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Statistical concepts for primary efficacy analysis in vertigo trials

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Trials performed in cooperation with the IBE:

**BEMED**
- **Trial Design**: Phase II, multicenter, placebo-controlled, double-blind, three-arm, parallel-group, dose-finding trial
- **Intervention**: Medical treatment of Menière’s disease with betahistine-dihydrochloride (2 dosages: 2.24 mg vs. 3.48 mg)
- **Primary efficacy endpoint**: number of attacks in the three treatment arms during the last 3 months of the 9-month treatment period

**PROVEMIG**
- **Trial Design**: Phase III, multicenter, placebo-controlled, double-blind, two-arm, parallel-group efficacy of treatment trial
- **Intervention**: Prophylactic treatment of definite vestibular migraine with metoprolol versus placebo
- **Primary Objective**: To demonstrate the superiority of metoprolol treatment regarding vertigo and headache attacks per month compared to placebo
- **Primary efficacy endpoints**: 1) number of vertigo attacks and 2) number of migraine attacks during the last 3 months of the 6-month treatment period (hierarchically tested)
- **Interim analysis**: to check assumptions of initial sample size calculation, optional sample size re-assessment

**BETAVEST**
- **Trial Design**: Phase II/III, multicenter, placebo-controlled, double-blind, two-arm parallel-group, efficacy of treatment trial
- **Intervention**: Medical treatment of acute vestibular neuritis with Betahistine-dihydrochloride (48 mg three times daily); Duration of treatment: 4 weeks
- **Primary Objective**: To demonstrate medium-term and short-term superiority of betahistine treatment regarding recovery of postural control or spontaneous nystagmus as compared to placebo
- **Primary endpoints**: "Total sway path" (length per time), and mean peak slow phase velocity of the spontaneous nystagmus. Measurements on day 10 (medium-term) and day 3 (short-term) after randomization
- **Interim analysis**: to check assumptions of initial sample size calculation, optional sample size re-assessment

Trial of 4-AP in EA2 and related familial episodic ataxias with 4-Aminopyridine

- **Trial Design**: randomized, placebo-controlled, double-blind, 2-way crossover (proof-of-concept)
- **Intervention**: Treatment of familial episodic ataxia with 4-Aminopyridine
- **Primary endpoint**: average number of ataxia attacks per month

**FAMPYRA™ trial [planned]**
- **Trial Design**: Phase III, monocenter, randomized, placebo-controlled, double-blind, three-way crossover trial
- **Intervention**: comparison of efficacy of 4-Aminopyridine (prolonged-release) vs. Azetazolamid in patients with EA2

Biometrical aspects & methodological considerations

Dealing with dropouts and informative missings

Methods to replace missing data for the scheduled examinations:
- LOCF principle (last observation carried forward)
- Pattern mixture modeling to handle non-ignorable monotone missing data

Modeling-based approach for longitudinal counts:
- Using Generalized Linear Mixed Models (GLMMs) to analyze longitudinal count data measured at key time-points (vs. single time point analysis)
- Random effects modeling to investigate how different patients respond to treatment
- Informed model choice for confirmatory analysis by using pilot/phase II data (Poisson-, negative binomial loglinear mixed models,... or variance-stabilizing transformation of attack frequency data)
- Research on the impact of model misspecification on the performance of inferential procedures (i.e. estimation of treatment effects) in GLMMs
- Predicting individual trajectories / longitudinal profiles
- Estimation of patient-specific treatment effects

Sample size re-assessment, design modifications for confirmatory analysis

- **BEMED trial**: calculation of a revised sample size: Estimation of new planning figures based on 2 data sources (1) baseline data (e.g. frequency of vertigo attacks) being independent of the trial data (2) pilot/phase II data to assess the anticipated individual trajectories and hence, determine parameters needed for sample size re-calculation
- Optional design modifications based on conditional rejection probability

Relevant publications


Münzer K, Damm B, Glaser M, Linn J, Adrion C, Mansmann U, Brandt T. BEMED trial: calculation of a revised sample size: Estimation of new planning figures based on 2 data sources (1) baseline data (e.g. frequency of vertigo attacks) being independent of the trial data (2) pilot/phase II data to assess the anticipated individual trajectories and hence, determine parameters needed for sample size re-calculation

Optional design modifications based on conditional rejection probability

Cooperation partners: Department of Neurology, CSC, LMU, SCS