# Post-authorisation Safety Study Report: 8822-001

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| Title | A Multicenter, Non-interventional, Observational, Post-Approval Safety Study of Updated ACCUSOL 35 Solutions in Continuous Renal Replacement Therapy (ACCUPASS) |
| Report version identifier | Final |
| Report version date | 08 SEP 2016 |
| 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 responsible for study | Baxter Healthcare Limited<br>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. |
| Country of study | United Kingdom |
| Author | Drew S. Jones, MD, MPH, MBA<br>Clinical Development Lead<br>Baxter Healthcare Corporation<br>One Baxter Parkway<br>Deerfield, IL 08815 USA |
| Marketing authorisation holder submitting report | NIKKISO Belgium bvba |
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# 1. 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: Final (08 SEP 2016)

Author: Drew S. Jones, MD, MPH, MBA
Clinical Development Lead
Baxter Healthcare Corporation

## Keywords

ACCUSOL 35, CRRT, precipitate, safety

## 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 Questions and Objectives

The updated ACCUSOL 35 formulations were developed to prevent calcium carbonate precipitate formation during CRRT administration. The objective of this study was 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 was a prospective, multicenter, non-interventional, uncontrolled, open-label, observational study in adult patients undergoing CRRT using any of the updated ACCUSOL 35 solutions.

CRRT therapy was to 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 KCl supplementation, was not allowed. The CRRT lines were to be inspected every 30 minutes for the duration of the therapy, as described in the labeling for ACCUSOL 35 solutions.

Study staff was to record the study data during administration of CRRT with ACCUSOL 35 solution. The planned maximum study observation period was 32 hours: from 40 hours after CRRT with the current circuit was started until 72 hours of treatment had been administered using that same circuit.

**Setting**

The study was performed at intensive care units that regularly treat CRRT patients using ACCUSOL 35 solutions.

**Subjects and Study Size**

The study was planned to include approximately 240 adult patients enrolled at approximately 20 to 25 European Union hospitals, with medical or surgical intensive care units that regularly treat CRRT patients using ACCUSOL 35 solutions. Male and non-pregnant female patients were eligible for enrollment if they were at least 18 years of age and had been undergoing CRRT using ACCUSOL 35 solution(s), without any concomitant medication added to the solution (except for supplemental potassium chloride [KCl], if required), with the same CRRT circuit for at least 40 hours. Patient enrollment in the study was to be terminated when it was confirmed that data had been collected from 58 evaluable patients.

Fifteen investigators at 16 centers screened 264 patients and enrolled 201 patients. Of the 201 patients enrolled, 70 patients completed the study, of which 65 were evaluable for the primary endpoint analysis of visible precipitate occurrence.

**Variables and Data Sources**

Variables analyzed for this study included demographic and baseline data, details of CRRT administration, details of administration of anticoagulants and supplemental KCl,

details of ACCUSOL 35 administration, occurrence of any visible precipitate in the CRRT lines, and occurrence of any adverse reactions to the study product.

Source data for this study comprised 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

**Results**

In this non-interventional, observational study, 201 enrolled patients received ACCUSOL 35, in one of 3 different formulations or a combination of 2 of the formulations, for CRRT. ACCUSOL 35 Potassium 4 mmol/L was used most frequently (42% of the enrolled patients), followed by ACCUSOL 35 (without potassium; 38% of the patients). Both ACCUSOL 35 and ACCUSOL 35 Potassium 4 mmol/L were administered to 17% of the patients, and ACCUSOL 35 Potassium 2 mmol/L was used for 2% of the patients.

No visible precipitate was observed in any CRRT lines for any of the patients that completed 72 hours of CRRT with a single CRRT circuit (0/65 patients; 95% confidence interval, 0.000-0.038). Furthermore, no visible precipitate was observed in any CRRT lines for any of the 201 enrolled patients with precipitate observation data.

No patient in the study experienced an adverse reaction. Two patients died while on study, as would be expected in a population of seriously ill patients. However, neither death was considered by the investigators to be the result of an adverse reaction to the study product.

**Discussion**

This post-approval safety study was designed to verify the successful minimization of the risk of precipitate formation with the updated ACCUSOL 35 solution. No visible precipitate was observed in the CRRT lines for any of the 65 evaluable patients, demonstrating with 95% confidence that the probability of precipitate formation in a CRRT treatment of 72 hours with a single circuit with ACCUSOL 35 solutions is not more than 3.8%. Since it is assumed that approximately 10% of all CRRT treatments will last 72 hours, this results in a probability of any CRRT treatment to both last 72 hours and develop visible precipitate of no more than 0.38%. This supports a proposal for

removal of the current recommendation (presented in the Patient Information Leaflet (PIL) and Summary of Product Characteristics (SmPC) for the ACCUSOL 35 solutions) to inspect the CRRT lines every 30 minutes for the presence of visible precipitate during the use of the products.

The lack of occurrence of any adverse reactions to ACCUSOL 35 solution in any of the treated patients supports the already established safety profile of the ACCUSOL 35 solutions.

## 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| CRRT | continuous renal replacement therapy |
| CVVH | continuous veno-venous haemofiltration |
| CVVHDF | continuous veno-venous haemodiafiltration |
| EC | ethics committee |
| eCRF | electronic case report form |
| EU PAS | European post-authorisation studies |
| KCl | potassium chloride |
| max | maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| min | minimum |
| PT | preferred term |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SOC | system organ class |
| WHODrug | World Health Organization Drug Dictionary |

## 3. INVESTIGATORS

The following table (see Table 1) presents information on the 15 investigators that enrolled patients at 16 centers in the study (Dr. Joyce Yeung served as investigator at 2 separate centers). Dr. Kiran Salaunkey from Papworth Hospital, Cambridge was the principal investigator for this study. All centers were located in the United Kingdom (UK).

**Table 1. Study Investigators**

| Center Number | Investigators (blue text links to investigator CV) | Institution | Number of Patients Enrolled |
|---|---|---|---|
| 001 | Kiran Salaunkey, MBBS, MD, DNB, FRCA | Papworth Hospital<br>Cambridge, UK | 8 |
| 002 | Philip Watt, MB, BS, FRCA, FFICM | Kettering General Hospital<br>Kettering, UK | 13 |
| 003 | Maurizio Cecconi, MD, FRCA, FFICM | St. George's Hospital,<br>General Intensive Care Unit<br>London, UK | 10 |
| 004 | David Brealey, BSc, PhD, MRCP, FRCA, FFICM | University College Hospital<br>London, UK | 12 |
| 005 | Christopher Thompson, MBChB, MRCP | Royal Stoke University Hospital<br>Stoke on Trent, UK | 30 |
| 007 | Ingeborg Welters, MD, PhD | Royal Liverpool University Hospital,<br>Intensive Care Unit<br>Liverpool, UK | 14 |
| 008 | Jonathan Bannard-Smith, MBChB, FRCA, FFICM | Manchester Royal Infirmary,<br>Department of Adult Critical Care<br>Manchester, UK | 26 |
| 009 | Daniel Martin, MBChB, FRCA, FFICM, PhD | Royal Free Hospital,<br>Intensive Care Unit<br>London, UK | 22 |
| 010 | Mohamed Ramali, MBBS, MD, FRCA, FFICM | Colchester General Hospital,<br>Intensive Treatment Unit<br>Colchester, UK | 9 |
| 011 | Catherine Plowright, MScN, MA | Medway Maritime Hospital<br>Gillingham, UK | 16 |
| 012 | Joyce Yeung, MBChB, FRCA, PhD[a] | Birmingham Heartlands Hospital,<br>Academic Department of Anesthesia, Critical Care, Resuscitation, and Pain<br>Birmingham, UK | 13 |

**Table 1. Study Investigators**

| Center Number | Investigators (blue text links to investigator CV) | Institution | Number of Patients Enrolled |
|---|---|---|---|
| 013 | Simon Fletcher, MBBS, FRCA, FRCPE | Norfolk and Norwich University Hospital,<br>Critical Care Complex<br>Norwich, UK | 5 |
| 014 | Joyce Yeung, MBChB, FRCA, PhD[a] | Good Hope Hospital,<br>Intensive Care Unit<br>Birmingham, UK | 5 |
| 015 | Julius Cranshaw, MBChB, MRCP, FRCA, PhD | Royal Bournemouth Hospital<br>Bournemouth, UK | 9 |
| 016 | Stuart McKechnie, MBChB, FRCA, PhD, DICM, FFICM | John Radcliffe Hospital<br>Oxford, UK | 2 |
| 017 | Robin Hollands, MBChB, DCH, FRCA | Royal Shrewsbury Hospital<br>Shrewsbury, UK | 7 |

Note: No patients were enrolled at Center 006.

[a] Dr. Yeung served as investigator at 2 separate centers (Centers 012 and 014) in Birmingham, UK.

Curricula vitae for the investigators are appended (refer to Appendix 16.1.4). Links to the individual curricula vitae are provided in the table above (see Table 1).

## 4. OTHER RESPONSIBLE PARTIES

| | |
|---|---|
| Sponsor Medical Monitor and Report Author | Drew S. Jones, MD, MPH, MBA<br>Senior Medical Director<br>Baxter Healthcare Corporation<br>One Baxter Parkway<br>Deerfield, IL 08815 USA |
| Qualified Person in Pharmacovigilance | Graeme Ladds, PhD<br>Operations Director & CEO<br>PharSafer Associates Ltd<br>PharSafer House, White Hart Meadows<br>Ripley, Surrey GU23 6ND UK |
| Contract Research Organization | PSI CRO UK Ltd.<br>Beaumont House, Langford Business Park, Langford Locks<br>Kidlington, Oxford OX5 1GG UK |

## 5. MILESTONES

**Table 2. Milestones**

| Milestone | Planned Date | Actual Date | Comments |
|---|---|---|---|
| Registration in the EU PAS register | JUN 2014 | 18 JUN 2014 | |
| Approval by responsible EC | not specified | 03 FEB 2015 | |
| Start of data collection | OCT 2014 | 19 MAR 2015 | First patient informed consent |
| End of data collection | APR 2016 | 31 JAN 2016 | Last patient visit |
| Final report of study results | AUG 2016 | 08 SEP 2016 | |

EC = ethics committee; EU PAS = European Union post-authorisation studies.

## 6. RATIONALE AND BACKGROUND

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 therapy (CRRT) lines during continuous veno-venous haemofiltration (CVVH) and continuous veno-venous haemodiafiltration (CVVHDF) 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 AUG 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 post-approval safety study was 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 was intended to 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 visible precipitate during the use of the products.

## 7. 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 was 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.

## 8. AMENDMENTS AND UPDATES

The original study protocol was dated 17 SEP 2014 (refer to Appendix 16.1.1, 8822-001 Protocol 2014 SEP 17).

The study protocol was amended once prior to the start of study conduct, at the request of the responsible ethics committee, to exclude the participation of pregnant patients in the study (see Table 3). For the protocol amendment and a description of the amendment changes, refer to Appendix 16.1.1, 8822-001 Protocol Amendment 1 2015 JAN 12 and 8822-001 Protocol Amendment 1 Description 2015 JAN 12, respectively.

**Table 3. Protocol Amendment and Updates**

| Number | Date | Sections of Study Protocol | Amendment or Update | Reason |
|---|---|---|---|---|
| 1 | 12 JAN 2015 | 4. Abstract (Study Population)<br>9.2.2 Study Population<br>9.2.2.1 Inclusion Criteria (Item 1) | Exclusion of pregnant females from study participation | Request from the responsible ethics committee |

## 9. RESEARCH METHODS

### 9.1 Study Design

This was 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 was 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 used the ACCUSOL 35 solutions from their available inventory; no ACCUSOL 35 solutions or any other approved medications or investigational products were provided to the study centers by the sponsor. CRRT therapy was administered in accordance with the intensive care unit's 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 potassium chloride (KCl) supplementation, was not allowed.

There were 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 supplemental KCl to the ACCUSOL 35 solution bag. Study patients were prospectively identified in that study data were only collected from patients treated after study enrollment at a site authorized by the responsible ethics committee (EC) and the sponsor.

Data were 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 needed to be changed or CRRT was completed (if either occurred sooner than 72 hours). The CRRT lines were to 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 visible precipitate through 72 hours of use was 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 had already been in use for 40 hours was intended to maximize the possibility of the studied CRRT circuits reaching 72 hours of use for inclusion in the primary analysis (see Section 9.9.2), while maintaining a reasonable overall study size by reducing the number of patients enrolled.

If precipitate was seen in a CRRT line during therapy administration, the therapy was to be stopped and proper procedures and monitoring (as recommended in the current ACCUSOL 35 solutions labeling) were to 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 was 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 was considered necessary to achieve the study objectives.

To review copies of the original and amended study protocols, refer to Appendix 16.1.1. To review a sample CRF, refer to Appendix 16.1.2.

### 9.2 Setting

The study was performed at 16 intensive care units in the UK (see Table 1) that regularly treat CRRT patients using ACCUSOL 35 solutions. Patient recruitment commenced on 05 MAR 2015 and ended on 29 JAN 2016 . The first patient was enrolled on 19 MAR 2015 and the last patient completed assessment on 31 JAN 2016.

### 9.3 Subjects

The study was planned to include approximately 240 adult patients enrolled at approximately 20 to 25 European Union hospitals, with medical or surgical intensive care units that regularly treat CRRT patients using ACCUSOL 35 solutions. Patient enrollment in the study was to be terminated when it was confirmed that data had been collected from 58 evaluable patients (ie, those whose CRRT circuits remained precipitate-free for 72 hours, and any patients in whose circuits visible precipitate was observed within 72 hours; see Section 9.9.2.1). The number of patients to be enrolled at each site was pre-specified to ensure that a small number of sites did not dominate the overall study enrollment.

Male and non-pregnant female patients were eligible for enrollment if they were at least 18 years of age and had 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) were excluded. The specific inclusion and exclusion criteria are listed below.

#### 9.3.1 Inclusion Criteria

Each patient had to meet all of the following criteria to be enrolled.

1. The patient was a male or non-pregnant female and at least 18 years of age.
2. The patient was undergoing CRRT using ACCUSOL 35 solution(s).
3. The patient’s CRRT had been ongoing for 40 hours using the same CRRT circuit; and the CRRT was anticipated to be continued for at least another 32 hours with the same circuit.
4. The patient, or their legally authorized representative, had 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).

### 9.3.2 Exclusion Criteria

Patients who met any of the following criteria were to be excluded from the study.

1. The patient had any contraindication(s) to treatment with ACCUSOL 35 solution(s).
2. An antibiotic or other medication (other than supplemental KCl) had 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 was currently, or was within the preceding 30 days, involved in a study of an investigational product or therapy.

### 9.3.3 Patient Withdrawal from the Study

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

## 9.4 Variables

Data were to 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 needed to be changed or CRRT was terminated (if either occurred sooner than 72 hours).

### 9.4.1 Demographic and Baseline Data

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

- Age
- Gender
- Weight

### 9.4.2 Concomitant Medication

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

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

No other concomitant medications data were to be collected in the study electronic case report form (eCRF) for study analysis. However, details of concomitant medications were to be included on the report form used for expedited reporting of any of adverse reactions (see Section 9.4.5).

### 9.4.3 Continuous Renal Replacement Therapy Details

The following information about the patient's CRRT was to 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

### 9.4.4 ACCUSOL 35 Administration

The following data on the administration of ACCUSOL 35 and the presence or absence of visible precipitate was to 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 occurred during the study (ie, before 72 hours of use were completed)
- The reason for termination of CRRT, if during the study (ie, before 72 hours of CRRT were completed)
- The reason for the end of the patient's study participation

### 9.4.5 Adverse Reactions

Details of any adverse reaction (non-serious or serious) that was noted in or reported by the study patient during the study data collection period (see Section 9.4) were to be collected in the eCRF.

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

#### 9.4.5.1 Definitions

The following definitions were to be used in identifying adverse reactions.

An *adverse event* was any untoward medical occurrence in a patient administered a medicinal product and which did not necessarily have to have a causal relationship with this treatment. An adverse event could therefore have been 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, were to be treated as such because they may have been reportable to regulatory authorities according to adverse event reporting requirements, whether or not considered causally associated with drug or biologic treatment, included 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* was a response to a medicinal product which was noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event was, at least, a reasonable possibility.

A *serious adverse reaction* was one that met one or more of the following criteria:

- Resulted in death (including fetal death);
- Was life-threatening (Note: “life-threatening” in the definition of “serious” referred to an adverse reaction in which the patient was at risk of immediate death at the time of the reaction. It did not refer to a reaction that might have caused death if it were more severe);
- Required inpatient hospitalization (Note: inpatient hospitalization refers to any inpatient admission, regardless of length of stay);
- Resulted in prolongation of ongoing hospitalization;
- Resulted in persistent or significant disability/incapacity (ie, a substantial disruption of a person’s ability to conduct normal life functions);
- Was a congenital anomaly/birth defect; or
- Was a medically important reaction that may not have been immediately life-threatening or resulted in death or hospitalization, but may have jeopardized the patient or required 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 did not result in hospitalization; or development of drug dependence or drug abuse).

### 9.4.5.2 Relationship to Study Drug

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

*Possibly related:*

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

*Probably related:*

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

### 9.4.5.3 Severity

The severity of an adverse reaction was 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 was to indicate their opinion on the severity of the event or reaction according to the following definitions. The assessment of severity was to be made irrespective of drug relationship or seriousness.

*Mild:*

- The reaction was a transient discomfort and did not interfere in a significant manner with the subject’s normal functioning level.
- The reaction resolved spontaneously or may have required minimal therapeutic intervention.

*Moderate:*

- The reaction produced limited impairment of function and may have required therapeutic intervention.
- The reaction produced no sequela(e).

*Severe:*

- The reaction resulted in a marked impairment of function and may have led to temporary inability to resume usual life pattern.
- The reaction produced sequela(e), which required (prolonged) therapeutic intervention.

#### 9.4.5.4 Expedited Reporting of Adverse Reactions, Precipitate Observation and Pregnancy

##### 9.4.5.4.1 Adverse Reactions

All adverse reactions (non-serious or serious) had to be reported to the sponsor or their designee within 1 business day of observation or notification of the event. Instructions and forms for reporting an adverse reaction were 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 was to be completed that provided detailed information about the reaction and was to be promptly forwarded to the sponsor or their designee as indicated in the instructions. The sponsor or their designee was to be responsible for appropriate reporting of adverse reactions that occurred in patients exposed to an ACCUSOL 35 solution to health authorities. The investigator was to 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.

##### 9.4.5.4.2 Precipitate Observation

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

##### 9.4.5.4.3 Pregnancy

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

### 9.5 Data Sources and Measurements

Data were obtained from the patient's medical record and study-specific worksheets.

Source data for this study comprised any of the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, 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.

### 9.6 Bias

This was a single-arm, open-label, non-interventional study specifically assessing the presence or absence of visible precipitate in the CRRT circuit lines during standard-of-care therapy.

### 9.7 Study Size

Based on published CRRT studies,[1-5] it was estimated that of those CRRT treatments that reached 40 hours with the same CRRT circuit, approximately 25% would continue with the same circuit through 72 hours of use. It was expected, therefore, that about 240 enrolled patients would provide data on approximately 60 treatments lasting 72 hours without CRRT circuit changes. If no visible precipitate was observed within that time in at least 58 evaluable treatments (ie, those in which CRRT circuits remained precipitate-free for 72 hours, and those in which visible precipitate was observed within 72 hours), the study would provide 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 was also considered reasonable to assume (based on the published studies[1-5]) that approximately 10% of all CRRT treatments would last 72 hours, regardless of whether the same CRRT circuit was in use the whole time. Multiplying the probabilities to account for both having a treatment last 72 hours and also having visible particulate formation (independent events) reduces the risk from 5.0% to 0.5%. Thus a sample size of 58 treatments with no observed precipitate would 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%.

### 9.8 Data Transformation

Not applicable. No data transformations were planned or performed.

### 9.9 Statistical Methods

#### 9.9.1 Main Summary Measures

The primary endpoint planned to evaluate safety was the incidence of visible precipitate in the CRRT lines during 72 hours of use of the single CRRT circuit.

The key safety variables to be collected for analysis included:

- 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

In addition, adverse reactions were to be summarized both by the total frequency of reactions and by the frequency and percentage of patients having at least one reaction.

#### 9.9.2 Main Statistical Methods

##### 9.9.2.1 Analysis Populations

The enrolled population included patients expected to receive CRRT with ACCUSOL 35 solution(s) using the same CRRT circuit for at least 72 hours. All analyses were to be performed on the enrolled population, except that the evaluable (per-protocol) patient population was to be used for the primary analysis of this study. Although not specifically stated in the protocol, the per-protocol population was to include patients:

- Who were treated with a single CRRT circuit and whose circuits remained precipitate-free for 72 hours, or in whose circuits visible precipitate was observed within 72 hours, and

- Whose study participation and treatment were not subject to any protocol deviations that may have substantially affected the primary safety endpoints (eg, missing information on visible precipitate at 72 hours, or at least 25% of planned time points)

#### 9.9.2.2 Visible Precipitate

The primary analysis was to evaluate the incidence of visible precipitate in the CRRT lines during 72 hours of use of the single CRRT circuit. If the upper bound of the 95% confidence interval on the true proportion of treatments having precipitate formation was 5% or less, then the primary objective of the study would be achieved. The Jeffreys method [6] was selected for generating the upper bound because normal approximation is not feasible when a zero rate is expected; and the Jeffreys method is considered appropriate for the planned sample size.

The number (n) and proportion of patients with visible precipitate in the CRRT lines during 72 hours of use of the single CRRT circuit were to be summarized along with the corresponding Jeffreys 95% confidence interval for the proportion.

#### 9.9.2.3 Adverse Reactions

Adverse reaction summaries were to be done overall and by MedDRA system organ class (SOC) and preferred term (PT). The specific adverse reactions were to be summarized by SOC and PT; adverse reactions by SOC, PT, and severity; and adverse reactions by SOC, PT, and relationship with study drug. The serious adverse reactions were to be summarized by SOC and PT; serious adverse reactions by SOC, PT, and severity; and serious adverse reactions by SOC, PT, and relationship with study drug. A listing was to be provided for adverse reactions.

The number (n) and percentage (%) of patients with at least 1 adverse reaction or serious adverse reaction were to be presented.

### 9.9.3 Missing Values

No imputation of missing values was planned or performed.

### 9.9.4 Sensitivity Analyses

No sensitivity analyses were planned or performed. Exploratory analyses were to be done only if visible precipitate was observed during 72 hours of use of ACCUSOL 35 solution with a single CRRT circuit.

The time to first occurrence was to be calculated (time from start of use of the CRRT circuit to time of observation of precipitate) and summarized using Kaplan-Meier methodology.

In addition, possible further analyses were to be considered 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 added 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.

Additional possible exploratory analyses pertaining to visible precipitate were also considered.

### 9.9.5 Amendments to the Statistical Analysis Plan

The first version of the statistical analysis plan (SAP) was approved on 12 JAN 2016 (refer to Appendix 16.1.9, 8822-001 Statistical Analysis Plan 2016 MAY 11).

Following test runs of tables and listings, version 2 of the SAP was approved as final on 11 MAY 2016 , before database lock (refer to Appendix 16.1.9, 8822-001 Statistical Analysis Plan Version 2.0 2016 MAY 11). The following minor changes were made:

- The following footnote was added to Table 14.1.3.1 (Summary of Demographic and Baseline Characteristics): “Demographic data is missing for some patients because informed consent was not obtained from the patient personally.”
- Data Listing 16.2.3.1 (Patients Excluded from Per-Protocol Population) was added (includes patients from whom consent was not properly obtained, as noted in the bullet above regarding Table 14.1.3.1)
- Data Listing 16.2.3.2 (Inclusion/Exclusion) was added
- Data Listing 16.2.5.1 (Concomitant Medications) was deleted as duplicative of information contained in other listings

## 9.10 Quality Control

Each investigator was responsible for the procurement of data and for the quality of data recorded in the patient’s eCRF. A validated eCRF system and detailed instructions for completing the eCRF were provided by the sponsor. All study personnel were trained on the protocol, study, and proper completion of the eCRF.

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

All information transcribed into the eCRF was expected to accurately reflect original data recorded in the patient's medical record and any applicable study worksheets. These were required to be available to the sponsor or their designee and/or appropriate health authorities.

Only authorized study site personnel were to record or change data in the eCRFs. Changes to an eCRF required documentation of the reason for each change, and an audit trail was created for all changes. An identical (electronic/paper) version of the complete set of eCRFs for each patient remained in the investigator file at the study site.

The handling of data by the sponsor or their designee, including data quality assurance, complied 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 were described in a data management plan.

A study database was created from the data in the eCRFs, using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 for adverse reaction coding, and the World Health Organization Drug Dictionary (WHODrug) of SEP 2014 for coding concomitant medications.

Programmatic and manual reviews of the database were performed to detect missing data, errors and inconsistencies. Queries on the detected problems were transmitted to the site, and responses were recorded in the database. After all database updates were completed and prior to any statistical analyses, the database was locked.

Quality assurance department representatives from the sponsor and/or their designee could visit a study center during or after the study to conduct a quality assurance audit. The audit would include a review of EC and informed consent documentation, data entry and validation processes, and adverse event reporting. Processes could be reviewed to ensure the study was conducted in compliance with the protocol, standard operating procedures, and all applicable legal requirements. To support an audit, the investigator was obligated to provide direct access to all relevant documents and to allocate adequate time to discuss findings and relevant issues.

Representatives of the contract research organization performed a routine good clinical practice audit of the second highest-enrolling center (Center 008; see Table 1) in JUL 2016. To view a copy of the audit certificate, refer to Appendix 16.1.8.

## 10. RESULTS

### 10.1 Participants

In this study, 15 investigators at 16 centers screened 264 patients and enrolled 201 patients. Patient disposition is summarized in the following table (see Table 4). For additional details (including reasons for screen failure, reasons for non-completion of the study, and reasons for exclusion from the per-protocol population), see Table 14.1.1 and Table 14.1.2.

**Table 4. Patient Disposition – All Screened Patients**

| Parameter | Number of Patients n (%)[a] |
|---|---|
| Patients screened[a] | 264 |
| Screen failures | 63 |
| Patients enrolled | 201 |
| Patients prematurely discontinued | 131 (65)[a] |
| Patients completing the study | 70 (35)[a] |
| Patients excluded from per-protocol population | 136 (68)[a] |
| Patients in per-protocol population | 65 (32)[a] |

[a] Denominator of the percentages is the number of patients enrolled.
Sources: See Table 14.1.1 and Table 14.1.2.

Of the 201 patients enrolled, 70 patients (35%) completed the study and 131 patients (65%) were prematurely discontinued. Among those prematurely discontinued, 91 patients (45.3% of those enrolled) had their CRRT terminated prior to 72 hours of use of the CRRT circuit, 37 (18.4%) had their CRRT circuit changed prior to 72 hours of use, 2 (1.0%) died, and 1 (0.5%) had their CRRT terminated because death was imminent (reason reported as “Other”).

Among the 136 patients excluded from the per-protocol population were the previously described 131 prematurely discontinued patients and 5 completing patients excluded for other reasons (2 for whom ACCUSOL 35 administration was not adequately documented, 1 for whom >25% of the visible precipitate observations were missed, 1 for whom the last 4 hours of visible precipitate observations were missed, and 1 whose

ACCUSOL 35 administration could not be verified and whose last 2 visible precipitate observations were not performed).

For individual data on patient disposition refer to Appendix 16.2.1, Data Listing 16.2.1. For individual data on the reasons for exclusion of patients from the per-protocol population, refer to Appendix 16.2.3, Data Listing 16.2.3.1.

### 10.1.1 Protocol Deviations

None of the enrolled patients were enrolled in violation of the study entry criteria (refer to Appendix 16.2.3, Data Listing 16.2.3.2).

Major and/or minor deviations were reported for 91 of the 201 patients enrolled in the study (refer to Appendix 16.2.2, Data Listing 16.2.2 for a list of the individual deviations). For 26 patients, demographic data could not be collected for study use as a result of the deviation. Reported deviations resulted in exclusion of a patient from the per-protocol population in only 8 cases (Patients 001-001, 002-005, 005-028, 007-006, 008-031, 010-005, 010-010 and 015-002). All other exclusions of patients from the per-protocol population were due to either early termination of CRRT or early change of the CRRT circuit. No major protocol deviations related to ACCUSOL 35 administration were reported (see Table 14.1.5.6).

Protocol deviations were reported for 19 of the 65 patients included in the per-protocol analysis (Patients 003-009, 005-012, 005-016, 005-020, 005-022, 007-011, 008-001, 008-002, 008-003, 008-020, 008-022, 008-024, 010-002, 013-002, 013-005, 013-010, 015-004, 015-005 and 015-006). In 17 of these cases, the deviation was considered minor and involved either a problem with informed consent or small amounts of missing data. In one of the other 2 cases (Patient 013-010), the deviation involved the patient having been enrolled for study data collection by a physician who was not a sub-investigator for the study, which was considered a major violation. In the other case (Patient 015-005), there were reported problems with legibility of patient signature information and the identity of the signing impartial witness on the amended informed consent form used when the patient was re-consented, which was considered a major violation. However, neither of these 2 deviations was considered cause to exclude the patient’s data from the per-protocol analysis.

## 10.2 Descriptive Data

### 10.2.1 Demographics

Age and gender data for the 201 patients enrolled are summarized in the following table (see Table 5). For the summary statistics on patient weight, see Table 14.1.3.1. Data are missing for those patients who did not give informed consent personally. For the 175 patients whose gender was reported, 115 (57%) patients were male, and 60 (30%) patients were female. For the 175 patients whose age was reported, patients ranged in age from 20 to 92 years, with a mean (standard deviation [SD]) age of 62 (16) years. Body weights ranged from 30 to 177 kg, with a mean (SD) weight of 80.5 (22.9) kg.

**Table 5. Summary of Demographics - Enrolled Population**

| | Statistic | ACCUSOL 35 (N=201) |
|---|---|---|
| Gender | | |
| Male | n (%) | 115 (57.2) |
| Female | n (%) | 60 (29.9) |
| Unknown[a] | n (%) | 26 (12.9) |
| Age | n | 175 |
| | mean (SD) | 62.3 (15.53) |
| | median | 65.0 |
| | min, max | 20, 92 |
| | missing[a] | 26 |

[a] Demographic data are missing for some patients because informed consent was not obtained directly from the patient.

Max = maximum; min = minimum; SD = standard deviation.

Source: see Table 14.1.3.1.

For summary demographic data for the 65 patients in the per-protocol population, see Table 14.1.3.2. For individual patient demographic data, refer to Appendix 16.2.4, Data Listing 16.2.4.

### 10.2.2 Other Baseline Characteristics

#### 10.2.2.1 Continuous Renal Replacement Therapy Details

The following table (see Table 6) summarizes the CRRT modes and ultrafiltration rates employed to treat the enrolled patients. The two modes of CRRT used to treat the 201 enrolled patients were CVVHDF, used for 162 patients (81%), and CVVH, used for

39 patients (19%). The mean (SD) CRRT ultrafiltration rate was 2.2 (0.75) L/h (range, 0.9 to 4.2 L/h).

**Table 6. CRRT Details - Enrolled Population**

| | Statistics | ACCUSOL 35 (N=201) |
|---|---|---|
| CRRT Mode Employed | | |
| Continuous venovenous hemofiltration | n (%) | 162 (80.6) |
| Continuous venovenous hemodiafiltration | n (%) | 39 (19.4) |
| Ultrafiltration rate (L/h) | n | 195 |
| | mean (SD) | 2.2 (0.75) |
| | median | 2.1 |
| | min, max | 0.9, 4.2 |
| | missing | 6 |

CRRT = continuous renal replacement therapy; SD = standard deviation.
Source: see Table 14.1.5.1 and Table 14.1.5.2.

For individual patient dialysis details (CRRT mode; ultrafiltration rate; circuit use times; and manufacturers and models of CRRT monitors, CRRT lines and haemofilters), refer to Appendix 16.2.5, Data Listing 16.2.5.4. For individual data on dialysis session interruptions, refer to Appendix 16.2.5, Data Listing 16.2.5.5.

### 10.2.2.2 Administration of Anticoagulant and Supplemental Potassium Chloride

The use of anticoagulation and supplemental KCl during CRRT treatment of the 201 enrolled patients is summarized in the following table (see Table 7). Anticoagulants were used for a total of 161 patients (80%), with heparin being the most frequently used agent.

Supplemental KCl was administered during CRRT in 71 (35%) of the cases. This was done for patients at Center 002 (all 13 patients), Center 005 (all 30 patients), Center 009 (19 of 22 patients) and Center 13 (all 5 patients), where the patients were treated with ACCUSOL 35 (without potassium) and had supplemental KCl added at 4 mmol/L; and at Center 7, where 4 patients treated with ACCUSOL 35 Potassium 2 mmol/L had supplemental KCl added at 2 mmol/L.

**Table 7. Anti-Coagulant and Potassium Chloride Administration - Enrolled Population**

| WHODrug Anatomic Therapeutic Class (Level 2) and Preferred Term | ACCUSOL 35 (N=201) n (%) |
|---|---|
| Antithrombotic agents | 161 (80.1) |
| Dalteparin | 5 ( 2.5) |
| Dalteparin sodium | 1 ( 0.5) |
| Epoprostenol | 4 ( 2.0) |
| Epoprostenol sodium | 14 ( 7.0) |
| Heparin | 122 (60.7) |
| Heparin sodium | 17 ( 8.5) |
| Tinzaparin | 6 ( 3.0) |
| Tirofiban | 1 ( 0.5) |
| Blood substitutes and perfusion solutions | 71 (35.3) |
| Potassium Chloride | 71 (35.3) |

Note: Every patient is counted a single time for each applicable specific anticoagulant and potassium chloride administration. A patient with multiple medications within a medication category is counted a single time for that category.

WHODrug = World Health Organization Drug Dictionary.

Source: see Table 14.1.4.

For individual data on anticoagulant administration (including agent, administration time, dose and route), refer to Appendix 16.2.5, Data Listing 16.2.5.1. For individual data on KCl administration (including administration time, concentration and route), refer to Appendix 16.2.5, Data Listing 16.2.5.2.

### 10.2.2.3 ACCUSOL 35 Solution Administration

The frequency of use of the different formulations of ACCUSOL 35 solution in the study is summarized in the following table (see Table 8). The most frequently used formulation was ACCUSOL 35 Potassium 4 mmol/L, administered to 84 (42%) of the enrolled patients, followed by ACCUSOL 35 (without potassium), administered to 76 patients (38%). Thirty five patients (17%) received both ACCUSOL 35 (without potassium) and ACCUSOL 35 Potassium 4 mmol/L, and 4 patients (2%) received ACCUSOL 35 Potassium 2 mmol/L alone. ACCUSOL 35 data for the other 2 enrolled patients (1%) were missing.

**Table 8. ACCUSOL 35 Solution Administration: Formulation Used – Enrolled Population**

| | Statistics | ACCUSOL 35 (N=201) |
|---|---|---|
| ACCUSOL 35 Potassium 4 mmol/L | n (%) | 84 (41.8) |
| ACCUSOL 35 | n (%) | 76 (37.8) |
| ACCUSOL 35 and ACCUSOL 35 Potassium 4 mmol/L | n (%) | 35 (17.4) |
| ACCUSOL 35 Potassium 2 mmol/L | n (%) | 4 ( 2.0) |
| Missing | n (%) | 2 ( 1.0) |

Source: see Table 14.1.5.3.

Dose rates of ACCUSOL 35 solution are summarized by site of introduction in the following table (see Table 9). For the 27 patients treated with the product via pre-filter introduction, the mean (SD) dose rate was 20.7 (5.43) ml/kg/hr. The mean dose rate for the 6 patients treated with the product via post-filter introduction was 34.7 (3.63) ml/kg/hr. The mean dose rate for the 116 patients treated with the product via both pre- and post-filter introduction was 32.4 (10.9) ml/kg/hr. The mean dose rate for the 47 patients treated with the product as dialysate was 35.7 (5.07) ml/kg/hr. Dose rate data were missing for 2 other patients.

## Table 9. ACCUSOL 35 Administration: Dose Rate (mL/kg/hr) by Site of Introduction – Enrolled Population

| Site of Introduction | Statistics | ACCUSOL 35 (N=201) |
|---|---|---|
| Pre-filter | n | 27 |
| | mean (SD) | 20.7 (5.43) |
| | median | 20.0 |
| | min, max | 10.0, 35.0 |
| | missing | 0 |
| Post-filter | n | 6 |
| | mean (SD) | 34.7 (3.63) |
| | median | 34.2 |
| | min, max | 30.1, 39.3 |
| | missing | 0 |
| Combination (Pre- and Post-filter) | n | 116 |
| | mean (SD) | 32.4 (10.91) |
| | median | 32.7 |
| | min, max | 11.9, 71.4 |
| | missing | 3 |
| As Dialysate | n | 47 |
| | mean (SD) | 35.7 (5.07) |
| | median | 35.5 |
| | min, max | 24.6, 48.7 |
| | missing | 0 |
| Unknown or Missing | missing | 2 |

SD = standard deviation

Source: see Table 14.1.5.4; and refer to Appendix 16.2.5, Data Listing 16.2.5.3.

The total volume of ACCUSOL 35 solution administered ranged from 1.0 L to 142.5 L (see Table 10). The mean (SD) total volume administered was 40.0 (29.2) L.

**Table 10. ACCUSOL 35 Administration: Amount Administered - Enrolled Population**

| | Statistics | ACCUSOL 35 (N=201) |
|---|---|---|
| Amount administered (L) | n | 195 |
| | mean (SD) | 40.0 (29.17) |
| | median | 35.0 |
| | min, max | 1.0, 142.5 |
| | missing | 6 |

SD = standard deviation.
Source: see Table 14.1.5.5.

For individual patient data on ACCUSOL 35 solution administration, refer to Appendix 16.2.5, Data Listing 16.2.5.3.

### 10.3 Outcome Data

Not applicable

### 10.4 Main Results

The primary endpoint of the study was the incidence of visible precipitate in the CRRT lines during 72 hours of use of a single CRRT circuit. No visible precipitate was observed in any CRRT lines for any of the patients that completed 72 hours of CRRT with a single CRRT circuit (0/65 patients; 95% confidence interval, 0.000-0.038) (see Table 14.3.1.1 and refer to Appendix 16.2.7, Data Listing 16.2.7.1). Furthermore, no visible precipitate was observed in any CRRT lines for any of the 200 enrolled patients with precipitate observation data (no precipitate observation data were collected for Patient 010-009 who had been enrolled but for whom no observation data were collected. So, 201 patients were enrolled, only 200 had precipitate observation data) (refer to Appendix 16.2.2, Data Listing 16.2.2).

### 10.5 Other Analyses

Not applicable; no other analyses were performed.

### 10.6 Adverse Events/Adverse Reactions

Safety data collection was limited to collection of details of adverse reactions (serious or non-serious). No adverse reactions (serious or non-serious) were reported for any patient in this study (see Table 14.3.1.2.1 and refer to Appendix 16.2.7, Data Listing 16.2.7.2.1 and Data Listing 16.2.7.3.1).

Two patients died while on study. However, neither death was considered by the investigators to be the result of an adverse reaction to the study product. The primary cause of death for patient 009-017 was gastrointestinal haemorrhage and pneumonia; and the primary cause for patient 014-002 was multiorgan failure (refer to Appendix 16.2.7, Data Listing 16.2.7.4).

## 11. DISCUSSION

### 11.1 Key Results

In this non-interventional, observational study, 201 enrolled patients received ACCUSOL 35, in one of 3 different formulations or a combination of 2 of the formulations, for CRRT. ACCUSOL 35 Potassium 4 mmol/L was used most frequently 42% of the enrolled patients), followed by ACCUSOL 35, which was administered to 38% of the patients. Both ACCUSOL 35 and ACCUSOL 35 Potassium 4 mmol/L were administered to 17% of the patients, and ACCUSOL 35 Potassium 2 mmol/L was used for 2% of the patients.

No visible precipitate was observed in any CRRT lines for any of the patients that completed 72 hours of CRRT with a single CRRT circuit (0/65 patients; 95% confidence interval, 0.000-0.038). Furthermore, no visible precipitate was observed in any CRRT lines for any of the 200 enrolled patients with precipitate observation data.

No patient in the study experienced an adverse reaction. Two patients died while on study, as would be expected in a population of seriously ill patients. However, neither death was considered by the investigators to be the result of an adverse reaction to the study product.

### 11.2 Limitations

As a non-interventional observational study, results depended on the quality of the data reported in medical records.

Safety data collection was limited to collection of details of adverse reactions (non-serious or serious) that may have occurred during the 72 hours of CRRT.

### 11.3 Interpretation

The updated ACCUSOL 35 formulations were developed to prevent calcium carbonate precipitate formation during CRRT administration. The results of this post-approval safety study confirm successful minimization of the risk of precipitate formation with the updated ACCUSOL 35 solution, demonstrating with 95% confidence that the probability of precipitate formation in a CRRT treatment of 72 hours with a single circuit with ACCUSOL 35 solutions is not more than 3.8%. Since it is assumed that approximately 10% of all CRRT treatments will last 72 hours (see Section 9.7), this results in a probability of any CRRT treatment to both last 72 hours and develop visible precipitate of no more than 0.38%.

This supports a proposal for removal of the recommendation presented in the current labeling for ACCUSOL 35 solutions that CRRT lines be inspected every 30 minutes for the presence of visible precipitate during the use of the products.

Source data were carefully examined to ensure that all possible information relevant to the safety of ACCUSOL 35 was captured. The lack of reports of adverse reaction occurrence in any of the patients treated in the study confirms the already established safety profile of the ACCUSOL 35 solutions.

### 11.4 Generalisability

The study design, wherein the data used for the analysis of the primary endpoint (appearance of visible precipitate in the CRRT circuit lines) were limited to those cases where a single circuit was used for a full 72 hours (the recommended limit for use of a single dialysis circuit), was intended to maximize the possibility of observing any precipitate formation (ie, a “worst-case” scenario).

In addition, this was an observational study conducted in a large number of hospitals, all 3 formulations of the ACCUSOL 35 solutions were used with 4 different sites of introduction into the CRRT circuit and a wide range of administration rates, and 2 different modes of CRRT (CVVH and CVVHDF) were employed using a wide range of ultrafiltration rates.

Given these conditions, the results of the study are considered to be generalisable to all intended use scenarios for the updated ACCUSOL 35 solutions.

## 12. OTHER INFORMATION

Not applicable; there is no other relevant information to add.

## 13. CONCLUSION

This post-approval safety study was designed to verify the successful minimization of the risk of precipitate formation with the updated ACCUSOL 35 solution. No visible precipitate was observed in the CRRT lines for any of the 65 evaluable patients, demonstrating with 95% confidence that the probability of precipitate formation in a CRRT treatment of 72 hours with a single circuit with ACCUSOL 35 solutions is not more than 3.8%. Since it is assumed that approximately 10% of all CRRT treatments will last 72 hours, this results in a probability of any CRRT treatment to both last 72 hours and develop visible precipitate of no more than 0.38%.

This supports 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.

The lack of occurrence of any adverse reactions to ACCUSOL 35 solution in any of the treated patients supports the already established safety profile of the ACCUSOL 35 solutions.

## 14. REFERENCES

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6. Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. *Stat Sci*. 2001;16(2):101-133.

# APPENDICES

## Annex 1. List of Stand-alone Documents

The appendix numbering follows the ICH E3 guideline. For that reasons the following numbers are not applicable for this study “16.1.3; 16.1.6; 16.1.7; 16.1.10; 16.1.11; 16.2.6”.

| Number | Document Reference Number | Date | Title |
|---|---|---|---|
| 1 | Appendix 16.1.1 | 08 SEP 2016 | Protocol and Amendments |
| 2 | Appendix 16.1.2 | 08 SEP 2016 | Sample Case Report Form |
| 3 | Appendix 16.1.4 | 08 SEP 2016 | Descriptions of Investigators Qualifications |
| 4 | Appendix 16.1.5 | 08 SEP 2016 | Report Signature Sheet |
| 5 | Appendix 16.1.8 | 08 SEP 2016 | Audit Certificates |
| 6 | Appendix 16.1.9 | 08 SEP 2016 | Documentation of Statistical Methods |
| 7 | Appendix 16.1.12 | 08 SEP 2016 | Publications Referenced in the Report |
| 8 | Appendix 16.2.1 | 08 SEP 2016 | Patient Disposition |
| 9 | Appendix 16.2.2 | 08 SEP 2016 | Protocol Deviations |
| 10 | Appendix 16.2.3 | 08 SEP 2016 | Patients Excluded From Analysis |
| 11 | Appendix 16.2.4 | 08 SEP 2016 | Demographic Data and Other Baseline Characteristics |
| 12 | Appendix 16.2.5 | 08 SEP 2016 | Product Exposure, Compliance and Concentration Data |
| 13 | Appendix 16.2.7 | 08 SEP 2016 | Safety Data |

## Annex 2. Additional Information

### *Tables Referred to, but not Included in the Text*

*Patient Disposition, Demographics and Other Baseline Characteristics*

**Table 14.1.1. Patient Disposition - All Screened Patients**

| | **Total n (%)** |
|---|---|
| Patients screened (a) | 264 |
| Number of screen failures | 63 |
| Reason if screen failure | |
| Acute Myocardial Infarction, Severe Coronary Artery Disease | 1 ( 0.4) |
| Cardiac Arrest | 1 ( 0.4) |
| Cardiac Arrest And Pea Arrest | 1 ( 0.4) |
| Clinical Decision Not To Restart The Filter, There Was A Break For A Ct Scan For The First Filter | 1 ( 0.4) |
| CRRT Clotted | 1 ( 0.4) |
| CRRT Keeps Clotting Nearer To The Time Of Enrollment | 1 ( 0.4) |
| Doctor's Decision To Use Intermittent Haemodialysis Instead On The Day The Patient Is Due For Enrollment | 1 ( 0.4) |
| Failure To Meet Eligibility Criteria | 48 (18.2) |
| Further Consent Not Collected After Loss Of Mental Capacity Patient Eventually Died | 1 ( 0.4) |
| Large Retroperitoneal Bleed With No Option For Surgical Management. | 1 ( 0.4) |
| Multi-Organ Failure  Sepsis | 1 ( 0.4) |
| Notes Unavailable | 1 ( 0.4) |
| Patient Did Not Reach The 40 Hours No Other Circuit Available | 1 ( 0.4) |
| Sepsis | 1 ( 0.4) |
| Staphylococcus Septicaemia, Cellulitis Of Leg | 1 ( 0.4) |
| Withdrawal Of Treatment Because Of Continuing Pneumonia Leading To Multi Organ Failure And Further Sepsis. | 1 ( 0.4) |
| Patients enrolled (b) | 201 |
| Patients in per-protocol population (b) | 65 (32.3) |
| Patients completed the study (b) | 70 (34.8) |

## Table 14.1.1. Patient Disposition - All Screened Patients

| | Total n (%) |
|---|---|
| Patients prematurely discontinued (b) | 131 (65.2) |
| Reason if discontinued (b) | |
| CRRT Circuit Changed (b) | 37 (18.4) |
| CRRT Terminated (b) | 91 (45.3) |
| Death (b) | 2 ( 1.0) |
| Other (b) | 1 ( 0.5) |

(a) Denominator of the percentages for screening failures is the number of patients screened.

(b) Denominator of the percentages is the number of patients enrolled.

## Table 14.1.2 Patients Excluded From the Per-Protocol Population - Enrolled Population

| | Total n (%) |
|---|---|
| Patients in Enrolled Population | 201 |
| Patients Excluded from Per-Protocol Population | 136 (67.7) |
| Reason, if excluded | |
| >25% OBSERVATIONS MISSED | 1 ( 0.5) |
| ACCUSOL ADMINISTRATION NOT DOCUMENTED | 2 ( 1.0) |
| CRRT CIRCUIT CHANGED | 37 (18.4) |
| CRRT TERMINATED | 91 (45.3) |
| DEATH | 2 ( 1.0) |
| LAST 4 HOURS OF OBSERVATION MISSED. ALSO NOT ABLE TO SDV ACCUSOL ADMINISTRATION - RECORDS INCOMPLETE | 1 ( 0.5) |
| LAST OBSERVATION MISSED (LAST 2) | 1 ( 0.5) |
| OTHER | 1 ( 0.5) |

Denominator of the percentage is the number of patients enrolled.

Source Data: Listing 16.2.3.1.

## Table 14.1.3.1 Summary of Demographic and Baseline Characteristics - Enrolled Population

| | Statistics | ACCUSOL 35 (N=201) |
|---|---|---|
| Gender | | |
| Male | n (%) | 115 (57.2) |
| Female | n (%) | 60 (29.9) |
| Unknown | n (%) | 26 (12.9) |
| | | |
| Age (years) | | |
| 18-35 | n (%) | 16 ( 8.0) |
| 36-45 | n (%) | 11 ( 5.5) |
| 46-55 | n (%) | 20 (10.0) |
| 56-65 | n (%) | 41 (20.4) |
| > 65 | n (%) | 87 (43.3) |
| Missing | n (%) | 26 (12.9) |
| | | |
| Age (years) | | |
| | n | 175 |
| | Mean (SD) | 62.3 (15.53) |
| | Median | 65.0 |
| | Min, Max | 20, 92 |
| | Missing | 26 |
| | | |
| Weight (kg) | | |
| | n | 201 |
| | Mean (SD) | 80.513 (22.9385) |
| | Median | 76.000 |
| | Min, Max | 30.00, 177.00 |

Denominator of the percentage is the number of patients in the Enrolled Population.

N: number of enrolled patients

Demographic data is missing for some patients because informed consent was not obtained from the patient personally.

## Table 14.1.3.2 Summary of Demographic and Baseline Characteristics – Per-Protocol Population

| | Statistics | ACCUSOL 35 (N=65) |
|---|---|---|
| Gender | | |
| Male | n (%) | 40 (61.5) |
| Female | n (%) | 19 (29.2) |
| Unknown | n (%) | 6 ( 9.2) |
| | | |
| Age (years) | | |
| 18-35 | n (%) | 8 (12.3) |
| 36-45 | n (%) | 6 ( 9.2) |
| 46-55 | n (%) | 6 ( 9.2) |
| 56-65 | n (%) | 12 (18.5) |
| > 65 | n (%) | 27 (41.5) |
| Missing | n (%) | 6 ( 9.2) |
| | | |
| Age (years) | | |
| | n | 59 |
| | Mean (SD) | 59.1 (17.22) |
| | Median | 63.0 |
| | Min, Max | 20, 85 |
| | Missing | 6 |
| | | |
| Weight (kg) | | |
| | n | 65 |
| | Mean (SD) | 80.531 (22.5697) |
| | Median | 77.000 |
| | Min, Max | 30.00, 177.00 |
| | | |

Denominator of the percentage is the number of patients in the per-protocol Population.

N: number of per-protocol patients

Demographic data is missing for some patients because informed consent was not obtained from the patient personally.

## Table 14.1.4 Anti-Coagulant and Potassium Chloride Administration - Enrolled Population

| ATC Level 2<br>Preferred Term | ACCUSOL 35<br>(N=201)<br>n (%) |
|---|---|
| | |
| Antithrombotic Agents | 161 (80.1) |
| Dalteparin | 5 ( 2.5) |
| Dalteparin Sodium | 1 ( 0.5) |
| Epoprostenol | 4 ( 2.0) |
| Epoprostenol Sodium | 14 ( 7.0) |
| Heparin | 122 (60.7) |
| Heparin Sodium | 17 ( 8.5) |
| Tinzaparin | 6 ( 3.0) |
| Tirofiban | 1 ( 0.5) |
| | |
| Blood Substitutes And Perfusion Solutions | 71 (35.3) |
| Potassium Chloride | 71 (35.3) |

Note: Every patient is counted a single time for each applicable specific anti-coagulant and potassium chloride administration.

A patient with multiple medications within a medication category is counted a single time for that category.
N: number of patients in the enrolled population.

## Table 14.1.5.1 CRRT Details: Ultrafiltration Rate - Enrolled Population

| | Statistics | ACCUSOL 35 (N=201) |
|---|---|---|
| Ultrafiltration rate (L/h) | n | 195 |
| | Mean (SD) | 2.2 (0.75) |
| | Median | 2.1 |
| | Min, Max | 0.9, 4.2 |
| | Missing | 6 |

## Table 14.1.5.2 CRRT Details: CRRT Mode - Enrolled Population

| | Statistics | ACCUSOL 35 (N=201) |
|---|---|---|
| Continuous Venovenous Hemodiafiltration (CVVHDF) | n (%) | 39 (19.4) |
| Continuous Venovenous Hemofiltration (CVVH) | n (%) | 162 (80.6) |

## Table 14.1.5.3 ACCUSOL 35 Administration: Formulation Used - Enrolled Population

| | Statistics | ACCUSOL 35 (N=201) |
|---|---|---|
| ACCUSOL 35 | n (%) | 76 (37.8) |
| ACCUSOL 35 Potassium 2 mmol/L | n (%) | 4 ( 2.0) |
| ACCUSOL 35 Potassium 4 mmol/L | n (%) | 84 (41.8) |
| ACCUSOL 35 and ACCUSOL 35 Potassium 2 mmol/L | n (%) | 0 ( 0.0) |
| ACCUSOL 35 and ACCUSOL 35 Potassium 4 mmol/L | n (%) | 35 (17.4) |
| ACCUSOL 35 Potassium 2 mmol/L and ACCUSOL 35 Potassium 4 mmol/L | n (%) | 0 ( 0.0) |
| Missing | n (%) | 2 ( 1.0) |

## Table 14.1.5.4 ACCUSOL 35 Administration: Dose Rate by Site of Introduction – Enrolled Population

| | Statistics | ACCUSOL 35 (N=201) |
|---|---|---|
| Dose rate - Pre-filter (ml/kg/hr) | n | 27 |
| | Mean (SD) | 20.7 (5.43) |
| | Median | 20.0 |
| | Min, Max | 10.0, 35.0 |
| | Missing | 0 |
| Dose rate - Post-filter (ml/kg/hr) | n | 6 |
| | Mean (SD) | 34.7 (3.63) |
| | Median | 34.2 |
| | Min, Max | 30.1, 39.3 |
| | Missing | 0 |
| Dose rate – As dialysate (ml/kg/hr) | n | 47 |
| | Mean (SD) | 35.7 (5.07) |
| | Median | 35.5 |
| | Min, Max | 24.6, 48.7 |
| | Missing | 0 |
| Dose rate - Other (ml/kg/hr) | n | 0 |
| | Mean (SD) | . (.) |
| | Median | . |
| | Min, Max | ., . |
| | Missing | 1 |
| Dose rate – Combination (ml/kg/hr) | n | 116 |
| | Mean (SD) | 32.4 (10.91) |
| | Median | 32.7 |
| | Min, Max | 11.9, 71.4 |
| | Missing | 3 |
| Dose rate – Missing site of introduction data (ml/kg/hr) | n | 0 |
| | Mean (SD) | . (.) |
| | Median | . |
| | Min, Max | ., . |
| | Missing | 1 |

## Table 14.1.5.5 ACCUSOL 35 Administration: Amount Administered - Enrolled Population

| | Statistics | ACCUSOL 35 (N=201) |
|---|---|---|
| Amount administered (L) | n | 195 |
| | Mean (SD) | 40.0 (29.17) |
| | Median | 35.0 |
| | Min, Max | 1.0, 142.5 |
| | Missing | 6 |

## Table 14.1.5.6 ACCUSOL 35 Administration: Incidence of Major Protocol Deviations - Enrolled Population

| | Statistics | ACCUSOL 35 (N=201) |
|---|---|---|
| No ACCUSOL 35 Administration related major protocol deviations were reported | | |

*Safety*

**Table 14.3.1.1 Analysis of Precipitate Formation - Per-Protocol Population**

| | ACCUSOL 35 (N=65) | |
|---|---|---|
| | **n (%)** | **95% CI** |
| Proportion of patients with visible precipitate during 72 hours of use of ACCUSOL 35 solution with a single CRRT circuit | 0 ( 0.0) | (0.000, 0.038) |

N:number of evaluable patients.

CI: Confidence Interval. Jeffrey's method is used to derive the confidence interval. The confidence limits are displayed as fractions of 1.

**Table 14.3.1.2.1 Overview of Adverse Reactions on Patient Level - Enrolled Population**

| | ACCUSOL 35 (N=201) n (%) |
|---|---|
| Patients with at least one AR | 0 ( 0.0) |
| Patients with at least one Serious AR | 0 ( 0.0) |
| Patients with at least one Drug-Related AR | 0 ( 0.0) |
| Patients with at least one serious Drug-related adverse reactions | 0 ( 0.0) |
| Patients with AR leading to discontinuation | 0 ( 0.0) |
| Patients with SAR leading to discontinuation | 0 ( 0.0) |

N: number of patients in the enrolled population

Note: Two patients died. Both deaths were not related to adverse events.