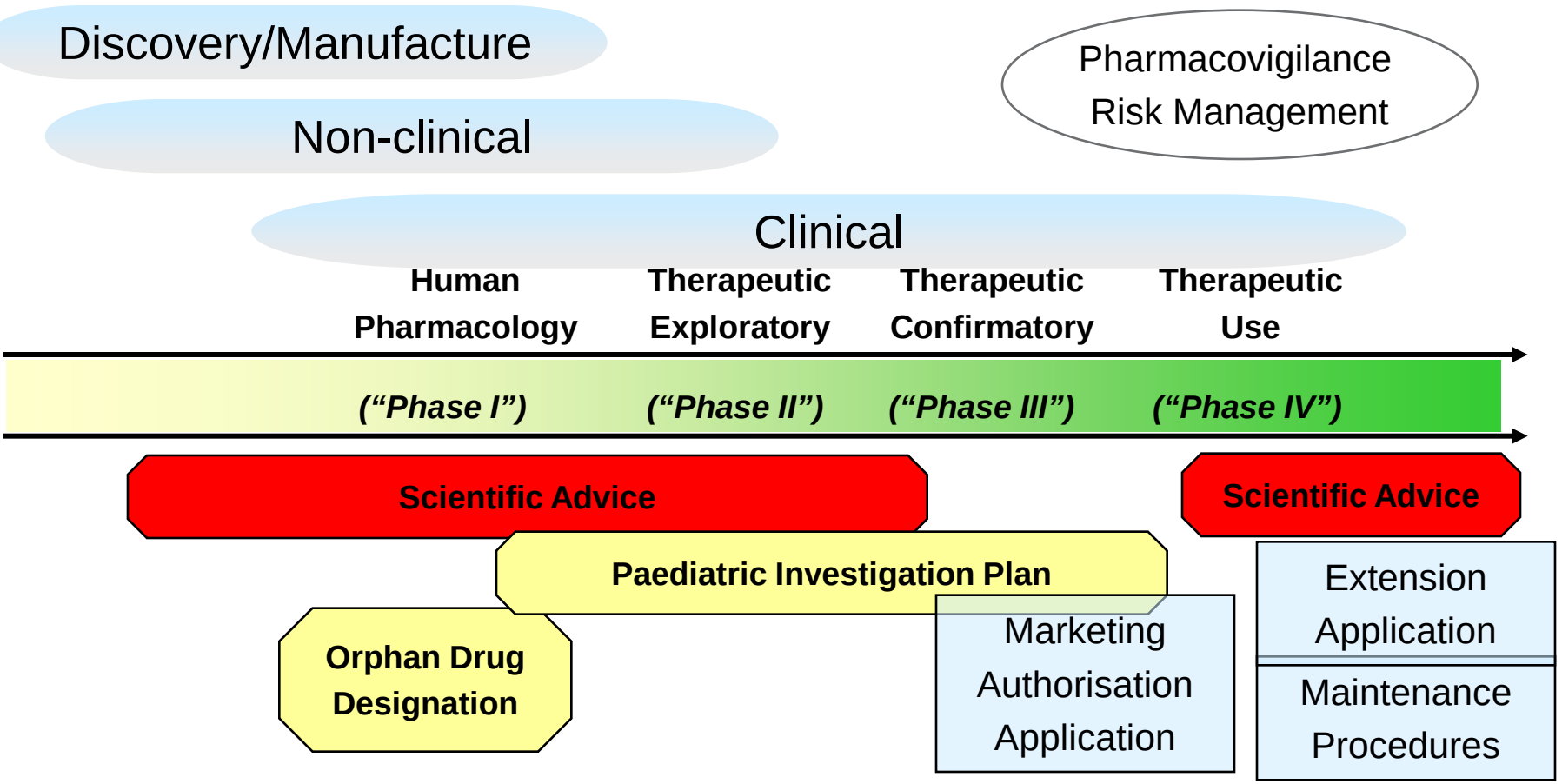
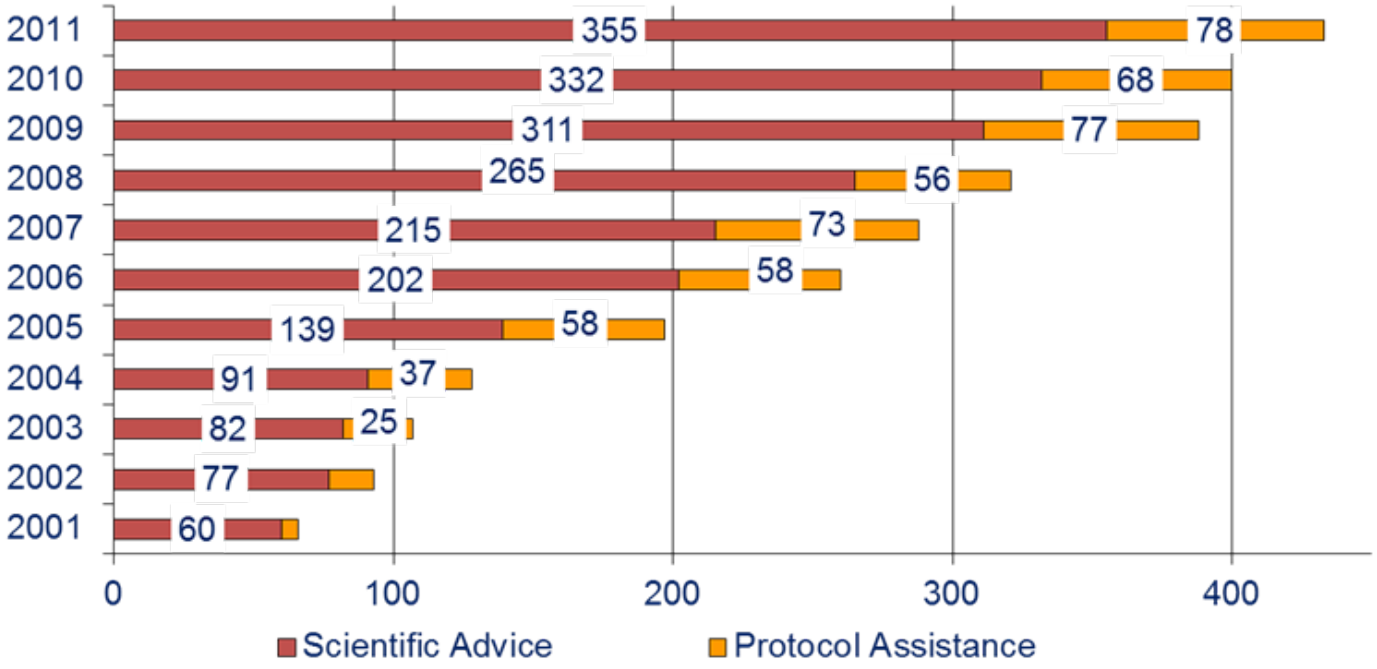


SAWP activities



- **Product related**
- **Qualification of novel methodologies**
- **HTA-EMA parallel advice**
- **FDA–EMA parallel advice**
- **Workshops**
- **1998-Sept 2012: 53 letters on CF products**

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Extrapolation of efficacy to CFTR mutations not studied in pivotal trials

Modulator of the mutant CFTR

Claim: Treatment of cystic fibrosis in patients with specific CFTR mutations

Pivotal safety / efficacy data on a specific CFTR mutation

Issues

Extrapolation of efficacy to patients harbouring other **CFTR mutations resulting in the same type of protein functional defect**

- Based on **in vitro data and one uncontrolled study with FEV1 % predicted as primary endpoint (PEP)**

Extrapolation of efficacy to patients harbouring other **CFTR mutations resulting in different types of protein functional defects with residual baseline CFTR activity**

- Based on **in vitro and placebo controlled underpowered study with FEV1 % predicted as PEP**

Modulator of the mutant CFTR

SAWP / CHMP

Extrapolation strategy **agreed** between mutations responsible for the **same type** of functional defect

Extrapolation across **different** CFTR protein functional defect **types**, but with residual baseline CFTR activity is **not possible** because mechanistic rational is missing. In this case failure to demonstrate **statistical significance** vs. control will make interpretation difficult

Modulator of the mutant CFTR

Alternative approach to identify patients that respond to treatment based on predefined sweat chloride response criteria. Exploratory analyses to assess the correlation between improvement in CFTR function (change in sweat chloride) and lung function (FEV1) and establish minimum threshold for response

SAWP/CHMP: Strategy to define **early predictors agreed**. Check also other biomarkers

Modulator of the mutant CFTR

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Open Questions

Extrapolation of efficacy across different CFTR mutations

- Study design, statistical significance
- How to qualify predictors for response to treatment

Eradication-Microbiology

Inhaled Antibiotic

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Claim: Treatment of early colonisation with PA

Issues

PEP for treatment of early colonisation with PA

Comparator (Nebulised colistin and oral ciprofloxacin, TOBI, IV antibiotics)

Microbiology

Company proposed time to recolonisation of lungs following effective anti-Pseudomonal therapy as primary endpoint

SAWP/CHMP

Initial eradication rate and time to recolonisation as **co-primary** endpoints

TOBI accepted as comparator

Avoid term eradication in indication

Fundamental **limitations** of all **respiratory tract sampling procedures and microbiological techniques** (e.g. false negative due to sampling problems, false positive due to contamination by organisms colonising the oropharynx)

Focus on culture results to define eradication and recolonisation

Initial eradication may be based on **negative cultures alone** but a secondary analysis should be performed in the subset of subjects who meet the culture-based criteria for initial eradication and have **negative antibody results**

The **phenotype** of all isolated P. aeruginosa should be determined and recorded. The presence or later appearance of strains with a **mucoid phenotype** is an important prognostic factor and should be evaluated as an exploratory endpoint

PCR detection of P. aeruginosa for exploratory analysis

Baseline isolates and positive cultures within the study period should be **genotyped** in order to specify **re-growth** vs. **new-colonisation**, i.e. colonisation by an exogenous isolate

Analysis of patients **colonised with other pathogens** should be addressed in protocol

Quantitative colony density counts not useful

Relationship between **MIC** and microbiological or clinical effect of inhaled therapy has rarely been claimed and has not been consistently or convincingly documented; this does not negate the collection of such data

Open questions

Primary endpoint and comparator for treatment of early PA colonisation

How to perform microbiology in CF lungs (sampling-microbiology techniques)?

Is microbiology predictive of clinical outcomes?

Generics / Hybrids / Biosimilars / me too

Inhaled Antibiotic

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Claim: Suppressive therapy of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis

Issue

Data requirements for a new formulation-device combination of an approved inhaled antibiotic

Background: Bioequivalence assessment performed in CF patients colonised with PA

SAWP/CHMP

For the purposes of comparing a new formulation-device of an inhaled antibiotic to the approved formulation-device, the CHMP agrees that **serum AUC** is a suitable primary endpoint

Concentrations in sputum are highly variable and could be analysed via descriptive statistics only. However, sputum sample data collected at several time points should be presented

Inhaled Antibiotic

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Open Questions

Is it important to disentangle effect of device from formulation?

How can regulators be kept up to date with new devices used in clinic, and update the requirement for control groups and SPCs?

Regulatory Awareness

The regulatory landscape changes when new orphan drugs are authorised for CF

Important to include endpoints/comparators to assess added benefit vs. current and expected to be authorised CF drugs

Pancreatic Enzyme Preparation (PEP)

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Me too PEP

Claim: Treatment of pancreatic exocrine insufficiency in CF

Issue

Conduct of a **non-inferiority** study requiring hospitalisation to compare investigational PEP to an approved active comparator in patients with CF and EPI, using **coefficient of fat absorption (CFA)** as the primary endpoint, exposes CF patients recruited in the study to **risks** that are not outweighed by the expected benefit of the investigational product compared to existing PEPs

SAWP/CHMP

In order to bridge data from approved PEP demonstration of Non Inferiority on CFA vs. approved comparator in CF patients is needed

Pancreatic Enzyme Preparation

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SAWP/CHMP

Modifications to the clinical trial in order to address ethical and feasibility concerns

- Inclusion of a relatively narrow age range (e.g. adults only, or only those from the age of 16) could not only help to dispel ethical concerns but also reduce variability
- Allow for full requirements/standard treatment of pulmonary disease, including inhaled and systemic antibiotics
- Conduct study in Ph I units
- Shorten treatment period

Open Question

Population and Endpoints for me too PEP

Feasibility

Ethics

28d on/off cycles

Inhaled Antibiotic

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Claim: Management of chronic pulmonary PA infections in cystic fibrosis patients

Issues

Assessment of Efficacy after a singe 28-day course

It would be unlikely that only one agent would be exclusively used in consecutive cycles, but rotated between other inhaled antimicrobial agents

Primary endpoint: Time to need for anti-pseudomonal antimicrobials (based on meeting pre-defined symptoms)

Key secondary: Spirometry

Placebo control

Inhaled Antibiotic

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SAWP/CHMP

PEP could be **supported** assuming that FEV1 will be a key secondary endpoint, but FEV1 is preferable as a primary endpoint

Long term efficacy should be demonstrated

Standard two arm trial vs. inhaled tobramycin of a minimum of 6 months (**3 on/off cycles**) proposed but open to alternative designs

Open Questions

How has the approval of new inhaled antibiotics shifted the therapeutic paradigm of 28d on/off cycles

Alternative designs and endpoints for long term efficacy

Qualification of Novel Methodologies

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CHMP Qualification Opinion

on the acceptability of a specific use of the proposed method (e.g. use of a BM) in a R&D context (non-clinical or clinical), based on the assessment of data, not product-specific

Qualification team, peer review, public consultation, publication

CHMP Qualification Advice

on future protocols and methods for further method development towards qualification, based on the evaluation of the scientific rationale and on preliminary data submitted, confidential

Thank You

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