This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. SYNOPSIS

SPONSOR COMPANY NAME: Cubist Pharmaceuticals, Inc. **NAME OF FINISHED PRODUCT:** Ecallantide® for injection **NAME OF ACTIVE INGREDIENT:** Ecallantide	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:** **VOLUME:** **PAGE:**	**(FOR NATIONAL AUTHORITY USE ONLY)**

TITLE OF STUDY:

CONSERV™ – 2 (***C**linical **O**utcomes a**n**d **S**afety Trial to Investigate **E**callantide's **E**ffect on **R**educing Surgical Blood Loss **V**olume*) – A Phase 2 Randomized Double-Blind Active-Controlled Study in Subjects Exposed to Cardio-pulmonary Bypass During Cardiac Surgery at High Risk of Bleeding

INVESTIGATORS AND STUDY CENTERS:

This was a multicenter study which was initiated at 46 study centers, including 5 in the United States (US), 17 in Poland and 24 in Germany; subjects were randomized at 36 of the 46 centers.

PUBLICATION (REFERENCE):

None

STUDY PERIOD:

Initiation Date (first subject enrolled): 30 June 2009
Early Termination Date (enrollment closed): 03 December 2009
Completion Date (last subject completed): 21 January 2010

PHASE OF DEVELOPMENT:

Phase 2

STUDY OBJECTIVES:

The primary objective was to evaluate the relative efficacy of ecallantide and Cyklokapron® in the reduction of blood loss in subjects undergoing cardiac surgery that included the use of cardiopulmonary bypass (CPB), associated with a high risk of bleeding.

Secondary objectives were:

- To assess the safety of ecallantide in subjects undergoing cardiac surgery including the use of CPB, associated with a high risk of bleeding;
- To explore clinical outcomes that may correlate with blood loss in subjects undergoing cardiac surgery including the use of CPB associated with a high risk of bleeding.

METHODOLOGY:

This was a Phase 2, randomized, double-blind, active-controlled, multicenter, multinational study designed to assess the efficacy and safety of ecallantide in the reduction of blood loss in subjects undergoing cardiac surgery including the use of CPB, associated with a high risk of bleeding.

Subjects were screened up to 14 days prior to surgery. Eligible subjects were randomized on a 1:1 basis to receive ecallantide or Cyklokapron® (tranexamic acid) on the day of surgery.

Subjects were monitored immediately prior to surgery (Study Day 1) through Study Day 4 (±1), and underwent follow-up evaluations at Study Day 7 (±1), or discharge from the hospital (whichever occurred first), and again 35 days (-7/+14) after dosing.

Screening assessments included medical and surgical history, physical examination, vital signs (temperature, heart rate, and blood pressure), left ventricular function assessment (LVEF; if not performed within the previous 90 days), 12 lead electrocardiogram (ECG), and clinical laboratory tests, including hematology, chemistry, coagulation studies, creatine kinase MB fraction (CK-MB), troponin T, and pregnancy test (if applicable).

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Peri- and post-operative assessments included physical examination, vital signs (temperature, heart rate, blood pressure, and oxygen saturation), ECG, chest tube drainage volume, transfusion requirements, and clinical laboratory tests.

The study design included oversight of the safety of treatment by a Data Safety Monitoring Board (DSMB) and central review of ECGs and cardiac enzymes for evaluation of events of myocardial infarction (MI).

NUMBER OF SUBJECTS (PLANNED AND ANALYZED):

Three hundred (300) subjects were planned to be randomized (1:1) to receive ecallantide or Cyklokapron® with approximately 150 subjects randomized into each treatment arm.

The study was terminated early by the Sponsor after the DSMB recommended temporary suspension in enrollment. During data review, the DSMB observed a statistical difference in mortality rates between the treatment arms. While overall mortality was consistent with expected outcomes for the subject population, more deaths were observed in the ecallantide arm. The Sponsor elected to end enrollment in this study and another Phase 2 ecallantide study (ECAL-PCPB-08-02), with nearly 500 subjects enrolled overall. At that time, a total of 242 subjects had been randomized in this study; 218 of these subjects received at least 1 dose of study treatment and are included in the Safety Population, including 109 subjects in both the ecallantide and Cyklokapron® groups.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Men or women ≥18 and ≤85 years of age undergoing cardiac surgery using CPB for one of the following: repeat sternotomy, surgery to repair or replace more than one valve, and combined coronary artery bypass graft (CABG) plus repair or replacement of at least one valve were candidates for this study. Subjects undergoing primary CABG, single valve repair or replacement surgery, or any off-pump procedure, or planned hypothermia or planned blood transfusion during peri-operative period, or planned use of desmopressin, lysine analogs, atrial natriuretic hormone, or recombinant activated Factor VII, were excluded from study participation.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, LOT NUMBER(S):

Ecallantide is a clear, colorless, sterile, preservative-free liquid suitable for IV infusion, supplied in a 2 mL glass vial containing 1.1 mL to 1.2 mL of a solution of ecallantide at a concentration of 10 mg/mL.

In order to maintain blinding, a dummy (placebo) test dose of 5 mL of normal saline was administered over at least 10 minutes after induction of anesthesia and insertion of a central venous line. The loading dose of ecallantide was administered after heparinization. Subjects received ecallantide at a target steady-state concentration of 2.25 mg/L. Administration of the study drug continued until skin dressing was applied or for 6 hours, whichever came first.

Ecallantide lot number: [redacted]

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, LOT NUMBER(S):

Cyklokapron® is a sterile liquid suitable for IV infusion, supplied at a concentration of 100 mg/mL.

A 5 mL test dose of Cyklokapron® was administered over at least 10 minutes after induction of anesthesia and insertion of a central venous line. The loading dose of 1 gram of Cyklokapron® was administered after heparinization only if there was no evidence of anaphylaxis following the test dose (as determined by the anesthesiologist responsible for the subject's care). Subjects received Cyklokapron® at dose of 400 mg/hr. Administration of the study drug continued until skin dressing was applied or for 6 hours, whichever came first. The first 24 subjects in Poland received approximately twice this dose before Cubist revised the protocol

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to use the dose of tranexamic acid recommended in the technical pamphlet for Cyklokapron® from Germany.
Cyklokapron® lot numbers: [redacted]

DURATION OF TREATMENT:

Subjects received a single dose of ecallantide or Cyklokapron® during cardiac surgery using CPB for 6 hours or until application of skin dressings; follow-up visits were conducted through Day 35.

CRITERIA FOR EVALUATION:

EFFICACY:

The key efficacy variable of interest was the volume of packed red blood cells (PRBCs) administered from the start of surgery up to 12 hours after the end of surgery. Results for this variable were also assessed during surgery, to 24 hours post-surgery and to hospital discharge.

SAFETY:

Safety was monitored throughout the study by observation or reports of adverse events (AEs), as well as changes in physical findings, vital signs, ECGs, and clinical laboratory tests.

STATISTICAL METHODS:

The efficacy analyses were evaluated in the modified intent-to-treat (mITT) population, defined as all randomized subjects who received any amount of study drug. Comparisons between the ecallantide and Cyklokapron® treatment groups were performed using the Wilcoxon rank sum test for variables with a continuous outcome. Fisher's exact test was used to compare proportions between treatment groups for variables with a dichotomous outcome. All tests performed were 2-sided conducted at the 0.05 significance level. There were no inferential adjustments for multiplicity.

The safety of ecallantide treatment was evaluated in the Safety Population, defined as all randomized subjects who received any amount of study drug. Evaluation of safety parameters was descriptive in nature.

SUMMARY AND CONCLUSIONS:

SUMMARY OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS:

The treatment groups were comparable with regard to demographic and baseline characteristics. Overall mean age was 69.6 years in the ecallantide group and 66.8 years in the Cyklokapron® group, with a range of 25 to 86 years across all 218 subjects. The majority of the subjects were male, 62% of subjects in both treatment groups; all subjects were Caucasian. Median body mass index was also comparable between treatment groups ranging 27.4 to 27.7 mg/m^2. More subjects in the ecallantide group had a history of smoking (58%) compared with the Cyklokapron® group (50%). Atrial fibrillation was reported at baseline more often in the Cyklokapron® group (33%) compared with the ecallantide group (23%).

Most subjects underwent CABG with valve replacement, primarily aortic valve and mitral valve surgeries (65% of subjects in the both treatment groups). Mean duration of CPB and aortic cross-clamp time were similar in the ecallantide the Cyklokapron® groups. Mean overall duration of surgery was 304 minutes in the ecallantide group and 310 minutes in the Cyklokapron® group. Mean total heparin dose administered during surgery was 45.5 and 47.8 x 1000 Units in the ecallantide and Cyklokapron® groups, respectively.

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SUMMARY OF EFFICACY:

Ecallantide was not as effective as Cyklokapron® in reducing blood loss in this study. Mean and median cumulative volume of PRBCs administered through 12 hours post-surgery were significantly higher in the ecallantide group (1223 and 900 mL, respectively) compared with the Cyklokapron® group (624 and 300 mL, respectively) ($p<0.001$). Furthermore, at all additional time points assessed, the cumulative volume of PRBCs administered was higher in the ecallantide group compared with the Cyklokapron® group; the results were statistically significant in favor of Cyklokapron® at 24 hours post surgery ($p<0.001$) and at discharge ($p<0.001$).

SUMMARY OF SAFETY:

A summary of the most commonly reported treatment-emergent adverse events (TEAEs) is provided in the following table.

Most Common (>10% of Subjects in Either Treatment Group) Treatment-emergent Adverse Events (Safety Population)

MedDRA Preferred Term	Ecallantide (N=109) n (%)	Cyklokapron® (N=109) n (%)
Atrial fibrillation	33 (30.3)	20 (18.3)
Hypotension	20 (18.3)	20 (18.3)
Anaemia	18 (16.5)	17 (15.6)
Procedural pain	17 (15.6)	25 (22.9)
Pleural effusion	15 (13.8)	17 (15.6)
Post procedural haemorrhage	13 (11.9)	8 (7.3)
Haemorrhage	11 (10.1)	4 (3.7)
Hyperglycaemia	11 (10.1)	15 (13.8)

The most commonly reported types of events were cardiac disorders, which were reported more often in the ecallantide group (61%) compared with the Cyklokapron® group (42%). The most commonly reported cardiac disorder was atrial fibrillation reported in 30% of subjects who received ecallantide compared with 18% of subjects who received Cyklokapron®. Other common TEAEs (≥10% incidence in either group) were hypotension (18% and 18%, in the ecallantide and Cyklokapron® groups, respectively), anemia (17% and 16%, respectively), procedural pain (16% and 23%, respectively), pleural effusion (14% and 16%, respectively), post-procedural hemorrhage (12% and 7%, respectively), hemorrhage (10% and 4%, respectively), and hyperglycemia (10% and 14%, respectively).

The majority of TEAEs were mild or moderate in intensity. The incidence of severe TEAEs was higher in the ecallantide group (35%) compared with the Cyklokapron® group (16%). The most commonly reported severe TEAEs (>5% incidence in either group) were post-procedural hemorrhage (7% and 3% of subjects in the ecallantide and Cyklokapron® groups, respectively) and hemorrhage (6% and 1%, respectively).

Seventeen subjects died during the study or in follow-up, including 13 (12%) subjects in the ecallantide group and 4 (4%) subjects in the Cyklokapron® group ($p=0.041$). All TEAEs leading to death in both the ecallantide and Cyklokapron® groups were considered by the Investigator to be unlikely related or not related to study drug. Nine of the 17 deaths occurred in the immediate post-surgical period (by the 2nd post-operative day); 3 of the deaths occurred more than 30 days post-treatment.

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Serious adverse events (SAEs) were reported in 41% of subjects who received ecallantide compared with 26% of subjects who received Cyklokapron®. This difference may be attributed to a higher incidence of serious cardiac disorders (22% and 10% in the ecallantide and Cyklokapron® groups, respectively) and reports of hemorrhage, including both post-procedural hemorrhage (10% and 6%, respectively) and hemorrhage (8% and 0%, respectively).

Protocol-defined massive postoperative bleeding occurred in 26% of ecallantide subjects and 13% of Cyklokapron® subjects (p=0.025). Subjects requiring re-thoracotomy for massive bleeding was also significantly higher in ecallantide subjects (18%) compared with Cyklokapron® subjects (8%; p=0.045), as was the proportion of subjects with chest tube drainage exceeding 1.125 L in 6 hours (14% versus 6%; p=0.038). Renal failure was reported in 5% of ecallantide subjects and 9% of Cyklokapron® subjects. Adjudicated MI occurred in 23% of ecallantide subjects and 21% of Cyklokapron® subjects (p=0.869). Prolonged ventilation, days on inotropic support and new onset neurological deficits also were not statistically different between treatment groups.

Two subjects in each of the treatment groups were discontinued due to adverse events: one subject due to cardiac failure in the operating room and one subject due to right ventricular failure in the ecallantide group; one subject due to ventricular tachycardia and one subject due to multi-organ failure in the Cyklokapron® group. All 4 of these adverse events were assessed as serious.

No differences were noted between the treatment groups in mean changes from baseline for hematology parameters. However, a higher proportion of subjects in the ecallantide group experienced thrombocytopenia with platelet count $<75 \times 10^9$/L (29%) compared with subjects in the Cyklokapron® group (17%). Differences in mean changes from baseline were noted between the treatment groups for alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin with higher mean changes observed in the ecallantide group compared with the Cyklokapron® group, reflecting the higher blood transfusion volumes in the ecallantide group. However, review of the proportion of subjects with ALT or AST >3 x upper limit of normal showed no differences between the treatment groups. The differences in mean values are likely related to several subjects with AST and ALT values >1000 U/L (5 subjects in the ecallantide group and 2 subjects in the Cyklokapron® group). There were no other clinically significant findings based on review of laboratory or vital signs data.

CONCLUSIONS:

Ecallantide was not as effective as Cyklokapron® in reducing blood loss in this study. There were significantly more deaths and massive bleeding events in ecallantide-treated subjects than Cyklokapron®-treated subjects.

DATE OF THE REPORT: 18 June 2010