EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Difficulties encountered – regulatory perspective:

Paediatric Investigation Plans

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EMA Workshop on endpoints for CF clinical trials
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Outline

- Paediatric Regulation
- Paediatric Investigation Plans for CF
- Challenges - Cystic Fibrosis Drug Development
- Potential new outcome measures

European Paediatric Regulation

The validation of a marketing authorisation application – even for adults only – will be refused unless an EMA decision on a Paediatric Investigation Plan (PIP) or waiver is included.

What is a PIP (Paediatric Investigation Plan)?

- Details of the measures and timing to demonstrate:
  - Quality
  - Efficacy
  - Safety

  Marketing Authorisation Criteria

  To be based on objective criteria
- Basis for development and authorisation of a medicinal product for children
- To be agreed by the Paediatric Committee (PDCO)
- Binding on company → compliance check

PIPs related to CF

17 PIPs related to Cystic Fibrosis submitted

- antibiotics: 8
- CFTR modulator: 3
- other: 6

10 PIPs agreed by PDCO

- enrolment of approx. **5000** CF patients (adults and children, including neonates)

3 under review

4 withdrawn by applicants

www.ema.europa.eu/htms/human/paediatrics/decisions

Paediatric investigation plans (PIPs)

- 4 PIPs agreed for **inhaled antibiotics** :

  - tobramycin: nebuliser solution/inhalation powder
  - colistimethate sodium: inhalation powder
  - amikacin: nebuliser suspension
  - aztreonam: nebuliser solution

- PIPs must address early *Ps.* infection/colonisation: Initial and sustained eradication to be assessed

- CHMP did not yet grant indication for treatment of early colonisation/infection

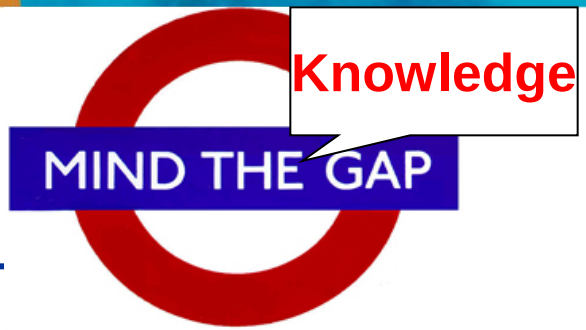
http://www.ema.europa.eu

Early infection

Endpoints under discussion by CHMP and PDCO

Initial and sustained eradication:

- Initial eradication: % patients with eradication at end of treatment
  - First time point to determine clearance of the airways ?
- Sustained eradication:
  - Time to re-colonisation as co-primary endpoint ?
  - to fulfil co-primary endpoint, patients should be free of *Pseudomonas* during 12 -24 (?) months following EOT
  - a positive *Ps. aeruginosa* sample within follow-up period to be considered a failure ?



Open Questions

- Lack of generally accepted definition of eradication

  At least three negative respiratory cultures within a 6-month period after the cessation of treatment in the presence of negative specific antibodies *(JCF 2004)*

  - 6 month period long enough ?

  - First time point to determine clearance of the airways ?

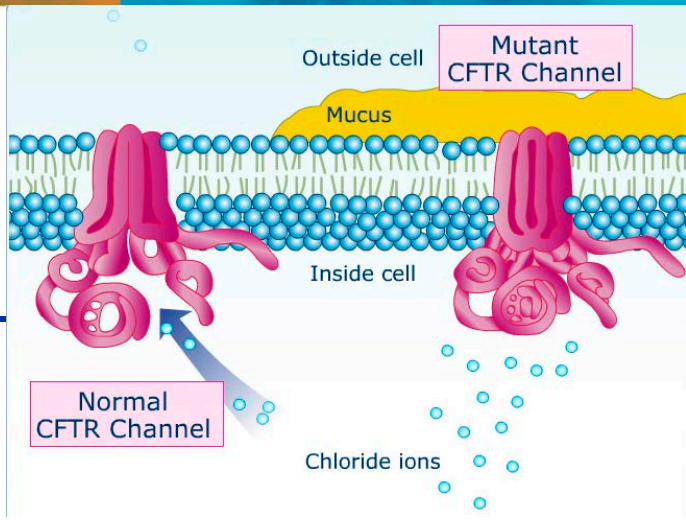
- Lack of international standardization of terms:

  colonization, chronic colonization, re-colonization, infection

  (European Consensus statement: ERS 2000; JCF 2011)

- Optimal Dose ?

PIPs - CFTR modulators:



At present 3 PIPs agreed for

- Ivacaftor
- Ivacaftor + Lumacaftor
- Ataluren

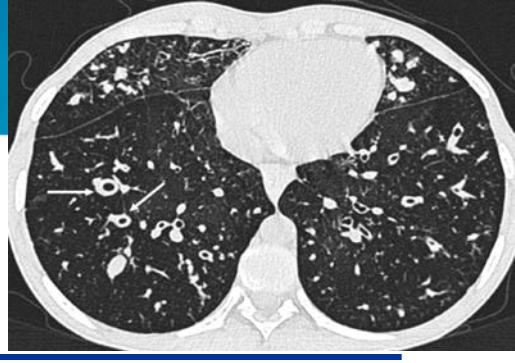
http://www.ema.europa.eu

Paediatric specific issues – CFTR modulators

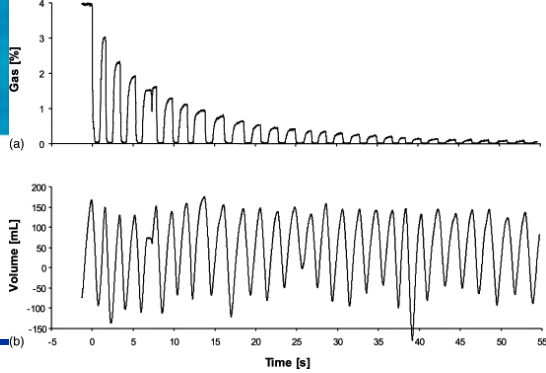
- Translation of disease improvement into improved organ function limited by level of irreversible damage
- Greatest benefit expected in young children
- Efficacy to be extrapolated from adults to young children ?
- Spirometry not optimal for evaluating novel therapies aimed at earliest stages of CF lung disease
- How to evaluate efficacy and safety of CFTR modulators in young children not yet able
  - to reliably perform lung function testing
  - who are clinically stable

→ new measures are needed

Imaging – HR-CT



- Clinical studies using CT scores as outcome parameter strongly suggest that CT scoring is more sensitive than lung function tests for detecting relevant disease progression in CF
- Bronchiectasis, progressive and irreversible in CF, the most relevant structural change on CT scans, can be scored reliably
- Need for standardized (low-dose) CT protocol and scoring system
- Need to demonstrate
  - preventing (progression of) bronchiectasis result in long-term clinical benefit to patients
  - long-term safety of repeated measurements



Lung clearance index

- marker of ventilation inhomogeneity within lung
- more sensitive than FEV1 to early lung disease
- narrow normal range of values, consistent across research centres
- good reproducibility and reliability
- objective surrogate marker
- Need to demonstrate:
  - sensitivity to meaningful changes in patient's health
  - improvement of LCI relates to long-term clinical benefit

Clinical outcomes:

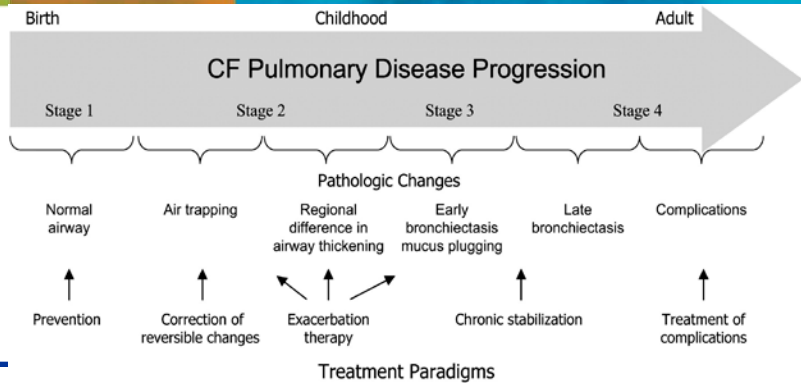
- Exacerbation rate
- Time to first pulmonary exacerbation requiring intravenous antibiotic therapy
- Need for

- universally accepted definition of exacerbation
- standardized criteria when to start iv antibiotic treatment
- PRO instrument for preschool children

Paediatric specific issues – CFTR modulators

- Can improvement of CFTR functions be quantified in the GI tract?
- Is it possible to define meaningful digestive endpoints?
- If yes, could they be used as surrogate for clinical efficacy in preschool children in whom repeat lung function tests are not (yet) feasible?

CFTR modulators – Impact on disease progression



- Need for long-term follow-up, including incidence of Diabetes mellitus and DIOS:

  - long-term observational studies ?

  - registries ?

- Need to evaluate effect of CFTR modulators on disease progression:

  - What endpoints ?

  - Comparison to historical control, to CF registries ?

Conclusion

- Need for new outcome measures
- Suitable for use in young children and infants
- Close collaboration between regulators, academia, patients/parents and industry