Advisory Board Meeting
21 July 2011

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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 betahistin EudraCT-Nr.: 2005-000752-32 *To be allocated: 186 total*

- 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 EudraCT No.: 2009-013701-34 *To be allocated: 266 total*

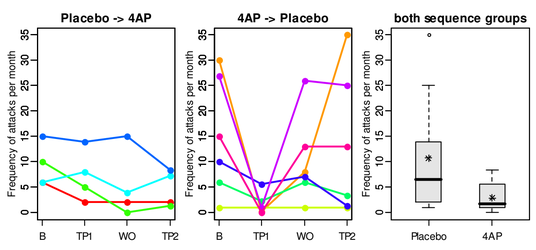
- Trial Design: Phase III, multicenter, placebo-controlled, double-blind, two-arm, parallel-group efficacy of treatment trial
- Intervention: Prophylactic treatment of definite **vestibular migraine** with metoprolol versus placebo
- Primary Objective: To demonstrate the superiority of metoprolol treatment 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

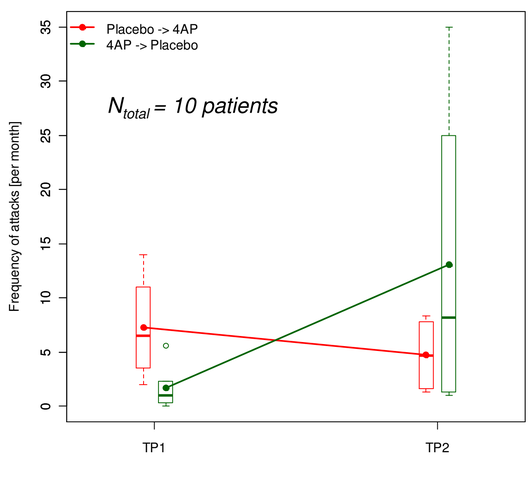
BETAVEST EudraCT No.: 2009-013702-14 *To be allocated: 210 total*

- 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

- 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





Poisson random intercept model revealed a significant treatment effect (p=0.03)

Left figure:
Boxplots illustrate the variation of the number of attacks in both groups for each treatment period TP1 and TP2.

Assessment of period effect and carry-over effect: The lines depict the mean number of attacks in each period (TP1: 1st treatment period, TP2: 2nd treatment period) for both groups (Placebo → 4-AP; 4-AP → Placebo). Small level differences for 4-AP versus Placebo can be observed indicating only a minor period effect (p=0.09). Differences of mean attacks for 4AP versus Placebo differ only marginal in both periods and there is no evidence for a carry-over effect.

(Strupp et al. *Neurology* 2011)

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

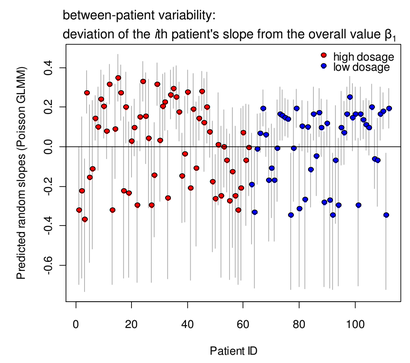
Dealing with dropouts and informative missings

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

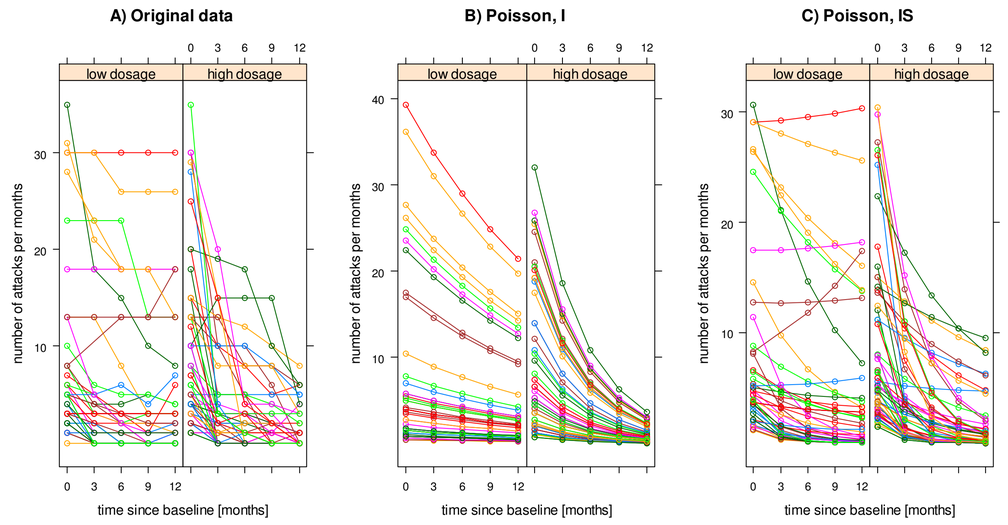
Modeling-based approach for longitudinal counts:

- 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



Poisson mixed model for subject-specific mean number of attacks measured over time:

$\log(\mu_{ij}) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})\cdot time_j + \beta_2 \cdot dosage_i \cdot time_j$ *i*: Patient, j: scheduled visit



(Strupp et al. *Acta Otolaryngol.* 2008)

Effect of Betahistine on the frequency of definitive episodes of vertigo in Ménière's disease for both treatment groups (low vs. high dosage)

A) Individual trajectories

B,C) Estimated conditional means for number of attacks, Poisson GLMM with patient-specific random intercept and slope.

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

Strupp M, Kalla R, Claaßen J, Adrion C, Mansmann U, Klopstock T, Freilinger T, Neugebauer H, Spiegel R, Dichgans M, Lehmann-Horn F, Jurkat-Rott K, Brandt T, Jen JC, Jahn K. 4-aminopyridine in episodic ataxia type 2 and other familial episodic ataxias with nystagmus. *Neurology* 2011;77:269-275.

Strupp M, Hupert D, Frenzel C, Wagner J, Hahn A, Jahn K, Zingler VC, Mansmann U, Brandt T. Long-term prophylactic treatment of attacks of vertigo in Menière's disease – comparison of a high with a low dosage of betahistine in an open trial. *Acta Otolaryngol*. 2008; 128(5):520-524.

Adrion C, Mansmann U. Bayesian model evaluation for longitudinal count data in a clinical trial setting: application to vertigo data. Submitted.

Hüfner K, Barresi D, Glaser M, Linn J, Adrion C, Mansmann U, Brandt T, Strupp M. Vestibular paroxysmia: diagnostic features and medical treatment. *Neurology* 2008; 71(13):1006-14.

Lezius F, Adrion C, Mansmann U, Jahn K, Strupp M. High-dosage betahistine dihydrochloride between 288 and 480 mg/day in patients with severe Menière's disease: a case series. *Eur Arch Otorhinolaryngol*. 2011; 268(8):1237-40.

Neugebauer H, Adrion C, Glaser M, Strupp, M. Long-term changes of central ocular motor dysfunction in patients with vestibular migraine. Under review.

Cooperation partners: Department of Neurology, CSC^{LMU}, CSC^{IFB}