Tuesday 8 December 2015

Workshop on gastrointestinal (GI) outcome measures to evaluate CFTR modulators for the treatment of cystic fibrosis (CF)

Tuesday, 8 December 2015, 13:30 – 16:30, meeting room 2E

Background

Recently introduced new CFTR modulator treatments target the basic defect of cystic fibrosis. CFTR modulators offer the potential of a curative treatment. Some CFTR modulators have currently been registered for clinical use in CF patient with specific CFTR mutations others or are under development or tested in several clinical trials.

The currently accepted primary outcome measures for clinical trials in CF are sweat chloride, FEV1 and weight gain. In practice also pulmonary exacerbation rate (FDA) and fecal elastase (EMA) have currently been accepted as secondary outcomes for use in clinical trials.

In practice the currently used set of outcome measures show some drawbacks:

1. Usability in young children with still well preserved lung function and nutritional status.
2. Absent or weak mutual correlation between sweat chloride (representing CFTR function), FEV1and weight gain.
3. The inability to perform dose finding studies.
4. No clear mechanistic explanation for the relation between CFTR correction and the measure outcome. E.g. treatment with Ivacaftor in CF patients with gating mutations resulted in significant weight gain. However, the mechanism behind the observed weight gain is not understood.
5. For individual patients, outcome measures may vary in effect size or effect direction. Indicating that a more personalized approach might be appropriate.
6. The potential presence or absence of additional treatment effects in other, by CF serious affected organ systems (intestinal malabsorption, exocrine pancreatic insufficiency and CF related diabetes) are not evaluated.

Evaluating Gastro intestinal (GI) outcome measures might help to elucidate some mechanisms and thus reduce the current knowledge gaps. (*Bodewes, Frank AJA, et al. "Cystic fibrosis and the role of gastrointestinal outcome measures in the new era of therapeutic CFTR modulation." Journal of Cystic Fibrosis 14.2 (2015): 169-177.)*

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Aim of the meeting:

To discuss and potentially reach agreement on gastrointestinal outcome measures to be included in clinical studies to evaluate efficacy (and safety) of CFTR modulators for regulatory submissions.

Agenda

Co-chairs: Frank Bodewes (University Medical Center Groningen) and Elmer Schabel (Chair CHMP GI-Drafting Group)

Topic	Speaker	Time
Welcome and registration		13:00
Brief overview of CFTR modifier pipeline	Tim Lee	10’
Potential of gastrointestinal outcome measures in CFTR modulation. Is it possible to define a core set that should be evaluated in all studies?	Frank Bodewes	15’
The role of intestinal organoids function for evaluation of CFTR modulators	Jeffery Beekman	15’
Discussion of predefined questions (and answers received)	All	
Wrap-up and conclusion/next steps	Co-chairs	
End of the afternoon session		16:30