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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-321**

**Medical Review(s)**

6/8/01

TO: NDA 21-321, 7.5% Icodextrin Peritoneal Dialysis Solution

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Subject: Medical Review

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### **EXECUTIVE SUMMARY**

Chronic ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) are currently performed using Dextrose in various concentrations as the osmotic agent to remove excess fluid and waste products from the system of End Stage Renal Disease (ESRD) patients. Because the osmotic gradient across the peritoneum decreases with Dextrose over the course of a long-dwell dialysis, Baxter has developed a different drug, Icodextrin, designed to maintain the gradient over the long-dwell period of peritoneal dialysis, and therefore increase the efficiency of dialysis.

Icodextrin is a high molecular weight glucose polymer derived from maltodextrin, and is administered with electrolytes. The dialysis solution contains 7.5 g per 100 ml, and 2.0 or 2.5 L are used for the long-dwell period of dialysis. Approximately 30-40% of Icodextrin is absorbed from a single exchange depending on dwell time (between 8-16 hours), and is systemically hydrolyzed to smaller oligosaccharides.

The clinical program compared the dialysis efficacy and safety to Dextrose for the long-dwell period in both CAPD and APD. No placebo controlled efficacy studies were performed.

Clinical studies 130, MIDAS and Pro-Renal demonstrated superiority of Icodextrin versus 1.5% or 2.5% Dextrose for net ultrafiltration and creatinine and urea clearance in long-dwell CAPD or APD. Superiority of Icodextrin versus 4.5% Dextrose was not demonstrated. Data to demonstrate that the increased ultrafiltration and creatinine and urea clearances benefited the patients clinically were not convincing, but it was clear that Icodextrin was an effective dialysis drug.

A serious **safety concern was raised by study 131**, a 52 week safety study with mortality as the primary endpoint, in which the mortality data were adverse for Icodextrin compared to Dextrose. **In the 13 month post-enrollment follow-up results, there were 20 Icodextrin deaths (n=175, 11.4%) and 9 Dextrose deaths (n=112, 8%).** Review of each case and exploratory subgroup analyses did not provide an explanation for the numerically adverse result. A pooling of all known deaths from all controlled trials did not replicate the adverse finding in study 131. Nevertheless, that result remains a concern.

Other adverse findings associated with Icodextrin were rash, decreased serum sodium and chloride, elevated alkaline phosphatase and AST (SGOT). A decline in serum amylase due to assay interference, and a slight decline in serum cholesterol was noted. No difference in effect on serum glucose, insulin requirements or HgA1C was found between treatments.

Considering the safety and efficacy data, a recommendation for approval for those patients inadequately responding to CAPD or APD with Dextrose for the long-dwell period is made. A post-marketing, long term, active-controlled, randomized mortality study should be considered.

## **CLINICAL REVIEW**

### **I. INTRODUCTION and BACKGROUND**

On 12/20/2000, Baxter Healthcare Corporation submitted an NDA for Extraneal (7.5% Icodextrin with electrolytes) peritoneal dialysis solution for the treatment of chronic renal failure. The drug is a designated orphan drug. The total submission consists of 155 volumes, SAS data sets for the Phase III clinical trials, and pdf files for the case report forms. Certifications re financial interests and arrangements with clinical investigators, and patent information covering the formulation, composition and/or method of use are included.

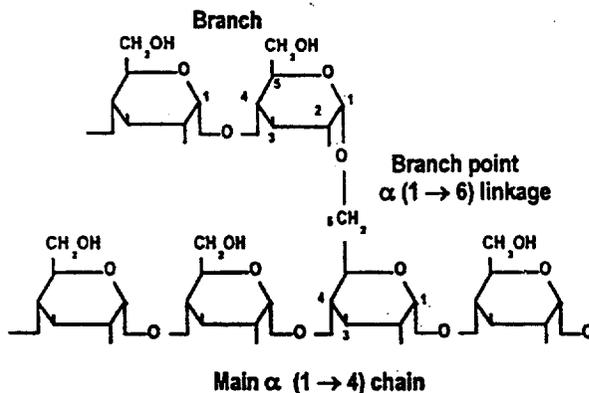
The medical portion of the submission includes volumes 1.1, 1.23-1.76 and 1.39A, and amendments dated 3/20 2001, 4/5/2001, 4/16/01, 4/18/01 and 5/3/01. On October 19,2000 a closed meeting of the CardioRenal Advisory Committee was held to discuss development of peritoneal dialysis solutions, at which meeting some of the data contained in this application was discussed. As a result of that discussion some additional data was gathered, analyzed and included in the application i.e. follow-up status of patients who participated in study RD 97-CA-131, a one year randomized safety study.

The drug is a new molecular entity, and has been approved in 17 European countries including the UK as well as in Canada. It is a designated orphan drug.

## **II. CLINICALLY RELEVANT INFORMATION RE: CHEMISTRY and NON-CLINICAL PHARMACOLOGY and TOXICOLOGY**

### **1. Chemistry**

Icodextrin is a soluble glucose polymer derived from maltodextrin that in turn was derived by partial hydrolysis of starch. It has an average molecular weight of 12000-20000 Daltons, and its molecular structure is represented as follows:



It is formulated as a 7.5% aqueous solution with electrolytes, and is manufactured by ML laboratories, PLC of Liverpool, England. The proposed fill volumes for various containers is 1.5L, 2.0L, and 2.5L. For the US, the composition of the electrolyte solution would be the same as for the currently available Dianeal PD-2 . The formulation proposed for marketing is:

<u>COMPONENT</u>	<u>COMPOSITION / 100 mL</u>
Icodextrin	7.5 g
Sodium Chloride, USP	535* mg
Sodium Lactate	448 mg
Calcium Chloride Dehydrate, USP	25.7 mg
Magnesium Chloride Hexahydrate, USP	5.08 mg
Hydrochloric acid	for pH adjustment
Sodium Hydroxide	for pH adjustment
Water for Injection, USP	qs

Approximate mEq per liter:

Lactate	40
Sodium	132
Calcium	3.5
Magnesium	0.5
Chloride	96

\* Approximately 0.6 mEq/L of 1.0 N sodium hydroxide is required to adjust the pH of the drug product which is equal to approximately 3.5 mg of sodium chloride.

For further information, see chemistry review.

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## 2. Non-Clinical Pharmacology and Toxicology

See Pharmacology review. Most studies were carried out using the ip route for 28 days, and blood levels were not detected in rats and low in dogs. A chart comparing those levels to man was provided as follows:

Species	Dose Details	Sample time (n)	Mean Plasma Levels (mg/ml)		
			G2	G3 - G10	G>10
Rat	4.0 & 6.0 g/kg IP twice daily for 28 days	Day 1:24h (4) Day 1:24h (4)	None detected		
Dog	6.0g/kg IP twice daily for 28 days (12g/kg/day)	Pre-dose (8)	0.02	0.02	0.10
		Day 1:5h (8)	0.11	0.52	0.17
		Day 1:24h (8)	0.02	0.22	0.13
		Day 21:5h (8)	0.05	0.33	0.18
		Day 21:24h (8)	0.02	0.24	0.16
		Day 28:5h (8)	0.03	0.28	0.14
		Day 1:24h (8)	0.02	0.26	0.16
Man (Davies,1994)	150 g once daily IP for 6 months (2.14 g/kg/day)	Pre-dose (91)	0.04	0.02	0.29
		1 month (80)	1.20	1.84	1.83
		3 months (72)	1.00	1.67	1.73
		6 months (53)	1.06	1.76	1.84

No carcinogenicity tests were performed. Ames test, CHO test and mouse micronucleus test were performed and no genotoxicity was observed. A reproductive study by ML Laboratories was not included in the NDA. The sponsor notes that maltodextrin is classied as GRAS as a food ingredient.

In metabolic animal studies it was shown that the route of elimination was renal, and icodextrin was hydrolyzed, probably by alpha amylase, to oligosaccharides including maltose and maltotriose.

## III. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

One single-dose and several multiple-dose studies evaluated the PK of Icodextrin. See the Pharmacology review for details of those studies.

Since Icodextrin is directly instilled into the abdominal cavity, bioavailability is assured. In the abdominal cavity the drug works as a colloid osmotic agent to effect ultrafiltration in peritoneal dialysis. The osmotic pressure created by Icodextrin is thought to be relatively constant with little loss of osmotic gradient during long-dwells.

As noted in the preclinical section, Icodextrin is hydrolyzed by alpha amylase and smaller oligosaccharides such as maltose, maltotriose and maltotetraose have been quantified in the plasma. Maltase further metabolizes the oligosaccharides to glucose.

During daily Icodextrin administration in single, long-dwell exchanges, plasma levels of 4-6.5 g/L of Icodextrin were found within one week and remained constant. Steady-state plasma levels of maltose ranged from 0.81 to 1.35 g/L. Steady state plasma levels of maltotriose were similar to maltose levels, and only small increases in plasma levels of larger metabolites were found. From a single dose of 150 g of Icodextrin, approximately 30-40% was absorbed, depending on dwell time. After discontinuation the plasma levels of Icodextrin and metabolites return to baseline in one to two weeks. Absorption from the peritoneal cavity into the blood follows zero order kinetics, and the drug is renally excreted, depending on residual renal function.

#### IV. DESCRIPTION of CLINICAL DATA

##### Clinical Trials

a) The sponsor identified 4 pivotal clinical trials which are outlined in the following chart.

Study	Description	N	Duration	Endpoint(s)
RD-97-CA-130 Vol. 1.31-1.37	Prospective, DB, Randomized comparison of Icodextrin and 2.5% Dextrose	Total=175 Ico=90 Dex=85 CAPD patients	4 weeks	Net UF
ML/1B/001 MIDAS Vol. 1.57-1.63	Open, Randomized comparison of Icodextrin and 1.5%, 2.5%, 4.5% Dextrose	Total=209 Ico=106 Dex=103 CAPD patients	6 months	Net UF
Pro-Renal-Reg-035 Vol. 1.54-1.56	Open, Randomized comparison of Icodextrin and 2.5% Dextrose	Total=39 Ico=20 Dex=19 APD patients	16 weeks	UF, Creatinine and Urea clearances
RD-97-CA-131 Vol. 1.38-1.53	Prospective, Randomized, DB Comparison of Icodextrin and 2.5% Dextrose	Total=287 Ico=175 Dex=112 CAPD and APD patients	52 weeks	Safety, Quality of Life

b) Supportive controlled clinical studies provided were:

ML/1B/004 (MIDAS-2): an open label long-term extension of MIDAS.

ML/1B/020 (DELIA): an open two-way crossover study comparing Icodextrin to a dry day.

ML/1B/011 (DIANA): an open, randomized comparison of Icodextrin to Dextrose in 38 APD patients for 2 years. 13 patients completed the 2 years.

RD-99-CA-060: an open single dose PK study of Icodextrin in a single exchange.

ML/1B/014: an open uncontrolled study of serum concentrations of drug and metabolites at steady state, after treatment cessation and after restarting.

ML/1B/002: an open randomized cross-over study of adding insulin to CAPD solutions in diabetics comparing Icodextrin and 1.5% glucose.

c) Cancelled studies due to slow enrollment were:

ML/1B/009 (IDEAL): an open, uncontrolled study that was to include 100 patients, but enrolled only 16 over more than a year.

PRO-RENAL-REF-037A: an open, uncontrolled study that was to include 80 patients but cancelled after 27 patients were enrolled. According to the sponsor analyses of the study are ongoing, and data were not included in the submission.

This review will consider the 4 pivotal studies in detail, and the others briefly.

## V. CLINICAL REVIEW

Each of the clinical studies provided by the sponsor is summarized in the following clinical review.

**1. RD-97-CA-130:** This randomized, double-blind study of 7.5% Icodextrin peritoneal dialysis solution compared to 2.5% Dextrose peritoneal dialysis solution was initiated on April 1, 1998 and completed on December 29, 1998, and conducted in the US and Canada. Dianeal PD-2 was used in the US, and Dianeal PD-4 was used in Canada each with 2.5% Dextrose (2.27% glucose). The composition of the Icodextrin solution was:

COMPONENT	Composition/100 mL
Icodextrin	7.5 g
Sodium Chloride, USP	535 mg *
Sodium Lactate	448 mg
Calcium Chloride Dihydrate, USP	25.7 mg
Magnesium Chloride Hexahydrate, USP	5.08 mg
Hydrochloric acid	for pH adjustment
Sodium Hydroxide	for pH adjustment
Water for Injection, USP	qs
COMPONENT	Approx. mEq/L
Lactate	40
Sodium	132
Calcium	3.5
Magnesium	0.5
Chloride	96

\* Approximately 0.6 mEq/L of 1.0 N sodium hydroxide is required to adjust the pH of the drug product, which is equal to approximately 3.5 mg of sodium chloride.

That of the PD-2 and PD-4 solutions were:

COMPONENT	PD-2	PD-4
Composition per 100 mL		
Sodium chloride, USP	538 mg	538 mg
Sodium lactate	448 mg	448 mg
Calcium chloride dihydrate, USP	25.7 mg	18.3 mg
Magnesium chloride hexahydrate, USP	5.08 mg	5.08 mg
Dextrose hydrous, USP	2.5 g	2.5 g
Water for injection, USP	qs	qs
Approximate mEq per liter		
Lactate	40	40
Sodium	132	132
Calcium	3.5	2.5
Magnesium	0.5	0.5
Chloride	96	95

The solutions were provided in Ultrabag, Twinbag or single bag configurations and the fill volume for each long-dwell dialysis was 2.0 or 2.5 liters.

The study was designed as a non-inferiority trial which in the August 13, 1998 protocol amendment was defined as established if the difference between groups was within 30% of the mean ultrafiltration (UF) in the long-dwell exchange for the control group. In the original December 5, 1997 protocol the non-inferiority definition used a 95% one-sided confidence interval with a lower bound greater than 150 ml. Secondary variables were peritoneal urea nitrogen exchange and peritoneal creatinine clearance. 175 patients were randomized: 90 to Icodextrin and 85 to control. Patients 18 years of age or older who had been on CAPD for at least 90 days, and who were treated by a long-dwell night exchange time of 12±4 hours with a fill volume of at least 2.0L but not more than 2.5L of 2.5% Dextrose were eligible. The randomization for each assignment was stratified for either 2.0 or 2.5L fill volumes. Eligible patients also needed to be requiring a minimum of 4 peritoneal dialysis exchanges per 24 hour period, one of which was a night exchange. Allergy to starch-based polymers, liver disease, and women who were pregnant, lactating or not using acceptable birth control methods were among the exclusion criteria.

Patients continued the same formulation of Dextrose during the other dialysis periods. If a patient was taking Dianeal PD-4, which contains less calcium chloride than PD-2, for the other exchanges, he or she would, if randomized to Icodextrin, get the PD-2 composition of electrolytes for the long-dwell.

Net ultrafiltration was determined by subtracting the inflow amount from the total weight of the long-dwell collection.

The sponsor provided a flowchart of procedures as follows:

VISIT NUMBER	SCREENING PERIOD	BASELINE	TREATMENT PERIOD (DIANEAL® OR ICODEXTRIN) 4 WEEKS	
	-1		1	2
WEEK	-2w	0	2w	4w
Intervals	7 d ± 7d	1 d	2w ± 3d	2w ± 3d
Informed Consent	X			
Selection Criteria	X			
Serum hCG <sup>1</sup>	X			
Medical History	X	X		
Physical Exam		X		X
Vital Signs		X	X	X
QoL Evaluation		X		
Lab Analyses <sup>2</sup>		X	X <sup>3</sup>	X
Chest X-Ray		X		
Concomitant Meds		X	X	X
Adverse Events	X <sup>4</sup>	X	X	X
Review Compliance		X	X	X
Randomization		X		
PET		X		
Total Cholesterol		X		X
24 hr. Urine		X		
Ico & met - plasma <sup>5</sup>		X		X
Ico - dialysate		X		X
12 ± 4 hr Dialysate		X	X	X
HbA <sub>1c</sub> <sup>4</sup>		X		X

<sup>1</sup> Women of child-bearing potential.

<sup>2</sup> To include biochemistry, hematology with differential and platelets, osmolality.

<sup>3</sup> These were considered pre-existing conditions.

<sup>4</sup> Diabetic patients only.

<sup>5</sup> Serum BUN and Creatinine only.

<sup>6</sup> The Icodextrin and metabolites blood sample were drawn at the end of the long dwell, just prior to draining.

VISIT	Screen	Baseline	Treatment	
	-1	0	1	2
Time Period	-1w	0	2w	4w
<b>BLOOD</b>				
Sodium		X		X
Glucose		X		X
Potassium		X		X
Chloride		X		X
HCO <sub>3</sub>		X		X
BUN		X	X	X
Creatinine		X	X	X
Phosphorus		X		X
Calcium		X		X
Total Bilirubin		X		X
SGOT (AST)		X		X
SGPT (ALT)		X		X
Alkaline Phosphatase		X		X
Osmolality		X		X
Albumin		X		X
Amylase		X		X
Hematology		X		X
Total Cholesterol		X		X
Serum hCG <sup>1</sup>	X			
Hb A <sub>1c</sub> <sup>2</sup>		X		X
PET		X		
Icodextrin & met. Analyses <sup>3</sup>		X		X
<b>DIALYSATE</b>				
12±4 hr. T. Drain Vol.		X	X	X
12±4 hr. urea nitrogen		X	X	X
12±4 hr. creatinine		X	X	X
Total Icodextrin		X		X
PET		X		
<b>URINE</b>				
24 hr. Collection-RRF		X		

<sup>1</sup> Women of child-bearing potential

<sup>2</sup> Diabetic patients only

<sup>3</sup> The Icodextrin and metabolites blood sample were drawn at the end of the long dwell, just prior to draining

The term PET in this context means peritoneal equilibrium test, and the baseline QoL test was added in the August 1998 amendment after the study had begun for comparison with a follow-up QoL test to be administered to some patients participating in the long term 52 week safety study RD-97-CA-131.

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The sponsor provided some baseline characteristics of the 175 randomized patients:

	Control Group		Icodextrin Group		All Patients		p-Value
	N	Percent	N	Percent	N	Percent	
<b>Gender</b>							0.317 *
MALE	26	30.6	34	37.8	60	34.3	
FEMALE	59	69.4	56	62.2	115	65.7	
<b>TOTALS</b>	<b>85</b>	<b>100.0</b>	<b>90</b>	<b>100.0</b>	<b>175</b>	<b>100.0</b>	
<b>Race</b>							0.584 **
CAUCASIAN	47	55.3	48	53.3	95	54.3	
HISPANIC	3	3.5	6	6.7	11	6.3	
ASIAN	3	3.5	2	2.2	5	2.9	
BLACK	27	31.8	30	33.3	57	32.6	
OTHER	3	3.5	4	4.4	7	4.0	
<b>TOTALS</b>	<b>85</b>	<b>100.0</b>	<b>90</b>	<b>100.0</b>	<b>175</b>	<b>100.0</b>	
<b>Primary Renal Diagnosis</b>							0.708 **
DIABETIC NEPHROPATHY	21	24.7	24	26.7	45	25.7	
HYPERTENSIVE NEPHROPATHY	19	22.4	24	26.7	43	24.6	
GLOMERULONEPHRITIS	16	18.8	14	15.6	30	17.1	
POLYCYSTIC KIDNEY DISEASE	3	3.5	2	2.2	5	2.9	
INTERSTITIAL NEPHRITIS	1	1.2	3	3.3	4	2.3	
OBSTRUCTIVE NEPHROPATHY	1	1.2	1	1.1	2	1.1	
AUTOIMMUNE DISEASE	3	3.5	1	1.1	4	2.3	
OTHER	21	24.7	21	23.3	42	24.0	
<b>TOTALS</b>	<b>85</b>	<b>100.0</b>	<b>90</b>	<b>100.0</b>	<b>175</b>	<b>100.0</b>	

\* Analysis of Variance used to test for treatment differences.

\*\* Pearson Chi-Square test used to test for treatment differences.

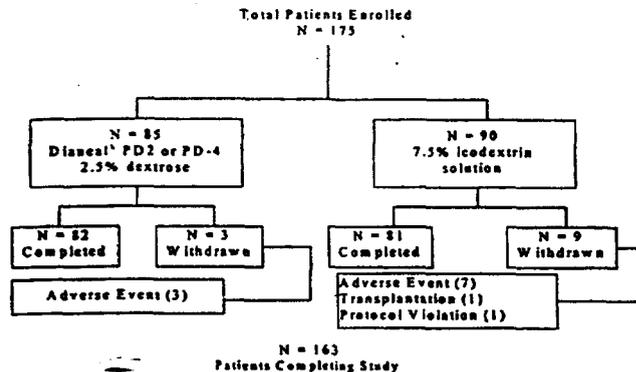
\*\*\* Fisher Exact test used to test for treatment differences because > 20% of the cells had expected counts < 5.

The groups were also well balanced at baseline for long-dwell glucose concentration and fill volume being used, as well as serum calcium.

Slightly more past episodes of peritonitis were reported for the Icodextrin group (1.2% versus 5.6%, p=0.076). and more months had elapsed from the last exit site infection for the Icodextrin group (mean 14.7 versus 9.1, p=0.062).

59 patients were diabetic (31 Icodextrin patients or 34.4% of the full cohort, and 28 of the Dextrose patients or 32.9%), mostly type II.

Patient disposition was provided by the sponsor as follows:



Details of the reasons for withdrawal were provided:

Treatment Group	Center	Patient	Age/Sex/Race*	Last Study Visit Completed	Last Study Day Completed	Reason for Withdrawal	Description
Control	23	06283	78/F/C	Baseline	15	ADVERSE EXPERIENCE	HOSPITALIZATION FOR MI
	35	15383	50/F/B	Week 3	34	ADVERSE EXPERIENCE	PERITONITIS
	123	19101	78/F/C	Baseline	9	ADVERSE EXPERIENCE	NAUSEA, VOMITING, ANOREXIA, GENERALIZED WEAKNESS, JOINT PAIN, AND SWELLING.
Icodextrin	16	24201	75/M/C	Baseline	13	PROTOCOL VIOLATION	NOT ON 1.5% LONG DWELL FOR 30 DAYS.
		24203	71/M/C	Week 2	36	ADVERSE EXPERIENCE	SEVERE DEHYDRATION AND HYPERKINESIA, PULMONARY EDEMA & BOWEL OBSTRUCTION
	20	21201	47/F/C	Baseline	13	TRANSPLANTATION	
	23	06203	35/F/B	Week 2	50	ADVERSE EXPERIENCE	HOSPITALIZATION FOR APPARENT GIB
	25	22101	51/F/C	Baseline	12	ADVERSE EXPERIENCE	RASH
	50	23200	52/F/B	Baseline	13	ADVERSE EXPERIENCE	HYPERPIGMENTATION BROWN/RED SKIN SPOTS < 2.0 CM IN SIZE X3 SPOTS. NO CO ITCHING
		23210	60/F/C	Baseline	14	ADVERSE EXPERIENCE	HIVES
	54	45102	72/F/C	Week 2	29	ADVERSE EXPERIENCE	BLOCKED CATHETER
	59	33104	34/F/C	Baseline	8	ADVERSE EXPERIENCE	RASH

\* Age in years / M=Male, F=Female / C=Caucasian, H=Hispanic, A=Asian, B=Black, O=Other

Results were provided for the evaluable population with additional analyses to demonstrate that the ITT results did not materially differ. Compliance was estimated by the number of days the bag was used and was over 80% in both groups. Changes in daytime dialysis prescriptions were similar for the groups. Time of the long-dwell averaged 10.44 hours for control and 10.63 hours for Icodextrin at week 4. Fill volume at that time was 2.2L for each treatment, and drain volumes were 2.6 L and 2.8 L for control and Icodextrin respectively.

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**EFFICACY**

**Primary Endpoint-Net UF**

At baseline, 2 and 4 week data on dwell start and stop times, volume infused and volume drained were collected on each patient's case report form. For weeks 2 and 4, data from 166 and 163 patients respectively were analyzed by the sponsor to provide the following net UF results:

Treatment Group	(Baseline) Week 0	Week 2	Week 4	
Control	No. of Patients	85	82	82
	Mean	328.718	389.793	379.988
	Standard Error	40.997	69.904	37.469
	Minimum			
	Maximum			
	Mean Change from Baseline		58.11	44.84
	Min Change from Baseline		-1049.0	-800.0
	Max Change from Baseline		5226.0	995.0
	Mean Pct Change from Baseline *		121.23	56.64
	p-Value for Change from Baseline		0.429	0.179
	Icodextrin	No. of Patients	90	84
Mean		261.922	578.060	605.827
Standard Error		37.514	35.234	31.305
Minimum				
Maximum				
Mean Change from Baseline			300.56	328.17
Min Change from Baseline			-820.0	-668.0
Max Change from Baseline			1568.0	1633.0
Mean Pct Change from Baseline *			356.25	392.75
p-Value for Change from Baseline			<0.001	<0.001
OVERALL ** (From Repeated Measures)		Icodextrin Adjusted Mean Change	294.60	
	Control Adjusted Mean Change	70.08		p-Value ***
	Difference (Icodextrin-Control) for Change	224.52		<0.001
	Std Error of Difference	50.68		
	Lower 90% Confidence Bound for Difference	140.68		
	Upper 90% Confidence Bound for Difference	308.35		

\* Means of individual percent changes from Baseline  
 \*\* The adjusted mean changes from the repeated measures analysis of covariance, with Baseline value as the covariate, for each treatment group.  
 A 90% confidence interval was constructed around the difference between Icodextrin and Control.  
 \*\*\* This p-value is from the two-sided test for treatment differences using the repeated measures analysis of covariance.

Mean dwell time was 10.36 hours and mean volume was 2222.55 ml for all patients with a slightly longer dwell time recorded for the Icodextrin patients but no difference in fill volumes between groups. One patient with an extreme value at week 2 was excluded in an alternative analysis with no change in results. Negative UF values occurred in 13.4% of the control patients versus 0% in the Icodextrin treated patients at 4 weeks (p<0.001).

Nondiabetics had slightly less net UF at 2 weeks versus diabetics, but similar results at 4 weeks. Icodextrin was significantly more effective than control at 2 and 4 weeks in both diabetics and nondiabetics with a somewhat larger net UF benefit for diabetics versus nondiabetics.

Negative UF

Analyses of negative and nonnegative ultrafiltration were carried out at baseline, 2 and 4 week timepoints with the following results:

Visit	Categories	Control Group		Icodestria Group		All Patients		p-Value
		N	Percent	N	Percent	N	Percent	
Long-Dwell UF (mL)								
BASELINE (Week 0)	Neg UF	16	18.8	18	20.0	34	19.4	0.844 *
	NonNeg UF	69	81.2	72	80.0	141	80.6	
	TOTALS	85	100.0	90	100.0	175	100.0	
WEEK 2	Neg UF	12	14.8	2	2.4	14	8.5	0.004 *
	NonNeg UF	69	85.2	82	97.6	151	91.5	
	TOTALS	81	100.0	84	100.0	165	100.0	
WEEK 4	Neg UF	11	13.4	0	0.0	11	6.7	<0.001 *
	NonNeg UF	71	86.6	81	100.0	152	93.3	
	TOTALS	82	100.0	81	100.0	163	100.0	

\* Pearson Chi-Square test used to test for treatment differences.

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Secondary Endpoints-Peritoneal Urea Nitrogen and Creatinine Clearance

Blood urea nitrogen and creatinine and dialysate urea nitrogen and creatinine data were collected at baseline, 2 and 4 weeks. Results of peritoneal urea and creatinine clearances (ml/min) were provided as follows:

Variable	Visit	Treatment Group	Baseline <sup>⊗</sup>			Data			Change from Baseline <sup>⊗</sup>						p Betw	
			Mean	N	Std Err	Min	Median	Max	Mean	Std Err	p W/in	Min	Median	Max		
Creatinine Clearance (mL/1.73 hrs)	Baseline	Control		85	2457.231	63.892		2459.36								0.733
	(Week 0)	Icodextrin		89	2488.271	63.895		2481.72								
		Control	2472.461	82	2478.179	81.684		2477.15								
	Week 2	Icodextrin	2483.888	84	2543.156	84.749		2376.37		461.338	76.616	<0.001		464.21		<0.001
		Control	2456.759	81	2523.948	94.904		2415.65		73.289	92.069	0.429		-19.78		0.001
	Week 4	Icodextrin	2474.555	81	2588.358	73.426		2135.26		481.287	55.382	<0.001		392.25		<0.001
		Control	2461.362	83	2501.684	69.685		2489.30		48.322	67.898	0.554		-54.39		<0.001
	Average * (Treatm)	Control	2483.085	84	2502.982	71.387		2387.23		418.639	58.713	<0.001		439.29		
		Icodextrin						3033.48								0.545
	Urea Nitrogen Clearance (mL/1.73 hrs)	Baseline	Control		85	3002.492	87.319		3033.48							
(Week 0)		Icodextrin		90	3022.692	88.026		3019.05								
		Control	3010.738	82	2947.799	94.107		2884.86								
Week 2		Icodextrin	3034.381	84	3281.972	75.577		3243.44		347.671	79.131	0.002		288.68		0.002
		Control	2992.524	82	2964.714	98.330		2881.22		-27.810	78.233	0.723		-65.44		0.004
Week 4		Icodextrin	3035.921	86	3268.710	82.168		3212.59		224.790	64.724	<0.001		228.84		<0.001
		Control	2996.830	83	2962.116	78.987		2989.88		-34.714	71.318	0.628		-46.28		0.001
Average * (Treatm)		Control	3034.381	84	3261.708	72.758		3248.68		227.407	69.527	0.002		288.78		
		Icodextrin						3248.68								

⊗ BASELINE is the Week 0 value.  
 \* The average was calculated for each patient during the treatment period. Any patients with data during that time is included.  
 p W/in p-value from the within treatment group paired t-test for significant mean change from baseline.  
 p Betw Baseline (Wk 0): p-value from analysis of variance testing for significant differences across treatment group means.  
 For baseline (Treatment: Wks 2,4): p-value from analysis of covariance testing for significant differences across treatment groups for mean changes.

These results support the sponsor's contention that Icodextrin is an effective peritoneal dialysis solution, and provides more net UF and peritoneal urea and creatinine clearance than 2.5% Dextrose for long-dwell dialysis.

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## SAFETY

175 patients were exposed to either Icodextrin or 2.5% Dextrose. 84.4% of the Icodextrin and 89.4% of the Dextrose patients were treated for more than 27 days. No deaths occurred.

### Withdrawals

The reasons for withdrawal were previously presented but is repeated below:

Treatment Group	Center	Patient	Age/Sex/Race *	Last Study Visit Completed	Last Study Day Completed	Reason for Withdrawal	Description
Control	22	04205	70/F/C	Baseline	15	ADVERSE EXPERIENCE	HOSPITALIZATION FOR MI
	35	15203	50/F/B	Week 2	24	ADVERSE EXPERIENCE	PERITONITIS
	123	29101	78/F/C	Baseline	9	ADVERSE EXPERIENCE	NAUSEA, VOMITING, ANOREXIA, GENERALIZED WEAKNESS, JOINT PAIN, AND SWELLING.
Icodextrin	18	24201	75/M/C	Baseline	12	PROTOCOL VIOLATION	NOT ON 2.5% LONG DWELL FOR 30 DAYS
		24203	71/M/C	Week 2	36	ADVERSE EXPERIENCE	SEVERE DEHYDRATION AND HYPERKINESIA, PULMONARY EDEMA & BOWEL OBSTRUCTION
	20	21201	47/F/C	Baseline	13	TRANSPLANTATION	
	23	04203	33/F/B	Week 2	50	ADVERSE EXPERIENCE	HOSPITALIZATION FOR APPARENT GIB
	25	22101	51/F/C	Baseline	12	ADVERSE EXPERIENCE	RASH
	50	23204	52/F/B	Baseline	15	ADVERSE EXPERIENCE	HYPERPIGMENTATION BROWN/RED SKIN SPOTS < 2.0 CM IN SIZE X3 SPOTS. NO CO ITCHING
		23210	60/F/C	Baseline	14	ADVERSE EXPERIENCE	HIVES
	54	45102	72/F/C	Week 2	29	ADVERSE EXPERIENCE	BLOCKED CATHETER
	59	33104	34/F/C	Baseline	8	ADVERSE EXPERIENCE	RASH

\* Age in years / M=Male, F=Female / C=Caucasian, H=Hispanic, A=Asian, B=Black, O=Other

### Serious Adverse Reactions

18 patients (9-Icodextrin, 9-Dextrose) reported serious adverse events with 7 Icodextrin and 8 Dextrose patients being hospitalized. The following list provides a brief primary problem description for each case.

Icodextrin	2.5% Dextrose
Confusion, hypercalcemia, Rocalcelrol dc'd	Chest pain, anterior MI
Unresponsive, seizures, bleeding	Abd. pain, nausea and vomiting, Kleb. in dialysate
Nausea and vomiting, bleeding	Flank pain, actinobacter in effluent
Elective renal transplant	Peritonitis
Chest pain	Peritonitis
Tremor, jerky movements, confusion, had Reglan	Peritonitis
Chest pain, CAD	Peritonitis
Pericarditis	Syncope, overuse of 2.5% Dextrose to lose weight
Blocked catheter	Peritonitis

Peritonitis seems to be more frequent as a cause of serious adverse events in the control group, but as noted for all adverse events whether serious or not, 13 or 15% was reported for the Dextrose group compared to 10 or 11% for the Icodextrin group.

### Other Adverse Reactions

135 patients reported adverse reactions; 77 Icodextrin (85.6%) versus 58 control (68.2%),  $p=0.006$ . Headache, rash and exfoliative dermatitis were more frequently reported in the Icodextrin group. The sponsor notes that rash and exfoliative dermatitis have been ascribed to the use of Icodextrin in the literature.

No difference between cohorts in the incidence of edema during treatment was noted.

**Laboratory Findings**

Significant changes from baseline values in each group and between groups were noted in the sponsor's chart:

Lab Assay	Visit	Treatment Group	Baseline @	Data		Change from Baseline @		p Betw
			Mean	N	Mean	Mean	p W/in	
SODIUM (MMOL/L)	Week 4	Control	137.988	82	138.061	0.073	0.860	<0.001
		Icodextrin	137.543	81	134.852	-2.691	<0.001	
CHLORIDE (MMOL/L)	Week 4	Control	95.317	82	96.134	0.817	0.031	<0.001
		Icodextrin	95.049	81	93.494	-1.556	<0.001	
CHOLESTEROL (MMOL/L)	Week 4	Control	5.481	82	5.435	-0.046	0.519	0.004
		Icodextrin	5.187	81	4.905	-0.282	<0.001	
AST (SGOT) (U/L)	Week 4	Control	20.500	82	19.931	-0.549	0.359	0.002
		Icodextrin	20.175	81	16.827	-3.313	<0.001	
AMYLASE (U/L)	Week 4	Control	100.695	82	98.012	-2.683	0.307	<0.001
		Icodextrin	103.086	81	16.136	-86.951	<0.001	
.ALK PHOS (U/L)	Week 4	Control	87.585	82	84.305	-3.280	0.075	<0.001
		Icodextrin	99.284	81	113.346	14.062	<0.001	

@ BASELINE is the Week 0 value.  
 p W/in= p-value from the within treatment group paired t-test for significant mean change from baseline.  
 p Betw= Baseline (Week 0): p-value from analysis of variance testing for significant differences across treatment group means.  
 Post-baseline (Treatment: Wks 2,4): p-value from analysis of covariance testing for significant differences across treatment groups for mean changes.

The sponsor claims that the decrease in sodium and chloride is dilutional due to the osmotic effect of Icodextrin and metabolites in the blood that drew water from the intracellular to intravascular compartment. While the slight reduction in cholesterol for the Icodextrin treated patients had been previously reported, it was not thought to be of clinical significance nor is a mechanism for this effect suggested. The slight decline in AST had not been previously reported had not been previously seen, but was not thought to be of clinical significance and the AST values were all within the normal range. The decline in serum amylase was ascribed to assay interference, and was previously reported as due to competition by Icodextrin for the substrate used in the assay. The increase in serum alkaline phosphatase had been previously reported in the PRO-RENAL study, was not associated with changes in other liver enzymes per the sponsor, and was not explained by assay interference. No explanation was proposed by the sponsor. Another significant shift from baseline to either higher or lower levels was found in the platelet counts for the Icodextrin group. The shifts however were modest and not to levels of clinical concern. There were changes from baseline glucose in both cohorts mainly from high to normal with no significant difference between cohorts. HgA1C remained normal for both cohorts.

Finally it should be noted that some patients completing the study entered the long-term safety study, RD-97-CA-131.

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**2. RD-97-CA-131:** This was a 52 week randomized, double-blind prospective safety study in 287 ESRD patients undergoing CAPD or APD. The study began on 4/1 98 and ended on 3/17/00. The original protocol was amended twice after study initiation. On 8/13/98 the protocol was amended to increase enrollment to allow inclusion of 60 patients from a European study that was never initiated, and on 1/29/99 to increase enrollment by 75 patients to include patients from study RD-97-CA-130 on the same assignment as designated in that study. The products involved were the same as described above for study RD-97-CA-130.

The primary endpoints were safety endpoints including mortality rates, changes in membrane transport characteristics, adverse reactions, laboratory abnormalities, clinical signs such as edema. The protocol specified reasons for removal of patients from therapy or assessment. These included withdrawal due to adverse event, protocol deviation, transplantation, transfer to hemodialysis and death. For patients terminating prematurely follow-up evaluation was to be completed no more than two weeks following the last dose administered.

No efficacy data was collected, but QoL questionnaires (KDQoL and SF-35) at baseline and at 13, 26, 39 and 52 week timepoints were added and evaluated for those who completed these at baseline and week 52. The sizing of the study was based on mortality estimates for the two groups with the hypothesis being that the mortality rates would be comparable. Mortality rates were to be calculated by determining number of deaths of any patient during the treatment or follow-up periods of the study, and comparing the rates for each group. In the 1/29/99 amendment a secondary analysis of mortality was added which was to do a survival analysis of time to death using a logrank test.

The schedule of study procedures was:

VISIT NUMBER WEEK	SCREENING PERIOD	BASELINE	TREATMENT PERIOD (DIANEAL® OR ICODEXTRIN) 52 WEEKS			
	-1	0	1	2	3	4
	-2	0	13	26	39	52
Intervals	7d ± 7d	1d	13wk 1w	13wk 1w	13wk 1w	13wk 1w
Informed Consent	X					
Selection Criteria	X					
Serum hCG <sup>1</sup>	X					
Medical History	X	X				
Physical Exam		X				X
Vital Signs		X	X	X	X	X
KDQoL Evaluation		X	X	X	X	X
Lab Analyses <sup>2</sup>		X	X	X	X	X
Chest X-ray		X				X
Concomitant Meds		X	X	X	X	X
Adverse Events	X <sup>3</sup>	X	X	X	X	X
Review Compliance		X	X	X	X	X
Randomization		X				
PET		X		X <sup>4</sup>		X <sup>4</sup>
24-hour Urine Collection		X		X		X
Plasma icodextrin and metabolites <sup>5</sup>		X	X	X	X	X
Hb A <sub>1c</sub> <sup>6</sup>		X	X	X	X	X

<sup>1</sup> Women of childbearing potential.

<sup>2</sup> To include biochemistry, hematology with differential and platelets, and osmolality.

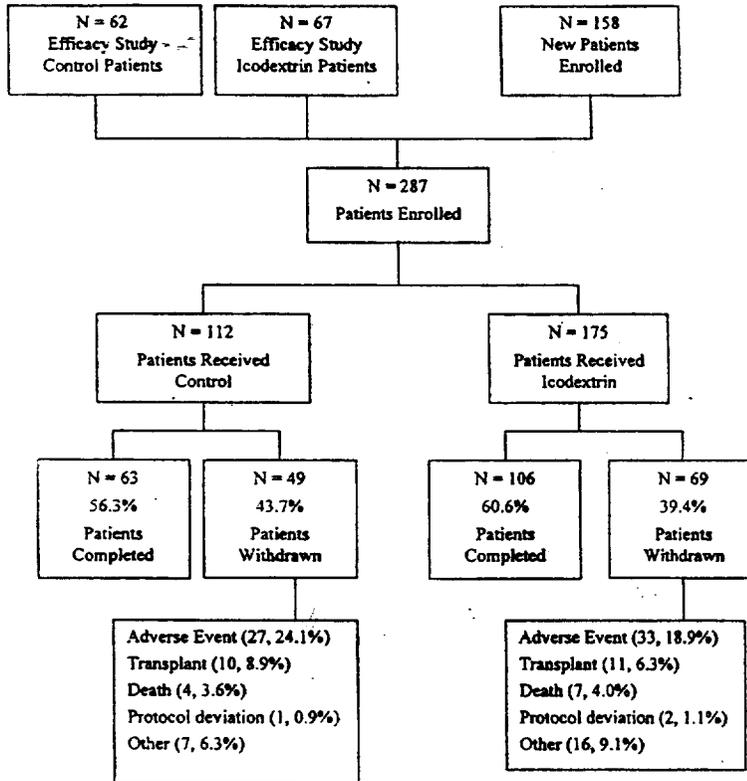
<sup>3</sup> These will be considered pre-existing conditions.

<sup>4</sup> The long dwell preceding the PET at the Week 26 and Week 52 Visits will be standardized to Dianeal® for all patients. The sample for icodextrin and metabolites that correlates with these visits must be drawn at the end of any investigational product long dwell in the week preceding the visit.

<sup>5</sup> Diabetic patients only.

<sup>6</sup> The icodextrin metabolites blood sample must be drawn at the end of the long dwell long prior to dialysis.

158 new patients were randomized and enrolled. 129 patients from other studies as described above were included in the study but not rerandomized. The disposition of subjects in the study was:



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Baseline demographics for the 287 patients entered into the study were:

	Control Group		Icodextrin Group		All Patients		p-Value
<b>AGE</b>							0.337*
N	112		175		287		
Mean ± SE	55.1 ± 1.23		53.5 ± 1.05		54.1 ± 0.80		
Min - Max	25 - 86		22 - 83		22 - 86		
	N	Percent	N	Percent	N	Percent	
<b>GENDER</b>							0.160*
Male	50	44.6	93	53.1	143	49.8	
Female	62	55.4	82	46.9	144	50.2	
Totals	112	100.0	175	100.0	287	100.0	
<b>RACE</b>							0.976**
Caucasian	70	62.5	110	62.9	180	62.7	
Hispanic	5	4.5	7	4.0	12	4.2	
Asian	4	3.6	9	5.1	13	4.5	
Black	31	27.7	46	26.3	77	26.8	
Other	2	1.8	3	1.7	5	1.7	
Totals	112	100.0	175	100.0	287	100.0	

\* Analysis of Variance used to test for treatment differences.

\* Pearson Chi-Square test used to test for treatment differences.

\*\* Fisher Exact test used to test for treatment differences because >20% of the cells had expected counts <5.

Primary renal diagnoses were balanced for the two cohorts:

	Control Group		Icodextrin Group		All Patients		p-Value
	N	%	N	%	N	%	
<b>Primary Renal Diagnosis</b>							0.660**
Diabetic Nephropathy	39	34.8	53	30.3	92	32.1	
Hypertensive Nephropathy	24	21.4	40	22.9	64	22.3	
Glomerulonephritis	20	17.9	27	15.4	47	16.4	
Polycystic Kidney Disease	3	2.7	7	4.0	10	3.5	
Interstitial Nephritis	0	0.0	6	3.4	6	2.1	
Obstructive Nephropathy	1	0.9	2	1.1	3	1.0	
Autoimmune Disease	4	3.6	5	2.9	9	3.1	
Other	21	18.8	35	20.0	56	19.5	
<b>TOTALS</b>	112	100.0	175	100.0	287	100.0	

\*\* Fisher Exact test used to test for treatment differences because >20% of the cells had expected counts of <5.

References: Table 14.1-1; Appendix 16.2.4.

As per the sponsor, the number of patients remaining in the study at the scheduled visits were:

Visit	Treatment Group		Total
	Control	Icodextrin	
	N	N	N
Baseline	112	175	287
Week 2 Visit	103	147	250
Week 4 Visit	103	147	250
Week 13 Visit	94	143	237
Week 26 Visit	83	130	213
Week 39 Visit	70	111	181
Week 52 Visit	62	104	166

References: Table 14.1-12; Appendix 16.4.

Exposure to study drug calculated from first dose to discharge or time in study was:

Time in Study	Control Group		Icodextrin Group		All Patients	
	N	Percent	N	Percent	N	Percent
≤ 2 weeks	1	0.9	5	2.9	6	2.1
> 2 - ≤ 4 weeks	2	1.8	7	4.0	9	3.1
> 4 weeks - ≤ 3 months	13	11.6	18	10.3	31	10.8
> 3 - ≤ 6 months	12	10.7	16	9.1	28	9.8
> 6 - ≤ 9 months	13	11.6	18	10.3	31	10.8
> 9 - < 12 months	10	8.9	10	5.7	20	7.0
12 months	61	54.5	101	57.7	162	56.4

References: Table 14.3.1; Appendix 16.4.

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### Mortality

The protocol called for a 30 day follow-up post-withdrawal or completion, In the original submission, it was stated that 5 patients in the control group and 13 in the Icodextrin group had died. This count was based on deaths occurring during the study or 30 days following the study or withdrawal. The sponsor's initial listing and brief synopsis of each patient who died follows:

Pt. #	Age/Sex/Race*	Days in Study	Adverse Events with Outcome "Death"
<b>CONTROL (n=5)</b>			
11102	59 / F / C	160	Cellulitis, cardiac arrest, hypoalbuminemia, wheezing
21205	66 / M / C	223	Cardiac arrest, cold feet, anorexia, constipation, decreased creatinine clearance, peripheral edema, bone pain, dyspnea, pruritus, skin disorder
22102	45 / F / C	303	Back pain, bowel obstruction, stomach ulcer, aspiration pneumonia, nervousness, hypoproteinemia, hypocholesterolemia, hypokalemia, hyponatremia
35101	58 / F / C	113	MI, hypoproteinemia
42301*	63 / F / C	367	CHF, heart failure, pneumonia, hypothyroid, skin ulcer
<b>ICODEXTRIN (n=13)</b>			
06102	46 / M / B	78	Retroperitoneal hemorrhage, syncope, electrolyte abnormalities, uremia, ileus, abnormal thinking, peritonitis, vascular disease, hypotension, cardiovascular disease, anemia, increased alkaline phosphatase, decreased weight, polycystic kidney disease, edema, increased AST
11501*	46 / M / C	133	Gangrene, sepsis, heart arrest, anemia, hypoproteinemia, neuropathy
18106	47 / F / B	148	Diabetic coma, heart arrest, cardiac murmur
22106*	59 / M / C	226	Sepsis, monilia, coronary artery disease, calcium disorder, hyperphosphatemia, hypocalcemia, dehydration, increased urea nitrogen, rash, cardiovascular disease, acidosis
22202	48 / M / C	324	Peritonitis, MI, stool abnormality, depression, insomnia, high serum osmolality, hyperphosphatemia, increased urea nitrogen, hypoproteinemia
26503*	63 / M / A	15	Sepsis
27102	65 / M / B	169	Heart arrest
30302	77 / F / C	164	CVA, peritonitis, anemia
32501*	68 / M / C	108	Heart arrest, artery occlusion, genital edema
35401*	82 / M / C	206	Pneumonia, CVA, diabetes mellitus
42302	63 / F / C	36	Hemorrhagic gm shock, MI, angina, intestinal necrosis, pneumonia, peripheral vascular disease, bursitis, peripheral neuritis, retinal disease, fibrocystic breasts
45401*	49 / M / C	15	Heart arrest, peritonitis, anemia, rash, stool abnormality, increased alkaline phosphatase, alopecia
62501	60 / F / B	49	Death secondary to MI

F=female, M=male, B=black, C=Caucasian, A=Asian. \* CABG=coronary artery bypass graft, CHF=congestive heart failure, CVA=cerebrovascular accident, MI=myocardial infarction. \*Patients who expired during the follow-up period.

10 of the 13 deaths on Icodextrin died before 6 months, while 2 of the 5 control patients died in that timeframe.

Of the Icodextrin patients who died 8 (62%) were diabetics compared to 1 (20%) in the Dextrose group. Alkaline phosphatase elevations were associated with transaminase elevations in 3 of the Icodextrin patients who died. History of hypertension and cardiovascular disease was frequently present in both cohorts. 5 Icodextrin patients who died had an episode of hypotension documented compared to 1 in the Dextrose group, however visits for evaluation in this study were infrequent.

The results for this initial mortality result were:

Treatment Group	Number Patients	Number Deaths	Percent Died	Quartiles for Survival (Days)			Mean Times to Death and 90% Confidence Intervals (Days)				p-Value*
				25th %	Median	75th %	Mean	Std Err	Lower	Upper	
Control	112	5	4.5	395	395	N/A	385.8 #	5.21	377.3	394.4	0.336
Icodextrin	175	13	7.4	N/A	N/A	N/A	343.3 #	5.48	336.3	354.1	
TOTAL	287	18	6.3	N/A	N/A	N/A	372.8 #	4.14	372.9	385.6	

\* p-Value is from the LogRank test comparing the survival curves between groups.  
 # The mean and standard error were underestimated because the largest observation was censored.  
 N/A: there were not enough deaths to estimate this quartile.

Mortality Rates (per Month and per Year) Based on Poisson Estimation

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	112	1027.3	5	0.005	0.000	0.128	0.06	0.08	1.44
Icodextrin	175	1600.3	13	0.008	0.000	0.156	0.10	0.09	1.88

90% Confidence Intervals are presented as specified in the protocol to estimate whether the two drugs had similar mortality risk associated with their use. Based on the initial results, it could not be concluded that the risk was similar, although the numerical difference was not statistically significant.

At the October 19, 2000 CRDAC meeting it was suggested that for the mortality analysis follow-up of all randomized patients should be done for the 52 week duration of the trial plus 30 days.

The sponsor therefore amended the protocol to provide a 13 month follow-up for all patients.

In the March 20, 2001 submission the sponsor provided final mortality results which included follow-up results on all but 3 of the randomized subjects. In this new tally it was noted that 16 patients had died (9-Icodextrin, 7-Control) in addition to the 18 already reported. A brief narrative for each of the new patients reported dead follows. A star following the patient number indicates that the death occurred later than 13 months post-enrollment of follow-up.

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**Patients assigned to Icodextrin:**

02401 was a 48 year old female Caucasian with type I diabetes. She entered on 12/14/98 and was withdrawn on 2/3/99 for pericarditis. She died on 6/7/99 from a CVA including intracranial hemorrhage.

19503 was a 50 year old Black male with hypertension who entered on 2/16/99 (BP 90/70). The patient was withdrawn on 4/20/99 due to a rash and itching (BP 118/60). The patient died on 11/21/99 of some unspecified cardiac problem.

24204\* was a 69 year old male Caucasian with type I diabetes who entered on 9/17/98 with a BP 141/68. On 11/20/98 complaints of hypotension, dizziness and chest pain were noted. The patient withdrew on 4/9/99 due to peritonitis, and died on 1/19/2000 of cardiac arrest. Death occurred after the 13 month post-enrollment period being considered.

24502\* was a 62 year old male Caucasian who entered on 8/17/98 and was withdrawn on 9/12/98 due to appendicitis. He died on 7/21/2000 from cardiac arrest.

32301 was a 37 year old female Caucasian with type I diabetes. She entered on 2/16/99, had a myocardial infarction on 4/7/99 and was noted to have a problem with diabetic control on 5/20/99. She withdrew on 6/3/99 for muscle aches, and died on 12/5/99 from diabetes, severe peripheral vascular disease and withdrawal from dialysis.

35301 was a 70 year old female Caucasian with type II diabetes and hypertension. She entered 10/16/98, and withdrew on 1/14/99 after her husband's death. She died 3/20/99 of renal failure.

38102 was an 82 year old male Caucasian with type II diabetes. He entered on 10/27/98 (BP 140/70), and was noted to have hypotension on 11/4/98. On 5/10/99 fluid overload was found, and the patient was withdrawn on 5/20/99 for membrane failure. The patient died of ESRD on 7/9/99.

38103 was a 74 year old male Hispanic with hypertension. He entered on 10/27/98 (BP 130/80), and developed hypotension and dehydration on 6/22/99. He was withdrawn for a cardiac mass on 7/7/99, and died on 10/25/99 with peripheral vascular disease noted.

61603 was a 66 year old male Caucasian with hypertension. He entered 11/13/98 (BP 170/80), and withdrew for joint aches on 1/12/99. He died on 6/20/99 of cardiac arrest.

**Patients assigned to control:**

01501 was a 50 year old Caucasian female with type I diabetes. She entered on 8/17/98, was withdrawn on 3/5/99 for hypoglycemia, and died on 4/13/99 from unknown cause.

15202 was a 42 year old Black female with type II diabetes. She entered on 7/24/98 and was withdrawn on 8/15/98 for peritonitis. She died on 12/17/98 from unknown cause.

24202\* was a 50 year old Black male with hypertension. He entered on 7/29/98 (BP 162/78), and died 12/9/99 of cardiac arrest/arrhythmia.

24501\* was a 60 year old Caucasian male with type I diabetes. He entered on 7/31/98, and withdrew on 9/23/98 for peritonitis. He died on 9/10/99 from cardiac arrest.

30601\* was a 69 year old Caucasian male with diabetes who entered on 11/16/98 and withdrew on 12/9/98 for unresolved peritonitis. He died on 5/26/00, no cause given.

32401 was a 64 year old Black male who entered on 1/14/99, withdrew on 10/14/99 for peritonitis, and died 1/7/2000 from cardiac arrest.

43403 was a 60 year old male Caucasian with type II diabetes. He entered 3/8/99, withdrew 7/23/99, and died 3/2/2000 from multisystem organ failure.

Although 16 new deaths were reported (7 on control and 9 on Icodextrin), only 11 (4 on control and 7 on Icodextrin) occurred 13 months post-enrollment. Therefore, the sponsor's analysis included 29 deaths: 20 (11.4%) randomized to Icodextrin and 9 (8.0%) to control. With these additional cases, the number of diabetics was 12 (60%) in the Icodextrin mortality group and 4 (44%) in the Dextrose group.

The sponsor provided a variety of analyses.  
 Their survival analysis indicating days to death or censoring was:

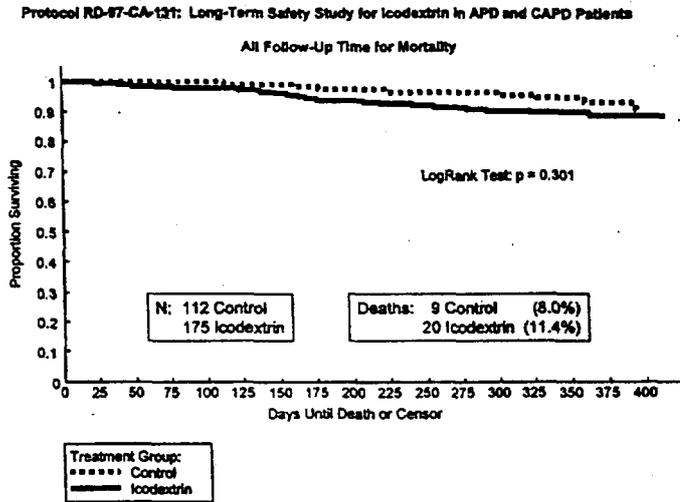


Table 1: Mortality Analysis Including Additional Follow-up Data  
 Based on Survival Times in Days -- Survivors Have Censored Times

Treatment Group	Number Patients	Number Deaths	Percent Died	Quartiles for Survival (Days)			Mean Times to Death and 95% Confidence Intervals (Days)			p-Value*	
				25th %	Median	75th %	Mean	Std Err	Lower		Upper
Control	112	9	8.0	N/A	N/A	N/A	384.8 #	4.40	376.2	393.4	0.301
Icodextrin	175	20	11.4	N/A	N/A	N/A	343.9 #	5.07	333.9	353.8	
TOTALS	287	29	10.1	N/A	N/A	N/A	376.6 #	3.86	369.0	384.1	

\* p-Value is from the LogRank test comparing the survival curves between groups.  
 # The mean and standard error were underestimated because the largest observation was censored.  
 N/A: There were not enough deaths to estimate this quartile.

Mortality rates per-month and per-year with 90% confidence intervals were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month <sup>@</sup>			Rates per Year <sup>@</sup>		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	112	1356.1	9	0.007	0.000	0.141	0.08	0.08	1.69
Icodextrin	175	2099.6	20	0.010	0.000	0.174	0.12	0.08	2.09

<sup>@</sup> the estimated mean and 90% confidence interval are displayed.

Table 3: Differences Between Mortality Rates (per Month and per Year) Based on Poisson Estimation  
 Equivalence of Icodextrin and Control Based on Ninety Percent (90%) Confidence Intervals

Icodextrin	Control	Difference	Std Error of Difference	Equivalence Based on Deaths per Month		Equivalence Based on Deaths per Year		
				Lower 90%	Upper 90%	(Ico - Cntl)	Lower 90%	Upper 90%
Mean	Mean	(Ico - Cntl)	Difference	Lower 90%	Upper 90%	(Ico - Cntl)	Lower 90%	Upper 90%
0.010	0.007	0.003	0.0031	-0.002	0.008	0.040	-0.022	0.102

Since there was some numerical difference in mortality rates suggesting a possible increased risk with Icodextrin, numerous subgroup analyses were done. These should be considered exploratory, and since the overall result was inconclusive, such further analyses should be considered with more scepticism than usual.

There were 4 prespecified randomized strata: 1) APD/2L, APD/2.5L, CAPD/2L, and CAPD/2/5L. The results for each stratum with 90% confidence intervals follows.

**APD MORTALITY**

77 patients underwent APD; 41 assigned to Icodextrin and 36 to control. There were 40 males, 37 females with a mean age of 53.5 years. 52 were Caucasian, 19 Black, 4 Asian and 1 Hispanic. 22 had diabetic nephropathy, 17 hypertensive nephropathy, 12 glomerulonephritis, 3 autoimmune disease and 23 other. 22 were Canadians. The demographics were well balanced between treatments.

Of these 77 patients, 50 completed the study, 5 withdrew for transplantation, 13 for an adverse experience, 1 for a protocol violation, 4 for other reasons, and 4 died in the per-protocol analysis.

In most respects the APD cohort behaved similarly to the CAPD cohort, though the sponsor notes that there was less evidence of any favorable trend in weight maintenance for Icodextrin. Also, comparing the Icodextrin CAPD group with the APD group, larger decreases in blood glucose levels in the APD Icodextrin group were noted.

The mortality rates with 90% CIs were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month <sup>ⓐ</sup>			Rates per Year <sup>ⓐ</sup>		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	36	428.8	4	0.009	0.000	0.168	0.11	0.00	2.02
Icodextrin	41	469.4	5	0.011	0.000	0.180	0.13	0.00	2.17

<sup>ⓐ</sup> the estimated mean and 90% confidence interval are displayed.

For the APD/2L stratum;

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month <sup>ⓐ</sup>			Rates per Year <sup>ⓐ</sup>		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	23	272.3	3	0.011	0.000	0.184	0.13	0.00	2.20
Icodextrin	30	339.3	4	0.012	0.000	0.190	0.14	0.00	2.28

<sup>ⓐ</sup> the estimated mean and 90% confidence interval are displayed.

For the APD/2.5L stratum:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month <sup>ⓐ</sup>			Rates per Year <sup>ⓐ</sup>		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	13	156.3	1	0.006	0.000	0.130	0.08	0.00	1.66
Icodextrin	11	129.9	1	0.008	0.000	0.152	0.09	0.00	1.82

<sup>ⓐ</sup> the estimated mean and 90% confidence interval are displayed.

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**CAPD MORTALITY**

210 patients underwent CAPD. 76 were assigned to Dextrose for the long-dwell, 134 were assigned to Icodextrin. The mortality rates for this cohort using the per-advisory committee follow-up database were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month <sup>@</sup>			Rates per Year <sup>@</sup>		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	76	927.3	5	0.005	0.000	0.126	0.06	0.00	1.51
Icodextrin	134	1540.3	15	0.010	0.000	0.172	0.12	0.00	2.06

<sup>@</sup> the estimated mean and 90% confidence interval are displayed.

For the CAPD/2L stratum, the results were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month <sup>@</sup>			Rates per Year <sup>@</sup>		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	34	413.0	2	0.005	0.000	0.119	0.06	0.00	1.43
Icodextrin	75	862.9	9	0.010	0.000	0.178	0.13	0.00	2.14

<sup>@</sup> the estimated mean and 90% confidence interval are displayed.

For the CAPD/2.5L stratum, the results were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month <sup>@</sup>			Rates per Year <sup>@</sup>		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	42	514.4	3	0.006	0.000	0.131	0.07	0.00	1.58
Icodextrin	59	677.3	6	0.009	0.000	0.164	0.11	0.00	1.96

<sup>@</sup> the estimated mean and 90% confidence interval are displayed.

Some patients entered from study 130 They continued on the assignment they were randomized to in that study and had successfully completed the 4-week treatment period of that study. To explore the mortality results of that cohort versus the newly randomized patients who entered study 131, the following analyses were done.

**STUDY 130 PATIENTS**

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month <sup>@</sup>			Rates per Year <sup>@</sup>		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	62	733.9	5	0.007	0.000	0.143	0.08	0.00	1.71
Icodextrin	67	777.3	7	0.009	0.000	0.165	0.11	0.00	1.98

<sup>@</sup> the estimated mean and 90% confidence interval are displayed.

**STUDY 131 PATIENTS**

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month <sup>@</sup>			Rates per Year <sup>@</sup>		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	50	622.3	4	0.006	0.000	0.138	0.08	0.00	1.64
Icodextrin	108	1232.4	13	0.011	0.000	0.180	0.13	0.00	2.15

<sup>@</sup> the estimated mean and 90% confidence interval are displayed.

The mortality rate for the control patients was 8% for each cohort. For those taking Icodextrin the mortality rate was 10.5% for study 130 patients, and 12% for study 131 patients. The difference is not large enough to suggest that results would have been significantly different had all new patients entered study 131.

**PD-2 and PD-4 MORTALITY**

One requested analysis was to compare mortality in those taking PD-2 electrolytes versus PD-4 electrolytes in the other exchanges. As previously stated, PD-4 has slightly less calcium chloride than PD-2, and might be selected for a patient who had elevated serum calcium. Since Icodextrin is supplied with PD-2 electrolytes only, during the long-dwell that patient would get the slightly greater amount of calcium chloride in that formulation.

The number taking PD-2 or PD-4 at entry was:

	U.S.		Canada	
	Control N (%)	Icodextrin N (%)	Control N (%)	Icodextrin N (%)
PD-2	42 (50%)	58 (45%)	0 (0%)	0 (0%)
PD-4	42 (50%)	71 (55%)	28 (38%)	46 (62%)

The mortality rate for those taking PD-2 at baseline was:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month <sup>@</sup>			Rates per Year <sup>@</sup>		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	42	502.6	4	0.008	0.000	0.153	0.10	0.00	1.36
Icodextrin	58	673.9	4	0.006	0.000	0.133	0.07	0.00	1.59

<sup>@</sup> the estimated mean and 90% confidence interval are displayed.

For those taking PD-4 at baseline the mortality rates were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month <sup>@</sup>			Rates per Year <sup>@</sup>		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	70	853.5	5	0.006	0.000	0.132	0.07	0.00	1.38
Icodextrin	117	1335.7	16	0.012	0.000	0.192	0.14	0.00	2.36

<sup>@</sup> the estimated mean and 90% confidence interval are displayed.

For the Icodextrin patients taking PD-2 at baseline the mortality rate was 6.9% versus 13.7% in those taking PD-4.

**CANADIAN AND US MORTALITY**

Since Canadians took only PD-4 at baseline a tabulation of their mortality rate was requested:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month <sup>@</sup>			Rates per Year <sup>@</sup>		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	28	338.1	2	0.006	0.000	0.132	0.07	0.00	1.59
Icodextrin	46	527.1	8	0.015	0.000	0.218	0.18	0.00	2.61

<sup>@</sup> the estimated mean and 90% confidence interval are displayed.

Their mortality rate was 17.3% on Icodextrin. Control mortality rate here was 7.1%.

The US results were also calculated:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month <sup>@</sup>			Rates per Year <sup>@</sup>		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	84	1018.0	7	0.007	0.000	0.143	0.08	0.00	1.72
Icodextrin	129	1482.5	12	0.008	0.000	0.156	0.10	0.00	1.87

<sup>@</sup> the estimated mean and 90% confidence interval are displayed.

**DIABETIC MORTALITY**

Since many of those who died were diabetic, a comparison of mortality rates for diabetes and no diabetes at baseline was requested. For diabetics these results were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	51	625.9	4	0.006	0.000	0.138	0.08	0.00	1.65
Icodextrin	68	754.4	10	0.013	0.000	0.203	0.16	0.00	2.43

@ the estimated mean and 90% confidence interval are displayed.

For nondiabetics results were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	61	730.2	5	0.007	0.000	0.143	0.08	0.00	1.72
Icodextrin	107	1255.2	10	0.008	0.000	0.155	0.10	0.00	1.86

@ the estimated mean and 90% confidence interval are displayed.

The mortality rate for those with diabetes at baseline and assigned to Icodextrin was 14.7% compared to 9.3% in nondiabetics assigned to Icodextrin.

None of these subgroup results are significant, and any hypotheses that might be considered would be speculative, needing prospective testing, at best.

**QUALITY OF LIFE**

The kidney disease quality of life (KDQoL) and short form 36 (SF-36) questionnaires were used. The KDQoL form contained a 35 symptom/problem list. SF-36 had 36 questions about the patient's general health covering mental and physical health. The protocol did not specify how these results were to be interpreted.

The KDQoL results for the 66 patients (41-Icodextrin and 25-Dextrose) who completed baseline and 52 week questionnaires as well as for 138 patients (63-Icodextrin, 75-Dextrose) for whom there was some data. There were no significant differences in overall score between treatments for either the KDQoL or SF-36 instruments for either cohort. Nor were changes from baseline to week 52 for individual questions such as soreness of muscles, trouble breathing significantly different between treatments.

A technical report from the \_\_\_\_\_ analyzed the data for clinically significant differences. They state "The determination of a clinically meaningful change score (also referred to as a minimally important difference) is a relatively recent pursuit by HRQOL scientists, and, as such, more research will be required before validated rules can be established for all HRQOL measures."

They note that guidelines from the SF-36 developer suggest that a 5-10 point change in any subscale is clinically meaningful, and using a —5 point difference between groups they provided the following results from the KDQoL data:

Treatment Advantage <sup>†</sup> for Problem/Symptom Items	
Icodextrin	Dianeal
m. Dry skin	e. Ache in bones
u. Lack of strength	h. Headaches
x. Numbness in hands or feet	n. Trouble getting your breath
aa. Trouble concentrating or thinking	o. Shortness of breath
	s. Dry mouth
	t. Excessive thirst
	ee. Trouble sleeping

From the SF-36 data they provided the following:

Domains	Within Group		Between-Group
	Control	Icodextrin	Differences
Physical Functioning	-7.2	-6.5	0.7
Role-Physical	-20.8	-6.0	14.8 *
Bodily Pain	-3.3	2.4	5.7 *
General Health	-6.5	-1.5	5.0 *
Vitality	-0.2	-5.5	-5.3 **
Social Functioning	-4.5	-4.9	-0.4
Role-Emotional	-7.2	-2.2	5.0 *
Mental Health	0.4	-0.2	-0.6
Physical Component Summary	-4.1	-1.5	2.6
Mental Component Summary	0.0	-0.4	-0.4

\*Clinically meaningful difference favoring Icodextrin Group.

\*\*Clinically meaningful difference favoring Control Group.

Additionally, a health transition frequency summary based on responses to the question "compared to one year ago, how would you rate your health in general now?" was provided for those with baseline and week 52 responses.

Response	Control Group (n=25)		Icodextrin Group (n=40)		p-Value**
	n	%	n	%	
Much better now than one year ago	1	4.0%	12	30.0%	0.030
Somewhat better now than one year ago	7	28.0%	6	15.0%	
About the same as one year ago	13	52.0%	19	47.5%	
Somewhat worse now than one year ago	4	16.0%	2	5.0%	
Much worse now than one year ago	0	0.0%	1	2.5%	

\*KDQoL Question 3: Compared to 1 year ago, how would you rate your health in general now?

\*\*Chi-Square and, when appropriate, Fisher's Exact test. Reference: Appendix 16.2.9.

It is not clear why 40 Icodextrin patients rather than 41 are included in this analysis, but whatever nominal significance was claimed in this analysis was not present at weeks 13, 26 and 39.

### ADVERSE REACTIONS

Serious adverse reactions were noted in 86 (51.2%) Icodextrin and 57 (51.4%) Dextrose patients. Hospitalization was the reason for classifying these events as serious in over 80% of cases with lesser percentages due to death or the life-threatening nature of the event. Hospitalization rates were similar for the two groups (17.1% for Icodextrin patients and 21.4% for the Dextrose patients). Events such as peritonitis, nausea and vomiting, MI were frequently noted in these patients as they were for other adverse reactions reported in this study.

60 patients (18.9% Icodextrin patients; 24.1% Dextrose patients) discontinued the study for adverse events. Most of these withdrawals were due to peritonitis, infection, dehydration, 5 Icodextrin patients withdrew for rash compared to none in the Dextrose group. Rash was reported 13 times in the Dextrose group versus 37 times in the Icodextrin group.

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The frequencies of adverse reactions in the treatment and follow-up periods of the study was:

COSTART Body System	Control Group				Icodextrin Group			
	Mild	Mod	Sev	Total	Mild	Mod	Sev	Total
BODY GENERAL	148	137	30	315	283	207	41	531
CARDIOVASCULAR	42	60	20	122	64	89	27	180
DIGESTIVE	68	71	7	146	133	88	15	236
ENDO	12	2	0	14	7	7	0	14
HEMATOLOGIC AND LYMPHATIC	28	27	2	57	55	34	7	96
METABOLIC AND NUTRITION	141	112	17	270	213	116	13	342
MUSCULOSKELETAL	21	22	1	44	39	24	8	71
NERVOUS	48	36	1	85	54	51	3	108
RESPIRATORY	64	33	2	99	117	39	7	163
SKIN	53	38	3	94	68	47	3	118
SPECIAL SENSES	23	7	1	31	27	12	1	40
UROGENITAL	18	20	2	40	31	21	4	56
— TOTALS —	659	557	86	1302	1091	735	129	1955

All Adverse Events per patient after Baseline are counted.  
Mod= Moderate, Sev= Severe

While overall the percentages in each costart category were similar, for specific terms where there was at least a 5% difference in incidence between groups, there were numerical differences that in most cases favored Icodextrin.

COSTART BODY SYSTEM	Control Group N=112		Icodextrin Group N=175	
	N	Percent	N	Percent
BODY GENERAL				
Exit Site Infection	24	21.4	28	16.0
Headache	9	8.0	25	14.3
Allergic Reaction	9	8.0	5	2.9
CARDIOVASCULAR				
Hypotension	27	24.1	25	14.3
DIGESTIVE				
Nausea	9	8.0	25	14.3
METABOLIC AND NUTRITIONAL				
Hypoproteinemia	20	17.9	22	12.6
Hypokalemia	26	23.2	21	12.0
Edema Peripheral	20	17.9	11	6.3
RESPIRATORY				
Dyspnea	17	15.2	13	7.4
SKIN				
Rash	13	11.6	33	18.9
Skin Disorder	15	13.4	9	5.1

Only one event per patient per preferred term was counted.  
Events are ordered within each Body System from highest to lowest incidence rates within the Icodextrin Group.

**EDEMA**

Concerning edema, the sponsor claimed a significant difference in the "no edema" category favoring Icodextrin at weeks 26 and 39 but not at week 52. As can be seen from the sponsor's table with these results, the number of patients reporting varies from period to period.

Visit	Categories	Control Group		Icodextrin Group		All Patients		p-Value
		N	Percent	N	Percent	N	Percent	
Week 26	0	58	65.9	112	81.8	170	75.6	0.007 **
	+1	14	15.9	18	13.1	32	14.2	
	+2	11	12.5	6	4.4	17	7.6	
	+3	5	5.7	1	0.7	6	2.7	
	TOTALS	88	100.0	137	100.0	225	100.0	
Week 39	0	49	65.3	95	79.2	144	73.8	0.021 **
	+1	21	28.0	20	16.7	41	21.0	
	+2	5	6.7	1	1.7	7	3.6	
	+3	0	0.0	3	2.3	3	1.5	
	TOTALS	75	100.0	120	100.0	195	100.0	
Week 52	0	49	75.4	79	76.7	128	76.2	0.866 *
	+1	9	13.8	13	12.6	22	13.1	
	+2	7	10.8	10	9.7	17	10.1	
	+3	0	0.0	1	1.0	1	0.6	
	TOTALS	65	100.0	103	100.0	168	100.0	

\* Pearson Chi-Square test used to test for treatment differences.  
 \*\* Fisher Exact test used to test for treatment differences because > 20% of the cells had expected counts < 5.

As noted above, more adverse events termed edema were noted in patients on control versus Icodextrin.

**BODY WEIGHT**

The sponsor stated that body weight increases were observed in the Dextrose group throughout the study which were significantly different from the Icodextrin group which showed a slight gain only at week 4. Their conclusion was based on the following data:

Vital Sign	Visit	Treatment Group	Baseline <sup>Ⓢ</sup>		Data					Change from Baseline <sup>Ⓢ</sup>					p Betw			
			Mean	N	Mean	Std Err	Min	Median	Max	Mean	Std Err	p W/in	Min	Median		Max		
Body Weight Before Drain (kg)	Baseline	Control		81	79.46	1.85		79.10									0.976	
	(Week 0)	Icodextrin		136	79.33	1.34		79.80										
	Week 2	Control	74.71	48	76.99	2.60		77.85			0.75	0.27	0.007		0.30		0.009	
		Icodextrin	79.48	54	79.11	2.07		78.60			-0.35	0.27	0.211		-0.60			
	Week 4	Control	74.68	49	77.19	2.36		78.20			1.05	0.35	0.004		0.58		0.425	
		Icodextrin	79.75	56	80.74	2.07		81.53			0.60	0.33	0.077		0.20			
	Week 13	Control	79.97	76	80.90	2.00		80.20			0.83	0.37	0.022		0.40		0.005	
		Icodextrin	79.01	116	78.79	1.39		78.05			-0.51	0.31	0.098		-0.50			
	Week 26	Control	80.49	65	80.54	2.07		81.00			0.44	0.46	0.337		0.23		0.204	
		Icodextrin	78.70	111	78.45	1.39		78.30			-0.27	0.39	0.492		-0.15			
	Week 39	Control	80.64	58	81.59	2.21		81.00			1.00	0.60	0.100		0.70		0.182	
		Icodextrin	77.40	96	77.24	1.49		76.50			-0.06	0.56	0.916		0.50			
	Week 52	Control	79.93	47	81.60	2.30		80.60			2.33	0.79	0.005		1.95		0.022	
		Icodextrin	77.64	88	77.53	1.55		77.25			-0.03	0.61	0.960		0.90			

Ⓢ BASELIned is the Week 0 value.  
 p W/in= p-value from the within treatment group paired t-test for significant mean change from baseline.  
 p Betw= Baseline (Week 0); p-value from analysis of variance testing for significant differences across treatment group means;  
 Postbaseline (Treatment; Wks 2-52): p-value from analysis of covariance testing for significant differences across treatment groups for mean changes.

These, however, were the before drain data. While the after drain data are sparse, those results do not support the sponsor's conclusion.

Body Weight After Drain (kg)	Visit	Treatment Group	Baseline <sup>Ⓢ</sup>		Data					Change from Baseline <sup>Ⓢ</sup>					p Betw			
			Mean	N	Mean	Std Err	Min	Median	Max	Mean	Std Err	p W/in	Min	Median		Max		
Body Weight After Drain (kg)	Baseline	Control		31	77.35	2.90	51.80	77.60	111.50								0.471	
	(Week 0)	Icodextrin		39	74.87	2.00	53.60	73.20	105.50									
	Week 2	Control	71.94	14	72.07	4.28	50.00	66.90	110.50			-0.55	0.46	0.256	-3.00	0.00	1.82	0.206
		Icodextrin	71.29	13	74.93	4.73	53.50	76.10	108.00			0.59	0.76	0.454	-4.00	0.00	4.00	
	Week 4	Control	71.94	13	72.45	4.55	50.45	67.20	109.00			-0.28	0.49	0.573	-4.30	0.00	1.50	0.095
		Icodextrin	68.91	11	70.19	3.64	52.00	67.00	90.00			1.28	0.68	0.091	-1.60	0.80	5.40	
	Week 13	Control	73.21	18	75.31	3.79	48.63	77.85	113.00			0.89	1.28	0.496	-3.17	-0.90	18.60	0.655
		Icodextrin	71.99	25	72.63	2.62	50.60	72.00	99.60			0.63	0.68	0.363	-5.00	0.13	6.70	
	Week 26	Control	72.28	17	77.10	3.87	51.36	81.10	105.00			1.85	1.73	0.305	-9.10	0.45	20.00	0.738
		Icodextrin	73.95	18	75.64	3.60	50.90	78.00	102.80			1.09	1.18	0.373	-5.00	0.48	8.19	
	Week 39	Control	68.48	11	67.75	3.66	49.09	64.00	84.54			-1.31	1.23	0.314	-8.70	-0.40	4.20	0.861
		Icodextrin	71.44	13	75.00	3.69	48.70	77.27	99.50			-1.85	0.88	0.043	-3.00	-1.79	1.82	
	Week 52	Control	72.10	13	75.88	4.53	50.00	77.30	108.20			1.13	2.15	0.608	-12.20	-0.80	21.10	0.199
		Icodextrin	71.39	16	71.53	3.35	50.90	72.45	92.70			-2.36	1.15	0.070	-10.00	-1.90	2.27	

**Laboratory Findings**

The following chart provides the sponsor's assessment of significant changes from baseline in laboratory values over time. The week 4 baseline values include the data of patients from RD-97-CA-130 who were rolled over into study RD-97-CA-131.

Lab Assay	Visit	Treatment Group	Baseline Mean <sup>®</sup>	Data		Change from Baseline		p Betw	
				N	Mean	Mean	p W/in		
Sodium (mmol/L)	Week 4	Control	138.000	62	138.161	0.161	0.752	<0.001	
		Icodextrin	137.642	67	134.910	-2.731	<0.001		
	Week 13	Control	138.457	94	138.436	-0.021	0.957	<0.001	
		Icodextrin	138.224	143	135.748	-2.476	<0.001		
	Week 26	Control	138.321	81	137.963	-0.358	0.475	<0.001	
		Icodextrin	138.313	128	135.148	-3.164	<0.001		
	Week 39	Control	138.386	70	137.643	-0.743	0.191	<0.001	
		Icodextrin	138.396	111	134.604	-3.793	<0.001		
	Week 52	Control	138.349	63	138.381	0.032	0.957	<0.001	
		Icodextrin	138.433	104	135.596	-2.837	<0.001		
	Chloride (mmol/L)	Week 4	Control	95.097	62	95.774	0.677	0.149	<0.001
			Icodextrin	95.299	67	93.493	-1.806	<0.001	
Week 13		Control	95.702	94	96.351	0.649	0.115	<0.001	
		Icodextrin	95.944	143	94.021	-1.923	<0.001		
Week 26		Control	95.704	81	96.086	0.383	0.420	<0.001	
		Icodextrin	96.117	128	94.133	-1.984	<0.001		
Week 39		Control	95.643	70	96.314	0.671	0.198	<0.001	
		Icodextrin	95.964	111	93.991	-1.973	<0.001		
Week 52		Control	95.619	63	96.714	1.095	0.070	<0.001	
		Icodextrin	95.923	104	94.798	-1.125	0.007		

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Lab Assay	Visit	Treatment Group	Baseline <sup>a</sup> Mean	Data		Change from Baseline		p Betw	
				N	Mean	Mean	p W/in		
AST (SGOT) (U/L)	Week 4	Control	21.145	62	20.919	-0.226	0.763	0.009	
		Icodextrin	19.773	67	17.030	-2.697	0.004		
	Week 26	Control	21.901	81	22.000	0.099	0.936	0.006	
		Icodextrin	20.039	128	18.414	-1.575	0.073		
	Week 39	Control	21.814	70	22.771	0.957	0.567	0.008	
		Icodextrin	19.555	111	18.423	-1.073	0.209		
Amylase (U/L)	Week 4	Control	96.645	62	93.435	-3.210	0.298	<0.001	
		Icodextrin	100.254	67	15.522	-84.731	<0.001		
	Week 13	Control	95.468	94	91.351	-4.117	0.194	<0.001	
		Icodextrin	98.986	143	16.902	-82.084	<0.001		
	Week 26	Control	95.630	81	87.358	-8.272	0.029	<0.001	
		Icodextrin	99.664	128	17.305	-82.359	<0.001		
	Week 39	Control	96.957	70	90.686	-6.271	0.035	<0.001	
		Icodextrin	98.342	111	13.793	-84.550	<0.001		
	Week 52	Control	97.397	63	93.079	-4.317	0.262	<0.001	
		Icodextrin	101.317	104	14.288	-87.029	<0.001		
	Osmolality (mOsm/kg)	Week 39	Control	315.971	70	311.257	-4.714	0.023	0.007
			Icodextrin	315.945	110	316.882	1.009	0.557	
Alkaline Phosphatase (U/L)	Week 4	Control	88.532	62	85.452	-3.081	0.146	<0.001	
		Icodextrin	87.403	67	102.343	14.940	<0.001		
	Week 13	Control	92.817	94	91.266	-1.183	0.826	0.002	
		Icodextrin	86.150	142	100.923	15.179	<0.001		
	Week 26	Control	93.913	81	90.704	-2.738	0.630	0.002	
		Icodextrin	85.683	128	101.164	15.833	<0.001		

<sup>a</sup> Baseline is the Week 0 value. Baseline means are calculated from patients with observations at each respective visit.  
p W/in = p-Value from the within treatment group paired t-test for significant mean change from Baseline.  
p Betw = Baseline (Week 0); p-Value from analysis of variance testing for significant differences across treatment group means (p<0.01). Post Baseline (Treatment Weeks 13, 26, 39, 52); p-Value from analysis of covariance testing for significant differences across treatment groups for mean changes (p<0.01).

As adverse events hyponatremia or hypochloremia were reported for 6.9% of the Icodextrin patients and 4.5% of the Dextrose patients. Increased alkaline phosphatase was reported in 6.9% and 5.4% of the Icodextrin and Dextrose groups respectively. One Icodextrin patient had cholestatic jaundice associated with the elevated alkaline phosphatase. Two Icodextrin patients who died were reported to have had elevated alkaline phosphatase. No significant differences between treatments in platelet shifts were reported in this study, but slight reductions in cholesterol at several timepoints were noted for the Icodextrin group. The sponsor postulated that the increases in plasma osmolality were due to low molecular weight metabolites of Icodextrin.

While there was no significant difference in serum calcium levels between treatments over time in either this study or study 130, one could not rule out a detrimental effect in certain patients such as those with hypercalcemia. A review of the case report forms for those assigned to Icodextrin who had been on the low calcium PD4 solution before admission did not reveal data to suggest a problem due to use of the PD 2 solution for the long-dwell.

### PET and MTAC

Results for the Peritoneal Equilibrium Test (PET) and the Mass Transfer Area Coefficient (MTAC) were presented.

PET is a test of peritoneal membrane transport of solutes and water. Dialysis/Plasma (D/P) ratios of urea, creatinine and glucose were determined at weeks 0, 26 and 52. If peritonitis developed, a minimum of 30 days had to elapse between resolution of the peritonitis and the PET. The PET was used to calculate the MTAC that provides a measure of diffusive solute mass transport based on membrane permeability and surface area.

The PET D/P ratios were not significantly different for each timepoint between treatments.

For glucose at week 52 there was a suggestion of a difference in the MTAC results as follows:

Lab Assay	Visit	Treatment Group	Baseline <sup>a</sup>	Data			Change from Baseline <sup>a</sup>			pBetw
			Mean	N	Mean	SE	Mean	SE	pW/in	
MTAC for Creatinine	Baseline (Week 0)	Control		105	9.954	0.276				0.381
		Icodextrin		169	0.306	0.267				
	Week 26	Control	9.913	82	10.223	0.290	0.365	0.230	0.116	0.929
		Icodextrin	10.276	126	0.460	0.264	0.226	0.277	0.416	
	Week 52	Control	9.663	62	9.970	0.345	0.308	0.263	0.247	0.559
		Icodextrin	10.272	101	10.512	0.334	0.279	0.354	0.432	
MTAC for Urea	Baseline (Week 0)	Control		105	18.500	0.367				0.880
		Icodextrin		168	18.575	0.315				
	Week 26	Control	18.577	81	18.271	0.394	-0.163	0.420	0.698	0.784
		Icodextrin	18.690	126	18.523	0.380	-0.084	0.394	0.832	
	Week 52	Control	18.118	62	17.880	0.466	-0.238	0.461	0.607	0.436
		Icodextrin	18.561	101	18.550	0.473	0.026	0.543	0.961	
MTAC for Glucose	Baseline (Week 0)	Control		105	10.725	0.341				0.993
		Icodextrin		169	0.721	0.264				
	Week 26	Control	10.676	83	10.696	0.315	0.029	0.292	0.920	0.018
		Icodextrin	10.504	124	11.381	0.354	1.017	0.282	<0.001	
	Week 52	Control	10.339	62	10.899	0.436	0.560	0.398	0.164	0.197
		Icodextrin	10.192	99	11.378	0.385	1.263	0.343	<0.001	

<sup>a</sup> Baseline is the Week 0 Value. pW/in=p-Value from the within treatment group paired t-test for significant mean change from Baseline. pBetw=Baseline (Week 0): p-Value from analysis of variance testing for significant differences across treatment group means. Postbaseline (Treatment Weeks 26, 52): p-Value from analysis of covariance testing for significant differences across treatment groups for mean changes.

#### Comments

This safety study raises a serious question because of a unfavorable numerical mortality result suggesting that Icodextrin might increase the risk of death in ESRD patients compared to 2.5% Dextrose. While the difference in mortality was not statistically significant, neither does it support the conclusion that the two drugs are similar in terms of mortality risk.

The data were provided to support a clinical benefit related to Icodextrin administration, i.e. Quality of Life, edema status, and weight were not convincing due to incomplete data, inconsistency over time, and selection of timepoints, endpoints and conditions post-hoc.

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**3. ML/1B/001 (MIDAS):** This was an open, randomized study performed at 11 centers in the UK with a product called Dextrin 20 that was essentially the same drug product as the Icodextrin formulation used in studies 130 and 131. Eligible patients were those adults on CAPD for at least three months, using 3-4 exchanges per 24 hours and free of peritonitis and mechanical drainage complications for at least 1 month prior to entry. The primary endpoint was the comparison of the median volume of ultrafiltrate at weeks 4, 13 and 21 (called special weeks by the protocol) produced after the long-dwell 12 hour dialysis with Dextrin 20 or the Dextrose solution (concentrations of 1.5%, 2.5% or 4.5%) as used prior to randomization for the ITT population (last value carried forward). Other secondary analyses involved different timepoints (weeks 3, 12 and 20 using an 8 hour long-dwell time), bag sizes (1.5 or 2.0L), subsets of the ITT population, and efficacy evaluable populations using the Bonferroni correction. Other analyses were done of "weak" glucose concentration i.e. 1.36%, "medium" i.e. 2.3%, and "strong" i.e. 4.25% versus Dextrin 20.

209 patients were randomized, 103 to control and 106 to Dextrin 20. Some demographic features of the population were:

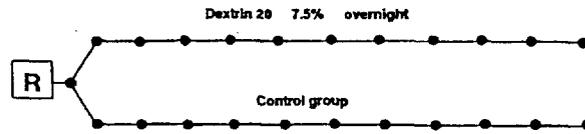
	Control n=103	Dextrin 20 n=106	Total n=209
Age, mean in years(SD)	55.2(15.0)	55.1(14.2)	55.2(14.6)
Male Female	65%/35%	66%/34%	66%/34%
Caucasian	93%	90%	91%
Diabetes(%)	11(10.7%)	15(14%)	26(12.4%)

The type and duration of renal disease was provided as follows:

**All Patients**

	Control	Dextrin 20	Total
<b>Number of Patients</b>	<b>103</b>	<b>106</b>	<b>209</b>
<b>Cause</b>			
Glomerulonephritis	16 (16%)	17 (16%)	33 (16%)
Polycystic Kidney Disease	10 (10%)	10 (9%)	20 (10%)
Hypertension	24 (23%)	24 (23%)	48 (23%)
Pyelonephritis	10 (10%)	11 (10%)	21 (10%)
Congenital	2 (2%)	0 (0%)	2 (1%)
Diabetes Mellitus	8 (8%)	11 (10%)	19 (9%)
Other	33 (32%)	33 (31%)	66 (32%)
<b>Duration (months)</b>			
Mean (s.d.)	96.0 (98.9)	98.0 (113.3)	97.0 (101.8)
Median	67.9	64.8	65.7
Minimum	4.1	4.3	4.3
Maximum	460.2	639.0	639.0
n	102	105	207

The plan for the study was:



Week	1	2	3	4	5	7	9	13	17	21	25	
Visit	1	2	3†	4†	5†	6	7†	8†	9	10†	11†	12
12 hr overnight exchange for 7 nights (week)				X (4)				X (13)		X (21)		
BP, weight	X	X	X	X	X	X	X	X	X	X	X	X
MEs* and symptoms	X	X	X	X	X	X	X	X	X	X	X	X
Medication/changes	X	X	X	X	X	X	X	X	X	X	X	X
Diary check		X	X	X	X	X	X	X	X	X	X	X
Physical check	X											X
Medical history	X											
Haematology & biochemistry		X		X		X		X	X	X	X	X
Plasma Dextrin 20		X				X‡		X‡				X
Fasting lipids		X										X
Eye, ECG, X-ray		X										X
R.E. tests§		X										X
Creatinine clearance		X										X

- R Randomisation
- § Optional
- † Dextrin 20 group only
- ‡ These visits may take place at the patient's home
- \* ME = Medical Event

The monitoring schedule for RD-97-CA-131, the long term US safety study described above, included scheduled visits for the newly randomized patients at baseline, week 13 and every 13 weeks to week 52. Those entering from study RD-97-CA-130 had data at 2 and 4 weeks post baseline from that earlier study. As can be seen from the chart above, the UK study design had a more frequent visit schedule, and at each visit medical events and CAPD symptoms were assessed which formed part of the safety database.

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The disposition of patients can be assessed from the chart below:

	Control	Dextrin 20
Number recruited	103	106
Number withdrawn permanently (up to/at Visit 2)	4 ( 4%)	10 ( 9%)
Loss of ultrafiltration	1	2
Problems with catheter	0	1
Apparently unrelated medical events	0	1
Patient wished to withdraw	1	2
Transplant	0	3
Other	2	1
Number in study at Visit 2	99	96
Number withdrawn temporarily	5 ( 5%)	11 (11%)
Number withdrawn permanently (after Visit 2)	28 (28%)	29 (30%)
Loss of ultrafiltration	1	3
Problems with catheter	1	1
Any adverse event	1	4
Patient out for 24 weeks	9	4
Patient wished to withdraw	3	4
Non-compliance	1	1
Transplant	5	6
Haemodialysis	2	2
Other	5	4
Number completing study	71 (72%)	67 (70%)

The case report forms included a temporary withdrawal form. Since patients were seen frequently where not only were diaries checked and symptoms elicited, where clinical circumstances indicated one temporary withdrawal period of up to a month to stabilize the patient on his/her usual pretrial CAPD regimen before reentering. To illustrate, patient 0608 was temporarily withdrawn on 6/21/91 for fluid overload, swollen ankles, shortness of breath and hypertension causing migraine, stabilized and reentered 7/15 91.

Results of the median ultrafiltrate volumes for the "total population and last values" at weeks 4, 13 and 21, where a 12 hour long-dwell time was used, were:

Special Week	n	Control Mean (s.d.)	n	Dextrin 20 Mean (s.d.)	Dextrin 20 - Control Difference in means (s.e.)	95% Confidence Interval
4	98	222.3 (420.9)	83	558.6 (284.8)	336.3 (54.8)	228.1 to 444.5
13	93	202.9 (408.6)	84	538.8 (283.4)	335.9 (53.4)	230.5 to 441.3
21	93	229.6 (416.8)	84	549.5 (288.8)	319.9 (54.5)	212.3 to 427.3

$p=0.73$  for test of non-constant treatment difference

$p<0.0001$  for test of overall treatment difference

At weeks 3, 12 and 20 where an 8 hour long-dwell time was used the overall results were similar.

This analysis subdivided by weak (1.36%) or medium or strong (2.27 or 3.84%) glucose concentrations suggested a larger benefit of Dextrin 20 versus those in the weak concentration group.

Special Week	n	Control Mean (s.d.)	n	Dextrin 20 Mean (s.d.)	Dextrin 20 - Control Difference in means (s.e.)	95% Confidence Interval
<b>Weak (1.36%/1.5%)</b>						
4	54	82.1 (342.5)	44	544.8 (296.4)	462.7 (65.5)	332.6 to 592.7
13	54	60.7 (334.0)	45	513.9 (289.0)	453.2 (63.5)	327.2 to 579.1
21	54	101.5 (349.9)	45	561.1 (293.3)	459.6 (65.7)	329.2 to 590.0
<b>Medium (2.27%/2.3%) or strong (3.86%/4.23%)</b>						
4	35	432.6 (453.6)	30	591.3 (246.5)	158.8 (92.8)	-26.6 to 344.1
13	35	405.4 (441.2)	30	593.3 (223.5)	187.9 (89.0)	10.0 to 365.8
21	35	413.6 (458.6)	30	552.5 (241.7)	138.9 (93.2)	-47.4 to 325.2

Weak : p = 0.93 for test of non-constant treatment difference  
p < 0.0001 for test of overall treatment difference

Medium/Strong : p = 0.63 for test of non-constant treatment difference  
p = 0.06 for test of overall treatment difference

The report does not provide the results for "medium" and "strong" glucose concentrations separately, and the literature report (Mistry et al: Kidney International, vol.46, 1994. Pp.496-503) gives the results as "weak: versus "strong" concentrations.

Regarding safety, there were 14 serious adverse events including 3 deaths; 2 in the Dextrose group and 1 in the Dextrin 20 group as detailed in the following chart:

	CONTROL		DEXTRIN	
M.I.	4	(0533) 0207* 0963* 0208	2	(0206) 0501
Cardiac failure	1	0317	1	0581**
Pneumonia	-		1	0724 ***
C.V.A.	-		2	0725# 0921
Severe hypertension	-		1	0902
Multiple emboli	1	0915	-	
Pulmonary embolism	-		1	(0913) @
	6		8	

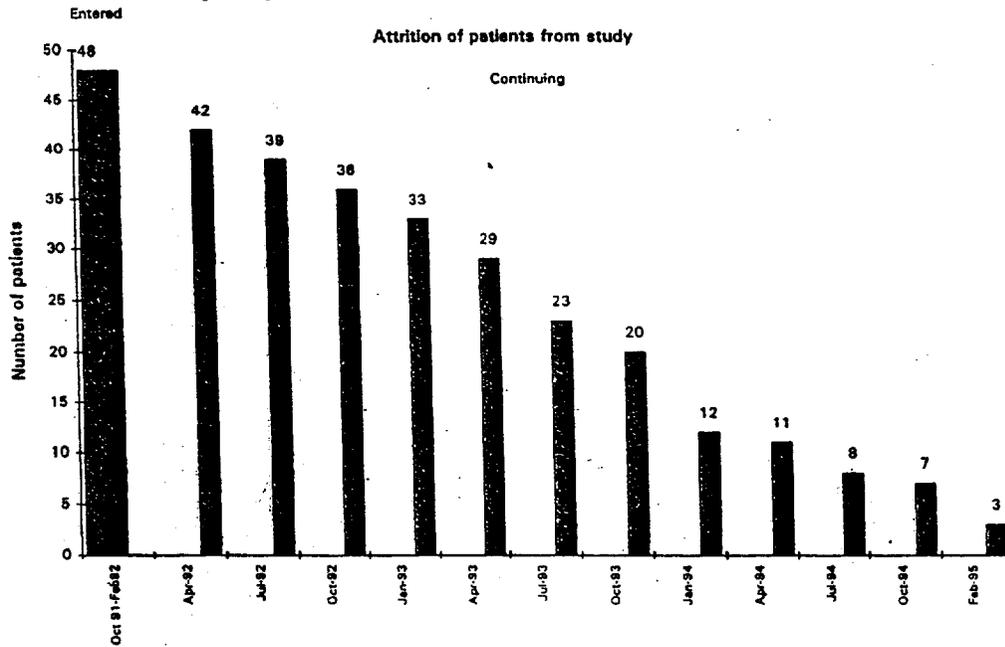
- \* Death
- \*\* Asystole secondary to cardiac failure
- \*\*\* Before Dextrin commenced
- () Patients not withdrawn
- @ After nephrectomy (off Dextrin for 7 days previously)
- # Died 7 days later

Other findings of interest were 28 skin medical events (9 in control, 19 in Dextrin), and slight but statistically significant decline in serum sodium and chloride.

4. ML/1B/004 MIDAS-2 was a long-term open, uncontrolled treatment extension of 48 Dextrin patients of the 67 Dextrin assigned completers from MIDAS. The report of MIDAS-2 covered 10/91 to 3/95 at which point 3 patients were continuing.

Of the 48 patients enrolled 36 were male and 12 were female. Their average age was 57 years and 8 were diabetics.

Attrition over time was portrayed as follows:



25 serious adverse events were reported including 12 deaths (three occurring after discontinuing Dextrin in patients 0266, 0961, 1202), and 5 withdrawals. The sponsor's listing of these cases was:

The following SAE has been reported since the report of 16 November 1994:

Patient No.	D.O.B.	Months of treatment	Date S.A.E.	S.A.E.	Outcome
0307	—	44	12.12.94	Continued ulcerated (R) toe	Withdrawn

For information, the previous SAE reports are given below together with information on total duration of icodextrin treatment:-

Patient No.	D.O.B.	Months of treatment	Date S.A.E.	S.A.E.	Patient Outcome
0104		14	00.06.92	Died at home	Deceased
0206		22	03.03.93	Bowel obstruction	Deceased
0211		23	00.05.93	Cardiac arrest	Deceased
0213		22	10.04.93	Bowel obstruction	Deceased
(0266)		23	30.06.93	Cardiac arrest	Deceased (♦)
0303		28	06.08.93	Skin cancer (R) forearm	Continued
0303		36	15.4.94	Necrotic leg ulcers	Continued
0303		40	13.7.94	Confusion/drowsiness (died 3.8.94)	Withdrawn
0307		21	02.12.92	(R) pleural effusions	Continued
0307		38	11.4.94	Proximal myopathy	Continued
0307		40	30.6.94	Infected R great toe	Continued
0309		18	24.09.92	Myocardial infarction	Continued
0316		33	25.01.94	Paralytic ileus	Continued
0316		34	14.02.94	Deep vein thrombosis	Deceased
0320		15	04.08.92	Bronchopneumonia	Deceased
0710		18	04.11.92	Respiratory arrest on haemodialysis	Withdrawn
0713		33	27.01.94	Cardiac arrest	Deceased
0907		28	04.08.93	Pleural effusions	Withdrawn*
0909		29	22.09.93	Died at home	Deceased
(0961)		7	17.03.92	Died at home	Deceased(®)
0964		25	09.07.93	Ischaemic (R) foot + gangrene	Continued
0964		26	09.08.93	Cardiac arrest after surgery	Deceased
(1202)		10	05.05.92	Cardiac arrest after surgery	Deceased(⊕)
1208		15	17.08.92	Severe dehydration	Withdrawn

- ♦ stopped icodextrin 00.05.93
- \* became named patient in compassionate use programme
- ® stopped icodextrin 10.01.92
- ⊕ stopped icodextrin 00.02.92

Patient 719 who died of a GI bleed should be included in the above listing.

A substudy of net ultrafiltration in 12 patients gave results as follows: 1 month  $424\text{ml} \pm 221\text{sd}$  (n=11); 3 months  $418 \pm 195$  (n=12); 6 months  $493 \pm 197$  (n=12); and 24 months  $480 \pm 280$  (n=12).

While uncontrolled, given the low mortality rate on Dextrin in the 6 months of the Midas study, this follow-up of 72% of the Dextrin completers from the MIDAS study showed no early increase in deaths that might suggest a reason for the low mortality found in MIDAS.

**5. PRO-RENAL:** This was an open, randomized study of Icodextrin versus 2.27% glucose all utilizing one 2 liter bag for the long-dwell day exchange in 39 chronic stable APD adult peritoneal dialysis patients. Patients who had been hospitalized, were pregnant or lactating, had chronic exit site infections, HIV positive as well as other reasons were excluded. The duration of the study was 16 weeks including a 2 week baseline period, a 12 week treatment period and a 2 week follow-up period during which all patients used the control solution for the long-dwell exchange. The Icodextrin was provided as a single 2 L bag with the following composition:

COMPONENT	g/L	COMPONENT	mmol/L
Icodextrin	75	Sodium	133
Calcium Chloride Ph Eur	0.257	Calcium	1.75
Magnesium Chloride BP	0.051	Magnesium	0.25
Sodium Chloride Ph Eur	5.4	Chloride	96
Sodium lactate	4.5	Lactate	40
Water for injection Ph Eur	q.s. ad 1000 mL		

The composition of the control solution was:

COMPONENT	g/L	COMPONENT	mmol/L
Anhydrous Glucose BP	22.7	Sodium	132
Calcium Chloride Ph Eur	0.184	Calcium	1.25
Magnesium Chloride BP	0.051	Magnesium	0.25
Sodium Chloride Ph Eur	5.4	Chloride	95
Sodium lactate	4.5	Lactate	40
Water for injection Ph Eur	q.s. ad 1000 mL		

The study began on 1/21/97 and ended on 1/12/98. Eight European centers including Germany, France, the Netherlands and Belgium participated. The primary efficacy measure was net ultrafiltration for the long-dwell exchange (14±2hours) with peritoneal clearance of creatinine and urea as secondary variables. The ITT population was defined as all randomized patients and at least 1 long-dwell dialysis with the assigned solution. The evaluable population completed the 2 week baseline period and at least the first 6 weeks of the treatment period. Change from baseline was assessed at weeks 1, 6 and 12 with between treatment results analyzed.

Safety was assessed during the study period and any patient experiencing a serious adverse event was followed-up for 3 months. In addition to the usual laboratory tests, the protocol included assessments of carbohydrate absorption, changes in insulin requirements for diabetic subjects and was amended to include determination of the sodium content of the dialysate during the long-dwell exchanges. This was added to assess whether the decrease in serum sodium with Icodextrin noted in other studies was due at least in part to greater loss of sodium during the treatment dialyses.

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The flowchart of procedures was:

WEEK	Baseline period		T	Treatment period			Follow-up period	
	-2	-1		+1	+6	+12	+13	+14
VISIT	-2	-1	0	+1	+2	+3	+4	+5
INTERVALS	day -14	11 d ± 3 d	day 0	day 1	day 6-12	day 13-14	day 15-16	day 17-18
Physical exam	#							
Vital signs	X	O					X	O
Lab analyses (1)	X	O						
Concurrent Meds	X	O					X	O
Review Compliance	X	O					X	O
AE review	X	O					X	O
RANDOMIZATION		X						
PET		X <sub>ph</sub>					X <sub>ph</sub>	
Urea		O			O	O		O
24 h urine coll.		O			O			
Acetamin/Para-Plasma		O			O	O	X	O
Acetamin - Dialysate		O			O	O		O
24 h dialysate coll. (UF & analyses)		O			O	O		O
Diabetic diary		O		O	O <sub>ph</sub>			
HbA1c		O		X	O	O		O

(1): To include biochemistry, hematology with differential and platelets, plasma osmolality.  
 (2): The PET must be performed the day after the dialysate & blood collections specified for the visit.  
 (3): If needed.  
 O = To be performed at the patient's home  
 # = To be performed by a physician

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41 patients were screened, and 39 patients entered: 19 assigned to Dextrose and 20 to Icodextrin. Patient disposition was noted as follows:

Study Site	Screened	Treatment group	N° of patients entered	N° of patients completed	N° of patients withdrawn	
					AE	Other
ALL SITES	41	Control	19	16	3	
		Icodextrin	20	17	1	2
S20: Hannover	5	Control	3	3		
		Icodextrin	2	1	1	
S21: Dusseldorf	12	Control	6	5	1	
		Icodextrin	6	6		
S22: Wurzburg	4	Control	2	2		
		Icodextrin	2	1		1
S23: Colmar	4	Control	2	2		
		Icodextrin	2	2		
S24: Ponteise	9	Control	3	2	1	
		Icodextrin	4	4		
S25: Amsterdam	1	Control	0	0		
		Icodextrin	1	1		
S26: Leuven	4	Control	2	1	1	
		Icodextrin	2	1		1
S50: Cherbourg	2	Control	1	1		
		Icodextrin	1	1		

The baseline characteristics of those randomized were:

	Control Group		Icodextrin Group		All Patients		p-value
Age (yrs)							0.882 @
Number of patients	19		20		39		
Mean	45.4		46.1		45.7		
Sd Error	3.45		3.01		2.25		
Minimum	26.0		27.0		26.0		
Maximum	75.0		74.0		75.0		
Gender	N	%	N	%	N	%	0.273 **
Male	13	68.4	17	85.0	30	76.9	
Female	6	31.6	3	15.0	9	23.1	
TOTAL	19	100.0	20	100.0	39	100.0	
Primary Renal Diagnosis	N	%	N	%	N	%	0.975 **
Diabetic nephropathy	2	10.5	2	10.0	4	10.3	
Hypertensive nephropathy	0	0.0	1	5.0	1	2.6	
Glomerulonephritis	7	36.8	9	45.0	16	41.0	
Polycystic kidney disease	2	10.5	1	5.0	3	7.7	
Interstitial nephritis	1	5.3	0	0.0	1	2.6	
Obstructive nephropathy	0	0.0	1	5.0	1	2.6	
Autoimmune disease	2	10.5	1	5.0	3	7.7	
Other	5	26.3	5	25.0	10	25.6	
TOTAL	19	100.0	20	100.0	39	100.0	
Race	N	%	N	%	N	%	1.000 **
Caucasian	19	100.0	19	95.0	38	97.4	
Asian	0	0.0	1	5.0	1	2.6	
TOTAL	19	100.0	20	100.0	39	100.0	

@ Analysis of Variance used to test for differences between treatment groups.

\*\* Fisher Exact test used to test for differences between treatment groups because > 20% of the considered table's cells had expected counts < 1.

As noted under renal diagnosis, 4 diabetics entered. 2 were assigned to Dextrose and 2 to Icodextrin.

**EFFICACY**

The results for the primary efficacy variable of net UF were:

Treatment Group		(Baseline) Week -1	Week 1	Week 6	Week 12
Control	No. of patients	19	19	18	17
	Mean	-135	-137	-113	-166
	Standard error	88	79	94	101
	Minimum				
	Maximum				
	Mean change from baseline		-2	10	-20
	Min change from baseline		-386	-336	-331
	Max change from baseline		500	419	556
	p-Value for change from baseline		0.966	0.822	0.712
	Icodextrin	No. of patients	20	20	18
Mean		-175	323	292	206
Standard error		55	64	48	38
Minimum					
Maximum					
Mean change from baseline			498	472	378
Min change from baseline			-251	-34	-105
Max change from baseline			1131	1200	851
p-Value for change from baseline			<0.001	<0.001	<0.001
OVERALL ** (From Repeated Measures)		Icodextrin Adjusted Mean Change			442
	Control Adjusted Mean Change			3	
	Difference (Icodextrin-Control) for Change			439	p-Value ***
	Std Error of Difference			67	<0.001
	Lower 90% Confidence Bound for Difference			328	
	Upper 90% Confidence Bound for Difference			551	

\*\* The adjusted mean changes from the repeated measures analysis of covariances as calculated, with baseline values as the covariates, for each treatment group.  
 A 90% confidence interval was constructed around the difference between Icodextrin and Control.  
 \*\*\* p-value from the one-sided test for treatment differences using the repeated measures analysis of covariance.

The means of the long-dwell time and of the infused volumes was presented in the following two charts.

Table 11.4.4-1: Means of the Long Dwell Time (hour) at Each Visit

Visit	Group	N	Mean	Std Dev	Min	Max
Baseline (Week -1)	Control	19	13.5	1.3		
	Icodextrin	20	13.5	0.9		
Week 1	Control	19	13.5	1.3		
	Icodextrin	20	13.8	1.3		
Week 6	Control	18	13.2	1.3		
	Icodextrin	18	13.4	1.3		
Week 12	Control	17	13.1	1.2		
	Icodextrin	17	13.3	0.8		
Follow-up (Week 14)	Control	17	13.5	1.2		
	Icodextrin	16	13.3	1.2		

Table 11.4.4-2: Means of the infused volume for the long dwell (hour) at Each Visit

Visit	Group	N	Mean	Std Dev	Min	Max
Baseline (Week -1)	Control	19	1964	47		
	Icodextrin	20	1933	73		
Week 1	Control	19	1937	46		
	Icodextrin	20	1902	38		
Week 6	Control	18	1924	58		
	Icodextrin	18	1876	74		
Week 12	Control	17	1901	131		
	Icodextrin	17	1891	73		
Follow-up (Week 14)	Control	17	1914	100		
	Icodextrin	16	1886	78		

For the secondary variables of peritoneal creatinine and urea clearances respectively, results were:

Treatment Group	(Baseline)	Week 1	Week 6	Week 12	
Control	No. of patients	19	19	18	17
	Mean	2.08	2.19	2.20	2.10
	Standard error	0.17	0.14	0.13	0.11
	Minimum				
	Maximum				
	Mean change from baseline		0.10	-0.00	-0.05
	Min change from baseline		-1.66	-0.51	-0.76
	Max change from baseline		1.67	0.43	0.72
	p-Value for change from baseline		0.511	0.999	0.553
	Icodextrin	No. of patients	20	20	17
Mean		2.10	2.53	2.64	2.54
Standard error		0.07	0.10	0.11	0.09
Minimum					
Maximum					
Mean change from baseline			0.45	0.58	0.46
Min change from baseline			-0.04	0.04	-0.07
Max change from baseline			1.23	1.58	0.99
p-Value for change from baseline			<0.001	<0.001	<0.001
OVERALL ** (From Repeated Measures)		Icodextrin Adjusted Mean Change		0.48	
	Control Adjusted Mean Change		0.04		p-Value ***
	Difference (Icodextrin-Control) for Change		0.43		<0.001
	Std Error of Difference		0.10		
	Lower 90% Confidence Bound for Difference		0.27		
	Upper 90% Confidence Bound for Difference		0.60		

\*\* The adjusted mean changes from the repeated measures analysis of covariance, with baseline value as the covariate, for each treatment group.

A 90% confidence interval was constructed around the difference between Icodextrin and Control.

\*\*\* This p-value is from the one-sided test for treatment differences using the repeated measures analysis of covariance.

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Treatment Group		(Baseline) Week -1	Week 1	Week 6	Week 12
Control	No. of patients	19	19	18	17
	Mean	2.21	2.28	2.34	2.27
	Standard error	0.19	0.14	0.13	0.14
	Minimum				
	Maximum				
	Mean change from baseline		0.07	0.01	-0.01
	Min change from baseline		-1.55	-0.50	-0.87
	Max change from baseline		1.66	0.49	0.80
	p-Value for change from baseline		0.637	0.846	0.957
Icodextrin	No. of patients	20	20	17	17
	Mean	2.17	2.62	2.74	2.63
	Standard error	0.08	0.10	0.12	0.09
	Minimum				
	Maximum				
	Mean change from baseline		0.45	0.59	0.47
	Min change from baseline		-0.23	-0.06	-0.17
	Max change from baseline		1.29	1.43	1.04
	p-Value for change from baseline		<0.001	<0.001	<0.001
OVERALL ** (From Repeated Measures)	Icodextrin Adjusted Mean Change			0.48	
	Control Adjusted Mean Change			0.06	p-Value ***
	Difference (Icodextrin-Control) for Change			0.42	<0.001
	Std Error of Difference			0.11	
	Lower 90% Confidence Bound for Difference			0.24	
	Upper 90% Confidence Bound for Difference			0.57	

\*\* The adjusted mean changes from the repeated measures analysis of covariance, with baseline value as the covariate, for each treatment group.  
A 90% confidence interval was constructed around the difference between Icodextrin and Control.  
\*\*\* This p-value is from the one-sided test for treatment differences using the repeated measures analysis of covariance.

As with other studies, this study confirmed that for the long-dwell dialysis Icodextrin removes more fluid, creatinine and urea than 2.27% glucose. The sponsor noted that the result exceeded the 250 ml difference proposed in the protocol as the smallest meaningful clinical difference, however data were provided that a clinical benefit was associated with this physiological change.

### SAFETY

Of the 39 randomized patients, 6 withdrew for adverse reactions for the following reasons:

Treatment Group	Patient N°	Last study visit completed	Reason for withdrawal	Description
Control	0210	Week 13	Adverse event	Inguinal hernia
	0502	Week 1	Adverse event	Intraperitoneal leakage diagnosed as hernia
	0702	Week 6	Adverse event	Perforation of the stomach
Icodextrin	0103	Week 1	Adverse event	Peritonitis
	0304	Week 6	Death	Acute heart failure
	0703	Week 1	Transplantation	?

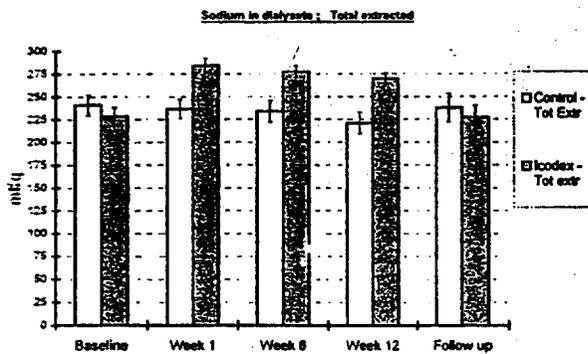
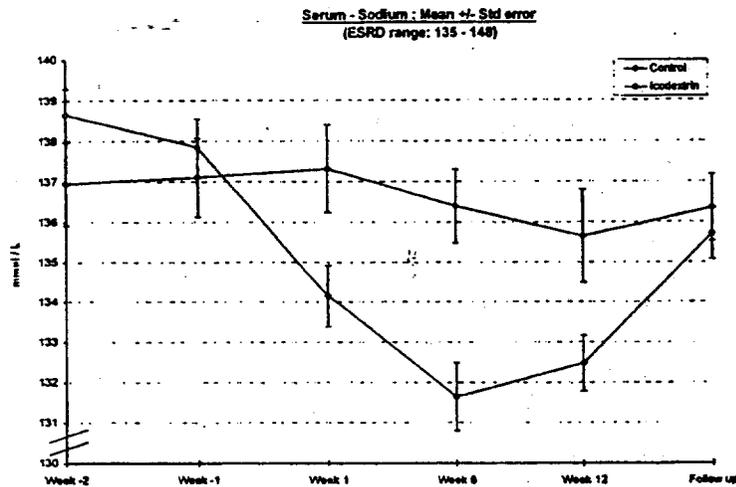
While 1 death was noted during the trial, there were 2 other deaths in the Icodextrin group shortly after the treatment period. No deaths occurred in the Dextrose group. A brief narrative of those deaths follows. Patient 0304 was a 29 year old Caucasian male who had a history of hypertension for 2 years prior to entry on 4/8/97. On 5/27/97 BP was 150/80. Developed acute cardiac failure on 5/29/97 and died. Post mortem showed marked LVH and circulatory failure was listed as the cause of death. No acute MI was found. Patient 0801 was a 53 year old Caucasian female who entered the trial on 10/21/97, developed hypertension on 2/2/98, was switched to the control solution and became normotensive on 2/9/98. No date or cause of death given. Patient 0212 was a 59 year old Caucasian diabetic male who entered the trial on 11/6/97, was noted to have hypertension on 2/4/98 and had a stroke on 2/15/98. Presumably that was the cause of death on 2/21/98. 6 additional patients with serious adverse reactions were identified; 5 taking Dextrose and 1 on Icodextrin. The reactions were extraosseous calcification (history of hyperparathyroidism), inguinal hernia, hyperhydration, hernia, stomach perforation in the Dextrose group, and peritonitis in the Icodextrin group. These reactions were classified as serious because of the need for hospitalization. 56 other adverse reactions were noted; 25 in the control group and 31 in the Icodextrin group, most thought unrelated to drug treatment.

Laboratory abnormalities were found for serum sodium, chloride, alkaline phosphatase, serum amylase, and serum AST (SGOT) in direction and degree consistent with the findings of other studies.

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The explorations of both serum and peritoneal sodium were more extensive with the following graphs depicting the patterns of change over time.



The change from baseline for carbohydrate absorption was somewhat greater in the Icodextrin arm compared to the Dextrose arm (+8gms/long-dwell versus +0.3gms/long-dwell,  $p=0.003$ ). Of the 4 diabetic patients, 1 in the Dextrose arm required an increase in insulin. These safety data are not reassuring, since there was a numerically greater number of deaths in the Icodextrin group compared to control in this study where reasonably frequent clinical observations were made.

**6. ML/1B/011 (DIANA):** This was an open, randomized parallel study of Icodextrin 7.5% versus Dextrose (1.36% or 2.27% or 3.86%) for long-dwell dialysis in 38 adult ESRD adult APD patients. The electrolytic composition of the Control in mmol/liter was Sodium 132, Chloride 102, Calcium 1.75, Lactate 35, and Magnesium 0.75. For Icodextrin it was Sodium 133, Chloride 97, Calcium 1.75, Lactate 40, and Magnesium 0.25.

The duration of the study was two years, and it was conducted in the Netherlands at two hospitals (Rotterdam and Haarlem). The primary purposes of this study were to:

- A. Evaluate the safety, efficacy and biocompatibility of Icodextrin compared to Dextrose.
- B. To evaluate whether there was less damage to host resistance (macrophage function, peritonitis episodes) and to the peritoneal membrane with Icodextrin.
- C. To assess "whether the glycation of peritoneal membrane" was less with Icodextrin.

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The following evaluations were to be made at approximately 3 month intervals:

**SCHEDULE FOR CLINICAL AND LABORATORY MEASUREMENTS**

Month	0	3	6	9	12	15	18	21	24
Visit	1	2	3	4	5	6	7	8	9
<b>General</b>									
Physical exam	0	0	0	0	0	0	0	0	0
weight	0	0	0	0	0	0	0	0	0
blood pressure	0	0	0	0	0	0	0	0	0
symptoms	0	0	0	0	0	0	0	0	0
medical events	0	0	0	0	0	0	0	0	0
<b>Laboratory measurements</b>									
Hb, ht, ery, plat, WBC	0	0	0	0	0	0	0	0	0
ASAT, ALAT	0	0	0	0	0	0	0	0	0
γGT, Alk.Phos	0	0	0	0	0	0	0	0	0
Creatinine	0	0	0	0	0	0	0	0	0
Urea	0	0	0	0	0	0	0	0	0
Ca, P	0	0	0	0	0	0	0	0	0
Albumin	0	0	0	0	0	0	0	0	0
Glucose	0	0	0	0	0	0	0	0	0
*Osmolality	0	0	0	0	0	0	0	0	0
HbA <sub>1c</sub>	0	0	0	0	0	0	0	0	0
Cholesterol	0	0	0	0	0	0	0	0	0
Triglycerides	0	0	0	0	0	0	0	0	0
HDL-cholesterol	0	0	0	0	0	0	0	0	0
<b>Dialysis related</b>									
*MTAC	0	0	0	0	0	0	0	0	0
*UF	0	0	0	0	0	0	0	0	0
Residual vol.	0	0	0	0	0	0	0	0	0
Kt/V	0	0	0	0	0	0	0	0	0
*Glucose load	0	0	0	0	0	0	0	0	0
Dextrin 20/metab	0	0	0	0	0	0	0	0	0
Peritonitis	0	0	0	0	0	0	0	0	0
Macrophage Fcγ receptor function	0				0				
<b>Urinary measurements in 24-hour samples</b>									
Volume	0	0	0	0	0	0	0	0	0
Creatinine	0	0	0	0	0	0	0	0	0
Dextrin 20 / metab	0	0	0	0	0	0	0	0	0
<b>In times of peritonitis</b>									
MTAC									
UF									
Dextrin 20 / metab									
<b>In vitro (effluent)</b>									
<b>* Peritoneal macrophage</b>									
IL-1 production	0	0	0	0	0	0	0	0	0
Opsonin	0	0	0	0	0	0	0	0	0
IL-6, IL-8	0	0	0	0	0	0	0	0	0
TGF-β, TNE	0	0	0	0	0	0	0	0	0
*CA-125	0	0	0	0	0	0	0	0	0
*Procollagen	0	0	0	0	0	0	0	0	0
*Glycated albumin	0	0	0	0	0	0	0	0	0
<b>Peritoneal histology</b>									
Percutaneous biopsy	0		0		0		0		0
Surgical biopsy - when possible									
* Primary endpoints									

No formal estimation of sample size was done, and corrections for multiple endpoints were to be made appropriately.

The demographics of the 38 randomized patients were:

	TOTAL	GLUCOSE	ICODEXTRIN
Number of patients	38	19	19
Sex:			
male	27	17	10
female	11	2	9
Race:			
Asian	4	1	3
Caucasian	31	16	15
Afro-caribbean	2	1	1
other	1	1	0
Age (years)			
mean	52.18	51.42	52.95
sd	13.28	15.38	11.18
min	21	21	31
max	70	68	70
Diabetic	2	2	0

RENAL DISEASE AND APD HISTORY

	GLUCOSE	ICODEXTRIN
Main cause of renal disease		
glomerulonephritis	8	6
polycystic kidney disease	3	4
hypertension	1	5
pyelonephritis	1	0
congenital	1	0
diabetes	1	0
other	4	4
New to APD	5	5
Duration of APD (months) for established CCPD patients		
mean	29	21
sd	28	18
min		
max		
n	14	14
Current daytime regime		
dry	2	1
dry+CAPD	0	2
1.36	3	4
2.27	10	11
3.86	3	1
2.27+CAPD	1	0

The number of patients assessed at each timepoint was:

Month	0	3	6	9	12	15	18	21	24
N on Icodex.	19	19	18	15	12	11	9	7	7
N on Control	19	16	14	13	13	12	8	6	6

ITT and completer analyses were done, but insufficient data was collected for the biocompatibility endpoints specified in the protocol, such as IL-6 or TNF- $\alpha$ , and where sufficient data were available, such as with macrophage function, no differences between groups were noted. The only efficacy endpoint that did show a significant difference was net UF. At baseline both groups showed negative net ultrafiltration volumes. While this negative direction continued in those receiving Dextrose for the log-dwell dialysis, the UF volumes became positive for those assigned to Icodextrin.

Of greatest interest in this study are the safety results.

5 patients died during the study and 1 died two and one-half months after withdrawal from the study. All were in the Dextrose group. A brief cause of death for each patient follows.

A006/0006 66 year old Caucasian male-infection and sepsis after toe amputation.

A017/0017 66 year old Caucasian male-CVA.

A019/0019 68 year old Asian female-dehydration, hypotension, transferred to nursing home and died 4 months later.

A025/0025 57 year old diabetic Caucasian male-peritonitis due to bowel ischemia.

A027/0027 67 year old Caucasian male-myocardial infarction.

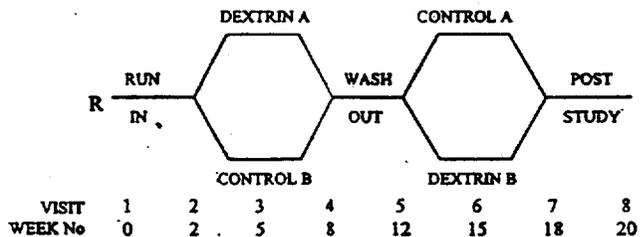
B010/0110 55 year old Caucasian male-acute necrotic pancreatitis.

While the Pro-Renal study results included 3 deaths all on Icodextrin, this study result shows an opposite numerical direction.

In addition to the deaths, 7 patients withdrew from the Dextrose group and 12 from the Icodextrin group. The major reason given was transplantation.

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**7. ML/1B 020 (DELIA):** This was an open, single center randomized crossover study in 11 adult ESRD undergoing APD which compared Icodextrin to a dry dwell. The design of the study was as follows:



Of the 11 randomized patients, all were Caucasian, 3 were male and mean age was 51.9 years $\pm$ 13.6. 7 patients completed both study periods, and diabetes was the most frequent cause of the renal disease. For the completers, there was no significant difference in 24 hour total ultrafiltration volume for the Icodextrin arm versus the control arm. There was a significant increase in creatinine clearance during the Icodextrin treatment compared to control (47.4l/week $\pm$ 12.0 versus 29.5 $\pm$ 8.7, p<0.01). Concerning safety, there were no deaths reported, there were 7 serious adverse reactions reported (4 in the Icodextrin period). 6 patients withdrew for peritonitis or diarrhea, 4 during the Icodextrin period.

**8. RD-99-CA-060 and ML/1B/014 (MIDAS Substudy)** were two pharmacokinetic studies; the first of a single Icodextrin exchange, and the second of Icodextrin levels at steady state, after stopping and after restarting Icodextrin. These will be reviewed in the Biopharmaceutics review, as will study ML1B/002 that evaluated insulin absorption when administered intraperitoneally during CAPD with Icodextrin or glucose.

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**9. ML/1B 009 (IDEAL):** This was an open, noncomparator study of Icodextrin in CAPD patients who had lost ultrafiltration across the peritoneum as defined by a PET study. Although the study planned to enroll 100 patients at 10 European centers and treat patients for 6 months, it was stopped after 16 patients enrolled in over a year. No efficacy data are presented, but safety data were reported.

8 males and 8 females entered at two centers; one in London, the other in Brussels. They ranged from 19 to 78 years of age. No other demographic data were presented.

Patient disposition was detailed as follows:

Patient #, Disposition	Study Solution Receipt	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
101, Completed	Feb. 24, 1995	March 27, 1995	April 04, 1995	May 22, 1995	June 19, 1995	July 18, 1995	Sept. 04, 1995
102, Completed	March 17, 1995	April 18, 1995	May 15, 1995	June 12, 1995	July 10, 1995	Aug. 03, 1995	Sept. 04, 1995
301, Completed	Jan. 24, 1995	Feb. 24, 1995	March 24, 1995	April 26, 1995	May 26, 1995	June 30, 1995	July 28, 1995
302, Completed	Jan. 23, 1995	Feb. 24, 1995	March 31, 1995	April 27, 1995	May 19, 1995	June 30, 1995	July 19, 1995
303, WD 03/29/1995	Feb. 02, 1995	March 02, 1995					
304, Completed	Feb. 02, 1995	March 02, 1995	March 30, 1995	April 21, 1995	May 10, 1995	June 20, 1995	July 27, 1995
305, WD 05/30/1995	Feb. 21, 1995	March 21, 1995	April 24, 1995	May 24, 1995			
306, Completed	March 15, 1995	Apr. 04, 1995	May 03, 1995	June 06, 1995	July 28, 1995	Aug. 25, 1995	Sept. 26, 1995
307, WD 11/17/1995	July 26, 1995	Aug. 25, 1995	Sept. 29, 1995	Oct. 24, 1995			
308, WD 03/07/1996	Sept. 17, 1995	Oct. 04, 1995	Nov. 06, 1995	Dec. UNK, 1995	Jan. 09, 1996	Feb. 13, 1996	
309, WD Date UNK	NA	—					
1101, WD 07/13/1995	May 19, 1995	June 16, 1995	July 13, 1995				
1102, Completed	May 31, 1995	June 12, 1995	July 31, 1995	Sept. 01, 1995	Dec. 01, 1995	Jan. 08, 1996	Feb. 08, 1996
1103, Completed	May 30, 1995	June 23, 1995	July 31, 1995	Sept. 01, 1995	Oct. 03, 1995	Oct. 27, 1995	Dec. 01, 1995
1104, WD 08/18/1995	July 31, 1995	—					
1105, WD 01/16, 1996	Dec. 12, 1995	Jan. 05, 1996					

WD = Withdrawn

UNK = unknown

NA=Not applicable

— Patient did not complete Visit 2

5 patients died. Those were:

patient 305-50 year old diabetic Caucasian female died after a myocardial infarction.

patient 307-77 year old Caucasian female had peritonitis and was not responding to dialysis.

patient 308-78 year old Caucasian male died after a myocardial infarction.

patient 1104-75 year old Caucasian male died in his sleep.

patient 1105-45 year old Caucasian male died after a cardiac arrest.

Each of these patients had a history of cardiovascular disease.

Other serious adverse reactions were reported by 5 patients. These included hypertension, CVA, overhydration, diabetic management problem, exit site infection, and peritonitis.

Without a randomized control group, it is difficult to assess the significance of these safety results.

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## VI. INTEGRATED REVIEW OF EFFICACY

The three controlled efficacy studies, 130, MIDAS, Pro-Renal, demonstrate That Icodextrin is an effective peritoneal dialysis drug, and is superior to 1.5% and 2.5% Dextrose for ultrafiltration amounts and creatinine and urea peritoneal clearance during the long-dwell period for CAPD and APD. Icodextrin long-dwell dialysis would be integrated into a daily treatment regimen which would still employ Dextrose for the other dialyses.

None of the patients entered were doing poorly on their regimen which consisted of Dextrose for all dialyses, but greater volumes of fluid and waste products were removed when Icodextrin was substituted for the long-dwell. The sponsor does not make a convincing case that this represents a clinical benefit were everyone to be treated with the new drug. In some cases excess fluid removal could lead to dehydration, hypotension, electrolyte imbalance. What attempts were made to show a clinical benefit, e.g QoL results, edema status, were not convincing because of incomplete cohort results, post-hoc selection of time points and scales, and inadequate statistical consideration of non-preplanned endpoints and multiple comparisons. That is not to say that the sponsor needs to prove that fluid and waste removal in ESRD is beneficial. Compared to historical expectations it is clear that Icodextrin is an effective dialysis drug, but compared to a currently used and well-tolerated drug there is no convincing data to demonstrate clinical superiority.

## VII INTEGRATED REVIEW OF SAFETY

840 patients were included in the sponsor's integrated summary of safety; 493 assigned to Icodextrin and 347 to control. The breakdown by study was as follows:

Study	Control Group	Extraneal Group	Total Patients
<b>Key Studies</b>			
RD-97-CA-130	85	90	175
RD-97-CA-131	112	175	287
ML/IB/001 (MIDAS)	103	106	209
PRO-RENAL-REG-035	19	20	39
<b>Total Key Studies</b>	<b>319</b>	<b>391</b>	<b>710</b>
<b>Supportive Studies</b>			
ML/IB/011 (DIANA)	19	19	38
ML/IB/020 (DELIA)	9	10	19*
ML/IB/014 (MIDAS-2)	--	48	48
RD-99-CA-060	--	13	13
ML/IB/014 (S-5)	--	12	12
<b>Total Supportive Studies</b>	<b>28</b>	<b>102</b>	<b>130</b>
<b>Total All Studies</b>	<b>347</b>	<b>493</b>	<b>840</b>

\*DELIA population data from Baxter. One patient received no drug and is not included in this table; 2 patients received icodextrin only; 1 received control only; a total of 12 patients were enrolled.

The duration of exposure was:

	Control Group N = 347	Extraneal Group N=493	All Patients N=840
<b>Duration (days)</b>			
Mean ± SE	174.3 ± 8.25	232.5 ± 11.06	208.5 ± 7.39
Minimum	--	--	--
Median	165.0	169.0	169.0
Maximum	--	--	--

Some demographic characteristics were:

	Control Group N = 347		Extraneal Group N = 493		All Patients N = 840	
<b>Age (yrs)</b>						
Mean ± SE	54.1 ± 0.76		53.9 ± 0.63		54.0 ± 0.48	
Range	19 - 86		18 - 83		18 - 86	
<b>Weight (kgs)</b>						
Mean ± SE	74.4 ± 0.82		75.6 ± 0.69		75.1 ± 0.53	
Range	44.4 - 145.4		37.0 - 140.5		37.0 - 145.4	
	Control Group		Extraneal Group		All Patients	
	n	%	n	%	n	%
<b>Age Categories</b>						
<35	33	9.5	52	10.5	85	10.1
35 - <45	63	18.2	70	14.2	133	15.8
45 - <55	65	18.7	113	22.9	178	21.2
55 - <65	91	26.2	135	27.4	226	26.9
65 - <75	76	21.9	102	20.7	178	21.2
≥75	19	5.5	21	4.3	40	4.8
<b>Gender</b>						
Male	175	50.4	278	56.4	453	53.9
Female	172	49.6	215	43.6	387	46.1
<b>Race</b>						
Caucasian	257	74.1	360	73.0	617	73.5
Hispanic	10	2.9	14	2.8	24	2.9
Asian	12	3.5	22	4.5	34	4.0
Black	62	17.9	90	18.3	152	18.1
Other	6	1.7	7	1.4	13	1.5

Reference: Appendix 8 Summary Table 3.0a.

Diabetic, hypertensive and hypertensive nephropathy subpopulations were represented as follows:

Table 3: Disease Subpopulations by Treatment Group		
	Control Group	Extraneal Group
<b>Patients with Diabetes</b>		
All Studies	94	132
Key Studies	92	116
Supportive Studies	2	16
<b>Patients with Hypertension</b>		
All Studies	147	243
Key Studies	134	188
Supportive Studies	13	55
<b>Patients with Primary Diagnosis of Hypertensive Nephropathy</b>		
All Studies	68	114
Key Studies	67	89
Supportive Studies	1	25

Reference: Appendix 8 Summary Tables 4.0a, 4.0.b, 4.0c

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Disposition of patients was:

	Control Group		Extraeal Group	
	n	%	n	%
<b>ALL STUDIES</b>	N=347		N=493	
Completed Study	246	70.9	323	65.5
Prematurely Discontinued Study	101	29.1	170	34.5
Transplantation	16	4.6	32	6.5
Adverse experience	41	11.8	66	13.4
Death	9	2.6	17	3.4
Protocol violation	11	3.2	7	1.4
Other	24	6.9	48	9.7
<b>KEY STUDIES</b>	N=319		N=391	
Completed Study	232	72.7	271	69.3
Prematurely Discontinued Study	87	27.3	120	30.7
Transplantation	10	3.1	13	3.3
Adverse experience	38	11.9	51	13.0
Death	4	1.3	8	2.0
Protocol violation	11	3.4	7	1.8
Other	24	7.5	41	10.5
<b>SUPPORTIVE STUDIES</b>	N=28		N=102	
Completed Study	14	50.0	52	51.0
Prematurely Discontinued Study	14	50.0	50	49.0
Transplantation	6	21.4	19	18.6
Adverse experience	3	10.7	15	14.7
Death	5	17.9	9	8.8
Protocol violation	0	0	0	0
Other	0	0	7	6.9

Reference: Appendix 8 Summary Table 1.0

The mortality comparisons did not include all patients who died during and following the study. This will be presented later.

**ADVERSE EVENTS**

For adverse events occurring in 5% or more of patients by treatment group and all patients were presented as follows:

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COSTART BODY SYSTEM Preferred Term	Control Group (N=347)		Extraneal Group (N=493)		All Patients (N=840)	
	n	%	n	%	n	%
<b>BODY GENERAL</b>						
Peritonitis	88	25.4	130	26.4	218	26.0
Exit site infect	58	16.7	73	14.8	131	15.6
Pain	43	12.4	48	9.7	91	10.8
Headache	23	6.6	43	8.7	66	7.9
Pain abdo	20	5.8	39	7.9	59	7.0
Flu synd	21	6.1	35	7.1	56	6.7
Injury accid	14	4.0	31	6.3	45	5.4
Asthenia	27	7.8	28	5.7	55	6.5
Lab test abnorm	12	3.5	25	5.1	37	4.4
Pain chest	12	3.5	25	5.1	37	4.4
Pain back	18	5.2	22	4.5	40	4.8
infect	19	5.5	21	4.3	40	4.8
<b>CARDIOVASCULAR</b>						
Hypertens	29	8.4	62	12.6	91	10.8
Hypotens	37	10.7	32	6.5	69	8.2
<b>DIGESTIVE</b>						
Diarrhea	33	9.5	40	8.1	73	8.7
Nausea	17	4.9	35	7.1	52	6.2
Nausea vomit	21	6.1	25	5.1	46	5.5
Dyspepsia	13	3.7	25	5.1	38	4.5
Vomit	19	5.5	22	4.5	41	4.9
<b>HEMATOLOGIC &amp; LYMPHATIC</b>						
Anemia	39	11.2	55	11.2	94	11.2
<b>METABOLIC &amp; NUTRITION</b>						
Hypokalem	37	10.7	34	6.9	71	8.5
Hypoproteinem	32	9.2	34	6.9	66	7.9
Hypervolem	20	5.8	28	5.7	48	5.7
Edema	17	4.9	28	5.7	45	5.4
Hyperphosphatem	26	7.5	25	5.1	51	6.1
Hyperglycem	12	3.5	25	5.1	37	4.4
Edema periph	29	8.4	18	3.7	47	5.6
<b>MUSCULOSKELETAL</b>						
Arthralgia	27	7.8	31	6.3	58	6.9

COSTART BODY SYSTEM Preferred Term	Control Group (N=347)		Extraneal Group (N=493)		All Patients (N=840)	
	n	%	n	%	n	%
<b>NERVOUS</b>						
Dizziness	19	5.5	27	5.5	46	5.5
<b>RESPIRATORY</b>						
Upper res infect	46	13.3	74	15.0	120	14.3
Cough inc	13	3.7	35	7.1	48	5.7
Dyspnea	24	6.9	26	5.3	50	6.0
<b>SKIN</b>						
Rash	16	4.6	50	10.1	66	7.9
Pruritus	23	6.6	27	5.5	50	6.0
Skin dis	18	5.2	11	2.2	29	3.5

Events are ordered within each Body System from highest to lowest incidence rates within the Extraneal group.

Some events of interest were peritonitis, hyperglycemia, edema and rash. Episodes of peritonitis were similar between groups as was hyperglycemia. Edema was more frequently noted in the control group, and has been discussed in the results of individual studies. Rash was approximately twice as frequent in the Icodextrin treated patients and deserves further comment.

A breakdown by study of skin adverse events leading to discontinuation was:

Study	Patient ID	Preferred Term	Study Day at Onset of AE	Relationship to Study Drug	Severity Assessment
RD-97-CA-131	37301	Derm exfol	19	Definite	Mild
RD-97-CA-131	2401	Pruritus	52	None	Mild
RD-97-CA-131	17201	Pruritus	51	Possible	Severe
RD-97-CA-130	22101	Rash	1	Probable	Mild
RD-97-CA-130	33106	Rash	6	Probable	Moderate
RD-97-CA-131	19503	Rash	7	Possible	Severe
RD-97-CA-131	24401	Rash	5	Probable	Severe
RD-97-CA-131	37301	Rash	5	Definite	Moderate
RD-97-CA-131	45401	Rash	9	Probable	Moderate
RD-97-CA-131	33305	Rash vesic bull	21	Possible	Moderate
RD-97-CA-130	23208	Skin discolor	8	Probable	Mild
MIDAS-2	303	Ulcer skin	1210	None	Severe
MIDAS-2	307	Ulcer skin	1334	None	Moderate
RD-97-CA-130	23210	Urticaria	9	Probable	Severe

Reference: Appendix 8 Summary Table 17.0

All were treated with Icodextrin although patient 307 had been assigned to Control in MIDAS-1 and Icodextrin in MIDAS-2.

For skin events judged related to study drug, 14 patients on control (4.0%) reported such events versus 49 patients on Icodextrin (9.9%;  $p < 0.001$ ).

By gender the following skin events were noted:

COSTART Preferred Term	Males				Females			
	Control Group (N=175)		Extraneal Group (N=278)		Control Group (N=172)		Extraneal Group (N=215)	
	n	%	n	%	n	%	n	%
Derm exfol	0	0	1	0.4	1	0.6	8	3.7
Eczema	0	0	2	0.7	1	0.6	4	1.9
Furunculosis	4	2.3	5	1.8	0	0	0	0
Herpes zoster	5	2.9	1	0.4	4	2.3	1	0.5
Nail dis	0	0	1	0.4	2	1.2	4	1.9
Pruritus	10	5.7	11	4.0	14*	8.1*	16	7.4
Rash	4	2.3	19	6.8	12	7.0	31	14.4
Rash vesic bull	5	2.9	5	1.8	4	2.3	1	0.5
Skin dis	6	3.4	5	1.8	12	7.0	6	2.8
Skin dry	1	0.6	8	2.9	2	1.2	2	0.9
Ulcer skin	3	1.7	9	3.2	10	5.8	7	3.3

\*Values for "pruritus" include one control patient with preferred term "pruritis"

Exfoliative dermatitis and rash appear to be more frequent complaints in females.

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Adverse events leading to discontinuation of the drug assigned were:

COSTART Body System Preferred Term-	Control Group (N=347)		Extraneal Group (N=493)		All Patients (N=840)	
	n	%	n	%	n	%
<b>BODY GENERAL</b>						
Peritonitis	14	4.0	18	3.7	32	3.8
Pain	3	0.9	1	0.2	4	0.5
Pain back	2	0.6	1	0.2	3	0.4
Asthenia	3	0.9	0	0	3	0.4
Pain abdo	3	0.9	0	0	3	0.4
Hernia	2	0.6	0	0	2	0.2
<b>CARDIOVASCULAR</b>						
Heart arrest	3	0.9	7	1.4	10	1.2
Infarct myocard	4	1.2	4	0.8	8	1.0
Hypotension	4	1.2	1	0.2	5	0.6
<b>DIGESTIVE</b>						
Obstruct intest	1	0.3	3	0.6	4	0.5
Hem GI	1	0.3	3	0.6	4	0.5
Nausea vomit	4	1.2	2	0.4	6	0.7
Anorexia	2	0.6	0	0	2	0.2
Nausea	2	0.6	0	0	2	0.2
<b>HEMATOLOGIC &amp; LYMPHATIC</b>						
Anemia	3	0.9	2	0.4	5	0.6
<b>METABOLIC &amp; NUTRITION</b>						
Dehydrat	4	1.2	3	0.6	7	0.8
Electrolyte abnorm	2	0.6	2	0.4	4	0.5
Hypervolem	2	0.6	1	0.2	3	0.4
Hypovolem	2	0.6	1	0.2	3	0.4
Hypokalem	4	1.2	0	0	4	0.5
Ultrafil dec	2	0.6	0	0	2	0.2
<b>NERVOUS</b>						
Insomnia	2	0.6	2	0.4	4	0.5
<b>SKIN</b>						
Rash	0	0	6	1.2	6	0.7

Only one event per patient per preferred term was counted.

Events are ordered within each Body System from highest to lowest incidence rates within the Extraneal group.

Proportions were similar between groups, though rash was a more frequent reason in Icodextrin treated patients.

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**SUBGROUPS: GENDER, AGE, RACE, DIABETES**

By gender and treatment group the comparative incidence of selected adverse events was:

COSTART Body System Preferred Term	Control Group				Extraneal Group			
	Male N=175		Female N=172		Male N=278		Female N=215	
	n	%	n	%	n	%	n	%
<b>CARDIOVASCULAR</b>								
Angina pectoris	2	1.1	3	1.7	11	4.0	1	0.5
Cardiac murmur	1	0.6	0	0	2	0.7	8	3.7
Heart arrest	1	0.6	2	1.2	10	3.6	1	0.5
Hypertension	16	9.1	13	7.6	28	10.1	34	15.8
Hypotension	13	7.4	24	14.0	23	8.3	9	4.2
<b>DIGESTIVE</b>								
Dyspepsia	9	5.1	4	2.3	13	4.7	12	5.6
Nausea	7	4.0	10	5.8	12	4.3	23	10.7
Vomit	10	5.7	9	5.2	8	2.9	14	6.5
<b>HEMATOLOGIC AND LYMPHATIC</b>								
Anemia	12	6.9	27	15.7	28	10.1	27	12.6
Leukocytosis	1	0.6	3	1.7	5	1.8	10	4.7
<b>METABOLIC AND NUTRITION</b>								
Edema	6	3.4	11	6.4	14	5.0	14	6.5
Edema periph	11	6.3	18	10.5	5	1.8	13	6.0
Hypercalcem	2	1.1	8	4.7	10	3.6	7	3.3
Hyperglycem	4	2.3	8	4.7	15	5.4	10	4.7
Hyperphosphatem	8	4.6	18	10.5	10	3.6	15	7.0
Hypervolem	7	4.0	13	7.6	11	4.0	17	7.9
Hypoglycem	0	0	9	5.2	4	1.4	2	0.9
Hypokalem	12	6.9	25	14.5	12	4.3	22	10.2
Hypoproteinem	6	3.4	26	15.1	17	6.1	17	7.9
<b>MUSCULOSKELETAL</b>								
Arthralgia	11	6.3	16	9.3	10	3.6	21	9.8
<b>NERVOUS</b>								
Neuritis periph	1	0.6	10	5.8	1	0.4	7	3.3
<b>RESPIRATORY</b>								
Cough inc	5	2.9	8	4.7	15	5.4	20	9.3
Dyspnea	6	3.4	18	10.5	11	4.0	15	7.0
Upper res infect	23	13.1	23	13.4	39	14.0	35	16.3
<b>SKIN</b>								
Derm exfol	0	0	1	0.6	1	0.4	8	3.7
Pruritus*	10	5.7	14	8.1	11	4.0	16	7.4
Rash	4	2.3	12	7.0	19	6.8	31	14.4
Skin dis	6	3.4	12	7.0	5	1.8	6	2.8
Ulcer skin	3	1.7	10	5.8	9	3.2	7	3.3
<b>SPECIAL SENSES</b>								
Ear dis	1	0.6	2	1.2	1	0.4	9	4.2
<b>UROGENITAL</b>								
Infect urin tract	4	2.3	12	7.0	9	3.2	4	1.9

\* Includes one female control patient with preferred term "pruritus."

Hypertension seemed more frequent in the Icodextrin treated females versus control females, but the hypotension result was in the opposite direction. Nausea was also somewhat more frequent in Icodextrin treated females compared to control treated females, but was similar to males treated with Icodextrin. Rash was most frequently reported in Icodextrin treated females.

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In the geriatric population versus all patients, the results were:

COSTART BODY SYSTEM Preferred Term	Control Group				Extraneal Group			
	≥ 65 years N=95		All Studies N=347		≥ 65 years N=123		All Studies N=493	
	n	%	n	%	n	%	n	%
<b>CARDIOVASCULAR</b>								
Hypertension	7	7.4	29	8.4	7	5.7	62	12.6
Hypotension	12	12.6	37	10.7	11	8.9	32	6.5
Vasc dis periph	8	8.4	13	3.7	7	5.7	17	3.4
<b>HEMATOLOGIC &amp; LYMPHATIC</b>								
Anemia	11	11.6	39	11.2	7	5.7	55	11.2
Leukocytosis	0	0	4	1.2	7	5.7	15	3.0
<b>METABOLIC &amp; NUTRITION</b>								
Dehydration	8	8.4	17	4.9	11	8.9	23	4.7
<b>NERVOUS</b>								
Dizziness	8	8.4	19	5.5	10	8.1	27	5.5
<b>SKIN</b>								
Pruritus	11	11.6	23	6.6	4	3.3	27	5.5
Rash	6	6.3	16	4.6	10	8.1	50	10.1

Reference: Appendix 8 Summary Tables 9.0a, 14.1a

Most results between groups were of comparable frequency.

Concerning race comparative results for Caucasian and Black were provided:

COSTART BODY SYSTEM Preferred Term	Control Group				Extraneal Group			
	Caucasian N=257		Black N=62		Caucasian N=360		Black N=90	
	n	%	n	%	n	%	n	%
<b>BODY GENERAL</b>								
Exit site infect	40	15.6	10	16.1	64	17.8	5	5.6
Flu syndrome	18	7.0	2	3.2	29	8.1	2	2.2
Headache	18	7.0	3	4.8	21	5.8	17	18.9
Pain chest	10	3.9	1	1.6	16	4.4	7	7.8
<b>CARDIOVASCULAR</b>								
Hypertens	19	7.4	7	11.3	32	8.9	23	25.6
Hypotens	18	7.0	14	22.6	21	5.8	9	10.0
Syncope	3	1.2	4	6.5	2	0.6	1	1.1
<b>DIGESTIVE</b>								
Diarrhea	21	8.2	10	16.1	31	8.6	6	6.7
Gastritis	1	0.4	6	9.7	5	1.4	3	3.3
Nausea	12	4.7	1	1.6	26	7.2	6	6.7
Nausea vomit	14	5.4	5	8.1	23	6.4	2	2.2
Vomit	19	7.4	0	0	17	4.7	3	3.3
<b>HEMATOLOGIC AND LYMPHATIC</b>								
Anetria	25	9.7	10	16.1	40	11.1	11	12.2
<b>METABOLIC AND NUTRITION</b>								
Edema	9	3.5	7	11.3	20	5.6	8	8.9
Edema periph	18	7.0	7	11.3	9	2.5	5	5.6
Hyperglycem	6	2.3	6	9.7	23	6.4	2	2.2
Hyperphosphatem	22	8.6	2	3.2	21	5.8	1	1.1
Hypoglycem	3	1.2	6	9.7	5	1.4	1	1.1
Hypokalem	23	8.9	13	21.0	18	5.0	13	14.4
Hypoproteinem	19	7.4	11	17.7	26	7.2	8	8.9
Hypovolem	2	0.8	4	6.5	6	1.7	2	2.2
Phosphatase alk inc	2	0.8	4	6.5	11	3.1	3	3.3
<b>MUSCULOSKELETAL</b>								
Arthralgia	23	8.9	2	3.2	21	5.8	6	6.7
<b>RESPIRATORY</b>								
Rhinitis	8	3.1	4	6.5	10	2.8	7	7.8
Upper res infect	36	14.0	7	11.3	59	16.4	10	11.1
<b>SKIN</b>								
Herpes zoster	3	1.2	4	6.5	2	0.6	0	0
Pruritus*	17	6.6	1	1.6	17	4.7	4	4.4
Rash	11	4.3	3	4.8	36	10.0	8	8.9

\* Includes one female Caucasian control patient with preferred term "pruritus."  
Reference: Appendix 8 Summary Tables 16.0a and 16.3a

Exit site infections seemed least frequent in Blacks on Icodextrin, while headache was most frequent in this group. Rather than put credence in these findings, one should be very cautious in any of the many numerical differences found in these exhaustive comparisons.

For diabetics versus all patients the results for selected adverse events were:

COSTART BODY SYSTEM Preferred Term	All Studies Population				Diabetic Subpopulation			
	Control Group (N=347)		Extraneal Group (N=493)		Control Group (N=94)		Extraneal Group (N=132)	
	n	%	n	%	n	%	n	%
<b>BODY GENERAL</b>								
Asthenia	27	7.8	28	5.7	12	12.8	13	9.8
Injury accid	14	4.0	31	6.3	6	6.4	16	12.1
Lab test abnorm	12	3.5	25	5.1	6	6.4	19	14.4
Pain back	18	5.2	22	4.5	8	8.5	3	2.3
<b>CARDIOVASCULAR</b>								
Hypotens	37	10.7	32	6.5	15	16.0	14	10.6
<b>DIGESTIVE</b>								
Diarrhea	33	9.5	40	8.1	15	16.0	11	8.3
Nausea	17	4.9	35	7.1	4	4.3	14	10.6
<b>HEMATOLOGIC &amp; LYMPHATIC</b>								
Anemia	39	11.2	55	11.2	14	14.9	25	18.9
Leukocytosis	4	1.2	15	3.0	3	3.2	12	9.1
<b>METABOLIC &amp; NUTRITION</b>								
Hyperglycem	12	3.5	25	5.1	11	11.7	21	15.9
Hypochlorem	3	0.9	8	1.6	0	0.0	7	5.3
Hypoglycem	9	2.6	6	1.2	8	8.5	6	4.5
Hypokalem	37	10.7	34	6.9	18	19.1	12	9.1
Hyponatrem	7	2.0	11	2.2	2	2.1	10	7.6
Hypoproteinem	32	9.2	34	6.9	14	14.9	21	15.9
<b>SKIN</b>								
Rash	16	4.6	50	10.1	5	5.3	14	10.6
Skin dis	18	5.2	11	2.2	10	10.6	7	5.3

Reference: Appendix 8 Summary Tables 9.0a and 33.0a

Since Icodextrin was developed with one expectation that it would provide less glucose load to diabetics and therefore be better tolerated, it is interesting that hyperglycemia was slightly more frequently reported in diabetics taking Icodextrin. Rash was also more frequent in this group.

Metabolic events were also compared in diabetics versus all patients:

COSTART Preferred Term	All Studies Population				Diabetic Subpopulation			
	Control Group (N=347)		Extraneal Group (N=493)		Control Group (N=94)		Extraneal Group (N=132)	
	n	%	n	%	n	%	n	%
Edema	17	4.9	28	5.7	9	9.6	12	9.1
Hypercalcem	10	2.9	17	3.4	2	2.1	8	6.1
Hypercholesterem	8	2.3	10	2.0	6	6.4	3	2.3
Hyperglycem	12	3.5	25	5.1	11	11.7	21	15.9
Hyperphosphatem	26	7.5	25	5.1	11	11.7	12	9.1
Hypochlorem	3	0.9	8	1.6	0	0.0	7	5.3
Hypocholesterem	1	0.3	6	1.2	0	0.0	6	4.5
Hypoglycem	9	2.6	6	1.2	8	8.5	6	4.5
Hypokalem	37	10.7	34	6.9	18	19.1	12	9.1
Hypomagnesem	4	1.2	7	1.4	4	4.3	2	1.5
Hyponatrem	7	2.0	11	2.2	2	2.1	10	7.6
Hypoproteinem	32	9.2	34	6.9	14	14.9	21	15.9
Phosphatase alk inc	6	1.7	14	2.8	5	5.3	6	4.5
Ultrafil dec	6	1.7	2	0.4	3	3.2	0	0.0

Reference: Appendix 8 Summary Tables 9.0a and 33.0a

For many comparisons diabetics had events more frequently than all patients (and nondiabetics by subtraction). Hypercalcemia and hyperglycemia was somewhat more frequent in diabetics treated with Icodextrin. Hypokalemia was more frequently reported in diabetics on the control drug.

## LABORATORY FINDINGS

The sponsor provided summary information on the following laboratory parameters: serum sodium, serum chloride, alkaline phosphatase, serum amylase, and osmolality which results are presented below.

### Serum Sodium

Table 27: Mean Values and Mean Changes From Baseline in Sodium (mmol/L) – All Studies

Visit	Treatment Group	N	Data		Change From Baseline	
			Mean	SE	Mean	SE
Baseline	Control	341	138.431	0.195	--	--
	Extraneal	472	138.530	0.160	--	--
One Month	Control	269	138.141	0.241	-0.242	0.209
	Extraneal	299	135.592	0.212	-2.744	0.217
3 Months	Control	217	138.180	0.234	-0.343	0.230
	Extraneal	265	135.694	0.211	-2.924	0.233
6 Months	Control	173	138.075	0.288	-0.578	0.320
	Extraneal	262	135.340	0.208	-3.597	0.224
1+ Year	Control	80	138.338	0.440	0.038	0.490
	Extraneal	157	135.752	0.245	-3.142	0.310
Last Visit	Control	329	138.161	0.214	-0.272	0.219
	Extraneal	451	135.796	0.156	-2.771	0.180

SE=standard error

### Serum Chloride

Table 28: Mean Values and Mean Changes From Baseline in Chloride (mmol/L) – All Studies

Visit	Treatment Group	N	Data		Change From Baseline	
			Mean	SE	Mean	SE
Baseline	Control	268	96.795	0.301	--	--
	Extraneal	374	96.902	0.275	--	--
One Month	Control	216	97.319	0.344	0.633	0.244
	Extraneal	253	94.747	0.296	-1.729	0.282
3 Months	Control	177	98.264	0.402	0.485	0.306
	Extraneal	227	95.203	0.298	-2.325	0.301
6 Months	Control	142	98.761	0.448	0.567	0.399
	Extraneal	210	95.862	0.333	-2.538	0.349
1+ Year	Control	79	97.165	0.514	0.764	0.584
	Extraneal	136	94.566	0.631	-2.435	0.803
Last Visit	Control	285	97.627	0.306	0.610	0.263
	Extraneal	395	95.149	0.291	-2.003	0.348

SE=standard error

### Alkaline Phosphatase

Table 31: Mean Values and Mean Changes From Baseline in Alkaline Phosphatase (U/L) – All Studies

Visit	Treatment Group	N	Data		Change From Baseline	
			Mean	SE	Mean	SE
Baseline	Control	214	89.107	3.667	--	--
	Extraneal	294	92.476	3.315	--	--
One Month	Control	167	85.383	3.547	-2.527	1.292
	Extraneal	192	110.068	5.164	15.142	2.194
3 Months	Control	116	92.724	5.169	1.096	5.034
	Extraneal	165	98.333	3.778	13.417	1.953
6 Months	Control	85	100.600	6.244	6.607	6.171
	Extraneal	132	100.924	3.902	15.800	3.700
1+ Year	Control	66	102.818	7.043	6.769	7.068
	Extraneal	104	111.423	10.401	24.864	10.525
Last Visit	Control	208	93.625	3.745	4.039	2.885
	Extraneal	278	111.428	5.251	19.073	4.247

SE=standard error

## Serum Amylase

**Table 30: Mean Values and Mean Changes From Baseline in Serum Amylase (U/L) – All Studies**

Visit	Treatment		Data		Change From Baseline	
	Group	N	Mean	SE	Mean	SE
Baseline	Control	216	96.444	3.577	--	--
	Extraneal	286	98.623	3.499	--	--
One Month	Control	169	107.527	8.508	-1.677	1.780
	Extraneal	136	19.435	1.314	-95.198	5.201
3 Months	Control	119	112.235	14.233	-4.414	2.590
	Extraneal	131	29.053	2.590	-81.115	5.630
6 Months	Control	89	118.921	16.947	-5.824	3.625
	Extraneal	92	21.837	2.576	-95.304	6.798
1+ Year	Control	66	92.985	6.063	-6.045	4.042
	Extraneal	61	17.311	1.304	-108.426	7.639
Last Visit	Control	212	105.524	7.659	-3.784	2.179
	Extraneal	221	27.517	1.972	-81.004	4.343

SE=standard error

## Plasma Osmolality

**Table 29: Mean Values and Mean Changes From Baseline in Osmolality (mOsm/kg) – All Studies**

Visit	Treatment		Data		Change From Baseline	
	Group	N	Mean	SE	Mean	SE
<b>Osmolality</b>						
Baseline	Control	325	313.571	0.800	--	--
	Extraneal	441	312.986	0.663	--	--
One Month	Control	264	312.061	0.843	-1.152	0.896
	Extraneal	286	316.465	1.011	4.011	1.020
3 Months	Control	212	313.571	1.183	0.172	1.223
	Extraneal	251	314.100	0.850	0.927	1.102
6 Months	Control	165	310.234	1.012	-2.525	1.170
	Extraneal	238	313.987	0.821	0.384	1.005
1+ Year	Control	78	312.206	1.692	-1.526	1.853
	Extraneal	150	315.167	1.110	0.901	1.456
Last Visit	Control	325	312.111	0.806	-1.451	0.873
	Extraneal	427	314.365	0.707	1.404	0.831
<b>Osmolality-Vapor Pressure</b>						
Baseline	Control	16	317.813	3.389	--	--
	Extraneal	18	310.500	1.833	--	--
One Month	Control	15	315.000	2.920	-2.333	1.489
	Extraneal	18	314.111	1.501	3.611	2.108
3 Months	Control	16	313.875	3.487	-3.938	2.957
	Extraneal	16	315.125	1.281	4.250	2.120
Last Visit	Control	16	313.875	3.487	-3.938	2.957
	Extraneal	18	314.944	1.159	4.444	1.910

SE=standard error

In studies 130 and 131 decreases in serum sodium and chloride as well as serum cholesterol, amylase and AST (SGOT), and increases in alkaline phosphatase and plasma osmolality were statistically significant. The decreases in serum sodium and chloride are more likely due to increased loss in the dialysate during Icodextrin treatment per the results in the Pro-Renal study.

**MORTALITY**

The mortality result of study 131 has been discussed in that section above. The initial results were provided for those who died during the study or within 30 days after completion or withdrawal. These initial results were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	112	1827.3	5	0.005	0.000	0.128	0.06	0.00	1.44
Icodextrin	175	1680.3	13	0.008	0.000	0.156	0.10	0.00	1.88

With follow-up for 13 months post-enrollment of all randomized patients, the results were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	112	1356.1	9	0.007	0.000	0.141	0.08	0.00	1.69
Icodextrin	175	2009.6	20	0.010	0.000	0.174	0.12	0.00	2.09

For all deaths reported in study 131, the results were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	112	1364.2	12	0.009	0.000	0.163	0.11	0.00	1.96
Icodextrin	175	2022.3	22	0.011	0.000	0.182	0.13	0.00	2.19

In this summary section all deaths reported in the controlled studies submitted in the NDA were evaluated. Overview tables follow:

**Controlled Studies**

Study	N in Study	Duration of Study	Icodextrin		Dextrose	
			Deaths	%	Deaths	%
131	287	52 weeks	22	12.6	12	10.7
MIDAS	206	6 months	1	0.9	2	1.9
PRO-RENAL	39	16 weeks	3	15	0	0
DIANA	32	2 years	0	0	6	31.6

**Uncontrolled Studies**

Study	N in Study	Duration of Study	Icodextrin	
			N	%
Ideal	16	6 months	5	31
Midas II	48	53 months	12	25

For all controlled studies, the sponsor provided an analysis of all deaths as follows:

Mortality Analysis Including Additional Follow-up Data  
Based on Survival Times in Days - Survivors Have Censored Times

Treatment Group	Number Patients	Number Deaths	Percent Died	Quartiles for Survival (Days)			Mean Times to Death and 90% Confidence Intervals (Days)					p-Value*
				25th %	Median	75th %	Mean	Std Err	Lower	Upper		
Control	285	20	7.0	481	558	N/A	568.0 #	12.62	487.3	528.8	0.929	
Icodextrin	366	26	7.1	704	N/A	N/A	636.3 #	17.68	607.2	665.4		
TOTALS	651	46	7.1	541	N/A	N/A	602.6 #	17.66	573.5	631.6		

\* p-Value is from the LogRank test comparing the survival curves between groups.  
# The mean and standard error were underestimated because the largest observation was censored.  
N/A: there were not enough deaths to estimate this quartile.

Mortality Rates (per Month and per Year) Based on Poisson Estimation

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	285	2368.7	20	0.009	0.000	0.163	0.11	0.00	1.96
Icodextrin	366	2926.7	26	0.009	0.000	0.164	0.11	0.00	1.97

@ the estimated mean and 90% confidence interval are displayed.

Differences Between Mortality Rates (per Month and per Year) Based on Poisson Estimation

Equivalence of Icodextrin and Control Based on Ninety Percent (90%) Confidence Intervals

Icodextrin Mean	Control Mean	Difference (Ico - Cont)	Std Error of Difference	Equivalence Based on Deaths per Month		Equivalence Based on Deaths per Year		
				Lower 90%	Upper 90%	(Ico - Cont)	Lower 90%	Upper 90%
0.009	0.009	0.000	0.0026	-0.004	0.004	0.001	-0.051	0.053

These pooled results do not support an increased mortality risk in patients treated with Icodextrin compared to control. None of the individual study or pooled mortality comparisons were statistically significant. However, no study was sized to demonstrate a significant difference, and the adverse numerical result in study 131 was something of a surprise. While the most likely explanation for that result is chance, what was set out to be demonstrated, i.e. that Icodextrin and control had similar mortality risks, was not demonstrated. Rather than dismiss the study 131 finding, an additional long-term mortality study should be considered with the objective to rule out some predetermined mortality risk increase, taking into account the size of the study needed to do that.

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## VIII DOSING, REGIMEN, AND ADMINISTRATION ISSUES

Each 100ml of the Icodextrin peritoneal dialysis solution contains 7.5g of Icodextrin. For each 2L long-dwell dialysis, 150 g of Icodextrin would be given. Of this 30-40% is absorbed depending on the duration of the long-dwell (12±2hours generally for CAPD). For 2.5L , 187.5g of Icodextrin would be given. Since efficacy was demonstrated for both 2L and 2.5L bag sizes and no dose-related toxicity was identified, the selection of what dose to give a particular patient can be based on clinical judgment.

Concerning efficacy relevant to the duration of the long-dwell, in MIDAS 8 hour dwells were used during weeks 3,12 and 20, while 12 hour dwells were used during weeks 4, 13 and 21. A 14±2 hours long-dwell time was used in Pro-Renal, and 12±4 hours was used for study 130. The glucose concentrations used in MIDAS were "weak", i.e. 1.36% glucose, or "medium" or "strong", i.e. 2.27 or 3.86% glucose respectively.

The comparative results were provided as follows:

Table 8: Repeated Measures Analyses of Mean Change in Net Ultrafiltration for the Long Dwell Exchange

Study	MIDAS/MIDAS				RD-97-CA-130	PRO-RENAL-REG-035
	8-hr Dwell	8-hr Dwell	12-hr Dwell	12-hr Dwell	12 ± 4 hr Dwell	14 ± 2 hr Dwell
	1.5% Dextrose versus Extraneal	2.5%/3.8% Dextrose versus Extraneal	1.5% Dextrose versus Extraneal	2.5%/3.8% Dextrose versus Extraneal	2.5% Dextrose versus Extraneal	2.5% Dextrose versus Extraneal
Extraneal Adjusted Mean Change*	430	-200	479	-128	295	442
Dextrose Adjusted Mean Change*	107	-46	40	-184	70	2
Difference (Extraneal - Dextrose) for Change	322	-154	439	56	225	439
Std Error of Difference	33	61	35	75	51	67
Lower 90% Confidence Bound Difference	234	-216	346	-48	141	328
Upper 90% Confidence Bound Difference	411	-12	532	181	308	551
p-value**	<0.001	0.066	<0.001	0.453	<0.001	<0.001

\* The adjusted mean changes from the repeated measures analysis of covariance, with Baseline values as the covariate, for each treatment group. A 90% confidence interval was constructed around the difference between Extraneal and dextrose.

\*\* This p-value is from the two-sided test for treatment differences using the repeated measures analysis of covariance.

Reference: Appendix 2 Summary Tables 5.1.1, 5.2.1, 5.3.1, 5.4.1, 5.5.1, and 5.6.1

Interpolating between trials it can be inferred that duration of the long-dwell does not much affect the net ultrafiltration benefit of Icodextrin versus 1.5% or 2.5% Dextrose.

Since the proposed market image of Icodextrin will include only the PD-2 electrolyte solution with contains 25.7mg/100ml calcium chloride, those patients who are taking Dextrose with PD-4 solution containing 18.3mg/100ml calcium chloride will be given the slightly higher calcium dose for the long-dwell. No case has been identified where this was associated with an adverse reaction. However, since a particular patient may be affected by the higher calcium dose, physician's should be informed that use of Icodextrin for the long-dwell will include the slightly higher calcium dose as well.

## IX. USE IN SPECIAL POPULATIONS

No children have been studied.

Analyses of the studies by age, Caucasian or Black race, gender, diabetic status, and hypertension have been carried out. All showed a similar direction of net ultrafiltration benefit compared to the total randomized population. Concerning Asian or Hispanic patients, too few were included to draw meaningful conclusions about efficacy or safety.

## X. CONCLUSIONS and RECOMMENDATIONS:

Icodextrin is an effective peritoneal dialysis drug based on historical expectations of patient outcome without it. It is more effective than 1.5% and 2.5% Dextrose in net ultrafiltration during the log-dwell dialysis period, but it has not been shown in the studies provided to provide a clinical benefit. However, it would be useful to have an alternative dialysis drug available for patients not adequately responding to their current regimen.

From a safety perspective, the mortality results in study 131 remain a concern. While this might be due to chance, it would be advisable to repeat that study. In addition to the mortality results, other findings such as rash and the laboratory abnormalities associated with the drug should be noted in the labeling.

Therefore, approval is recommended for the treatment of ESRD patients undergoing CAPD or APD during the single daily long-dwell 8-16 hours periods for those not adequately responding to their current regimen. A phase 4 commitment to repeat a mortality study similar to study 131.

**XI. LABELING**

The sponsor's draft labeling with additional comments on the medical sections follow.

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this page is the manifestation of the electronic signature.**

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/s/

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Stephan Fredd  
6/8/01 08:32:51 AM  
MEDICAL OFFICER

12/28/01  
TO: NDA 21321  
FROM: Stephen Fredd M.D.  
Subject: Safety Update

In response to the approvable letter of 10/22/01, Baxter submitted a safety update for Icodextrin peritoneal dialysis solution on 12/11/01.

This one volume submission contains safety information from two completed Japanese studies: BLR-PG21 and BLR-PG22.

BLR-PG21 was an open labeled, uncontrolled study of Icodextrin used for 6 weeks in 18 CAPD patients. 15 patients reported 51 adverse events including URIs, cough, pruritis, anorexia. One serious adverse event (pneumonia with hospitalization) was reported. No patient died or was discontinued for an adverse experience.

BLR-PG22 was a multicenter, randomized comparison of Icodextrin and Dianeal in 54 CAPD patients treated for 6 weeks. No deaths were reported. One patient in each treatment group withdrew for an adverse experience; for peritonitis in the Icodextrin treated patient, and pulmonary carcinoma in the control patient. Another Icodextrin treated patient developed infectious enteritis as a serious adverse event but was not withdrawn. Of the non-serious events reported 67 occurred in the Icodextrin patients and 71 in the control patients. Of these skin events were more frequent in the Icodextrin patients than control (23.1% versus 3.6%). Chemistry changes occurred in the Icodextrin group compared to the control patients as was noted in the original NDA studies. These included elevations of alkaline phosphatase, decreases in serum amylase as well sodium and chloride.

The safety results in this update do not reveal new or different findings than already documented in the NDA medical review.

Of the published articles submitted, one, CLINICAL EXPERIENCE WITH ICODEXTRIN IN CHILDREN: ULTRAFILTRATION PROFILES AND METABOLISM, Pediatric Nephrology (2000) 15:21-24, suggests usefulness of Icodextrin in children with chronic renal disease necessitating peritoneal dialysis.

Finally the sponsor provides a summary of foreign spontaneous reports including 26 of pain on infusion/abdominal pain/ discomfort and 8 of cloudy effluent/sterile peritonitis.

Conclusions: The safety data provided in this update is consistent with what has been noted in review of the original NDA studies.

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this page is the manifestation of the electronic signature.**

/s/

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Stephan Fredd  
12/28/01 10:18:44 AM  
MEDICAL OFFICER

**Safety Update**

Per the sponsor, the safety update is "To be filed as required." The sponsor is awaiting the action letter before they submit the Safety Update.

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