

Attachment to the Access to Data and Information Research Proposal Form

Title: Retracing compliance patterns from blood samples: a comparison with medication event monitoring system recordings

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Statistical Analysis Plan (SAP)

Population and sample: as in the publication resulting from the study data analysis (Vrijens et al.) and described above. We do not mean to have a representative sample of any specific population.

Statistical approach:

Descriptives

Basic descriptive statistics will be obtained for all of the variables. Graphs of the blood sample concentration as a function of the sampling time will be produced per individual. Potential outliers will be flagged and used for sensitivity analyses at the end of the modeling process.

Retrieving compliance patterns from blood sample data

We will use a Bayesian statistical procedure; from *a priori* distribution of compliance patterns, we estimate the *a posteriori* distribution conditioned on blood sample knowledge. The detailed procedure is described in reference #1: "A Bayesian approach for the estimation of patient compliance based on the last sampling information". The method relies on a pop-PK model of the drug. See below for a description of how we plan to obtain such model from the data. For each individual, the output (i.e. retrieved compliance pattern from blood sample) will be compared to the measured compliance pattern as obtained via the MEMS.

Obtaining a population pharmacokinetics model from the data

Mimicking the procedure described in the publication resulting from the study data analysis (Vrijens et al.), a pop-PK model will be obtained. In other words: 1) we will assume a 1-compartment model with first-order absorption and first-order elimination; 2) we will consider the volume of the central compartment (V), elimination rate constant (k_e), and absorption rate constant (k_a) as model parameters; 3) we will assume a lognormal model for the between-patient variability in k_e and V , while k_a will be considered fixed across the population. NONMEM 7 will be used in order to obtain the necessary parameter estimates.

Endpoints (variables) to be analyzed: The probability of having retrieved the accurate compliance pattern of the participants as a function of study data being used.

Covariates and Analysis of subgroups: we will investigate if socio-demographic factors can influence the probability of retrieving accurate compliance patterns.

Statistical tests and power: We do not wish to infer conclusions to a population, but only to test the performance of the method on the sample. Therefore, no statistical test will be performed. We will, however, compute a confidence interval around our endpoint.

Handling of missing data: We plan on testing if and which kind of missing data can impact the method's performance.