FULL METHODS

Trial design

The low glucose clinical study program consisted of the IMPENDIA (Improved Metabolic control of Physioneal, Extraneal, and Nutrineal (P-E-N) versus Dianeal only treatment in DIAbetic peritoneal dialysis [PD] patients) and EDEN (Evaluation of Dianeal, Extraneal, and Nutrineal (D-E-N) in diabetic PD patients) clinical trials. IMPENDIA was a Phase III protocol in Canada, Australia, and New Zealand (Clinicaltrials.gov registration NCT00567398) and a Phase IV protocol in Europe and Asia (NCT00567489). The EDEN trial was a Phase III protocol performed in Colombia (NCT01219959). The EDEN trial was added as a result of insufficient enrollment into the IMPENDIA study. However, because of the unavailability of the Physioneal solutions in Colombia, Dianeal was used instead. The Phase III nature of the trials in Canada, Australia, New Zealand and Colombia were due to country-specific regulatory requirements for the use of Nutrineal. Both IMPENDIA and EDEN were randomized, controlled, open label, parallel group, multi-center trials that compared the effects of a P-E-N or D-E-N PD regimen to a Dianeal only regimen in diabetic continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) patients over a 6 month study period.

In the IMPENDIA study, patients were randomized to control (Dianeal only) or test (P-E-N) using a centralized randomization scheme and implemented using a web based automated randomization system. Patients were assigned the next available patient number at the time of randomization. A 1:1 stratified randomization scheme was carried out in which randomization was stratified by centers and by Informed Consent status (i.e., Informed Consent to participate in the sub-group evaluation, yes or no) in a manner designed to maintain approximate balance between the two treatment groups (Dianeal only versus P-E-N) both within and between centers and within the sub-group of patients who consent to the sub-group evaluations.

In the EDEN study, patients were randomized to control (Dianeal only) or test (D-E-N) using a centralized randomization scheme and implemented using a web based automated randomization system. Patients were assigned the next available patient number at the time of randomization. A 1:1 stratified randomization scheme was carried out in which randomization was stratified by center in a manner designed to maintain approximate balance between the two treatment groups (Dianeal only versus D-E-N) within and between centers.

The primary efficacy endpoint of the glucose-sparing clinical trial program was change in HbA1c from baseline to 6 months. Secondary efficacy endpoints included:

- Change from baseline value in metabolic control parameters, including total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, very low density lipoprotein, triglycerides, lipoprotein(a), apolipoprotein A1, apolipoprotein B, pro-insulin, insulin, and c-peptide.

- Change in glycemic control mediation usage as defined by change in medication dose and usage (assessed using a 7-day glycemic-control medication usage diary).

- Change in the number of severe hypoglycemic events requiring medical intervention, as defined according to the criteria used in the Diabetes Control and Complications Trial.

- Change from baseline value in nutritional status, as measured by the Subjective Global Assessment test, total protein, serum albumin, body mass index, and drained body weight (measured after the drainage of PD effluent).

- Quality of life as measured by the Diabetes Symptom Checklist and the European Quality of Life 5 Dimensions (EuroQol-5D) score.

- Change in composition and distribution of abdominal fat and in left ventricular structure and function as measured by abdominal and cardiac magnetic resonance imaging, respectively. This secondary endpoint was only assessed in a pre-specified subgroup of study participants.

Assessment of the primary and secondary outcome parameters occurred at screening and baseline visits, a mid-study visit (for the majority of subjects this occurred 3 months after start of study solutions), and an end-of-study visit 6 months after the start of study solutions. HbA1c and other biochemical secondary endpoint parameters were obtained with subjects fasting for 10 hours (nil per os and no dwelling PD solution) and were measured at a central lab (Baxter's Clinical Laboratory Services, Round Lake, IL, USA) using validated techniques. For the HbA1c measurement, a Tina-quant® immunological assay (Roche Diagnostic) suitable for samples from end-stage renal disease patients, including patients with icodextrin metabolites, was utilized.

The sample size for the glucose-sparing clinical study program was based on the goal to detect a 10% difference in the mean change from the baseline value of HbA1c between subjects randomized to the intervention and control groups. To calculate the sample size required to detect this 10% difference, the following assumptions were made: 1) the mean HbA1c would be between 7.1 and 7.9 with a standard deviation of 2.0, and a correlation between the baseline value and 6-month HbA1c of 0.50; 2) the control group would have a mean HbA1c at baseline of 7.5, with no change anticipated over the 6 months of follow-up; 3) the intervention group would have a mean HbA1c of 7.5 at the baseline measurement and a 10% reduction (i.e., an average absolute decline of 0.75 in HbA1c) in the average HbA1c over the 6 months of follow-up. Based on a two-group repeated measures analysis of variance (RM-ANOVA) F-test carried out at the 5% level of significance, a sample of 100 evaluable subjects per group would provide 90% power to detect a 10%, in aggregate, average difference in the mean change from the baseline value for HbA1c. It was anticipated that an annual dropout rate of approximately 30% would occur during the study. Therefore, to achieve a target of 100 evaluable subjects per group, randomization of 118 subjects per group would be necessary, for a desired total sample of 236 subjects.

The eligible study population included incident and prevalent Type 1 and Type 2 diabetic patients, aged 18 years or older, who had been performing CAPD or APD for at least 30 days. Patients using only Dianeal and/or Physioneal solutions were included. To prevent volume depletion if randomized to the intervention group (which included one bag of Extraneal daily), eligible patients were also required to have at least one exchange daily of 2.5% or 4.25% dextrose (2.27% or 3.86% glucose) during screening to reduce the risk of hypovolemia induced by Extraneal. Eligibility criteria also included a HbA1c level >6.0% but ≤12.0%, a blood hemoglobin concentration of ≥8.0 g/dL but ≤13.0 g/dL, and a total weekly Kt/V ≥1.7. Patients entering into the study were expected to remain on PD for at least 6 months, the duration of the study period.

Patients were excluded from consideration if they had any of the following at time of screening: blood urea nitrogen > 95 mg/dL; exposure to Extraneal within 60 days of screening; mean arterial pressure ≥ 125 mm Hg or <77 mm Hg at screening; peritonitis, exit-site or tunnel infection treated with antibiotics within the last 30 days; cardiovascular event within the last 30 days; ongoing clinically significant congestive heart failure (New York Heart Association class III

or IV); allergy to starch-based polymers, glycogen storage disease or isomaltose/maltose intolerance; or receiving rosiglitazone maleate.

Subjects randomized to the intervention received a 24-hour combination of Physioneal (1-3 exchanges daily for CAPD patients, up to 16L for APD patients), Nutrineal (1 exchange daily), and Extraneal (the long dwell exchange daily). (In the EDEN trial, subjects randomized to the intervention group received Dianeal instead of Physioneal. Both Dianeal and Physioneal have similar glucose concentrations, thereby assuring that the glucose-sparing hypotheses was tested in a similar manner for IMPENDIA and EDEN subjects). Subjects randomized to the control group continued on Dianeal for all exchanges in a 24-hour period, with 3 to 5 daily exchanges permitted for CAPD subjects and up to 20L daily for APD subjects. Dry periods were not allowed in the 24-hour prescriptions of either group. The prescribed fill volume (1.5-3.0 L) of the solutions, or number of cycles, was based on the subject's pre-randomization prescription and could be modified by the investigator as clinically required. Subjects were required to remain on their dialysis modality (CAPD or APD) in use at the time of randomization. PD prescriptions in both treatment arms were tailored to reach a minimum target total Kt/V of 1.7 per week throughout the study as per local standards of care.

The IMPENDIA trial commenced enrollment of eligible CAPD patients in February 2008. The study protocol was amended in November 2008 to address lower than anticipated recruitment. The following key changes were made to the protocol to increase the rate of recruitment:

- Inclusion criteria were broadened to include patients treated by APD
- The inclusion upper limit value for HbA1c was raised to ≤12.0% (from ≤10.0%,)
- The inclusion lower limit value for hemoglobin was lowered to ≥8.0 g/dL (from ≥9.0 g/dL) to reflect standard of practice at some sites.
- The inclusion criteria requiring subjects to use glycemic-control medication was deleted.
- The visit schedule was changed to have fewer clinic visits to reduce the burden on the subjects and the clinical sites. Study visits for months 2 and 4 were replaced by a singular visit at month 3.

To further improve recruitment, while maintaining the need to test the glucose-sparing hypothesis, the EDEN trial commenced enrollment for eligible subjects in October 2010. Enrollment was complete in January, 2011 for both the IMPENDIA and EDEN trial, and the last

subject finished all study-related procedures in July, 2011. The IMPENDIA trial was conducted at 37 sites distributed as follows: Russia (7), Hong Kong (4), Korea (6), Australia (8), New Zealand (2), Canada (4), Taiwan (2), Singapore (2), France (1), and Portugal (1). The EDEN trial was conducted at 16 sites in Colombia.

All subjects were required to provide informed consent after the nature of the study had been explained, but prior to the initiation of any trial-related activities. Ethics approval for the IMPENDIA and EDEN trials was obtained from the local research ethics boards in all participating centers prior to study initiation and patient enrollment. The studies were conducted in accordance with the Declaration of Helsinki and applicable International Conference on Harmonisation (ICH) guidelines, and all study coordinators and investigators followed international good clinical practice guidelines.

Statistical methods

Prior to completion of either clinical trial or database lock, the statistical plan was developed to combine both clinical trials in order to achieve the desired sample size for the primary endpoint.

Two populations were identified for the efficacy analysis on the primary endpoint: (1) the intention-to-treat (ITT) population included all subjects who were randomized and for whom, at a minimum, the baseline value of HbA1c measured at screening was determined and one PD exchange using a study solution was performed, and (2) the per-protocol (PP) patient population which included all ITT subjects who completed the study and had, at a minimum, their 6-month HbA1c value measured. A safety ITT analysis was also performed which included all subjects who were randomized regardless of subsequent measurement of HbA1c or exposure to study solutions.

The primary efficacy analysis was carried out for both the ITT and PP patient population. A RM-ANOVA was carried out comparing the HbA1c mean change from the baseline profile between the two groups using a generalized estimating equations (GEE) approach. Under the GEE approach, a common standard deviation and common correlation across the repeated measurements was assumed through the specification of a patient-specific random intercept. Under the RM-ANOVA, time (t=0, mid-study and 6 months where t=0 refers to baseline value), treatment group (Dianeal only versus P-E-N/D-E-N) and their interaction (time $\times$ treatment group) served as the primary independent class variables. No confounding baseline variables

were found so no additional covariates were added to the model. Mean change from baseline value at mid-study and 6 months was summarized for each treatment group and comparisons between the two groups were made based on the RM-ANOVA model. To safeguard against model misspecification with respect to assumptions about the standard deviation and common correlation (compound symmetry) over time, all analyses (e.g., confidence intervals, tests of hypotheses) were done using robust standard error estimates. A *P* value of <0.05 for either the treatment effect or the treatment by time interaction was evidence that the treatment groups were different.

For the secondary efficacy endpoints a RM-ANOVA was also carried out that is consistent with the generalized linear model (GLIM) and link function appropriate to the particular endpoint analyzed. Specifically, one of the following general analytical approaches was applied depending on the type of secondary endpoint (i.e., continuous, binary, ordinal, or count data) analyzed:

1. For continuous longitudinal data, RM-ANOVA was done assuming a GLIM with an identity link for normally distributed data. A common standard deviation and common correlation across the repeated measurements was assumed through specification of a patient-specific random intercept. When necessary, analyses of select continuous variables were used based on a log-transformation (or some other suitably determined transformation) depending on departures from an assumed Gaussian distribution.
2. For discrete longitudinal binary data, RM-ANOVA was done assuming a GLIM with a logit link for binary data. This was carried out using a logistic regression model with a working independence correlation structure.
3. For discrete longitudinal ordinal data, RM-ANOVA was done assuming a GLIM with a cumulative logit link for multinomial data. This was carried out using a proportional odds logistic regression model with a working independence correlation structure.
4. For discrete longitudinal count data, RM-ANOVA was done assuming a GLIM with a log link for count data. This was carried out using a Poisson regression model with working independence structure.

In each case, RM-ANOVA incorporated time (corresponding to those visits when the endpoint of interest was measured), treatment group (Dianeal only versus P-E-N/D-E-N), and their

interaction (time × treatment group) as the primary independent class variables. Results were summarized at each time point and, when appropriate (i.e., for endpoints measured after baseline), results were also summarized in terms of change from baseline. For binary and ordinal data, percentages and odds ratios were summarized together with corresponding 95% confidence intervals while count data, mean counts and rate ratios were summarized together with corresponding 95% confidence intervals. To safeguard against model misspecification with respect to assumptions about the standard deviation and correlation structure over time, all analyses (e.g., confidence intervals, tests of hypotheses) were conducted using robust standard errors.

Subject Baseline Characteristics (IMPENDIA only)

Variable[a]	Control Group (Dianeal only) (*n* = 91)	Intervention Group (P-E-N) (*n* = 89)
Age, years	58 ± 14	57 ± 12
Female	45 (50)	44 (49)
Male	46 (50)	45 (51)
Race		
Asian	41 (45)	42 (47)
Caucasian	41 (45)	41 (46)
Hispanic	0 (0)	0 (0)
Other	9 (10)	6 (7)
Country		
Australia	8 (9)	9 (10)
Canada	6 (7)	3 (3)
France	1 (1)	0 (0)
Hong Kong	21 (23)	19 (21)
Korea	13 (14)	12 (13)
New Zealand	9 (10)	8 (9)
Portugal	1 (1)	0 (0)
Russia	29 (32)	30 (34)
Singapore	1 (1)	2 (2)
Taiwan	2 (2)	6 (7)
BMI, kg/m^2	27 ± 5	26 ± 4
CAPD	82 (90)	87 (98)
Diabetes		

Type 1	20 (22)	26 (29)
Type 2	71 (78)	63 (71)
Dialysis vintage, yrs	1.5 ± 1.8	1.5 ± 2.1
SGA classification		
Well nourished	69 (76)	60 (68)
Mild to moderate malnutrition	22 (24)	29 (32)
Severe malnutrition	0 (0)	0 (0)
Blood pressure, mmHg		
Systolic	138 ± 19	140 ± 19
Diastolic	76 ± 12	78 ± 12
HbA_{1c}, %	7.5 ± 1.1	7.6 ± 1.2
Hemoglobin, g/L	106 ± 15	109 ± 13
Blood urea nitrogen, mmol/L	21 ± 6	21 ± 6

BMI, body mass index; CAPD, continuous ambulatory peritoneal dialysis; SGA, Subjective Global Assessment.

[a]Data are presented as *n* (%) or mean ± standard deviation.

Subject Baseline Characteristics (EDEN only)

Variable[a]	Control Group (Dianeal only) (*n* = 36)	Intervention Group (D-E-N) (*n* = 35)
Age, years	59 ± 10	58 ± 12
Female	14 (39)	20 (57)
Male	22 (61)	15 (43)
Race		
Asian	0 (0)	0 (0)
Caucasian	0 (0)	0 (0)
Hispanic	32 (89)	31 (89)
Other	4 (11)	4 (11)
Country		
Colombia	36 (100)	35 (100)
BMI, kg/m^2	26 ± 4	27 ± 4
CAPD	36 (100)	35 (100)
Diabetes		
Type 1	1 (3)	1 (3)
Type 2	35 (97)	34 (97)
Dialysis vintage, yrs	2.4 ± 2.5	1.4 ± 0.8
SGA classification		
Well nourished	34 (95)	28 (80)
Mild to moderate malnutrition	2 (5)	7 (20)
Severe malnutrition	0 (0)	0 (0)
Blood pressure, mmHg		
Systolic	139 ± 18	146 ± 16

Diastolic	80 ± 12	82 ± 9
HbA_{1c}, %	7.9 ± 1.3	8.0 ± 1.4
Hemoglobin, g/L	114 ± 13	114 ± 12
Blood urea nitrogen, mmol/L	19 ± 6	19 ± 7

BMI, body mass index; CAPD, continuous ambulatory peritoneal dialysis; SGA, Subjective Global Assessment.

[a]Data are presented as *n* (%) or mean ± standard deviation.

Primary and secondary outcomes (IMPENDIA only)

Endpoint[a]	Control group (Dianeal only)			Intervention group (P-E-N)			Treatment difference between groups[b]		
	Baseline	Month 3	Month 6	Baseline	Month 3	Month 6	Control - intervention	95% CI	*P* value
Glycemic control									
HbA_{1C}, %	7.5 ± 1.1	7.7 ± 1.4	7.4 ± 1.2	7.6 ± 1.2	7.3 ± 1.3	7.2 ± 1.2	0.3	0.0–0.7	0.07
Metabolic control									
Total cholesterol, mmol/L	5.2 ± 1.6	5.3 ± 1.7	5.1 ± 1.7	5.1 ± 1.5	4.8 ± 1.4	4.7 ± 1.3	0.4	0.0–0.8	0.08
LDL cholesterol, mmol/L	2.8 ± 1.2	3.0 ± 1.3	2.8 ± 1.3	2.9 ± 1.3	2.7 ± 1.1	2.7 ± 1.1	0.1	-0.3–0.5	0.58
HDL cholesterol, mmol/L	1.1 ± 0.4	1.1 ± 0.3	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	0.0	-0.1–0.1	0.51
VLDL cholesterol, mmol/L	0.9 (0.2–12.6)	0.8 (0.3–6.0)	0.8 (0.1–7.7)	0.8 (0.3–6.8)	0.8 (0.2–2.7)	0.8 (0.2–2.9)	0.3	0.1–0.6	0.009
Serum TG, mmol/L	2.0 (0.4–27.7)	2.0 (0.6–13.2)	1.8 (0.5–16.9)	1.9 (0.6–15.0)	1.8 (0.4–6.0)	1.7 (0.7–6.3)	0.8.	0.2–1.3	0.005
Apolipoprotein A1, mg/dL	136 ± 29	137 ± 28	132 ± 28	138 ± 27	132 ± 27	129 ± 26	3.4	-4.8–11.5	0.42
Apolipoprotein B, mg/dL	96 ± 30	100 ± 34	95 ± 33	95 ± 28	89 ± 27	87 ± 28	9.2	0.2–18.3	0.05
Lipoprotein(a), mg/dL	14 (2–125)	14 (2 –149)	13 (2–171)	15 (2–102)	22 (2–113)	18 (2–140)	-3.7	-10.6–3.3	0.30
Pro-insulin, pmol/L	14 (3–1187)	14 (3–193)	14 (3–1475)	15 (3–240)	17 (3–752)	19 (3–285)	20.3	-10.4–50.9	0.19
Insulin, pg/mL	488 (137–3674)	510 (137–3436)	443 (137–6190)	430 (137–7354)	561 (137–4592)	513 (137–8155)	-59	-365–247	0.71
C-peptide, pg/mL	3432 (69–20058)	3149 (69–20743)	3238 (69–16940)	2630 (69–17287)	3620 (69–22325)	3382 (69–19087)	124	-1149–1397	0.85
Glycemic control medications									
Daily insulin use, units	20 (0–224)	20 (0–398)	24 (0–706)	28 (0–168)	22 (0–168)	24 (0–168)	14.3	-4.2–32.7	0.13

Severe hypoglycemia									
Number of events	0		0	0		3	NA	NA	NA
Nutritional status[c]									
Serum albumin, g/L	35.4 ± 4.3	35.6 ± 4.5	36.1 ± 4.2	35.2 ± 4.1	35.7 ± 3.7	35.0 ± 4.1	1.1	-0.1–2.4	0.07
Total protein, g/L	65.5 ± 6.8	65.4 ± 6.7	66.2 ± 6.4	65.1 ± 6.3	65.6 ± 6.0	64.9 ± 5.6	1.3	-0.5–3.1	0.14
Body mass index, kg/m^2	26.9 ± 5.0	26.9 ± 5.0	27.2 ± 5.0	26.4 ± 4.2	26.3 ± 4.4	26.1 ± 4.4	1.1	-0.3–2.5	0.12
Drained body weight, kg	71.7 ± 16.0	71.6 ± 15.6	72.3 ± 15.5	70.6 ± 13.7	70.1 ± 14.7	69.7 ± 14.7	2.5	-1.8–6.9	0.26
Quality of life									
EuroQOL-5D health status	56.7 ± 25.3	54.9 ± 26.2	55.9 ± 27.1	55.2 ± 27.3	56.5 ± 28.3	58.8 ± 28.9	-3.1	-11.2–5.1	0.46
EuroQOL-5D index	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.0	-0.1–0.0	0.14
Abdominal fat composition									
Visceral fat volume, mL	234 (71–885)		197 (42–906)	227 (77–858)		150 (33–510)	55	-7–118	0.08
Subcutaneous fat volume, mL	307 (107–693)		326 (115–664)	245 (99–828)		270 (85–664)	25	-47–96	0.50
LV mass and function									
LV mass, g	128 ± 37		132 ± 60	128 ± 45		124 ± 39	2.3	-18.9–23.4	0.83
Ejection fraction, %	59 ± 14		58 ± 17	57 ± 14		58 ± 14	-0.2	-5.3–7.7	0.72

[a]Data are presented as mean ± standard deviation or median (range).

[b]Difference between groups calculated using analysis of variance with repeated measures and represents the comparison of change from baseline between groups.

[c]Subjective Global Assessment was also a secondary endpoint within the nutritional status category. Results are not shown in this table due to the ordered ordinal nature of the data. Using a proportional odds logistic regression model with a working independence correlation structure, no difference was observed between treatment groups.

LDL = low density lipoprotein; HDL = high density lipoprotein; VLDL = very-low density lipoprotein; TG = triglycerides; EuroQOL-5D = European Quality of Life 5 Dimensions; LV = left ventricular

Primary and secondary outcomes (EDEN only)

Endpoint[a]	Control group (Dianeal only)			Intervention group (D-E-N)			Treatment difference between groups[b]		
	Baseline	Month 3	Month 6	Baseline	Month 3	Month 6	Control - intervention	95% CI	*P* value
Glycemic control									
HbA_{1C}, %	7.9 ± 1.3	7.8 ± 1.3	7.8 ± 1.5	8.0 ± 1.4	7.0 ± 1.1	7.1 ± 1.4	0.8	0.1–1.5	0.03
Metabolic control									
Total cholesterol, mmol/L	4.9 ± 0.8	5.0 ± 1.4	5.0 ± 1.3	5.4 ± 1.3	4.8 ± 1.2	4.9 ± 1.2	0.2	-0.4–0.8	0.54
LDL cholesterol, mmol/L	2.6 ± 0.8	2.9 ± 1.2	3.0 ± 1.2	3.2 ± 1.0	2.8 ± 1.0	3.0 ± 1.0	0.1	-0.5–0.6	0.82
HDL cholesterol, mmol/L	0.9 ± 0.2	0.9 ± 0.3	0.9 ± 0.3	1.1 ± 0.3	1.1 ± 0.4	1.0 ± 0.3	-0.1	-0.2–0.1	0.38
VLDL cholesterol, mmol/L	1.0 (0.3–3.9)	1.0 (0.4–3.8)	1.1 (0.3–2.9)	1.0 (0.4–2.8)	0.7 (0.2–2.4)	0.8 (0.3–3.3)	0.2	-0.1–0.5	0.17
Serum TG, mmol/L	2.2 (0.7-8.6)	2.3 (0.9–8.5)	2.4 (0.6–6.0)	2.2 (0.8–6.2)	1.7 (0.4–5.2)	1.8 (0.7–7.3)	0.4.	-0.2–1.0	0.18
Apolipoprotein A1, mg/dL	129 ± 16	124 ± 19	124 ± 16	130 ± 19	116 ± 21	113 ± 21	10	1–19	0.03
Apolipoprotein B, mg/dL	88 ± 21	96 ± 33	107 ± 32	96 ± 24	87 ± 20	101 ± 28	6	-8–19	0.40
Lipoprotein(a), mg/dL	11 (2–89)	13 (2 –91)	26 (2–144)	9 (2–82)	11 (2–99)	19 (2–139)	2	-12–16	0.78
Pro-insulin, pmol/L	23 (3-244)	19 (3–187)	17 (3–125)	19 (3–69)	20 (4–377)	19 (3–241)	5	-26–16	0.62
Insulin, pg/mL	459 (70–2347)	386 (137–4119)	491 (137–3080)	402 (87–1284)	420 (131–3142)	414 (137–3403)	49	-268–366	0.76
C-peptide, pg/mL	4130 (69–15410)	4190 (69–15856)	4468 (69–19581)	3071 (325–15390)	3685 (392–10463)	4782 (334–23126)	172	-1692–2037	0.85
Glycemic control medications									
Daily insulin use, units	21 (0–110)	29 (0–244)	28 (0–140)	20 (0–131)	20 (0–154)	22 (0–258)	-1.7	-21–18	0.86

Severe hypoglycemia									
Number of events	0		0	0		1	NA	NA	NA
Nutritional status[c]									
Serum albumin, g/L	33.4 ± 4.4	32.1 ± 5.6	33.2 ± 5.3	33.5 ± 4.4	31.3 ± 5.0	31.7 ± 4.8	2.0	-0.5–4.6	0.12
Total protein, g/L	60.9 ± 5.2	59.7 ± 6.3	61.5 ± 5.4	61.7 ± 5.9	61.4 ± 4.3	60.0 ± 4.5	1.8	-0.7–4.3	0.17
Body mass index, kg/m^2	25.8 ± 4.2	25.5 ± 3.9	25.3 ± 4.0	27.5 ± 4.1	27.9 ± 4.5	28.3 ± 4.6	-1.7	-3.7–0.3	0.09
Drained body weight, kg	67.7 ± 13.5	67.0 ± 13.2	66.7 ± 13.9	71.5 ± 13.6	73.9 ± 14.5	74.5 ± 15.0	-4.0	-10.5–2.6	0.23
Quality of life									
EuroQOL-5D health status	80.9 ± 16.4	76.3 ± 15.9	75.8 ± 18.5	77.3 ± 16.8	69.3 ± 20.0	69.7 ± 21.5	7.2	-2.3–16.7	0.14
EuroQOL-5D index	0.8 ± 0.2	0.7 ± 0.2	0.7 ± 0.3	0.8 ± 0.2	0.7 ± 0.3	0.7 ± 0.3	0.0	-0.1–0.2	0.53

[a]Data are presented as mean ± standard deviation or median (range).

[b]Difference between groups calculated using analysis of variance with repeated measures and represents the comparison of change from baseline between groups.

[c]Subjective Global Assessment was also a secondary endpoint within the nutritional status category. Results are not shown in this table due to the ordered ordinal nature of the data. Using a proportional odds logistic regression model with a working independence correlation structure, no difference was observed between treatment groups.

LDL = low density lipoprotein; HDL = high density lipoprotein; VLDL = very-low density lipoprotein; TG = triglycerides; EuroQOL-5D = European Quality of Life 5 Dimensions

Adverse events and serious adverse events by treatment group (IMPENDIA study)

Category		All adverse events, *n* (related adverse events, *n*)[a]		Serious adverse events, n (related serious adverse events, *n*)[a]	
		Control group *n* = 91	Intervention group *n* = 89	Control group *n* = 91	Intervention group *n* = 89
Cardiovascular					
Ischemic heart disease		6 (1)	2	2	2
Edema/fluid overload		36 (7)	18 (3)	7 (2)	7 (1)
Hypertension		13 (1)	7	1 (1)	1
Hypotension/dehydration		6	8 (3)	3	1 (1)
Peripheral vascular		6	1	4	1
Hypertensive crisis/urgency/encephalopathy		0	0	0	0
Heart failure		1	2	1	2
Cardiac arrest/sudden death		0	1	0	1
Other		2 (2)	2	0	0
	Subtotal	**70 (11)**	**41 (6)**	**18 (3)**	**15 (2)**
Infectious					
Peritonitis		19	15	7	11
Respiratory		10	13	4	2
Abscess/cellulitis		1	6	0	5
Catheter site/exit site infection		5	5	0	0
Other		12	12	5	4
	Subtotal	**47 (0)**	**51 (0)**	**16 (0)**	**22 (0)**
Gastrointestinal and hepatobiliary					
Pain and discomfort		11	20 (1)	3	2
Nausea, vomiting or decreased appetite		12	13	0	0
Malnutrition		3	5	0	0
Other		7	9	0	2
	Subtotal	**33 (0)**	**47 (1)**	**3 (0)**	**4 (0)**
Endocrine					
Hypoglycemia		1 (1)	13 (4)	0	3 (1)
Hyperglycemia		3 (1)	4 (2)	2 (1)	1
Hyperparathyroidism or increased PTH		5	1	0	0
Other		9 (1)	4	2	1

	Subtotal	**18 (3)**	**22 (6)**	**4 (1)**	**5 (1)**
Neuromuscular/musculoskeletal					
Pain		7	10 (1)	0	1
Peripheral neuropathy		7	4	1	0
Cerebrovascular		4	1	4	1
Dizziness		3	2	1	0
Seizures		0	1	0	1
Headache		0	2	0	0
Other		5	7	1	2
	Subtotal	**26 (0)**	**27 (1)**	**7 (0)**	**5 (0)**
Respiratory					
Cough		8	4	0	0
Other		5	5	0	0
	Subtotal	**13 (0)**	**9 (0)**	**0 (0)**	**0 (0)**
Non-specific skin rash and other skin disorders		6	11 (3)	0	1
Allergic/immune system disorders		0	1	0	0
Abnormal blood tests, not otherwise specified		17	18	2	1
Non-infectious catheter or exit site complications		9	7	2	3
Eye, ear and throat disorders		12	9	1	2
Blood and lymphatic system disorders		6	8	2	2
Other		18	23 (3)	3	3
	TOTAL	**275 (14)**	**274 (20)**	**58 (4)**	**63 (3)**
Number of subjects with any adverse event or serious adverse event (% of total group sample)		**71 (78%)**	**68 (76%)**	**29 (32%)**	**36 (40%)**

[a]Relatedness to the study PD solutions was judged by the clinical trial site investigator

PTH = parathyroid hormone

Adverse events and serious adverse events by treatment group (EDEN study)

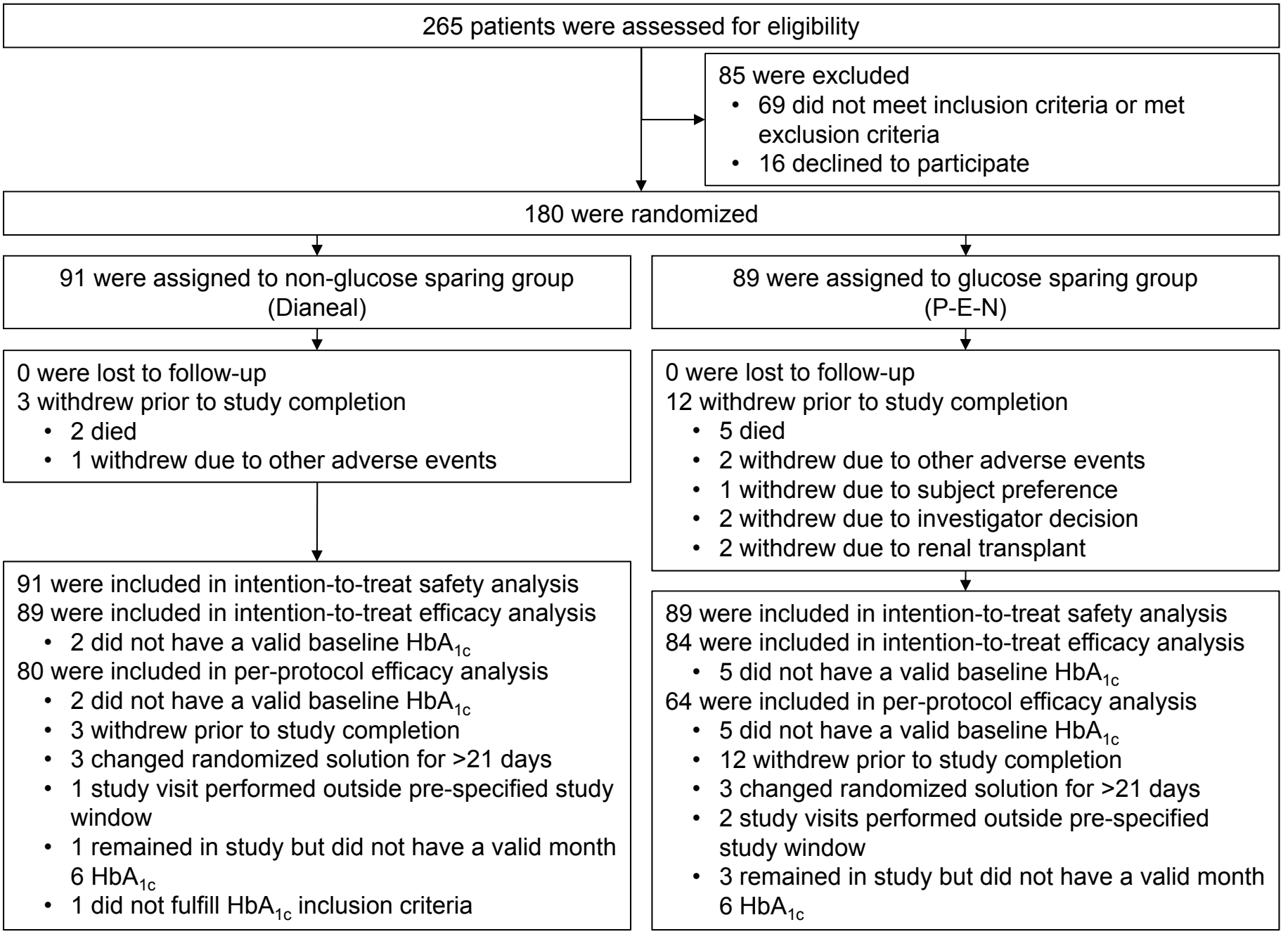
Category		All adverse events, *n* (related adverse events, *n*)[a]		Serious adverse events, *n* (related serious adverse events, *n*)[a]	
		Control group *n* = 36	Intervention group *n* = 35	Control group *n* = 36	Intervention group *n* = 35
Cardiovascular					
Ischemic heart disease		3	0	3	0
Edema/fluid overload		2	1	0	1
Hypertension		1	1	0	0
Hypotension/dehydration		2	0	0	0
Peripheral vascular		2	4	1	2
Hypertensive crisis/urgency /encephalopathy		1	7	1	7
Heart failure		0	4	0	4
Cardiac arrest/sudden death		1	2	1	2
Other		3	3	0	0
	Subtotal	**15 (0)**	**22 (0)**	**6 (0)**	**16 (0)**
Infectious					
Peritonitis		10	12	4	6
Respiratory		0	5	0	4
Abscess/cellulitis		3	4	3	3
Catheter site/exit site infection		1	2	0	0
Other		10	8	5	3
	Subtotal	**24 (0)**	**31 (0)**	**12 (0)**	**16 (0)**
Gastrointestinal and hepatobiliary					
Pain and discomfort		2	6 (2)	0	2
Nausea, vomiting or decreased appetite		2	7 (3)	0	0
Malnutrition		2	2	0	0
Other		4	2	0	0
	Subtotal	**10 (0)**	**17 (5)**	**0 (0)**	**2 (0)**
Endocrine					
Hypoglycemia		3	2 (1)	0	1 (1)
Hyperglycemia		1	1	0	0
Hyperparathyroidism or increased PTH		0	0	0	0
Other		0	1	0	0
	Subtotal	**4 (0)**	**4 (1)**	**0 (0)**	**1 (1)**

Neuromuscular/musculoskeletal					
Pain		5	2 (2)	2	0
Peripheral neuropathy		0	3	0	1
Cerebrovascular		0	0	0	0
Dizziness		0	0	0	0
Seizures		0	2	0	2
Headache		0	1 (1)	0	0
Other		2	1	0	0
	Subtotal	**7 (0)**	**9 (3)**	**2 (0)**	**3 (0)**
Respiratory					
Cough		0	0	0	0
Other		0	1	0	1
	Subtotal	**0 (0)**	**1 (0)**	**0 (0)**	**1 (0)**
Non-specific skin rash and other skin disorders		0	1	0	1
Allergic/Immune system disorders		0	4 (1)	0	2 (1)
Abnormal blood tests, not otherwise specified		2	2	0	0
Non-infectious catheter or exit site complications		1	3	0	0
Eye, ear and throat disorders		0	0	0	0
Blood and lymphatic system disorders		2	1	0	0
Other		5	4 (4)	0	0
	TOTAL	**70 (0)**	**99 (14)**	**20 (0)**	**42 (2)**
Number of subjects with any adverse event or serious adverse event (% of total group sample)		**30 (83%)**	**30 (86%)**	**12 (33%)**	**22 (63%)**

[a]Relatedness to the study PD solutions was judged by the clinical trial site investigator.

PTH = parathyroid hormone

Enrollment, randomization and follow-up of study participants (IMPENDIA only)



Enrollment, randomization and follow-up of study participants (EDEN only)