Study Plan

of a Non-Interventional Observational Study

Infusion of gelatine solutions in pediatric patients aged up to 12 years

GPS - Gelatine in **P**ediatric Patient**S**

Study ID No.: HC-O-H-1406

NCT02495285

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Marketing Authorisation Holder:

B. Braun Melsungen AG
Germany

Organized and Financed by:

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STUDY OVERVIEW

Title	Infusion of gelatine solutions in pediatric patients aged up to 12 years *Acronym:* **G**elatines in **P**ediatric patient**S** (**GPS**)
Product under investigation	Plasma volume replacement solutions containing gelatine (Gelaspan® 4% & Gelofusine® 4%)
Study design	Prospective, non-interventional, international, multicentric observational cohort study
Number of sites, countries	≥ 10 European centers (e.g., Austria, France, Germany, Italy)
Phase	Post-authorization, non-interventional, clinical study voluntarily performed by Marketing Authorization Holder (MAH)
Indication	Treatment of hypovolemia and shock
Primary objective and variable	To gain additional information (dosing used during different surgeries) during routine clinical practice when used in pediatric population
Secondary objectives and variables	Further evaluation of safety and efficacy based on routinely measured clinical parameters: <u>Safety:</u> • blood gas analysis (pH, HCO_3^-, pCO_2, sO_2, BE, Hb, Hct, lactate, Na^+, K^+, Ca^{2+}, Cl^-, glucose) • serum prolin • renal function (serum creatinine) • (serious) adverse events / reactions including severity of an allergy and prick-test results in case of an anaphylactic/anaphylactoid reaction <u>Efficacy:</u> • hemodynamic measures (heart rate, mean arterial pressure) <u>Other:</u> • demographic data • medical diagnosis leading to intervention • concomitant disease • pre-operative abnormalities • indication for the administration of gelatine solution • hemodynamics and hemodynamic monitoring • concomitant infusions/medication (crystalloids, colloids, blood products, vasoactive drugs) • surgery related data • follow-up (post-operative bleeding complications and renal failure) • final evaluation
Patient population ▪ inclusion criteria	• age ≤ 12 years • American Society of Anesthesiologists (ASA) risk score: ≤ III • peri-operative infusion of gelatine solutions

▪ exclusion criteria	• informed consent and/or data protection declaration signed by parents/legal guardians (according to local requirements) • inclusion in another investigational study in the field of volume replacement which could interfere with the routine clinical practice regarding the administration of the gelatine solutions In addition contraindications as outlined in the valid local Summaries of Product Characteristics (SmPCs) have to be considered.
Observational period per patient	Observation period will start two hours prior first infusion of gelatine solutions and will end two hours after the last gelatine infusion stopped. A follow up will be furthermore recorded at discharge from the hospital or in-hospital 3 months after start of gelatine infusion, whatever occurs first.
Study duration / milestones	60 months after first patient in or termination after treatment of a maximum of 1500 patients, whatever occurs first. Interim analysis should be conducted after enrolment of at least 600 patients.
Sample size	At least 1000 patients and in total a maximum of 1500 patients.

Statistical Analysis and Evaluation

All data will be analyzed by means of tables, figures, listings and statistical tests if appropriate. The final programming will be performed after closure of the database by use of an appropriate statistical software package like SAS or SPSS.

Deviations from the study plan will be assessed as plan violations if at least one of the inclusion or exclusion criteria is not fulfilled. All patients who received the product at least once will be included in the intention-to-treat analysis. All patients who received the product under investigation at least once without any plan violation will be included in the per protocol analysis.

The patient data will be identified by the patient number assigned during data management, the study center, the treatment time and age of patient.

The following statements are valid throughout the statistical analysis:
Variables with metric or ordinal scale will be summarized with

- number of patients (N)
- minimum (Min)
- maximum (Max)
- median (ordinal variables)
- mean (metric variables)
- standard deviation (SD)
- *(optional)* frequency in the case of ordinal scale (n/%)
- *(optional)* upper and lower quartile (Q3 and Q1)
- 95% confidence interval of the median/mean
- number of missing data (N_{miss})

Categorical variables will be summarized with

- N
- frequency (n,%)
- N_{miss}

Missing data will be analyzed as such and will not be replaced by estimates.

The following standard procedures for the comparison of subgroups (e.g. study center, country and age) are planned:

- Fisher's exact test for binary data
- χ^2 test for kx2 tables (k > 2)
- U test according to Wilcoxon-Mann-Whitney
- t-test for metric data
- ANOVA (analysis of variance)
- in case of small cell expectations occurring in the majority of the test situations data of ordinal scale will be analyzed by means of the U test instead of the χ^2 test.

All statistical tests will be performed two-tailed with the pre-specified significance level of α = 5%.

An interim analysis will be performed after treatment of at least 600 patients.

The following tables inclusively descriptive statistics (see above) are planned:

- demographic data
- medical diagnosis leading to intervention
- concomitant disease(s)
- pre-operative abnormalities
- indication for and time of administration of gelatine solutions
- gelatine solution application

    - dosage in relation to efficacy and safety during different kind of surgeries
- hemodynamic monitoring
- concomitant infusion/medication
- hemodynamic data
- blood gas analysis
- serum proline
- serum creatinine
- surgery related data
- AEs
- ARs
- SAEs / SARs
- follow-up at hospital discharge or in-hospital 3 months after first infusion of gelatine solutions, whatever occurs first
- personal review
- remarks and final conclusion

Where appropriate corresponding figures (e.g. box-plot, bar-chart) will be presented.