1. TITLE PAGE

A STUDY TO EVALUATE THE EFFICACY AND SAFETY OF EXTRANEAL PHYSIOLOGICAL pH COMPARED WITH CURRENT EXTRANEAL IN PATIENTS RECEIVING CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD)

Product Name or Number:	EXTRANEAL Physiological pH Peritoneal Dialysis Solution
Protocol Number:	PRO-RENAL-REG-062
Developmental Phase:	III
Indication Studied:	Subjects with end-stage renal disease treated by continuous ambulatory peritoneal dialysis
Date First Subject Enrolled:	February 16, 2005
Date Last Subject Completed:	May 29, 2006
Sponsor:	Baxter R&D Europe SCRL
Sponsor's Responsible Medical Officer:	[redacted], MD Baxter World Trade S.A. Renal Global Clinical Affairs Brussels, Belgium Tel: +[redacted] Fax: +[redacted]
Date of Report:	December 21, 2006

Quality Assurance Statement

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

2. SYNOPSIS

Name of Sponsor/Company: Baxter R&D Europe SCRL	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: EXTRANEAL Physiological pH Solution for peritoneal dialysis		
Name of Active Ingredient: Icodextrin (7.5%), sodium chloride (5.73 g/L), calcium chloride dihydrate (0.257 g/L), magnesium chloride hexahydrate (0.051 g/L), sodium bicarbonate (2.10 g/L), sodium (S)-lactate (1.12 g/L)		

Title of Study: A Study to Evaluate the Efficacy and Safety of EXTRANEAL Physiological pH Compared With Current EXTRANEAL in Patients Receiving Continuous Ambulatory Peritoneal Dialysis (CAPD)

Investigators: Thirty-six investigators enrolled subjects into the study (see Appendix 16.1.4 for a list).

Study Center(s): The study was conducted at 36 sites: Canada (5 sites), Denmark (2 sites), Sweden (10 sites), the Netherlands (3 sites), and the United Kingdom (16 sites) (see Appendix 16.1.4 for a listing of the institutions at which the study was conducted).

Publications (reference): None as of the time of this report.

Studied Period: February 2005 - May 2006 **Date First Subject Enrolled:** February 16, 2005 **Date Last Subject Completed:** May 29, 2006	**Phase of Development:** III

Objectives:

Primary Objective: The primary objective was to demonstrate the non-inferiority of EXTRANEAL Physiological pH compared with current EXTRANEAL with regard to long-dwell ultrafiltration (UF).

Secondary Objectives: The secondary objectives were to demonstrate:

- The equivalence of EXTRANEAL Physiological pH to current EXTRANEAL with regard to acid-base status.
- The non-inferiority of EXTRANEAL Physiological pH compared with current EXTRANEAL with regard to long-dwell peritoneal creatinine clearance.

Methodology: This was a phase III, prospective, parallel-group, randomized, multicenter study of EXTRANEAL Physiological pH and current EXTRANEAL (7.5% icodextrin) in subjects with end-stage renal disease (ESRD) that was treated by continuous ambulatory peritoneal dialysis (CAPD). The study included a 2-week screening period; a 2-week baseline period; and an 8-week treatment period. During the screening and baseline periods, all of the subjects used current EXTRANEAL for the long dwell and either PHYSIONEAL 40 or DIANEAL PD4 for the short dwell. Between baseline (Week -2) and the start of the treatment period (Day 1), subjects were randomized in a 1:1 ratio to receive either the control solution, current EXTRANEAL, or the test solution, EXTRANEAL Physiological pH, during the 8-week treatment period. To ensure that the 2 groups were balanced with respect to the short-dwell peritoneal dialysis (PD) solution, randomization was stratified by the prestudy short-dwell solution.

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Thus, subjects received 1 of the following 4 regimens during the 8-week treatment period: (1) current EXTRANEAL for the long dwell and PHYSIONEAL 40 for the short dwell; (2) current EXTRANEAL for the long dwell and DIANEAL PD4 for the short dwell; (3) EXTRANEAL Physiological pH for the long dwell and PHYSIONEAL 40 for the short dwell; or (4) EXTRANEAL Physiological pH for the long dwell and DIANEAL PD4 for the short dwell.

No changes in the short-dwell prescription were allowed during the study. The fill volumes and durations of the long dwell during the treatment period (current EXTRANEAL or EXTRANEAL Physiological pH) were to be the same as those used during the baseline period. The calcium carbonate prescription was to remain unchanged during the study, and subjects were not allowed to add sodium bicarbonate to their dialysis bag or to take sodium bicarbonate orally during the study period.

Study participation comprised 7 study visits over an approximate 12-week period: a screening visit (Visit 0, Week -4), a baseline visit (Visit 1, Week -2), a visit to initiate the randomized treatment (Visit 2, Day 1), and 4 visits during the treatment period (Visits 3, 4, 5, and 6) that were conducted at 2-weekly intervals (i.e., at 14 ± 3 day intervals). Ultrafiltration (the primary efficacy endpoint) was determined by weighing the overnight dialysis bag, before infusion and after drainage, for 7 days before the baseline and treatment period visits and calculating the mean of the measurements; the net UF (in milliliters) was calculated as the difference of the bag weights. Blood samples for determination of serum levels of sodium, potassium, phosphorus, ionized calcium, total calcium, chloride, urea, creatinine, C-reactive protein, alkaline phosphatase, albumin (bromocresol green or purple method), total protein, amylase, and glucose were obtained at baseline and at each clinic visit during the treatment period; blood gases were determined at 37ºC on a venous whole blood sample at baseline and at each clinic visit during the treatment period. A physical examination was done at baseline and at the final visit (Visit 6). Adverse events were monitored continuously throughout the study

Number of Subjects (Planned and Analyzed): The study was planned to include approximately 120 subjects (to ensure 51 evaluable subjects per treatment group). A total of 135 subjects were screened of whom 122 were enrolled in the study (60 in the current EXTRANEAL group and 62 in the EXTRANEAL Physiological pH group). One hundred eighteen subjects (59 in each treatment group) were included in the intent-to-treat (ITT) population. Of these, 101 were included in the evaluable UF population (52 in the current EXTRANEAL group and 49 in the EXTRANEAL Physiological pH group), 107 were included in the evaluable plasma bicarbonate population (54 in the current EXTRANEAL group and 53 in the EXTRANEAL Physiological pH group), and 109 (54 in the current EXTRANEAL group and 55 in the EXTRANEAL Physiological pH group) were included in the evaluable peritoneal creatinine clearance population.

Diagnosis and Main Criteria for Inclusion: Subjects aged 18 years and older that were using current EXTRANEAL for the long dwell and either PHYSIONEAL 40 or DIANEAL PD4 for the short dwell and who had been using these solutions for at least 60 days before the baseline visit (Week -2) were eligible for the study. Subjects that had received antibiotics for the treatment of an episode of peritonitis in the 30-day period before the screening visit (Week -4), those that had had an acute or chronic exit-site

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or tunnel infection in the past 14 days (counted as the last day of infection to the screening visit), those that routinely added sodium bicarbonate to their dialysis bag, or those that had other serious, active, or uncontrolled illnesses were excluded from the study, as were women who were pregnant or lactating. Other exclusion criteria included major illness or injury that had required hospitalization within the 30-day period before the baseline visit; severe malnutrition; routine use of NUTRINEAL (1.1% amino acid-based solution), which could not be omitted from the regimen during the study; allergy to starch-based polymers; and glycogen-storage disease. All subjects gave written informed consent.

Test Product, Dose, Mode of Administration, and Batch Number(s): EXTRANEAL Physiological pH was administered intraperitoneally at fill volumes of 2.0 or 2.5 L once daily for 8 weeks for the long-dwell exchange. The supplies were provided in 2.0-L or 2.5-L VIAFLEX, 2-chamber twin bags and were taken from batch numbers BX04341, BX04341R, BX04342, BX04342R, BX04345, and BX04346 (2.0-L supplies) and from batch numbers BX04351, BX04351R, BX04352, BX04352R, BX04355, and BX04356 (2.5-L supplies).

Duration of Treatment: The planned duration of participation in the study was 10 weeks, including a 2-week baseline period during which all subjects received current EXTRANEAL for the long dwell and an 8-week treatment period during which subjects received their randomized treatment (current EXTRANEAL or EXTRANEAL Physiological pH) for the long dwell.

Reference Therapy, Dose, Mode of Administration, and Batch Number(s): Current EXTRANEAL was administered intraperitoneally at fill volumes of 2.0 or 2.5 L once daily for 8 weeks for the long-dwell exchange. The supplies were provided in 2.0-L or 2.5-L VIAFLEX, single-chamber bags and were taken from batch numbers BX04321 and BX04322 (2.0-L supplies) and from batch numbers BX04331, BX04332, and BX04333 (2.5-L supplies).

Criteria for Evaluation:

Efficacy: Efficacy data were analyzed for 2 populations: (1) The ITT population included all subjects who received at least 1 dose of the test or control solution during the treatment period. (2) The evaluable (or per-protocol) population included only those subjects who had at least 1 measure of UF, plasma bicarbonate, or long dwell peritoneal creatinine clearance before starting study treatment (Week –2 and/or Day 1) and at least 2 measures of UF, plasma bicarbonate, or long dwell peritoneal creatinine clearance during the treatment period of the study. Subjects who had changes in their dialysis prescription had the UF measurements from those visits excluded for determining the evaluable population. Subjects who had changes in calcium-containing phosphate binders and subjects who used oral or intraperitoneal sodium bicarbonate were excluded from the evaluable population for the analysis of plasma bicarbonate.

Safety: Safety data were analyzed for the ITT population.

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Statistical Methods:

Main Efficacy Analyses. Long-dwell UF, the primary efficacy endpoint, was evaluated using a repeated measure analysis of covariance model (ANCOVA). The response variable was the change from baseline, and the covariates were the baseline measures of the subjects and the baseline solution for the short dwell (PHYSIONEAL 40 or DIANEAL PD4). Comparisons were made between the treatment groups for the difference between baseline and the Weeks 2, 4, 6, and 8 visits. A contrast (or point estimate) of the difference between the treatment groups of the adjusted mean UF change from baseline was constructed. The subject identification (ID) was used as a random effect to account for repeated measures across time points (weeks). A lower one-sided 97.5% confidence interval (CI) on the difference of the 2 treatment groups for the change from baseline was calculated for UF. If the lower limit was greater than -150 mL, then EXTRANEAL Physiological pH was considered to be non-inferior to current EXTRANEAL. An analysis of UF rate was also performed. The UF rate from each exchange was calculated as the UF value divided by the long-dwell time. In this analysis, EXTRANEAL Physiological pH was considered to be non-inferior to current EXTRANEAL if the lower limit of the 97.5% CI was greater than -14.1 mL/hour

Plasma bicarbonate and peritoneal creatinine clearance were analyzed similarly to UF. A 2-sided 95% CI on the difference of the 2 treatment groups for the change from baseline was calculated for plasma bicarbonate. If the upper limit of the CI was less than +3 mmol/L and the lower limit was greater than -3 mmol/L, then EXTRANEAL Physiological pH was considered to be equivalent to the current EXTRANEAL. A lower one-sided 97.5% CI on the difference of the 2 treatment groups for the change from baseline was calculated for peritoneal creatinine clearance. If the lower limit of the CI was greater than -0.6 mL/min, then EXTRANEAL Physiological pH was considered to be non-inferior to current EXTRANEAL.

Secondary Efficacy Analyses. A secondary analysis of the primary and secondary efficacy endpoints in which any missing data were imputed using the last value carried forward was conducted only at the Week 8 time point.

Safety. The incidence of adverse events was tabulated by seriousness, severity, and relationship to treatment. Adverse events were summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and by preferred term symptom. Rates of adverse events were estimated and tabulated on a per-subject basis (number of events of a specific adverse event per subject) and on a per-subject-month basis (number of events of a specific adverse event per subject month of exposure). Descriptive rather than inferential statistical comparisons were used to compare the 2 treatment groups within each system and symptom. Descriptive statistics (mean, standard deviation, minimum and maximum) were used to summarize blood chemistry parameters and vital signs by treatment group and visit. The change from baseline for current EXTRANEAL and the change from baseline for EXTRANEAL Physiological pH were assessed using a Student's t test. A simple comparison for change from baseline between the current EXTRANEAL and EXTRANEAL Physiological pH groups was

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made using an ANCOVA, with the covariate being the subject's baseline measure.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Long-dwell UF (Primary Endpoint). The primary analysis of long-dwell UF failed to demonstrate the non-inferiority of EXTRANEAL Physiological pH relative to current EXTRANEAL for either the ITT (lower limit of 97.5% CI, -156.4 mL) or evaluable (lower limit of 97.5% CI, -164.1 mL) subjects. The secondary analysis of long-dwell UF at Week 8 in which missing data were imputed using the last observation carried forward also failed to demonstrate the non-inferiority of EXTRANEAL Physiological pH relative to current EXTRANEAL for either the ITT or evaluable subjects. Additionally, statistically significant differences, favoring better long-dwell UF for current EXTRANEAL than for EXTRANEAL Physiological pH, were observed in the mean change from baseline in UF at Weeks 2, 4, 6, and 8 (early termination) both for the ITT and evaluable subjects. The results of the analysis of long-dwell UF rate — an additional analysis of UF — were consistent with those of the analysis of long-dwell UF. A post hoc analysis, which was done to correct the data for the differences in bag weights between the treatment groups, failed to provide a full explanation of the observed differences.

Acid-base Status (Secondary Endpoint). The primary analysis of acid-base status demonstrated that EXTRANEAL Physiological pH was equivalent to current EXTRANEAL with regard to acid-base status both for the ITT (point estimate, -0.08; 2-sided 95% CI: -0.567, 0.412) and evaluable (point estimate, -0.17; 2-sided 95% CI: -0.669, 0.328) subjects. The secondary efficacy analysis (last observation carried forward at Week 8) confirmed the findings of the primary analysis. No statistically significant differences were observed between the current EXTRANEAL and EXTRANEAL Physiological pH groups in the mean change from baseline in plasma bicarbonate at Weeks 2, 4, 6, or 8 (early termination) for either the ITT or evaluable subjects, thereby providing further support of the equivalence of the 2 treatments.

Peritoneal Creatinine Clearance (Secondary Endpoint). The primary efficacy analysis demonstrated the non-inferiority of EXTRANEAL Physiological pH relative to current EXTRANEAL with regard to peritoneal creatinine clearance both for the ITT (point estimate, -0.19; lower 97.5% CI: -0.349) and evaluable (point estimate, -0.16; lower 97.5% CI: -0.324) subjects. The secondary efficacy analysis (last observation carried forward at Week 8) confirmed the findings of the primary analysis. No statistically significant differences were observed between the current EXTRANEAL and EXTRANEAL Physiological pH groups in the mean change from baseline in peritoneal creatinine clearance at Weeks 2, 6, or 8 (early termination) for either the ITT or evaluable subjects. A transient statistically significant difference was observed between treatment groups at Week 4.

SAFETY RESULTS: Both current EXTRANEAL and EXTRANEAL Physiological pH were well tolerated when used once daily as part of a CAPD regimen for up to 8 weeks:

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- No relationship was observed between the study treatment (current EXTRANEAL or EXTRANEAL Physiological pH) and the incidence of any adverse event, any serious adverse event, any related adverse event, withdrawals due to adverse events, or withdrawals due to peritonitis.
- The incidence of drug-related adverse events was low and comparable between the current EXTRANEAL (5.1%; 3/59) and EXTRANEAL Physiological pH (3.4%; 2/59) groups.
- The incidence of peritonitis (nonspecific causes) was 6.8% (4/59) in the current EXTRANEAL group and 0% (0/59) in the EXTRANEAL Physiological pH group. Bacterial peritonitis was reported in 1 (1.7%) subject in each treatment group. Two (3.4%) subjects in the current EXTRANEAL group discontinued from the study because of peritonitis (nonspecific causes), and 1 (1.7%) subject in the EXTRANEAL Physiological pH group discontinued from the study because of bacterial peritonitis.
- One (1.7%) death was reported in each treatment group. Neither death (attributed to cardiac arrest in the current EXTRANEAL group and to congestive heart failure in the EXTRANEAL Physiological pH group) was suspected to be related to the study treatment.
- The incidence of serious adverse events was low and comparable between the current EXTRANEAL (8.5%; 5/59) and EXTRANEAL Physiological pH (6.8%; 4/59) groups. Serious adverse events in both treatment groups were primarily related to cardiac disorders and to infections. None of the serious adverse events in either treatment group was suspected to be related to the study treatments.
- Little fluctuation was observed in serum sodium, potassium, phosphorus, ionized calcium, total calcium, chloride, urea, creatinine, C-reactive protein, alkaline phosphatase, albumin (bromocresol green or purple method), total protein, amylase, or glucose or in the blood gas determinations of actual bicarbonate (HCO_3), standard HCO_3, partial pressure of carbon dioxide (PCO_2), total carbon dioxide (TCO_2), or pH. Statistically significant mean changes from baseline were observed in some tests at isolated time points during the study in each treatment group, but the magnitude of the changes was small and not clinically significant. No clinically significant differences were observed between treatment groups in the mean change from baseline at Week 2, 4, 6, or 8 (early termination) for any laboratory test.
- Little fluctuation was observed in sitting or standing blood pressure, respiratory rate, temperature, pulse, or actual weight (after draining dialysis fluid) in either treatment group during the study. No clinically significant differences were observed between treatment groups in the mean change from baseline at Week 2, 4, 6, or 8 (early termination) for any vital sign.

Overall, the results of this study demonstrate that the safety profile of EXTRANEAL Physiological pH is consistent with and comparable to that of current EXTRANEAL.

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CONCLUSION: This phase III, prospective, parallel-group, randomized, multicenter study failed to demonstrate the non-inferiority of EXTRANEAL Physiological pH relative to current EXTRANEAL with regard to long-dwell UF, the primary efficacy endpoint. The study did, however, demonstrate that EXTRANEAL Physiological pH is equivalent to current EXTRANEAL with regard to acid-base status and non-inferior to current EXTRANEAL with regard to peritoneal creatinine clearance. Both treatments were well tolerated when used once daily for up to 8 weeks as the long-dwell exchange solution as part of a CAPD regimen. The safety profile of EXTRANEAL Physiological pH was consistent with and comparable to that of current EXTRANEAL.		
Date of the Report: December 21, 2006		