Post-authorisation Safety Study Protocol: Study 8822-001

Title	A Multicenter, Non-interventional, Observational, Post-Approval Safety Study of Updated ACCUSOL 35 Solutions in Continuous Renal Replacement Therapy (ACCUPASS)
Protocol version	Amendment 1 (2015Jan12)
EU PAS register number	ENCEPP/SDPP/6800
Active substances	Calcium chloride dihydrate, magnesium chloride hexahydrate, sodium chloride and sodium bicarbonate in all 3 formulations; and potassium chloride and glucose monohydrate in 2 of the 3 formulations
Medicinal products	ACCUSOL 35; ACCUSOL 35 Potassium 2 mmol/L; and ACCUSOL 35 Potassium 4 mmol/L
Product references	UK license numbers: PL 00116/0414; PL 00116/0415; and PL 00116/0416
Procedure numbers	MRP numbers: UK/H/0813/001; UK/H/0839/001; and UK/H/0839/002
Marketing authorisation holder	Baxter Healthcare Limited Caxton Way, Thetford, Norfolk, UK IP243SE
Joint PASS	No
Research question and objectives	As a result of prior reports of visible calcium carbonate precipitate in continuous renal replacement therapy (CRRT) lines during administration of ACCUSOL 35 solutions, the formulations of the products were updated. The objective of this study is to confirm the prevention of precipitate formation during CRRT by the use of the updated ACCUSOL 35 solutions.
Countries of study	4 to 5 EU countries (possible candidates include Austria, Belgium, Czech Republic, Denmark, France, Germany, Ireland, Netherlands, Spain, Sweden and United Kingdom)
Author	Drew S. Jones, MD, MPH, MBA Senior Medical Director Baxter Healthcare Corporation Round Lake, IL, USA Telephone: +1 (224) 270 2659
MAH contact person	James D. Motley Director, Pharmacovigilance, UK, Ireland and Malta Direct telephone: +44 (0) 1635 206437 Mobile telephone: +44 (0) 7717 542284 Direct fax: +44 (0) 1635 206281 e-mail: james_motley@baxter.com

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

CRF	case report form
CRRT	continuous renal replacement therapy
EC	ethics committee
ICH GCP	International Conference on Harmonisation guidelines for Good Clinical Practice
ICU	intensive care unit
KCl	potassium chloride
MedDRA	Medical Dictionary for Regulatory Activities dictionary
WHODRUG	World Health Organization drug dictionary

3. RESPONSIBLE PARTIES

Protocol Author and Sponsor Medical Monitor	Drew S. Jones, MD, MPH, MBA Senior Medical Director Baxter Healthcare Corporation Round Lake, IL, USA Direct telephone: +1 (224) 270 2659
Qualified Person in Pharmacovigilance	Johan Hellmér, MD, PhD Deputy EU Qualified Person for Pharmacovigilance Baxter Medical AB Kista, Sweden Direct telephone: +46 (0) 8 632 64 68) Direct fax: +46 (0) 8 752 01 12

The list of investigators and contact information for them will be maintained by the study Sponsor in a separate document (see Section 14.1).

4. ABSTRACT

Title

A Multicenter, Non-interventional, Observational, Post-Approval Safety Study of Updated ACCUSOL 35 Solutions in Continuous Renal Replacement Therapy (ACCUPASS)

Study Number: 8822-001

Version: Original (2014Sep17)

Author: Drew S. Jones, MD, MPH, MBA
Senior Medical Director
Baxter Healthcare Corporation
Round Lake, IL, USA
phone: +1 224-270-2659

Rationale and Background

ACCUSOL 35 solutions are indicated for the treatment of acute and chronic renal failure, as substitution solution in haemofiltration and haemodiafiltration, and as dialysis solution in haemodialysis and haemodiafiltration. Due to an increase in the number of product quality complaint reports related to the presence of white precipitate (calcium carbonate) formed during continuous veno-venous haemofiltration and continuous veno-venous haemodiafiltration in the continuous renal replacement therapy (CRRT) lines during the use of ACCUSOL 35 solutions, Baxter Healthcare Corporation updated the formulations of the products. The marketing authorization holder subsequently committed to perform this post-approval safety study with the updated solutions to monitor the safety of the updated formulations, specifically to address the risk of calcium carbonate precipitate formation.

Research Question and Objectives

The updated ACCUSOL 35 formulations were developed to prevent calcium carbonate precipitate formation during CRRT administration. The objective of this study is to confirm the prevention of calcium carbonate precipitate formation during CRRT by the use of the updated ACCUSOL 35 solutions under normal clinical use conditions.

Study Design

This is a multicenter, non-interventional, single-arm, observational, post-approval safety study in adult patients undergoing CRRT using any ACCUSOL 35 solution(s).

CRRT therapy will be administered in accordance with the intensive care unit's usual clinical practice and the recommendations in the current labeling for the ACCUSOL 35 solutions. Addition of antibiotics or any other medications to the ACCUSOL 35 solution bag, except for potassium chloride (KCl) supplementation, will not be allowed (see "Population"). The CRRT lines will be inspected every 30 minutes for the duration of the therapy, as described in the labeling for ACCUSOL 35 solutions.

Study staff will record the study data (see "Variables") during administration of CRRT with ACCUSOL 35 solution. The planned maximum study observation period is 32 hours: from 40 hours after CRRT with the current circuit was started until 72 hours of treatment has been administered using that same circuit.

Population

The study will include approximately 240 adult patients enrolled at approximately 20 to 25 hospitals, with medical or surgical ICUs that regularly treat CRRT patients using ACCUSOL 35 solutions, in 4 to 5 European Union countries (possible candidates include Austria, Belgium, Czech Republic, Denmark, France, Germany, Ireland, Netherlands, Spain, Sweden and United Kingdom).

Male and non-pregnant female patients will be eligible for enrollment if they are at least 18 years of age and have been undergoing CRRT using any ACCUSOL 35 solution (without any concomitant medication added to the solution, except for supplemental potassium chloride, if needed), with the same CRRT circuit for at least 40 hours. Patients with any contraindication to treatment with an ACCUSOL 35 solution, patients involved in any study with another investigational product or therapy (in the prior 30 days or during participation in this study), and patients who were previously included in the study will be excluded.

Variables

The key safety variables to be collected for analysis include:

- Amount of ACCUSOL 35 solution delivered through the CRRT circuit observed during the study
- Start- and end-of use times for the CRRT circuit used during the study
- Presence or absence of visible precipitate in the CRRT lines used during the study
- Time of observation of visible precipitate (if applicable)
- Color of precipitate observed (if applicable)

- Reason for terminating the use of the CRRT circuit, if during the study
- Reason for terminating the CRRT, if during the study
- Reason for end of patient's study participation

Data Sources

Data will be collected from the medical records of the enrolled patients and from observation of the patients and CRRT lines during the study period.

Study Size

The study will enroll approximately 240 patients. Data from at least 58 evaluable CRRT patients (ie, those whose CRRT circuits remained precipitate-free for 72 hours and those in whose circuits visible precipitate was observed within 72-hours) are needed to meet the study objective (see "Data Analysis").

Data Analysis

The primary analysis will be to generate the upper bound of the 95% confidence interval on the true proportion of treatments having precipitate formation, based on the data from the evaluable treatments. If no visible precipitate is observed in at least 58 evaluable treatments, the study will have provided 95% confidence that the probability of visible precipitate formation during 72 hours of CRRT with ACCUSOL 35 solution using the same CRRT circuit is not more than 5.0%. Based on the assumption that only 10% of all CRRT treatments will last 72 hours (regardless of whether the same circuit is in use the whole time), and combining the probabilities of both having a treatment last 72 hours and also having visible particulate formation, the result will have demonstrated with 95% confidence that the probability of visible precipitate formation in all CRRT treatments of any length with ACCUSOL 35 solutions, is not more than 0.5%.

Appropriate summary statistics will be calculated for other applicable variables to describe the variability of the therapy methods and materials involved in the study.

Milestones

Planned registration in the EU PAS register: June 2014

Planned start of data collection: October 2014

Planned end of data collection: April 2016

Planned final report of study results: August 2016

5. AMENDMENTS AND UPDATES

Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
1	2015Jan12	4. Abstract (Study Population) 9.2.2 Study Population 9.2.2.1 Inclusion Criteria (Item 1)	Exclusion of pregnant females from study participation	Request from the responsible ethics committee

6. MILESTONES

Milestone	Planned Date
Registration in EU PAS Register	June 2014
Start of data collection	October 2014
End of data collection	April 2016
Final Report of Study Results	August 2016

7. RATIONALE AND BACKGROUND

ACCUSOL 35 solutions are indicated for the treatment of acute and chronic renal failure, as substitution solution in haemofiltration and haemodiafiltration, and as dialysis solution in haemodialysis and haemodiafiltration. The product is presented in 3 formulations, 1 without potassium chloride (KCl) and 2 containing KCl (at concentrations of 2 mmol/L and 4 mmol/L). All 3 formulations contain calcium chloride dihydrate, magnesium chloride hexahydrate, sodium chloride and sodium bicarbonate. The 2 KCl formulations also contain glucose monohydrate.

In 2008, Baxter Healthcare Corporation (Baxter; the manufacturer of ACCUSOL 35 solutions) received an increased number of product quality complaint reports related to the presence of white precipitate observed in the continuous renal replacement (CRRT) lines during continuous veno-venous haemofiltration and continuous veno-venous haemodiafiltration during the use of ACCUSOL 35 solutions. In 2009, Baxter's root cause investigation identified that the precipitate was calcium carbonate, and a change in the pH of the mixed solution (supersaturation) was acknowledged as the major contributing factor to precipitate formation. Further investigation revealed that the addition of a low amount of phosphate salt as an excipient and lowering the pH of the mixed solution could inhibit the formation of calcium carbonate.

As part of their responses on 27 August 2009, Baxter made a commitment to the Pharmacovigilance Working Party to perform a post-approval safety study with the updated solution to monitor the safety of the updated formulation, specifically to address the risk of calcium carbonate precipitate formation.

This protocol presents the details of the post-approval safety study designed to verify the successful minimization of the risk of precipitate formation with the updated ACCUSOL 35 solution. The confirmation of the prevention of precipitate formation will support a proposal for removal of the current recommendation (presented in the labeling for the ACCUSOL 35 solutions) to inspect the CRRT lines every 30 minutes for the presence of precipitate during the use of the products.

8. RESEARCH QUESTION AND OBJECTIVES

The updated ACCUSOL 35 formulations were developed to prevent calcium carbonate precipitate formation during CRRT administration. The objective of this study is to confirm the prevention of calcium carbonate precipitate formation during CRRT by the use of the updated ACCUSOL 35 solutions.

9. RESEARCH METHODS

9.1 Study Design

This study is a prospective, multicenter, non-interventional, uncontrolled, open-label, observational study in adult patients undergoing CRRT using any of the updated ACCUSOL 35 solutions. The study is intended to capture data on the absence or presence of visible precipitate during 72 hours of use of ACCUSOL 35 solution with a single CRRT circuit.

Study centers will use the ACCUSOL 35 solutions from their available inventory; no ACCUSOL 35 solutions or any other approved medications or investigational products will be provided to the study centers by the Sponsor. CRRT therapy will be administered in accordance with the intensive care unit's (ICU) usual clinical practice and the recommendations in the current labeling for ACCUSOL 35 solutions. Addition of antibiotics or any other medications to the ACCUSOL 35 solution bag, except for KCl supplementation, will not be allowed.

There will be no randomized or non-randomized treatment assignments; no diagnostic, therapeutic, or experimental interventions; and no restrictions on use of concomitant medications or other treatments, except as noted above for the restriction on addition of medications other than KCl supplementation to the ACCUSOL 35 solution bag. Study patients will be prospectively identified in that study data will only be collected from

patients treated after study enrollment at a site has been authorized by the responsible ethics committee (EC) and the Sponsor.

Data will be collected at patient enrollment (at approximately 40 hours of CRRT with the same CRRT circuit) and periodically up to 72 hours of CRRT with the same circuit, or until the CRRT circuit needs to be changed or CRRT is completed (if either occurs sooner than 72 hours). The CRRT lines will be inspected every 30 minutes for the duration of the therapy, as recommended in the labeling for the ACCUSOL 35 solutions.

Observation of the CRRT circuit for precipitate through 72 hours of use is intended to represent a worst-case situation, since 72 hours is the maximum intended use period for a single CRRT circuit. Enrollment of patients whose CRRT circuit has already been in use for 40 hours is intended to maximize the possibility of the studied CRRT circuits reaching 72 hours of use for inclusion in the primary analysis (see Section 9.5), while maintaining a reasonable overall study size by reducing the number of patients enrolled.

If precipitate is seen in a CRRT line during therapy administration, the therapy will be stopped and proper procedures and monitoring (as recommended in the current ACCUSOL 35 solutions labeling) will be performed in order to return the circuit blood back to the patient and immediately set up a new CRRT circuit to continue therapy.

This study is strictly a non-interventional observational safety study assessing the presence or absence of visible precipitate in the CRRT lines with the specific products being studied. Therefore, no control group is considered necessary to achieve the study objectives.

9.2 Setting

9.2.1 Study Treatment

9.2.1.1 Study Drug

Patients enrolled in the study can be treated with ACCUSOL 35, ACCUSOL 35 Potassium 2 mmol/L, ACCUSOL 35 Potassium 4 mmol/L, or any combination of the solutions. Given the observational nature of this study, no ACCUSOL 35 solutions, or any other approved medications or investigational products, will be provided to study sites. All patients will be treated with ACCUSOL 35 solutions according to the patients' medical needs and the standard of care at the participating ICU.

No ACCUSOL 35 solution bag should be used for more than 24 hours after mixing of the two chambers as indicated in the approved labeling for the products.

9.2.1.2 Concomitant Therapy

There will be no restrictions on the use of concomitant medications or non-drug therapies, with the single exception being that only supplemental KCl may be added directly to the ACCUSOL 35 solution bag being used to treat a study patient. All patients will otherwise be treated according to their medical needs and the standard of care at the participating ICU.

9.2.2 Study Population

The study will include approximately 240 adult patients enrolled at approximately 20 to 25 hospitals, with medical or surgical ICUs that regularly treat CRRT patients using ACCUSOL 35 solutions, in 4 to 5 European Union countries (possible candidates include Austria, Belgium, Czech Republic, Denmark, France, Germany, Ireland, Netherlands, Spain, Sweden and United Kingdom). Patient enrollment in the study will be terminated when it has been confirmed that data have been collected from 58 evaluable patients (ie, those whose CRRT circuits remained precipitate-free for 72 hours, and those in whose circuits visible precipitate was observed within 72 hours; see Section 9.7.3). The number of patients to be enrolled at each site will be pre-specified to ensure that a small number of sites do not dominate the overall study enrollment.

Male and non-pregnant female patients will be eligible for enrollment if they are at least 18 years of age and have been undergoing CRRT using ACCUSOL 35 solution(s), without any concomitant medication added to the solution (except for supplemental KCl, if required), with the same CRRT circuit for at least 40 hours. Patients with any contraindication to treatment with an ACCUSOL 35 solution, and patients involved in any study with another investigational product or therapy (in the prior 30 days or during participation in this study) will be excluded. The specific inclusion and exclusion criteria are listed below.

9.2.2.1 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

1. The patient is male or non-pregnant female and at least 18 years of age.
2. The patient is undergoing CRRT using ACCUSOL 35 solution(s).
3. The patient's CRRT has been ongoing for 40 hours using the same CRRT circuit; and the CRRT is anticipated to be continued for at least another 32 hours with the same circuit.
4. The patient, or their legally authorized representative, has provided informed consent for inclusion of their medical data in the study (unless the responsible EC has provided the Investigator a written waiver of the need to obtain consent due to the observational nature of the study).

9.2.2.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study.

1. The patient has any contraindication(s) to treatment with ACCUSOL 35 solution(s).
2. An antibiotic or other medication (other than supplemental KCl) has been added to the ACCUSOL 35 solution(s) used for the patient's CRRT.
3. The patient previously participated in the study (ie, one of the patient's CRRT circuits has already been observed as part of this study).
4. The patient is currently, or was within the preceding 30 days, involved in a study of an investigational product or therapy.

9.2.2.3 Patient Withdrawal from the Study

Patients, or their legally authorized representatives, may terminate their consent for collection of their medical data for use in the study at any time. Should a patient or their legally authorized representative do so, site study personnel will record the time of and the reason provided for the withdrawal. The data collected on withdrawn patients will be used in the analyses, as applicable, and included in the clinical study report.

9.2.2.4 Study Termination

The Sponsor may prematurely terminate this study at any time for any reason. It may also terminate a single study center from participation in the study at any time for various reasons such as:

- inadequate rate of patient enrollment into the study
- noncompliance with protocol requirements or data collection methods
- noncompliance with Good Clinical Practice guidelines; applicable national and local laws; and/or applicable guidelines or regulations for protecting the rights, safety, and welfare of patients
- knowingly submitting false information to the Sponsor or designee.

If the study is prematurely terminated, all collected study data must be provided to the Sponsor.

9.3 Variables

Data will be collected at patient enrollment (at approximately 40 hours of CRRT with the same CRRT circuit) and periodically up to 72 hours of CRRT with the same circuit, or until the CRRT circuit needs to be changed or CRRT is terminated (if either occurs sooner than 72 hours).

9.3.1 Demographic and Baseline Data

The following data will be obtained from the patient's medical record:

- age
- gender
- weight

9.3.2 Concomitant Medication

Details (product, dosage and timing) of any anticoagulants used will be collected.

The concentration of any supplemental KCl added to the ACCUSOL 35 solution(s) will be recorded.

No other concomitant medications data will be collected on the study CRF for study analysis. However, details of concomitant medications will be included on the report form used for expedited reporting of any of adverse reactions (see Section 11.3)

9.3.3 CRRT Details

The following information about the patient's CRRT will be collected:

- the manufacturer and model of the CRRT monitor used
- the manufacturer and model of the CRRT lines used
- the manufacturer and model of the haemofilter used
- the CRRT mode employed
- the ultrafiltration rate(s) used

9.3.4 ACCUSOL 35 Administration

The following data on the administration of ACCUSOL 35 and the presence or absence of visible precipitate will be collected:

- the formulation(s) (ACCUSOL 35, ACCUSOL 35 Potassium 2 mmol/L, ACCUSOL 35 Potassium 4 mmol/L) and lot number(s) of ACCUSOL 35 solution(s) administered
- the ACCUSOL 35 solution dose rate(s) (mL/kg/hr) by site of introduction (pre- or post-filter or as dialysate)
- the start- and end-of-use times for the CRRT circuit used during the study
- the presence or absence of visible precipitate in the CRRT lines used during the study
- the time of observation of the observed precipitate, if applicable
- the formulation (ACCUSOL 35, ACCUSOL 35 Potassium 2 mmol/L or ACCUSOL 35 Potassium 4 mmol/L) and lot number of the ACCUSOL 35 solution in use at the time of the observation of the precipitate, if applicable
- the color of the observed precipitate, if applicable
- the reason for termination of the use of the CRRT circuit used during the study, if it occurs during the study (ie, before 72 hours of use are completed)

- the reason for termination of CRRT, if during the study (ie, before 72 hours of CRRT are completed)
- the reason for the end of the patient's study participation

9.4 Data Sources

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study that are necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study may comprise any of the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, study patient files and worksheets, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study.

9.5 Study Size

Based on published CRRT studies[1-5], it is estimated that of those CRRT treatments that have reached 40 hours with the same CRRT circuit, 25% will continue with the same circuit through 72 hours of use. It is expected, therefore, that about 240 enrolled patients will provide data on approximately 60 treatments that last 72 hours without CRRT circuit changes. If no visible precipitate is observed within that time in at least 58 evaluable treatments (ie, those in which CRRT circuits remains precipitate-free for 72 hours, and those in which visible precipitate is observed within 72-hours), the study will have provided 95% confidence that the probability of visible precipitate formation during 72 hours of CRRT with ACCUSOL 35 solution using the same CRRT circuit is not more than 5.0%.

It is also reasonable to assume (based on the published studies[1-5]) that approximately 10% of all CRRT treatments will last 72 hours, regardless of whether the same CRRT circuit is in use the whole time. Combining the probabilities of both having a treatment last 72 hours and also having visible particulate formation reduces the risk from 5% to 0.5%. Thus a sample size of 58 treatments with no observed precipitate will demonstrate, with 95% confidence, that the probability of precipitate formation in all CRRT treatments with ACCUSOL 35 solutions of any length (and not necessarily with the same CRRT circuit) is not more than 0.5%.

9.6 Data Management

The Investigator is responsible for the procurement of data and for the quality of data recorded on the patient's case report form (CRF). CRFs will be provided by the Sponsor in paper or electronic form. Detailed instructions for completing the CRF will be provided by the Sponsor All study personnel will be trained on the protocol, study, and proper completion of the CRF. Data will be obtained from the patient's medical record and, if applicable, study-specific worksheets.

The Investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

All information transcribed onto the CRF is expected to accurately reflect original data recorded in the patient's medical record and any applicable study worksheets. These must be available to the Sponsor or designee and/or appropriate health authorities.

If paper-format CRFs are provided by the Sponsor, all required study data, including corrections, will be clearly and accurately recorded by authorized study site personnel on the CRFs. The CRFs will remain at the site until they are reviewed by the Sponsor's study monitor. All original CRFs will be collected by the study monitor, and an identical copy of the complete set of CRFs for each subject will remain in the investigator file at the study site.

If electronic-format CRFs are provided by the Sponsor, only authorized study site personnel will record or change data on the CRFs. Changes to a CRF will require documentation of the reason for each change, and an audit trail will be created for all changes. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site.

The handling of data by the Sponsor, including data quality assurance, will comply with regulatory guidelines and the Sponsor's, or designee's, standard operating procedures. Data management and control processes and data management software specific to the study will be described in a data management plan (see Section 14.1).

A study database will be created from the data on the CRFs, using the Medical Dictionary for Regulatory Activities dictionary (MedDRA) for adverse event coding and the World Health Organization drug dictionary (WHODRUG) for coding concomitant medications.

Programmatic and manual review of the database will be performed to detect missing data, errors and inconsistencies. Queries on the detected problems will be forwarded to the site, and the responses returned from the site will be used by data management personnel to update the database as needed.

After all database updates are completed and prior to any statistical analyses, the database will be locked.

Quality assurance department representatives from the Sponsor and/or a contract research organization designated by the Sponsor, may visit a study site during or after the study to conduct a quality assurance audit. During a visit, EC and informed consent documentation, data entry and validation processes, and adverse event reporting may be reviewed. Processes may be reviewed to ensure the study is conducted in compliance with the protocol, standard operating procedures, and all applicable legal requirements. During these visits, the Investigator is obligated to provide direct access to all relevant documents and to allocate adequate time to discuss findings and relevant issues and, after the visit, to complete appropriate corrective actions when necessary.

9.7 Data Analysis

9.7.1 General Considerations

The methods and software to be used for the analyses and the responsible individual(s) who will perform these analyses will be identified in a data analysis plan (see Section 14.1) prior to database lock. Deviations from the planned analyses, if any, will be described in the clinical study report.

All data collected (see Sections 9.3 and 11) will be presented in data listings.

9.7.2 Analysis Populations

The enrolled population will be patients expected to receive CRRT with ACCUSOL 35 solution(s) using the same CRRT circuit for at least 72 hours. All analyses will be performed on the enrolled population, except as otherwise noted below.

9.7.3 Primary Analysis

For purposes of this study, the incidence of visible precipitate in the CRRT lines during 72 hours of use of the CRRT circuit will be examined. Data from the evaluable patients (ie, those whose CRRT circuits remains precipitate-free for 72 hours, and those in whose circuits visible precipitate is observed within 72-hours) will be used for this analysis. Data from patients whose CRRT was interrupted or terminated prior to 72 hours with no

observation of visible precipitate in the lines (ie, non-evaluable patients) will be excluded from this analysis.

The primary analysis will be to estimate the upper bound of a 95% confidence interval on the true proportion of treatments having precipitate formation. If the upper bound of the 95% confidence interval is 5% or less, then the primary objective of the study will have been achieved. That result will have demonstrated, with 95% confidence, that the probability of visible precipitate formation in all CRRT treatments with ACCUSOL 35 solutions of any length (and not necessarily with the same CRRT circuit), is not more than 0.5%. (see Section 9.5).

9.7.4 Other Assessments and Analyses

Categorical data (eg, gender) will be summarized using counts and percentages. Continuous data (eg, age) will be summarized using descriptive statistics for measures of central tendency and dispersion (number of patients, mean, standard deviation, minimum, median, maximum, and number missing).

Demographic and baseline characteristics include age, gender, and weight. Frequency and percentages will be provided for age as a categorical variable (eg, 18-35 years, 36-45 years, 46-55 years, 56-65 years and > 65 years) and gender. Weight will be summarized by descriptive statistics for measures of central tendency and dispersion.

Adverse reactions will be summarized both by the total frequency of reactions and by the frequency and percentage of subjects having at least one reaction. These adverse reaction summaries will be done overall and by MedDRA system organ class and preferred term.

Other data recorded (eg, concomitant anticoagulant used, CRRT details, ACCUSOL 35 administration details other than occurrence of precipitate) will not be summarized.

9.7.5 Potential Exploratory Analyses

If visible precipitate is observed, the time to first occurrence will be calculated (time from start of use of the CRRT circuit to time of observation of precipitate). In addition, further analyses may be performed to explore contributing factors (eg, ACCUSOL 35 solution formulation(s) and lot(s) administered; dose rate(s) and amount of ACCUSOL 35 delivered through the circuit; frequency of use and concentration of KCl add to the ACCUSOL 35 solution; manufacturer and model of CRRT lines used; haemofilter used; use and type of anticoagulant; CRRT mode; or ultrafiltration rate), as appropriate.

9.8 Quality Control

9.8.1 Investigator's Responsibility

The Investigator will comply with the protocol, the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH GCP), and applicable regulatory requirements. The Investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the responsible party. The term "Investigator" as used in this protocol as well as in other study documents, refers to the Investigator or authorized study personnel that the Investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the Investigator, except where the Investigator's signature is specifically required.

9.8.2 Direct Access to Source Data/Documents

The Investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the Sponsor or its designee, review by the EC, and inspections by applicable regulatory authorities.

9.8.3 Training

The study monitor will ensure that the Investigator and study site personnel understand all requirements of the protocol and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the Investigator and will serve as the liaison between the study site and the Sponsor.

9.8.4 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, and applicable regulatory guidelines/requirements. The Investigator will permit the study monitor to visit the study site at appropriate intervals. Monitoring processes specific to the study will be described in the Clinical Operations Plan (see Section 14.1).

9.8.5 Auditing

The Sponsor and/or their designee may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site.

9.8.6 Non-compliance with the Protocol

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the Sponsor may terminate the investigator's participation. The Sponsor will notify the responsible EC and applicable regulatory authorities of any such investigator termination.

9.9 Limitations of the Research Methods

The non-controlled observational study design is considered suitable to achieve the study purpose, which is to confirm that the updated ACCUSOL 35 solutions do not present a significant risk of calcium carbonate precipitate formation. If there are statistical limitations, it is the inability to generalize to any specific CRRT patient population, which is typically the case for an observational study.

If precipitate is actually observed during the study, the study data will not be adequate to determine the cause of that occurrence, although the data collected may be helpful in developing hypotheses for further in vitro or clinical studies.

9.10 Other Aspects

Not applicable; all aspects of the study are described in the other sections of this protocol.

10. PROTECTION OF HUMAN SUBJECTS

10.1 Ethical Conduct of the Study

This study will be conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki and its revisions, ICH GCP, good pharmacovigilance practices and all national and local laws. The Investigator will be responsible for ensuring that this study is conducted according to the investigational plan and for protecting the rights, safety, and welfare of study patients under the Investigator's care.

10.2 Ethics Committee Approval

Prior to enrolling any patients in the study, the Investigator must obtain approval from the responsible EC and, if required, the responsible health authority for the protocol and any amendments, the informed consent form (if applicable), and any other information intended to be presented to the patient in order to obtain informed consent (if applicable). All changes in the research activity and all unanticipated problems involving risk to study patients or others will be reported to the responsible EC and, if required, to the responsible health authority. No changes in the research will be implemented without the

responsible EC's and, if required, to the responsible health authority's prior approval, except where necessary to eliminate apparent immediate hazards to study patients.

10.3 Patient Information and Consent

Written informed consent will be obtained from each patient or (if the patient is unable to provide informed consent) the patient's legally authorized representative prior to the patient's participation in the study, unless the responsible EC has granted a waiver from the requirement for informed consent based on the observational nature of the study.

In obtaining and documenting informed consent, the Investigator will comply with all Good Clinical Practice and applicable legal requirements, and with the ethical principles that have their origin in the Declaration of Helsinki. Neither the Investigator, nor the site staff, will coerce or unduly influence a patient or their representative, to participate or to continue to participate in the study. The patients or the patient's representative may refuse participation or withdraw consent at any time and for any reason during the study.

Neither the written informed consent form, nor any other information presented to the patient or the patient's representative in order to obtain consent for participation in the study, will contain language that causes the patient or their representative to waive or to appear to waive any legal rights, or that releases the Investigator, the institution, or their agents from liability for negligence.

The Investigator or designee will fully inform the patient or the patient's representative of all pertinent aspects of the study. Before informed consent is obtained, the Investigator or their designee will answer all questions about the study to the satisfaction of the patient or the patient's representative. The Investigator or designee will inform the patient or the patient's representative that they are free to refuse to participate in the study without affecting the quality of the patient's medical care. The language used in all communications regarding the study will be as non-technical as practical so that it is understandable to the patient or the patient's representative.

If a patient is unable to read or to provide written informed consent by him/herself, the patient's representative will sign on behalf of the patient; in addition to which an impartial witness, who was present throughout the informed consent process ,will also sign and date the form. Prior to the patient's participation in the study, the patient or the patient's representative will be given a copy of the signed and dated written informed consent form and any other written information intended to be provided to the patient.

10.4 Patient Confidentiality

Every effort will be made to maintain confidentiality of all patient data included in the CRF. At the time of study enrollment study personnel will assign each patient a patient identification number, which will be used to identify the patient in the CRF. The Investigator will maintain a patient identification list (patient study identification numbers with the corresponding patient names) to enable source records to be identified.

Patients will be informed that information about them is being entered into the study database. Patients will be informed that all protected health information and clinical data will be maintained in a confidential manner.

All study data will be stored in electronic databases that are confidential, password-protected, and access-restricted. Information that may be made available for inspection by authorized health authorities will be handled in the strictest confidence. No information that could uniquely identify individual patients will be submitted to the Sponsor.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Definitions

An *adverse event* is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc), disease (eg, peritonitis, bacteremia, etc) or outcome of death temporally associated with the use of a medicinal product, whether or not considered associated with this medicinal product. Other events that, while not necessarily meeting the definition of adverse events, should be treated as such because they may be reportable to regulatory authorities according to adverse event reporting requirements, whether or not considered causally associated with drug or biologic treatment, include the following:

- drug or biologic overdose, whether accidental or intentional
- drug or biologic abuse
- an event occurring from drug or biologic withdrawal
- any failure of expected pharmacological action
- exposure to a drug or biologic during pregnancy

- inadvertent or accidental drug or biologic exposure (eg, product leaking or being spilled onto a patient or caregiver)
- unexpected therapeutic or clinical benefit from the drug or biologic product
- medication errors (eg, incorrect route of administration, incorrect dosage, use of incorrect product)

An *adverse reaction* is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is, at least, a reasonable possibility.

A *serious adverse reaction* is one that meets one or more of the following criteria:

- results in death (including fetal death);
- is life-threatening (Note: "life-threatening" in the definition of "serious" refers to an adverse reaction in which the patient was at risk of immediate death at the time of the reaction. It does not refer to a reaction that might have caused death if it were more severe);
- requires inpatient hospitalization (Note: inpatient hospitalization refers to any inpatient admission, regardless of length of stay);
- results in prolongation of ongoing hospitalization;
- results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions);
- is a congenital anomaly/birth defect; or
- is a medically important reaction that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or requires intervention to prevent one of the other outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependence or drug abuse).

11.2 Recording of Adverse Reactions

Details of any adverse reaction (non-serious or serious) that is noted in or reported by the study patient during the study data collection period (see Section 9.3) will be collected in the CRF.

Whenever possible, the Investigator will present a diagnosis based on the presenting signs and symptoms, rather than just presenting a sign or symptom.

11.2.1 Relationship to Study Drug

The Investigator will indicate their opinion on the relationship of the reaction to ACCUSOL 35 according to the following definitions.

Possibly related:

The reaction follows a reasonable temporal relationship to the administration of the study drug, and an alternative etiology is equally or less likely compared to the potential relationship to the study drug.

Probably related:

The reaction has a strong temporal relationship to the administration of the study drug and an alternative etiology is unlikely or significantly less likely compared to the potential relationship to the study drug.

11.2.2 Severity

The severity of an adverse reaction is defined as a qualitative assessment by the Investigator of the degree of intensity of the adverse reaction observed or reported to him/her by the patient. The Investigator will indicate their opinion on the severity of the event or reaction according to the following definitions. The assessment of severity will be made irrespective of drug relationship or seriousness.

Mild:

- The reaction is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
- The reaction resolves spontaneously or may require minimal therapeutic intervention.

Moderate:

- The reaction produces limited impairment of function and may require therapeutic intervention.
- The reaction produces no sequela(e).

Severe:

- The reaction results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.

- The reaction produces sequela(e), which require(s) (prolonged) therapeutic intervention.

11.3 Expedited Reporting of Adverse Reactions, Precipitate Observation and Pregnancy

11.3.1 Adverse Reactions

All adverse reactions (non-serious or serious) must be reported to the Sponsor or designee within one business day of observation or notification of the event. Instructions and forms for reporting an adverse reaction will be provided to the Investigator, including the name(s) and contact details of the individual(s) who should be contacted regarding safety issues or questions regarding the study.

An adverse reaction form will be completed that provides detailed information about the reaction and will be promptly forwarded to the Sponsor or designee as indicated in the instructions. The Sponsor or designee will be responsible for appropriate reporting of adverse reactions that occur in patients exposed to an ACCUSOL 35 solution to health authorities. The Investigator will promptly notify the responsible EC of all adverse reactions occurring at the Investigator's site, in accordance with the requirements of the EC, including any significant follow-up information.

11.3.2 Precipitate Observation

If the Investigator or study staff observes visible precipitate in any study CRRT line, it will be reported within one business day of becoming aware of the precipitate observation. Instructions and forms for expedited reporting of precipitate observation will be provided to the Investigator.

11.3.3 Pregnancy

Although it is not expected based on the population included in this study, if the Investigator or study staff becomes aware of the pregnancy of a study patient during their study participation, the pregnancy will be reported within one business day of becoming aware of the pregnancy, and the pregnancy will be followed-up at 1 year post-delivery, if feasible. Instructions and forms for reporting pregnancy will be provided to the Investigator.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Information concerning study treatment, patent applications, formulation, manufacturing processes, unpublished scientific data, and other pertinent information is confidential and remains the property of the Sponsor. Details will be disclosed only to persons involved in

the conduct of the study. The Investigator may use this information for the purposes of the study only.

It is understood by the Investigator that the Sponsor may use the information derived from this study and may share this information, as required, with other clinical investigators or health authorities. To allow for the use of the information and to ensure complete and thorough analysis, the Investigator is obligated to provide the Sponsor with complete study data.

The results of this study may be considered for publication or presentation at symposia and congresses. Individual investigators are encouraged to publish or disclose the data generated at their respective sites; but only after the collective data are presented or published as a single study, or two years following either the conclusion of the study at all sites or database lock, whichever occurs first. All publication manuscripts, abstracts, prepared transcripts, and texts and visual material for presentation (eg, slide sets) must be submitted to the Sponsor at least 60 days prior to the intended submission. This is necessary to prevent premature disclosure of trade secrets or patent-protected information, and is in no way intended to restrict publication of facts or opinions formulated by the Investigator. The Sponsor will inform the Investigator in writing of any objections or questions arising within 30 days of receipt of the proposed presentation materials.

The results of the study will be summarized on the EU PAS register after completion of the study report.

13. REFERENCES

1. Monchi M, Berghmans D, Ledoux D, Canivet J-L, Dubois B, Damas P. Citrate vs. heparin for anticoagulation in continuous venovenous hemofiltration: a prospective randomized study. Intensive Care Med. 2004;30:260-265. doi:10.1007/s00134-003-2047-x.

2. Kutsogiannis DJ, Gibney RT, Stollery D, Gao J. Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. Kidney Int. 2005;67:2361-2367. doi:10.1111/j.1523-1755.2005.00342.x

3. Morabito S, Pistolesi V, Tritapepe L, et al. Regional citrate anticoagulation in cardiac surgery patients at high risk of bleeding: a continuous veno-venous hemofiltration protocol with a low concentration citrate solution. Critical Care. 2012;16:R1111. doi:10.1186/cc11403.

4. Hetzel GR, Schmitz M. Wissing H, et al. Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial. *Nephrol Dial Transplant*. 26(1):232-239. doi:10.1093/ndt/gfq575.

5. Betjes MGH, van Oosterom D, van Agteren M, van de Wetering J. Regional citrate versus heparin anticoagulation during venovenous hemofiltration in patients at low risk for bleeding: similar hemofilter survival but significantly less bleeding. *J Nephrol*. 2007;20(5):602-608.

14. ANNEXES

14.1 List of Stand-alone Documents

Number	Document Reference Number	Date	Title
1	to be assigned	to be determined	Study Investigators
2	to be assigned	to be determined	Clinical Operations Plan
3	to be assigned	to be determined	Data Management Plan
4	to be assigned	to be determined	Statistical Analysis Plan
5	to be assigned	to be determined	Safety Plan

14.2 ENCePP Checklist for Study Protocol

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
A Multicenter, Non-interventional, Observational, Post-Approval Safety Study of Updated ACCUSOL 35 Solutions in Continuous Renal Replacement Therapy (ACCUPASS)

Study reference number:
8822-001

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☐	☒	☐	10
1.1.2 End of data collection[2]	☐	☒	☐	10
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☒	☐	10
1.1.6 Final report of study results.	☐	☒	☐	10

Comments:

No study progress or interimg progress reports were requested by the responsible regulatory authority.

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	13-14
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This study is observational and therefore does not include hypothesis testing.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	11-12
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	19-20
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	19

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	13
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	11-12
4.2.2 Age and sex?	☒	☐	☐	13
4.2.3 Country of origin?	☒	☐	☐	13
4.2.4 Disease/indication?	☒	☐	☐	13
4.2.5 Co-morbidity?	☒	☐	☐	13-14
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	13-14

Comments:

Seasonality has no bearing on this study's population or design.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	16

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

The time during which direct observations are made for the occurrence of the study endpoint is fixed. Based on the endpoint, the use of time windows is not appropriate for the planned analyses. The study does not examine in-vivo exposure and the endpoint is not based on a pharmacologic response.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	15-16
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	17

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

The primary study endpoint is absence or observation of a physicochemcal phenomenon in the study product outside the patient, rather than a therapeutic or pharmacologic effect on the patient.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	16-17
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	16-17
8.1.3 Covariates?	☒	☐	☐	16-17
8.2 Does the protocol describe the information available from the data source(s) on:				

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	15-16
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	15-16
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	15-16
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	18
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	18
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	23

Comments:

Based on study design, data on the patients' diseases are not collected for analysis.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	17

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	19-20
10.3 Are descriptive analyses included?	☒	☐	☐	19-20
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

The primary study endpoint is absence or observation of a physicochemcal phenomenon in the study product outside the patient, rather than a therapeutic or pharmacologic effect on the patient.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	17-18
11.3 Are methods of quality assurance described?	☒	☐	☐	17-18

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☐	☒	
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

The primary study endpoint is absence or observation of a physicochemcal phenomenon in the study product outside the patient, rather than a therapeutic or pharmacologic effect on the patient.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☐	☐	☒	
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	
12.3 Does the protocol address other limitations?	☒	☐	☐	21-22

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	22
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	23-24

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	10

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	7, 27
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	27-28

Comments:

ENCePP Checklist for Study Protocols (Revision 2) 5

Name of the main author of the protocol: Drew S Jones MD

Date: 16/Jun/2014

Signature: Drew S Jones MD

14.3 Additional Information

Investigator Acknowledgement

Study Title:	A Multicenter, Non-interventional, Observational, Post-Approval Safety Study of Updated ACCUSOL 35 Solutions in Continuous Renal Replacement Therapy (ACCUPASS)
Study Number:	8822-001
Version:	Amdement 1
Date:	2015Jan12

I have read the protocol described above, and I agree to abide by all provisions set forth therein.

I agree to obtain written and dated approval from the responsible Ethics Committee (EC) and, if required, the responsible health authority for the protocol and (unless the EC has granted a written waiver of the requirement for informed consent) the informed consent form, any consent form updates, and any other written information to be provided to the patients before collection of their medical information for use in this study.

I agree to provide sufficient resources for the foreseen duration of the study and to conduct the study properly, ethically, and safely. I agree to ensure that all persons assisting in this study are adequately informed about the protocol and I agree to permit direct monitoring and auditing by the Sponsor, Sponsor's representatives, and authorized health authorities.

I agree to ensure that the confidential information contained in this document will not be disclosed to others without prior written authorization from Baxter Healthcare Limited, except to the extent necessary to obtain approval of the EC and, if required, the responsible health authority.

Signed:_____ Date:_____

Printed Name:_____