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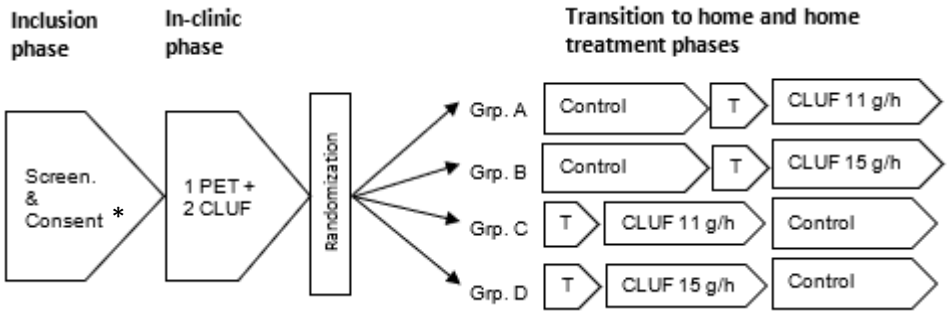
CLINICAL INVESTIGATION PLAN (CIP)

Study Title	A clinical study with the Carry Life® UF system in continuous ambulatory peritoneal dialysis (CAPD) patients
Study No.	Tmed-010
EUDAMED No.	CIV-23-03-042555
Clinical Investigation Medical Device(s)	Carry Life® UF system
Indication	Peritoneal dialysis and ultrafiltration in end-stage kidney disease (ESKD) patients
Class	Carry Life® UF Cycler: Class IIb, Rule 12 per MDR 2017/745 Carry Life® UF Line set: Class IIa, Rule 2 per MDR 2017/745
Document Version	V6.0
Issue Date	Feb 08 2024
Coordinating Investigator	Dr Olof Heimburger, Chief Physician Mottagning Njurmedicin Rosenlund Karolinska Universitetssjukhuset Tideliusgatan 12, 118 69 Stockholm, Sweden
Investigators and Investigation Sites	A list of investigators, investigation sites, and external organizations involved with this clinical investigation is found in Attachment A. An up-to-date list will be maintained by the Sponsor. The final list will be provided with the Clinical Investigation Report.
Sponsor	Triomed AB Scheelevägen 20, 223 63 Lund, Sweden

1 SYNOPSIS

STUDY TITLE	A clinical study with the Carry Life® UF system in continuous ambulatory peritoneal dialysis (CAPD) patients
STUDY TYPE	Pre-market, prospective, multicenter, randomized, crossover study.
STUDY SITES	Six (6) to twelve (12) European sites will participate in this clinical investigation.
STUDY PERIOD	Estimated time for clinical investigation completion: Approximately one (1) year. Participation of each study subject: Approximately twelve (12) weeks.
OBJECTIVES	**Primary objective:** To demonstrate that a 5-hour Carry Life® UF treatment at home results in an increased ultrafiltration (UF) volume compared to a 5-hour 2.27% glucose CAPD dwell in adult CAPD patients. **Secondary objectives:** • To evaluate the overall safety of the Carry Life® UF system used by the patient at home as measured by rates of adverse events (AEs) and serious adverse events (SAEs) in adult CAPD patients. • To demonstrate that treatment with the Carry Life® UF system at home results in increased sodium removal compared to a 2.27% glucose CAPD dwell in adult CAPD patients. • To demonstrate that treatment with Carry Life® UF system at home results in a more glucose efficient peritoneal fluid removal compared to a 2.27% glucose CAPD dwell in adult CAPD patients. • To evaluate if the peak glucose concentration during a Carry Life® UF treatment is lower than the glucose concentration of a 2.27% glucose peritoneal dialysis (PD) solution. **Exploratory objectives:** • Evaluation of peritoneal urea and creatinine removal. • Evaluation of overall weekly UF volumes based on the patient diary.
ENDPOINTS	**Primary endpoint:** • UF volume during treatments at home (Carry Life® UF treatment vs. a 2.27% glucose CAPD dwell). **Secondary endpoints:** • AE and SAE rates. • Peritoneal sodium removal. • Glucose UF efficiency. • Peak dialysate glucose concentration. **Exploratory endpoints:** • Peritoneal creatinine and urea removal. • Weekly UF volumes.

METHODOLOGY	The study consists of the following five (5) phases: 1. Inclusion phase. 2. In-clinic treatment phase for dose determination and safety evaluation. 3. Randomization phase. 4. Transition to home treatment phase. 5. Home treatment phase for efficacy and safety evaluation. CAPD patients need to use the Baxter PD system and have a PD prescription of at least one 1.5-2.0 L 2.27% glucose day dwell to be included in the study. Throughout the study, the subject will use the fill volume they normally use, both for the standard PD prescription and for the Carry Life® UF treatments. However, for the peritoneal equilibrium test (PET), a 2 L fill volume will be used. The in-clinic phase consists of one 2.27% CAPD dwell and two Carry Life® UF treatments; one with a 11 g/h glucose dose and one with a 15 g/h glucose dose. The Carry Life® UF treatments will be used for a safety evaluation and based on the UF volumes achieved with the Carry Life® UF treatments, the Carry Life® UF glucose dose for the home treatment phase will be determined. After completion of the in-clinic treatment phase, subjects will be randomized to start the home treatment phase either with the control treatment arm or with the Carry Life® UF treatment arm. Subjects in the control arm will continue their standard CAPD treatment as prescribed. In the Carry Life® UF arm, for three days of the week one 2.27% glucose CAPD dwell per day will be replaced by a Carry Life® UF treatment. For the remaining four days of the week, one 2.27% glucose CAPD dwell will be replaced with a 1.36% glucose CAPD dwell. Immediately before the subject starts using the Carry Life® UF device at home, there will be a transition to the home treatment phase during which the patient will be trained in how to use the Carry Life ® UF system. AEs, SAEs, and Carry Life® UF device malfunctions will be recorded throughout the study. A nurse at each participating clinic who has undergone education and training necessary for thorough AE collection will be responsible for the recording of AEs i.e., education in Good Clinical Practice (GCP) will be required and training with respect to the electronic case record form (eCRF) for AE reporting. In case of an AE or Carry Life® UF device malfunction during the home phase, the subject will be instructed to immediately contact the clinic. Furthermore, the clinic will contact the subject weekly and specifically ask about the occurrence of any AE or Carry Life® UF device malfunction. Any changes in medications or PD prescriptions will be recorded during the study. If changes to diuretic prescription or PD prescription are made, the reason for the change will be documented. If a study participant discontinues the clinical study the reason for this will be documented in detail.

	A flow diagram of the study design is shown below (Figure 1). Refer to Table 1 for the schedule of activities at each visit. **Figure 1. Study flow chart**  Abbreviations: CLUF = Carry Life® UF; Grp. = Group; PET = peritoneal equilibration test; Screen. = Screening; T = Transition to home phase with device training. * A run-in period of at least two weeks may be performed in order to make an approved adjustment the PD prescription so that it can meet the study inclusion criteria
STUDY FOLLOW UP	The subject will be followed up for one (1) week for new or continuing AEs after the end-of-study visit. The follow-up will be in the form of a phone call or a physical meeting as required.
NUMBER OF SUBJECTS	Approximately 25 patients will be enrolled with a goal of 19 completing the study per protocol.
STUDY POPULATION	Adult subjects with end-stage kidney disease (ESKD) treated with CAPD.
INCLUSION/EXCLUSION CRITERIA	**Inclusion criteria** 1. Age ≥ 18 years. 2. Subjects with ESKD treated with PD for at least three (3) months. 3. A PD prescription of 2–4 CAPD dwells/day unchanged for a minimum of two (2) weeks, with at least one 1.5–2L, 2.27% glucose day dwell daily. 4. Subjects must be able to tolerate a 2 L PD fill volume for the PET. 5. Subjects using the Baxter PD system with a MiniCap transfer set. 6. In the opinion of the Investigator, the subject has the capacity to learn how to use the Carry Life® UF system or has a caregiver who can do so. 7. Obtained written consent to participate in the study. **Exclusion criteria** 1. A PD prescription including a regular 3.86% glucose day dwell. 2. An episode of peritonitis within the last three (3) months. 3. Serum potassium > 6 mmol/l within the last three (3) months. 4. Serum urea > 35 mmol/l within the last three (3) months. 5. Clinical signs of dehydration. 6. Systolic blood pressure < 100 mmHg within the last month. 7. Known diagnosis of clinically significant aortic stenosis. 8. Clinical condition of unstable diabetes. 9. Subjects with a life expectancy of < six (6) months. 10. Evidence of any other diseases or medical conditions that may interfere with the planned treatment or affect participant compliance.

	11. Participation in clinical trials, interfering with the present study, within the previous month. 12. Anticipated living donor kidney transplantation within six (6) months of screening. 13. Pregnant, breastfeeding, or women of childbearing potential who are not using an effective method of contraception (hormonal contraceptives or barrier contraceptive methods).
INDICATIONS FOR USE	The Carry Life® UF system is indicated for PD and UF in adult patients with ESKD.
DURATION OF TREATMENT	Each subject's participation will last approximately 12 weeks. The study schedule will include 8 to 13 visits depending on the individual device training requirements. Only the in-clinic visits and the visits during the home treatment phase have been assigned a specific visit number: 1. Inclusion phase – Screening & consent (Visit 1). 2. In-clinic treatment phase (Visits 2–4; approximately 2 weeks). 3. Randomization phase – No visit. 4. Transition to home treatment phase – Visit T1 to T7 (2 to 7 visits; approximately 1 week). 5. Home treatment phase – Visit 5 and 6 (8 weeks; 4 weeks in the control arm and 4 weeks in the treatment arm).
CRITERIA FOR EVALUATION / STATISTICAL METHODS	**Primary endpoint** • The UF volume of the control CAPD dwell and the Carry Life® UF treatment will be measured per protocol at each efficacy evaluation treatment (two days per treatment arm) during the home treatment phase. • Each subject is expected to have two efficacy evaluations per treatment arm. Subjects with one or more evaluations in each arm will be included in the primary endpoint analysis. Both the PP and ITT populations will be analyzed. Excluded subjects will be tabulated with narratives as to why they missed efficacy evaluations. • A UF volume during the Carry Life® UF treatment exceeding with ≥ 250 ml the UF volume obtained with the 2.27% glucose CAPD dwell is considered clinically relevant. **Secondary endpoints** • AE and SAE rates: Based on all safety data gathered during the home treatment phase of the study for the Intent-To-Treat (ITT) dataset, AE and SAE occurrences will be collected, summarized, and presented. • Peritoneal sodium removal: ○ Based on data gathered from the efficacy evaluation treatments during the home treatment phase of the study, peritoneal sodium removal will be calculated and summarized. ○ Each subject is expected to have two efficacy evaluations per treatment arm. Subjects with one or more evaluations in each arm will be included in the endpoint analysis. Excluded subjects will be tabulated with narratives as to why they missed efficacy evaluations. ○ A statistically significant increase in sodium removal between the Carry Life UF treatment and the 2.27% glucose CAPD dwell will be determined by a t-test.

	• Glucose UF efficiency:
	  ○ Based on data gathered from the efficacy evaluation treatments during the home treatment phase of the study, glucose UF efficiency will be calculated and summarized.
	  ○ Each subject is expected to have two efficacy evaluations per treatment arm. Subjects with one or more evaluations in each arm will be included in the endpoint analysis. Excluded subjects will be tabulated with narratives as to why they missed efficacy evaluations.
	  ○ A statistically significant increase in glucose UF efficiency between the Carry Life UF treatment and the 2.27% glucose CAPD dwell will be determined by a t-test.
	• Peak dialysate glucose concentration:
	  ○ During the in-clinic treatment phase the peak peritoneal glucose concentration during each glucose dose of the Carry Life® UF treatments will be determined.
	  ○ Each subject is expected to have one in-clinic Carry Life UF treatment per glucose dose with hourly dialysate sampling points during the treatment. Subjects with dialysate glucose data from one or more sampling points will be included in the endpoint analysis. Excluded subjects will be tabulated with narratives as to why they missed the endpoint evaluation.
	A t-test will be used to determine that the peak dialysate glucose concentration during the Carry Life® UF treatment is lower than 2.27%.
	A subject may be excluded for one or more secondary endpoints, that is, exclusions are made independently for each endpoint.

SAMPLE SIZE JUSTICATION	The sample size is calculated using the UF volume data from a previous pilot study (Tmed-007). The difference between the Carry Life® UF and the control 2.27% CAPD dwell had a mean value of 574 ml and a standard deviation of 236 ml. The aim is to demonstrate superiority over the control by a margin delta (δ), of 250 ml. Assuming a standard deviation of 236 ml, an expected difference of 574 ml and a superiority margin of 250 ml requires a sample size of 3 to obtain 80% power for the superiority test (α = 0.025) using a one sample superiority (one-sided) t-test sample size calculation. We also consider a more extreme case where we assume a standard deviation of 1.4 times the previous standard deviation, or 330 ml. Further, we lower our assumed mean difference to 400 ml (about 0.7s below the previous observed value). With these assumptions (standard deviation of 330 ml, an expected difference of 400 ml, and a superiority margin of 250 ml) we require a sample size of 19 to obtain 80% power for the superiority test (α = 0.025). The study size of 25 was selected based on the conservative sample size with additional subjects to account for possible dropouts.

Figure 2. Clinical investigation visits

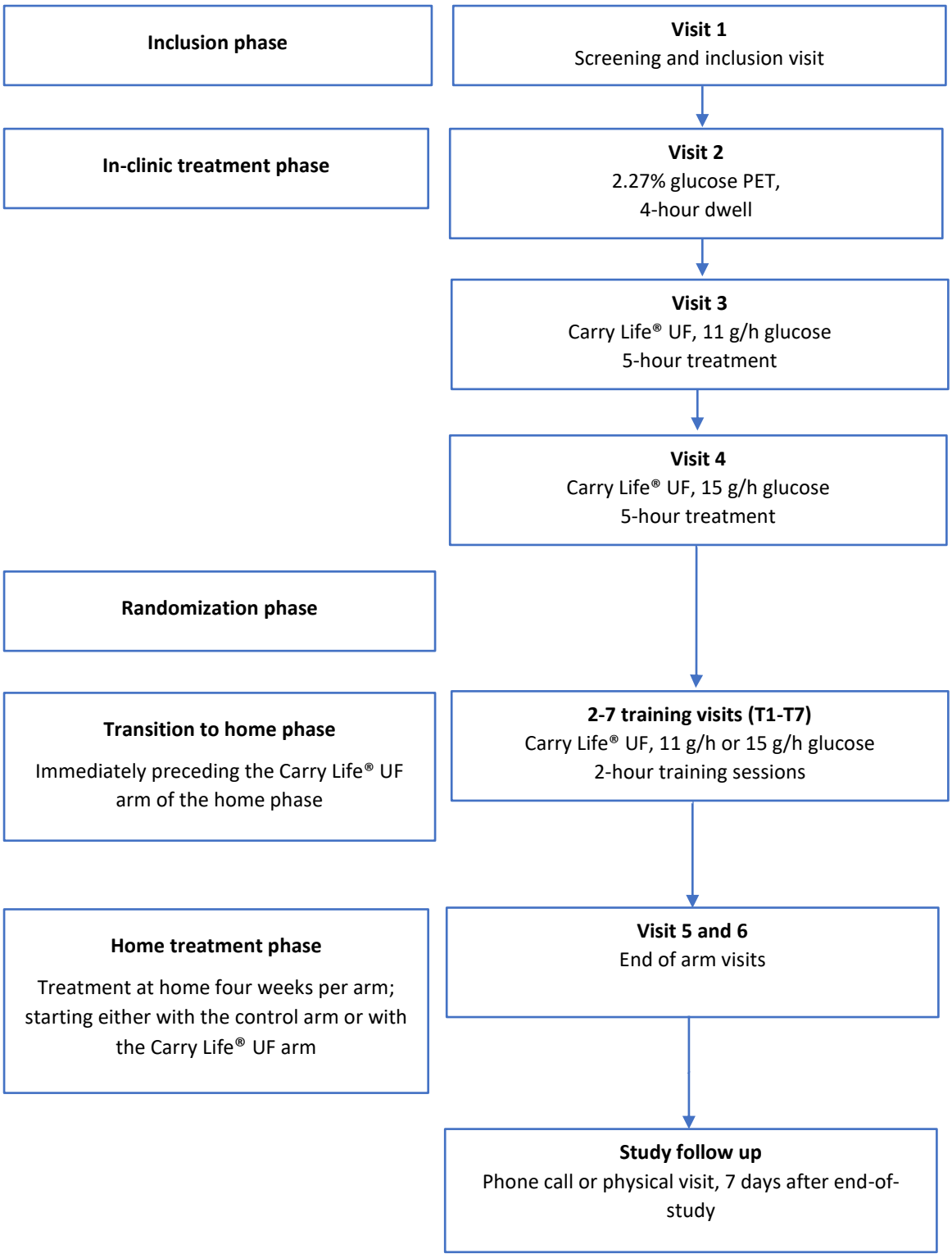


Table 1. Schedule of activities

Visit		**V1 Screening & Inclusion**	**V2-V4 (In-clinic treatments)**	**Randomization**	**T1-T7 (Device training)**	**Home treatment (two sampling days)**	**V5**	**T1-T7 (Device training)**	**Home treatment (two sampling days)**	**V6/End of study**
Time point/duration	Group A, B	-14–0 Days	Week 1–2	Week 2		Week 3–6	Week 6	Week 7	Week 8–11	Week 11/After premature ending of study
	Group C, D				Week 3	Week 4–7	Week 7			
Informed consent		X								
Inclusion and exclusion criteria		X								
Demographics[a]		X								
Medical history[b]		X								
Concomitant medications[c]		X	X		X	X	X	X	X	X
Baseline PD prescription[d]		X								
Fluid restriction[e]		X	X		X	X	X	X	X	X
Randomization				X						
Vital signs & body weight[f]			X			X	X		X	X
Food intake and fluid intake & urinary output[g]			X							
Blood samples[h]			X				X			X
Dialysate samples[i]			X			X			X	
PD bags used[j]			X			X			X	
Fill and drain volumes[k]			X			X			X	
24-hour urine sample[l]			X (V2 only)				X			X
24-hour UF volume[m]						X			X	
Carry Life® UF safety assessment[n]			X							

Visit	V1 Screening & Inclusion	V2-V4 (In-clinic treatments)	Randomization	T1-T7 (Device training)	Home treatment (two sampling days)	V5	T1-T7 (Device training)	Home treatment (two sampling days)	V6/End of study
Transition to home evaluation		X							
Device competency assessment				X			X		
Subject clinical evaluation[o]					X			X	
AEs and SAEs[p]		X		X	X	X	X	X	X
Device malfunctions[q]		X		X	X		X	X	

Footnotes:

a. Year of birth, age, gender, ethnicity, height, body weight.
b. Cause of end-stage kidney disease (ESKD), year of diagnosis of kidney disease, start of peritoneal dialysis (PD), start of ESKD therapy other than PD (if applicable) and comorbidities.
c. Concomitant medications will be recorded. Any changes in prescription of medications will be recorded throughout the study, for diuretics and diabetes medication, the reason for change of prescription will be documented.
d. Baseline PD prescription: volumes and glucose concentration for the day dwells, volume for the icodextrin, and volume and glucose concentration for glucose-based night dwell, as applicable).
e. Any changes in fluid restriction will be recorded throughout the study. The reason for change in fluid restriction will be documented.
f. **In-clinic phase**: Body weight, systolic and diastolic blood pressure and heart rate will be measured before and after treatment.
Home phase: The subjects will record body weight, systolic and diastolic blood pressure, and heart rate daily.
g. **In-clinic phase**: Food intake and fluid intake as well as urinary output during the in-clinic visits will be documented.
h. **In-clinic phase and home phase**: The following blood chemistry parameters will be analyzed at visit 2 (baseline), visit 5, and visit 6: Sodium, potassium, magnesium, calcium (ionized), phosphate, albumin, creatinine, urea and parathyroid hormone. Creatinine and urea at visit 2, 5, and 6 will be used for calculation of residual renal function. Plasma creatinine before the PET will be used for calculation of D/P creatinine.
In addition, blood glucose will be measured before the treatment, at 30 min, at 1 h and then hourly until the end of treatment for the three in-clinic treatments.
i. **In clinic phase**: PET: Dialysate samples will be collected at 0, 1, 2 and 4 hours for analysis of dialysate glucose and creatinine for determination of peritoneal membrane transfer type (4 h D/P creatinine and D/D0 glucose ratios). Sodium concentration at each time point will also be analyzed. After the completion of infusion (T0) and at the 1- and 2-hour dwell time, 200 mL of dialysate will be drained. A 10 mL sample will be taken, and the remaining 190 will be infused back into the peritoneal cavity.

Carry Life® UF treatments: 10 ml dialysate samples at 0, 1, 2, 3, 4 and 5 hours will be analyzed for dialysate glucose and sodium for evaluation of dialysate glucose and sodium concentrations during treatment. All PD fluid automatically drained (and any additional drains) during the Carry Life® UF treatment will be pooled. The pooled PD fluid, plus the final peritoneal drain will be analyzed for dialysate glucose, sodium, potassium, calcium, phosphate, albumin, creatinine, and urea for calculation of glucose ultrafiltration (UF) efficiency, glucose absorption and peritoneal removal of the listed substances.

Home phase efficacy evaluation days, during week 2 and week 4 or each arm: Drained dialysate from the control and Carry Life® UF efficacy evaluation treatments (Carry Life® UF drain bag + final peritoneal drain) will be collected by a research assistant for analysis of dialysate glucose, sodium, potassium, calcium, phosphate, albumin, creatinine, and urea, for calculation of glucose absorption, glucose UF efficiency, and peritoneal removal of the listed substances.

j. **In-clinic phase**: The volume and glucose concentration of PD bags used for the PET and Carry Life® UF treatments will be recorded.
Home treatment phase: The subjects will record information of all PD bags used (volume and glucose concentration for glucose-based solutions and volume for icodextrin).

k. **In-clinic phase:** The PD bag and glucose bag will be weighed by a clinical professional before the treatment and the drain bag(s) will be weighed after the treatments for calculations of fill volume, drained volume and UF volume.
Home treatment phase: Subject will record fill and drain weights of all dwells every day during the home phase.
Home treatment phase efficacy evaluation days: A research assistant will weigh the solution bags (PD bag and glucose bag), and the drain bags for calculations of fill volume, drained volume and UF volume.

l. 24-hour urine volume and urine concentration of creatinine and urea will be collected for calculation of residual renal function.

m. The patient will weigh the PD bag, glucose bag and drain bag(s) for each CAPD dwell/Carry Life® UF treatment during the home phase of the study for evaluation of weekly UF volume.

n. To assess the Carry Life® UF safety at the different glucose doses, each in-clinic Carry Life® UF treatment will be evaluated for the following:
    1) a systolic blood pressure of < 100 mmHg.
    2) an UF rate higher than 20 ml/kg body weight/treatment.

o. Subjects will be contacted weekly for evaluation of body weight, blood pressure, volume status and clinical symptoms.

p. A nurse adequately trained in AE reporting will specifically ask the subject for occurrences of AEs and SAEs during a weekly call.

q. The nurse will specifically ask the subject for occurrences of Carry Life® UF device malfunctions weekly.

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LIST OF ABBREVIATIONS AND DEFINITIONS

ADE	Adverse device effect
AE	Adverse event
APD	Automated peritoneal dialysis. APD uses a cycler and is divided into APD with a day dwell and "day dry". APD is also known as nocturnal intermittent peritoneal dialysis (NIPD) as it is often performed at night
BNP	B-type natriuretic peptide. BNP is produced as a response to increased mechanical load and wall stretch by the ventricles of the heart. It protects the heart from adverse consequences of overload by increasing natriuresis and diuresis, relaxing vascular smooth muscle, inhibiting the renin-angiotensin-aldosterone system, and by counteracting cardiac hypertrophy and fibrosis
Bpm	Beats per minute
CA	Competent Authority
CAPD	Continuous ambulatory peritoneal dialysis. Performed manually at 4 hourly intervals and dialysate is constantly present in the peritoneal cavity
CI	Confidence interval
CFPD	Continuous flow peritoneal dialysis
CKD	Chronic kidney disease
eCRF	electronic Case Report Form
D/P sodium or D/P creatinine	The D/P sodium is the rate at which sodium or creatinine equilibrates between the dialysate and plasma
DD	Device deficiency
Dialysate	Is the term used for PD solutions once dialysis has occurred, although the term "dialysate" is commonly used for fresh as well as for used or "spent" solution. In this document dialysate and intraperitoneal fluid are used interchangeably
Dry weight	Dry weight for PD is the weight that gives a well-tolerated normotensive, edema-free status
Dwells in PD	The length of time that the PD solution remains in the peritoneal cavity
EDC	Electronic data capture
Edema	Is swelling caused by excess fluid in the body's tissues and predominant affects the hands, arms, feet, ankles, and legs. If untreated it can result in shortness of breath called pulmonary edema which is serious and can be life threatening
Electrolyte	In this document electrolytes refers to Sodium (Na^+), Potassium (K^+), Magnesium (Mg^{2+}), Calcium (Ca^{2+}), Phosphate (PO_4^{3-}), bicarbonate (HCO_3^-), lactate, base excess (BE)
ePROM	Electronic patient-reported outcome measure
ETO	Ethylene oxide
GDPR	General data protection regulation
HD	Hemodialysis
HR	Heart rate
Hemodynamic instability	Is the term most commonly associated with an abnormal or unstable blood pressure, especially hypotension
Hypotension	Is abnormally low blood pressure
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFU	Instructions for use
IP	Intraperitoneal fluid. Is the term used for the PD solution in the peritoneal cavity
ISF	Investigator site file

ISO	International Organization for Standardization
ITT	Intent-to-treat
MDR	Medical device regulation
NCA	National Competent Authority
Net fluid loss	The sum of the total fluid intake minus the total fluid output
NIPD	Nocturnal intermittent peritoneal dialysis. See APD
NTPD	Nightly tidal peritoneal dialysis. Is a technique in which, after an initial fill of the peritoneal cavity, only a portion of dialysate is rapidly cycled
Osmotic gradient	Osmotic gradient is the difference in concentration between two solutions on either side of a semipermeable membrane
PD	Peritoneal dialysis
PET	Peritoneal Equilibrium Test. A semiquantitative assessment of peritoneal membrane transport in patients on peritoneal dialysis
POM	Polyoxymethylene
PP	Per protocol
PTH	Parathyroid hormone
PVC	Polyvinyl chloride
Reflection coefficient	Is the term used to reflect the osmotic agent's effectiveness to diffuse out of the dialysis solution into the peritoneal capillaries and the range is between 0 and 1
RRF	Residual renal function
SADE	Serious adverse device effect
SAE	Serious adverse event
SCPD	Steady concentration peritoneal dialysis
SD	Standard deviation
Sieving effect	Each solute has a sieving coefficient that depends on the molecular weight and charge. Higher sieving coefficients indicate lower permeability of the solute.
Study session	The term study sessions refer to both the Baseline and Carry Life® UF sessions
TMF	Trial master file
Tonicity	Tonicity is a measure of the effective osmotic pressure gradient of a solution
UF	Ultrafiltration is the removal of fluid during PD primarily by osmotic pressure gradient
USADE	Unanticipated serious adverse device effect

REVISION HISTORY

This section records all changes made to controlled versions of the Clinical Investigation Plan (CIP).

Revision	Date	Revision Author, Organization	Comments/Changes
V1.0	Mar 01 2023	Original Version	N/A
V2.0	May 09 2023	Charlotte de Leon, Triomed	Update base on MHRA pre-clinical assessment May 04 2023. Minor corrections.
V3.0	May 17 2023	Charlotte de Leon, Triomed	Update based on MHRA pre-clinic assessment May 15 2023, Statistical analysis clarifications.
V4.0	May 25 2023	Charlotte de Leon, Triomed	Update based on MHRA pre-clinic assessment May 23 2023. Statistical analysis update, change from alpha 0.05 to 0.025.
V5.0	Aug 1 2023	Charlotte de Leon, Triomed	Update to clarify that icodextrin overnight PD-dwell before visit 2 (PET) should be replaced by a 2.27% glucose PD dwell. This is in alignment with other documents (CIP attachment D and the patient information sheet).
V6.0	Feb 08 2024	Charlotte de Leon, Triomed	Adding a run-in period to allow a change of PD prescription to meet inclusion criteria. Increasing the number of sites to up to 12.

2 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

2.1 SUMMARY DESCRIPTION OF THE INVESTIGATIONAL DEVICE AND ITS INTENDED PURPOSE

The intended use of the Carry Life® UF system is for peritoneal dialyses (PD) and ultrafiltration (UF). The therapeutic concept of the Carry Life® UF system is to maintain a stable intraperitoneal (IP) glucose concentration and thereby achieving a stable peritoneal UF. The Carry Life® UF system is indicated for PD and UF in adult patients with end-stage kidney disease (ESKD). Treatment with the Carry Life® UF system is prescribed by the treating physician and intended for use in dialysis clinics or in the home environment.

The Carry Life® UF system consists of the following parts:

- Carry Life® UF Cycler.
- Carry Life® UF Line set.
- Carry Life® UF Carrying bag.
- Carry Life® UF Storage bag.
- Battery and battery charger.

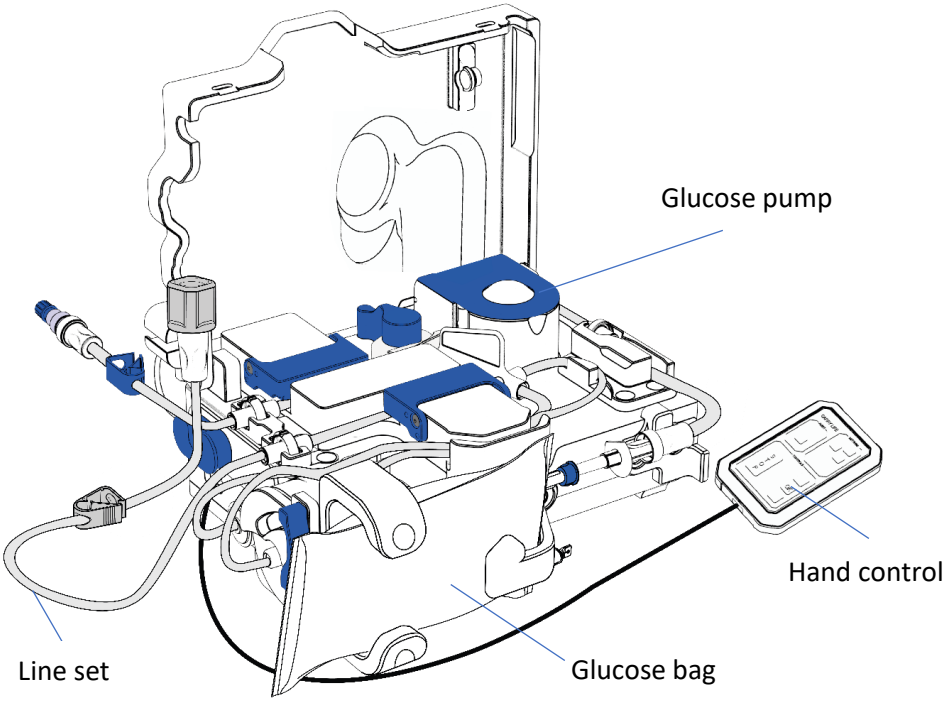
Treatment with the Carry Life® UF system also requires the following products:

- A standard PD catheter.
- A standard Baxter MiniCap extended life PD transfer set with twist clamp for access to the intraperitoneal catheter.
- A PD belt (Frank Stubbs).
- A 13.6 mg/ml glucose (1.36 %), 1.5 or 2L Baxter Peritoneal Dialysis solution.
- A 500 mg/ml, 500 ml Glucose Fresenius Kabi solution for infusion.

In this clinical investigation, subjects will already have a standard PD catheter and an extension set, and use the PD bags provided in their standard PD prescription. For participation in this clinical investigation, the Sponsor, or their designee, will provide the PD belt, and the glucose PD solution.

The Carry Life® UF Cycler with line set and glucose bag attached is illustrated in Figure 3.

Figure 3. The Carry Life® UF system



Refer to the Investigator's Brochure (IB) and Instructions for Use (IFU) for further details.

2.2 MANUFACTURER OF THE INVESTIGATIONAL DEVICE

Triomed AB
Address: Scheelevägen 20, 223 63 Lund, Sweden
Contact telephone: +46 46 460 20 00

2.3 DEVICE REGULATORY STATUS AND CLASSIFICATION

The Carry Life® UF system is not CE-marked and is considered an investigational device in this clinical investigation.

- Carry Life UF® Cycler: Class IIb per MDR 2017/745, Rule 12.
- Carry Life UF® Line set: Class IIa per MDR 2017/745, Rule 2.
- Carry Life® UF Carrying bag: Accessory, Class I per MDR 2017/745, Rule 1.
- Carry Life® UF Storage bag: N/A.
- Battery and battery charger: N/A.

2.4 IDENTIFICATION AND TRACEABILITY OF THE DEVICES

Devices will be delivered to the study subjects by the Investigator, or its delegate. Any special procedures, such as calibration and maintenance of the devices, will be conducted per the device label. If a device breaks, malfunctions, or is lost, a replacement device will be provided to the site by the Sponsor, or its delegate, for the study subject to continue participation in the clinical investigation.

Table 2. Device and accessory identification and traceability

Device/Accessories	Ref.	Traceability recorded in CRF
Cycler delivery kit*	**321100**	**Lot number**
Carry Life® UF Cycler	321101 (SW version 100C11_1.2.2, 100C12_1.2.1)	Serial number
Battery	RCC2054	Serial number
Battery charger and adaptor	110115-01	Serial number
Carry Life® UF Carrying bag	321121	Lot number
Carry Life® UF Storage bag	321222	Lot number
Carry Life® UF - B Line set	321106	Lot number
PD belt (Frank Stubbs)	XS, S, M, L or XL	Lot number

* All components of the delivery kit will be traceable from the lot number of the delivery kit.

2.5 Intended Purpose

The Carry Life® UF system is indicated for PD and UF in adult patients with ESKD treated with continuous ambulatory peritoneal dialysis (CAPD) with the objective of providing PD and UF.

In this clinical investigation the device will be used by clinical professionals in a clinical setting in the hospital environment and by the patient or caregiver in the home environment.

2.6 General Description of the Carry Life® UF system

In CAPD, the glucose concentration of the PD fluid is reduced as the glucose is absorbed across the peritoneal membrane, resulting in a reduced UF rate or even fluid re-absorption by the end of the dwell.

The Carry Life® UF is a novel system that performs peritoneal dialysis with the method of steady concentration PD. Throughout the 5-hour Carry Life® UF treatment glucose is administered to the dialysate in the patient's peritoneal cavity to compensate for glucose absorption. By doing this the glucose concentration in the dialysate is sustained and the peritoneal UF is maintained throughout the treatment. Treatment with Carry Life® UF will result in an increased UF volume compared to a 2.27% CAPD dwell. Furthermore, removal of low molecular weight solutes may occur during the treatment as these will follow with the fluid, i.e., with convective solute transport.

The Carry Life® UF treatment starts with an initial fill of the peritoneal cavity with a 1.5 L or 2 L 1.36% glucose PD solution. Following dressing of the Carry Life® UF cycler with the line set and connecting the 50% glucose solution in accordance with the instructions in the IFU, the device is connected to the patient and priming of the line set is performed using a small amount of the IP fluid from the initial fill which is emptied into the drainage bag.

During the treatment a small volume of IP fluid is transferred back and forth between the peritoneal cavity and the device. Glucose is mixed and diluted in the IP fluid, which is transferred into a reservoir bag (pressure chamber bag) inside the pressure chamber of the device The addition of glucose occurs in 13.5-minute cycles during which approximately 70 ml of IP fluid is transferred at 30 second

intervals to and from the device. When the glucose volume to be dosed each cycle has been administered, the glucose pump remains stopped until the next cycle begins. The device automatically drains approximately 180 ml of dialysate every hour into a drainage bag resulting in approximately 900 ml UF being drained during the 5-hour treatment.

The device can administer two different glucose doses: 11 g and 15 g glucose per hour.

2.6.1 Carry Life® UF Cycler

The cycler controls the intermittent transfer of the IP fluid into and out of the patient as well as addition of the glucose solution. This is done by means of a pressure chamber, a peristaltic pump, and valves that control the fluid direction. The pressure chamber is the driving force for the fluid movement, into and out from the pressure chamber bag. The cycler is operated by a hand control and powered by a standard rechargeable battery, which is delivered with the device. The chassis of the cycler is made of plastic (POM) and lids and glucose pump is made of anodized aluminum.

2.6.2 Carry Life® UF Line set

The line set connects to the patient's PD catheter extension set and the IP fluid is channeled to the pressure chamber bag in a closed circuit and back to the patient, or to the drain bag. The disposable line set is made of polyvinyl chloride (PVC) and is ethylene oxide (ETO) sterilized. The line set is not made of latex and components in the fluid path are not made with phthalates. The line set is delivered sterile and individually packed in a sterile pouch labelled "CAUTION! Exclusively for Clinical Investigation" / "FÖRSIKTIGHET! Enbart för Klinisk Prövning".

The line set contains five tubes, which are connected to a line organizer:

- Patient line.
- Glucose line.
- Drain line.
- Pressure bag line.
- Pressure sensor line.

All lines except the pressure sensor line have a protective cap which is removed before connection. The pressure sensor line ends with a transducer protector which has a sterile filter incorporated.

The flow path of the line set is in contact with the IP fluid and the material in the flow path is thereby in indirect contact with the peritoneal cavity/membrane of the patient during treatment. All materials in the line set with fluid contact are medical grade and the line set has undergone *in vitro* and *in vivo* testing and a biological evaluation according to EN ISO 10993:2018. Figure 4 shows the Carry Life® UF line set with its components.

Figure 4. The Carry Life® UF line set

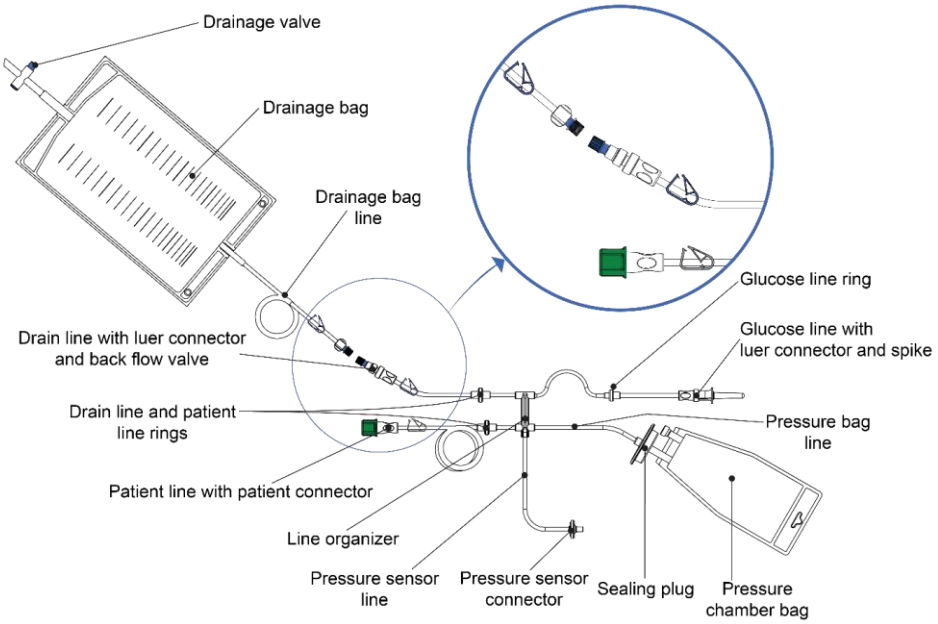


Table 3 below shows the materials of the different components with human body fluid contact. Refer to the IB for further details.

Table 3. Main components in the Carry Life® UF Line set: Supplier of component, raw materials, raw material supplier and tests performed by material supplier

Component	Supplier	Raw material description / supplier	Biocompatibility tests performed by raw material supplier
Pressure bag	Qosina, standard component	PVC EH-222 from Renolit	Material fulfills USP class VI test requirements. Material fulfills the following ISO 10993:2018 test requirements: • Cytotoxicity. • Sensitization. • Intracutaneous irritation. • Acute systemic toxicity. • Implantation.
Spike	Qosina, standard component	Lustran ABS M205FC-011220 from Elix Polymers	Supplier's equivalent material fulfills USP class VI test requirements, and the following ISO 10993:2018 test requirements: • Pyrogenicity. • Systemic toxicity. • Hemocompatibility, hemolysis. • Implantation. • Cytotoxicity. • Sensitization. • Intracutaneous irritation. • Mutagenicity (AMES).
Transducer protector (26) 320340D	LUC & BEL, standard component (0.2 µm hydrophobic membrane filter), Part no. A00820610W	Housing: PVC AM22 W17, AM22 W1645 from TPV Compound S.R.L. Membrane: MMT-323 Gore (PTFE on polyester support) from W.L. Gore. The membrane has undergone bacterial filtration efficiency testing at an increased challenge level by an independent accredited laboratory (Nelson laboratories, Protocol No.	All materials fulfill USP class VI test and ISO 10993:2018 cytotoxicity test requirements. PVC AM22 materials additionally fulfill the following ISO 10993:2018 test requirements: • Sensitization. • Intracutaneous irritation. • Acute systemic toxicity. • Hemolysis.

Component	Supplier	Raw material description / supplier	Biocompatibility tests performed by raw material supplier
		2003010708- 01; Laboratory No. 249167).	
Sealing plug Line organizer Patient connector Glucose connector Tube rings	Västra Karaby Plast (VKP) Custom made components	PVC AM22W17 from TPV Compound S.R.L.	PVC AM22W17 material complies with USP VI test requirements, and fulfills the following ISO10993:2018 test requirements: • Sensitization. • Intracutaneous irritation. • Acute systemic toxicity. • Hemolysis. • Genotoxicity.
Tubing	National Bredaryd Custom made	PVC HY-VIN XH77863 Sh 62 and HY-VIN XH79214 Sh 68 from Ineos	Material XH77863 fulfills USP class VI and ISO 10993:2018 cytotoxicity tests requirements. Material XH79214 consists of the same ingredients at slightly different concentration levels.

2.6.3 Carry Life UF Carrying bag

The cycler is placed in a plastic (polyurethane) carrying bag during treatment.

2.6.4 Peritoneal dialysis solution

The peritoneal cavity is pre-filled with a standard Baxter 1.36% glucose-based PD solution (Dianeal or Physioneal) before treatment with the Carry Life® UF device is initiated.

2.6.5 Glucose solution

The Carry Life® UF system is designed to be used with a standard Fresenius Kabi 50% glucose solution in a 500 ml soft polypropylene FreeFlex bag with injection port, suitable for connection to the spike connector of the Carry Life® UF line set.

2.7 SUMMARY OF REQUIRED EXPERIENCE/TRAINING

The participating clinical investigation sites are required to be experienced in the treatment of patients receiving PD therapies for ESKD. The medical care of patients with ESKD is commonly prescribed and supervised by a nephrologist and usually involves a dedicated clinical PD team. This is the case for all the sites participating in the study.

To use the Carry Life® UF system in the dialysis clinic, training in the set-up and handling of the device is required. A description of the therapeutic principles of the device and the specific training requirements will be outlined in connection with the site initiation visit. Training sessions will be scheduled and performed according to the IFU by Triomed AB, or their representative.

A site-specific PD nurse will be responsible for managing the connections to the PD catheter and for performing and managing the baseline and Carry Life® UF treatments at the clinic as well as assessing the subject's device competency before the home phase of the study. Training of the patient may be performed by a Triomed representative under the supervision of the dialysis clinic or by a dialysis clinic team member who has been adequately trained in the Carry Life® UF system.

A Triomed representative will be available at the clinic to assist with device related questions during the first Carry Life® UF treatment(s) at each clinic, if requested by the clinic. Documentation of the training format and the participants will be contained in the training log in the investigator site file (ISF) and in the trial master file (TMF).

2.8 DESCRIPTION OF SPECIFIC MEDICAL PROCEDURES INVOLVED IN THE USE OF THE INVESTIGATIONAL DEVICE

There are no specific medical procedures required for use of the Carry Life® UF system.

3 RATIONALE FOR THE DESIGN OF THE CLINICAL INVESTIGATION

3.1 BACKGROUND

Chronic kidney disease (CKD) poses a high economic burden for health care systems and to individuals affected by the disease. The causes of CKD are many and can be due to age related decline of renal function compounded by hypertension, diabetes, and primary renal disorders. The global prevalence of CKD is estimated to be between 11-13%.[1]

CKD can progress to ESKD where dialysis therapy or a kidney transplant is required. PD has been used for treatment of ESKD for more than thirty years and despite that many patients choose PD as their initial therapy of choice, as many as 35% are reported to transfer to hemodialysis (HD) yearly.[2] Issues that may cause patients to leave PD are multifactorial and include: peritonitis, inadequate dialysis, catheter related problems, patient burn-out, and fluid overload due to insufficient UF. The Carry Life® UF system aims to provide an effective management of fluid overload which is associated with increased mortality, hospitalization and technique failure.

3.2 OVERVIEW OF FLUID OVERLOAD IN PATIENTS USING PD THERAPIES

The prevalence of fluid overload in PD patients is in the range of 56-73%,[3-5] with 25% of patients expressing severe fluid overload.[5] Fluid overload in PD patients occurs when an insufficient amount of fluid is removed by the kidneys and the dialysis regimen, and is associated with increased mortality and technique failure.[6,7] Changes in peritoneal membrane transport characteristics are associated with decreased UF over time, e.g., due to faster reduction of glucose levels in the dialysate.[6,8] Moreover, as ESKD patients experience a reduction in residual renal function (RRF) during course of time, an effective peritoneal UF becomes even more important as the dialysis treatment should optimally compensate for the potential decrease in urine production.

Fluid overload in PD patients can manifest as generalized edema, pulmonary congestion, and hypertension. It contributes to left ventricular hypertrophy and is a major contributor to cardiovascular disease, the leading causes of death in all dialysis patients. It is also associated with hypoalbuminemia, malnutrition, inflammation, and atherosclerosis and is a significant contributor to technique failure.

The assessment of fluid status is often based on clinical examination and the target body weight (so called “dry weight”), which represents a state of normal blood pressure and the absence of edema. Fluid status may further be determined by: bioimpedance, serum levels of B-type natriuretic peptide (BNP), and ultrasound of the inferior vena cava or lungs.[9]

Causes of fluid overload in PD therapies are multifactorial and can be a combination of the following:

1. Inappropriate PD prescription for the membrane transport status.
2. Long glucose-containing daytime or nocturnal dwells.
3. Failure to use icodextrin solutions.
4. Inadequate sodium removal.
5. Non-compliance with PD prescription regarding salt and fluid restriction.
6. Loss of residual renal function.

7. Peritoneal membrane deterioration associated with the use of hypertonic glucose-based PD solutions.
8. Catheter malfunction.

3.3 CURRENT STRATEGIES TO MANAGE FLUID OVERLOAD

General measures to treat fluid overload in PD entail: regular assessment of the peritoneal membrane and the adjustment of PD regimes to meet clinical needs, patient education, frequent clinical assessment, control of blood glucose, regular assessment of RRF, and the correcting of catheter problems.

Increased fluid removal in PD patients can be achieved by the following:

1. Maximizing the osmotic gradient by using higher tonicity dwells (e.g., 3.86% glucose).
2. Shorter duration dwells (e.g., automated peritoneal dialysis [APD]).
3. Larger dwell volumes.
4. An osmotic agent with a higher reflection coefficient (e.g., icodextrin).
5. Increasing urine output (e.g., diuretics).

Maximizing the osmotic gradient increases UF, due to the glucose concentration being sustained for a longer period of time. However, this may be problematic as it may increase the glucose absorption (Table 4) and can contribute to or aggravate metabolic disturbances, such as hyperglycemia, hyperinsulinemia, insulin resistance, dyslipidemia and the promotion of obesity.[10]

Table 4. The approximal absorption of glucose in high/high average transports with different glucose concentrations during a 4-hour dwell

Absorption of glucose with different glucose concentrations PD solutions				
Concentration	**Glucose/2 liters**	**Absorption**	**Absorption 4 exchanges/day**	**Caloric load (3.7 kcal/g glucose)**
1.36% Glucose	27.2 g/2 liter	19 g	76 g/day	281 calories/day
2.27% Glucose	45.4 g/2 liter	32 g	128 g/day	473 calories/day
3.86% Glucose	77.2 g/2 liter	54 g	216 g/day	799 calories/day

Another factor of importance for glucose absorption is the characteristics of the peritoneal membrane. The transport across the peritoneal membrane is classified as slow to fast transport characteristics as is determined by a peritoneal equilibrium test (PET). The clinical impact of the transport characteristics is associated with how rapidly the glucose is absorbed and the solutes equilibrate. Patients with a fast transport characteristics require frequent exchanges with short duration dwells to preserve the glucose concentration as they absorb glucose rapidly, whereas patients with low transport characteristics utilize longer dwells as the dialysate glucose concentration and hence the UF are maintained for longer periods.[9] It is, however, recommended that dialysis regimes routinely utilizing 3.86% glucose PD solutions should be avoided and icodextrin is proposed as a once-a-day alternative to hypertonic PD solutions.[11] Icodextrin is iso-osmolar and induces UF by its oncotic effect. It is mainly absorbed via the lymphatic system and since this absorption is much slower than the absorption of glucose the oncotic effect and hence the UF will be sustained for a longer period of time. Icodextrin is used for long dwells as it is less effective than glucose when used for shorter dwell times. The effect on peritoneal UF of increasing the dwell volumes in PD therapies

tends to be modest, possibly because of the increased intraperitoneal (IP) pressure which tends to increase fluid absorption.

The urinary output is important in dialysis patients and one of the advantages with PD compared to HD is that RRF is better preserved.[9] The loss of urinary output varies over time and clinically significant changes can occur rapidly. Strategies to preserve RRF and urinary output include the use of diuretics and the avoidance of episodes of dehydration. PD patients who are overhydrated and consistently achieve a daily peritoneal UF of less than 750 ml should be closely monitored and may benefit from a change in modality.[11] In the management of fluid status it is recommended that the peritoneal membrane function, the RRF, and the achieved UF volumes are monitored regularly.[11] Fluid overload is a complex issue in PD therapies and there is an unmet need for a more effective peritoneal fluid removal which could be provided by the Carry Life® UF system.

3.4 PERITONEAL ULTRAFILTRATION AND SURVIVAL

During the past decades the importance of peritoneal UF has emerged as a major factor for patient and technical survival of PD patients, whereas previously more attention was put on the clearance of uremic toxins.[4] Indeed, observational studies have consistently shown that reduced peritoneal UF is associated with increased mortality.[12-15]

In a non-anuric PD population, fluid removal was shown to be related to survival, total hospitalization, and cardiovascular hospitalization.[12] In this study, 125 PD patients were followed for three years from the start of treatment. Based on quartiles for total fluid removal, the patients were divided into four groups and the survival for each group was analyzed. In summary the study showed that the three-year patient survival rates were different among the groups, with a survival rate of 61.5% in the patients with a total fluid removal in the 1st quartile (<1265 ml/24 h/1.73 m^2), while for patients in the 4th quartile (>2035 ml/24h/1.73m^2) the survival was 96.3%. The peritoneal UF volume was on average found to constitute 78% of the total fluid removal.

In anuric PD patients, studies have shown that UF volumes below 0.75 L/day[13] and below 1.0 L/day[15] are associated with decreased survival. In the NECOSAD study[14], peritoneal UF was significantly associated with mortality in anuric patients. In the EAPOS study[13], the two-year survival was approximately 83% in patients with an UF volume above 750 ml/day compared to about 57% in those with an UF volume below 750 ml/day, i.e., about 26 percentage points higher. In a multivariate Cox regression model, baseline UF volume was shown to be a significant predictor of survival. In the study by Lin *et al*., the four-year survival in patients with an UF volume of ≥1 L24h was approximately 53% compared to about 16% in patients with an UF volume <1 L/24h, i.e., about 37% higher.[15] Median survival was 42.4 vs 27.2 months in the in the two groups, respectively. In a multivariate Cox regression analysis, the relative risk of death per daily 100 ml UF difference was 0.80 (p<0.001). In anuric PD patients, targets for peritoneal UF volumes of 0.75 - 1.0 L/day have been suggested by international guideline bodies.[11,16]

3.5 PERITONEAL GLUCOSE LOAD

The most common osmotic agent used for PD is glucose. Glucose, or its degradation products, are believed to have a negative impact on the peritoneal membrane integrity, and the significant peritoneal glucose absorption of up to 200 g of glucose per day[13] that may occur with glucose-based

PD is associated with systemic and metabolic effects such as insulin resistance, new onset diabetes and cardiovascular disease, as well as mortality[9,10,16,17]. Therefore, the objective of PD must be to obtain the required UF with as low glucose absorption possible, i.e., using a method that optimizes the glucose UF efficiency.

3.6 PERITONEAL SODIUM REMOVAL

Adequate sodium balance is crucial for the management of PD patients. Low sodium removal in PD patients is associated with increased mortality and hospitalization.[18] An efficient peritoneal sodium removal is complicated by the phenomenon known as sodium sieving. Sodium sieving occurs when water is transported through the aquaporins in the peritoneal membrane, which does not allow passage of electrolytes. Thereby sodium is retained in the blood and the UF fluid generated is hypotonic with regards to sodium. Sodium retention is associated with the use of glucose as the osmotic agent and in particular when using high glucose strength PD solutions. The sodium retention, results in a reduced dialysate sodium concentration, which enables sodium to move more efficiently over the membrane via diffusion. If the dwell is maintained for a duration sufficient for the dialysate sodium concentration to reach a level close to the blood sodium concentration the net sodium retention is minimized.

APD is characterized by shorter dwell times than CAPD; after approximately 40–90 minutes the fluid is typically exchanged with fresh PD solution. This may increase the UF volume and the removal of uremic toxins, but comes at the expense of sodium removal[4,19,20] as the dialysate is not allowed sufficient time to equilibrate, which results in the removal of a sodium hypotonic UF fluid.

3.7 EXPLORATORY STUDIES WITH MAINTAINED INTRAPERITONEAL GLUCOSE CONCENTRATION

Therapeutic concepts similar to the Carry Life® UF system such as continuous flow PD (CFPD) and steady concentration PD (SCPD) have been described in the literature. The features of CFPD are that the IP volume is fixed and that dialysate rapidly and continuously flows in and out of the peritoneal cavity, creating a stable IP glucose concentration. Studies performed with CFPD have demonstrated that CFPD results in a significantly higher UF volume compared to standard PD therapies.
In the study on adult PD patients by Freida *et a*l.[21] the UF volume in the PET (2.27% glucose), achieved 270 mL, whereas the mean UF in CFPD was 587 mL with a 1.36% PD solution. UF and net sodium removal extrapolated to eight hours of treatment was also much higher with CFPD (1175 ml UF; 212 mmol sodium removal) compared to 8 hours APD treatment APD (427 ml UF; 66 mmol sodium removal). Glucose absorption was not significantly different between the CFPD and APD session but the glucose UF efficiency (UF/absorbed glucose) was higher with the CFPD (33.5 ml/g) compared to APD (11.4 ml/g).

In a study by Pérez-Díaz a PD treatment concept close to that of the Carry Life® UF system was used.[22] In the study a 50% glucose solution, at a dose of 20-30 g/h, was continuously administered to the IP fluid during four-hour dwells in PD patients with symptomatic fluid overload that could not be adequately treated with available PD methods. IP glucose concentrations at the end of the PD dwell was 1.89 ± 0.42%. The highest IP glucose concentration was 2.7%. The treatment reversed all episodes of fluid overload, and serum glucose levels were stable and remained within safe levels during the study. The SCPD achieved high UF volumes in the four-hour sessions (653 ± 363 ml/4 h) and achieved twice the UF volume compared to the patients' PET tests (300 ± 251 ml/4 h) and

6 times that of their regular PD regime (100 ± 123 ml/4 h). The achieved UF volumes varied in the study participants, despite identical treatments being performed, which was partly explained by a correlation of UF to fluid overload. The conclusion of the Pérez-Díaz study was that SCPD may provide an effective and safe tool to manage UF in PD, opening new therapeutic possibilities to optimize and increase the flexibility of PD treatments.[22]

Conclusions of the reviewed literature for CFPD and SCPD are that when a stable IP glucose concentration is maintained during the PD dwell the UF is increased compared to standard PD therapies. CFPD is also associated with a higher sodium removal and a more efficient use of the glucose.

3.8 Clinical experience with the Carry Life® UF device

Two clinical studies have been performed with the Carry Life® UF device in PD patients (Tmed-004 and Tmed-007). The therapeutic concept of both clinical investigations was to maintain a stable IP glucose concentration to achieve peritoneal UF.

In Tmed-004, a 20% glucose solution was used and a glucose dose of approximately 10 g/h was administered during the 8-hour treatments. Five patients were included in the study and two treatments were performed for each patient. A stable IP glucose concentration of around 1.27% was maintained throughout the treatment. The average UF volume with the Carry Life® UF treatment was 586 ± 685 ml which compared with the patients' average UF volume of 860 ± 640 ml for 24 hours. The Carry Life® UF hence achieved an UF volume in eight hours in the same range as the UF volume normally achieved by the patients 24-hour CAPD regime. However, there was high variability in the UF volume outcome, both between patients and between the two treatments for the same patient.

Due to the high variability in UF outcome in the Tmed-004 study, the Carry Life® UF glucose dose setting was adjusted to enable a glucose dose up to 20 g/h. The system software (SW) was updated for use with a 50% glucose solution instead of the 20% glucose solution. The Tmed-007 study was performed with the updated device in order to determine the UF efficacy of three different glucose doses (11, 14, and 20 g/h) during a 5-hour treatment in comparison to a standard 4-hour 2.27% glucose CAPD dwell. The study included eight subjects of high (H) and high average (HA) peritoneal membrane transport characteristics and the results showed a significantly increased UF volume compared to the 2.27% CAPD dwell at all three doses. The UF volume with the Carry Life® UF treatment was 646 ± 256, 739 ± 312, and 863 ± 380 ml with the 11, 14, and 20 g/h glucose doses, respectively, compared with 162 ± 242 ml for the control CAPD dwell. Glucose UF efficacy was significantly higher with Carry Life® UF treatments, being 17.0 ± 10.6, 14.5 ± 7.7 and 12.4 ± 6.8 ml UF/g glucose absorbed with the 11, 14 and 20 g/h glucose doses, respectively, compared with standard 5.9 ± 7.8 ml UF/g glucose absorbed with the control CAPD dwell. The sodium removal was proportional to the fluid removal, resulting in a sodium removal with the Carry Life® UF treatments which was 4-5 times higher than the CAPD dwell (86 ± 27, 92 ± 33, 110 ± 37 mmol/treatment with the 11, 14 and 20 g/h glucose doses, respectively, vs. 21 ± 33 mmol/treatment with the control CAPD dwell). The dialysate glucose concentration was maintained between 1.6% to 2.2% glucose throughout the treatments in a dose dependent manner.

There were no incidents of adverse therapy or adverse device effects in Tmed-004. In Tmed-007 there was one adverse device effect where the subject felt light-headed after the 11 g/h Carry Life® UF treatment. The incident resolved after a short rest. All patients tolerated the treatment well and there was no discomfort associated with the intermittent transfer of IP fluid during the investigations.

Since the Tmed-007 study, the Carry Life® UF cycler has been updated in order to improve the robustness and usability of the system, including:

- The auto-drain function has been added.
- The highest dose of 20 g/h has been removed. There are now two glucose doses, 11 g/h and 15 g/h instead of the 11, 14 and 20 g/h doses that were used in the Tmed-007 study.
- The SW has been updated in accordance with the updated functionality and in order to avoid false alerts.
- The user interface (hand control) has been updated.
- The pinch valves have been made more robust.
- The cycler chassis is modified to improve usability.

Please also refer to the IB for a further description of the device updates that was done after the Tmed-007 study.

3.9 RATIONALE FOR THE CLINICAL INVESTIGATION

The Carry Life® UF system has been verified and validated according to Triomed's quality system and meets applicable regulatory standards. Verifications and validations have been performed for the following system components:

- Line set.
- Labeling.
- Software.
- Cycler and System.

For details on the verification and validation testing, refer to the IB.

The following conclusions for the verification and validation testing has been made:

Line set:
All verification and validation testing performed on the Carry Life® UF line set met pre-determined acceptance criteria as defined in design inputs, product specifications, and applicable standards. The line set performed as expected and all testing results suggest with high statistical probability that the device will perform as intended in the clinical environment. None of the deviations from prescribed methods in the protocol adversely affected the outcome of the tests.

Labeling:
All verification and validation testing performed on the Carry Life® UF labeling met pre-determined acceptance criteria as defined in design inputs, product specifications, and applicable standards.

Software:
All verification and validation testing performed on the Carry Life® UF software met pre-determined acceptance criteria as defined in design inputs, product specifications, software requirements, software design documents and applicable standards. The software performed as expected and all testing results indicate that the device is expected to perform as intended in the clinical environment. None of the deviations from prescribed methods in the protocol adversely affected the outcome of the tests.

Cycler / system conclusion:
All verification and validation testing performed on the Carry Life® UF cycler and system met pre-determined acceptance criteria as defined in design inputs, product specifications, and applicable standards. The cycler and system performed as expected and all testing results suggest with high statistical probability that the device will perform as intended in the clinical environment. None of the deviations from prescribed methods in the protocol adversely affected the outcome of the tests.

The previous clinical investigation Tmed-007 showed in eight PD patients that the Carry Life® UF treatment, at glucose doses between 11 g/h and 20 g/h, can be used to significantly increase the UF volume, increase the peritoneal sodium removal and increase the glucose UF efficiency (i.e., more UF per glucose amount absorbed) compared to a 2.27% CAPD dwell. The study also showed that the device was safe to use in a clinical setting when handled by PD nurses. The Carry Life® UF system is intended for use by the patient or caretaker in the home environment.

The aim for the present clinical investigation is: 1) to show that a Carry Life® UF treatment performed by the patient (or caregiver, if a caregiver normally assists the subject's PD treatment) in the home environment generates an increased UF compared to the control treatment and 2) to evaluate the overall safety of the Carry Life® UF treatment when incorporated in the subjects' current CAPD regime in the home environment and when used by the patient/caregiver in the home environment.

The proposed design of the clinical investigation is a crossover study where all subjects will perform both the control arm, which includes a baseline PD regimen including one 2.27% CAPD day dwell, and the Carry Life® UF treatment arm. Subjects will start with either the control arm or Carry Life® UF arm based on the randomization. During the Carry Life® UF arm one 2.27% glucose CAPD dwell will be replaced with Carry Life® UF treatment during three days of the week. For the remaining four days of the week, the 2.27% glucose dwell will be replaced by a 1.36% glucose dwell. With this design Triomed expect that the subject's weekly UF volume will be reasonably stable. The PD prescription can be changed as required during the study to obtain an adequate fluid removal.

All the steps required for the use of the Carry Life® UF system are described in the IFU. When using the Carry Life UF® system at home the patient/caretaker would need to perform the following activities listed in Table 5.

The Carry Life® UF System has been validated in a summative usability study on 15 PD nurses and 15 PD patients. While the report from the study is not completed, there study has passed all acceptance criteria including the acceptance criteria of no critical use errors allowed.

Table 5. Patient/caregiver activities performed at home to use the Carry Life® UF System

Activity	Comment
Cleaning the work surface.	Same as before standard CAPD treatment.
Weighing of solution bags.	Weighing of solution bags is clinical practice for many patients in their standard CAPD treatment.
Inspecting all disposables and solutions used for the treatment.	Same as for their standard CAPD treatment.
Setting up the Carry Life UF® system: • Inserting the battery in the cycler. • Attaching the line set in the cycler. • Connecting the glucose bag to the line set and attaching glucose bag to cycler. • Starting the device function check (pressing the OK button).	Training will be performed and patients will be required to pass a device competency evaluation by a site PD nurse before using the system at home.
Performing a standard CAPD fill.	Same as for standard CAPD treatment.
Attachment of the PD belt.	Same as for standard CAPD treatment (if they use a PD belt).
Connecting the Carry Life UF® line set to the catheter transfer set.	Similar to what the CAPD patients normally do when they perform a PD fluid exchange. Same type of connection.
Securing the patient connection (connection between the extension set and Carry Life UF® line set) in the PD belt.	Similar to what the CAPD patients normally do, normally the transfer set would be secured in the PD belt.
Priming the Carry Life UF® system (by pressing the OK button after function check is completed).	Training will be performed and patients will be required to pass a device competency evaluation by a site PD nurse before using the system at home.
Starting treatment with the Carry Life UF® device (after priming is completed).	Training will be performed and patient will be required to pass a device competency evaluation by a site PD nurse before using the system at home.
Managing device alerts (according to description and troubleshooting guide in the IFU).	Training will be performed and patient will be required to pass a device competency evaluation by a site PD nurse before using the system at home.
Performing additional drains (not normally needed).	Training will be performed and patient will be required to pass a device competency evaluation by a site PD nurse before using the system at home.
Disconnecting from device after completing treatment.	Similar to what the CAPD patients normally do when they disconnect after a PD fluid exchange. Same type of connection.
Performing a standard PD drain after treatment.	Same as for standard CAPD treatment.
Removing used disposables from the Carry Life UF® line set.	Training will be performed and patients will be required to pass a device competency evaluation by a site PD nurse before using the system at home.
Weighing and emptying drain bags after treatment.	The CAPD patients are used to weighing and emptying the drain bags. A different scale will be used if patient does not normally use a desk top scale.
Discarding of disposables.	Same as for standard CAPD treatment.
Removing an and re-charging the Carry Life UF® battery in the provided battery charger.	Training will be performed and patient will be required to pass a device competency evaluation by a site PD nurse before using the system at home.
Cleaning the Carry Life UF® cycler and carrying bag.	Training will be performed and patient will be required to pass a device competency evaluation by a site PD nurse before using the system at home.

4 THE RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

4.1 ANTICIPATED CLINICAL BENEFITS

Carry Life® UF system is intended as a complement to standard PD therapies, performed by the patient or a caregiver at home, with the anticipated clinical benefit of improved fluid management through an efficient fluid and sodium removal enabled by the sustained IP glucose concentration. Inadequate fluid management is associated with technique failure, and higher total fluid removal and total sodium removal are both associated with decreased morbidity and mortality in PD patients. Introducing Carry Life® UF treatment for PD patients may enable patients to stay longer on PD therapy, and allowing for less strict fluid restrictions. By mitigating the need for use of hypertonic glucose-based PD solutions, which are associated with peritoneal membrane deterioration resulting in higher solute transport and reduced peritoneal fluid removal, the UF capacity of the peritoneal membrane may be preserved.

In Tmed-007, the Carry Life® UF doses of 11 and 14 g/h resulted in a dialysate glucose concentration around 1.6% and 1.9%, i.e., lower peak glucose concentration than with hypertonic glucose-based PD solutions. With lower peak dialysate glucose concentration, the peak glucose absorption rate will be lower, which may lead to less impact from the Carry Life® UF treatment on blood glucose levels in diabetic patients compared to the standard hypertonic PD-dwells.

Because of the more efficient use of glucose (more UF per amount of glucose absorbed) compared to 2.27% glucose PD dwells, Carry Life® UF may reduce the total peritoneal glucose uptake from the patients PD regimen.

In summary, the clinical advantages of the Carry Life® UF system are:

- UF can be maintained throughout the treatment session leading to a larger fluid removal which enables improved volume management.
- An efficient use of glucose, i.e., higher UF volume per amount of glucose absorbed which may reduce the total glucose absorption from the PD regimen.
- Increased sodium removal.
- A reduced use of hypertonic glucose PD solutions.
- Increased technique survival.

4.2 ANTICIPATED BENEFITS FOR PARTICIPANTS

There are no immediate clinical benefits for the patients participating in the clinical investigation. Subjects may achieve increased UF volume during the clinical investigation study sessions compared to their standard PD regime and less glucose may be absorbed during the 4 weeks treatment with the device at home, however, these benefits cannot be guaranteed.

At present the Carry Life® UF system is not commercially available, and patients will not be able to continue with the therapy even if it was shown beneficial in the clinical investigation. When the device is commercially available it is intended for the patient population included in the clinical investigation.

4.3 ANTICIPATED ADVERSE DEVICE EFFECTS

The anticipated adverse device effects of the Carry Life® UF system are related to the adverse effects of standard PD treatment performed by the patient/caregiver at home, which are well known and documented. Table 6 below lists the adverse effects associated with standard PD treatment compared to the Carry Life® UF system and the study mitigations.

Table 6. The anticipated adverse events with the Carry Life® UF compared to standard PD treatment and their mitigations

Anticipated adverse device effect	Frequency in standard PD treatment	Estimated relative risk for Carry Life® UF vs standard PD treatment	Carry Life® UF risk mitigations
Infection: Exit site/catheter tunnel infection Peritonitis	Exit site and catheter tunnel infections are major predisposing factors for PD related peritonitis which is a well-known risk associated with PD. The peritonitis rate is between 0.2 to 0.6 episodes/patient/year, or 1 episode per 20-60 patient months of PD.	Contamination of the fluid path may cause infection and peritonitis and is primarily associated with connections of PD bags and line sets performed by the user. Carry Life® UF system connections have been developed in order to minimize the risk of contamination and the risk is therefore assessed as comparable to standard PD therapies. Each Carry Life® UF treatment adds one patient connection, when the catheter extension set is connected to the Carry Life® UF line set. Since flush-before-fill is utilized with the Carry Life® UF system, (the PD solution instilled in the peritoneal cavity is used to flush the system) the added risk of contamination is assessed as minimal. Exit site infection and catheter tunnel infection may be caused by tear at the exit site. The connection to the Carry Life UF cycler adds a risk for pulling of the catheter and tear of the exit site compared to a standard CAPD treatment but may be comparable to the risk associated with APD treatment, where the patients also are connected	The design of line set and connectors mitigates the risk of contamination. The system flushes the system with IP fluid after device connection which reduce the risk for contamination. The study subjects prevalent CAPD patients who performs their standard CAPD treatment at home and who are proficient is aseptic techniques. The subject/caretaker have to undergo training on the device to ensure they can operate the device safely and autonomously before continuing to the home treatment phase. The IFU contains clear instructions regarding the use of aseptic technique with the system. The length of the patient line and securing of the patient connection in a PD belt mitigates the risk for pulling of the catheter and tearing of the exit site. The securement of the patient connection in the PD belt has been verified to prevent pulling of the

Anticipated adverse device effect	Frequency in standard PD treatment	Estimated relative risk for Carry Life® UF vs standard PD treatment	Carry Life® UF risk mitigations
		to a device throughout the treatment.	catheter in case the cycler is dropped.
Fibrosis of the peritoneal membrane	Deterioration of the peritoneal membrane is a long-term consequence of PD.	The risk with the Carry Life® UF system is possibly lower as the peritoneal membrane is exposed lower peak dialysate glucose concentration.	N/A
Hernia	Hernia occurs in 10-20% of PD patients at some point during the treatment period due to the intraperitoneal fluid volumes.	The same or lower as standard CAPD as the system remove dialysate from the system hourly during treatment which based on the Tmed-007 study prevents an increase in IP volume in most patients.	Hourly drains to limit increases in IP volume resulting from the UF fluid.
Encapsulating peritoneal sclerosis	Encapsulating peritoneal sclerosis is a rare but devastating complication of long-term PD occurring in 1-3% of PD patients, usually after approximately 5 years of PD therapy. The mechanism of this complication is unclear, but the duration of PD therapy is the strongest risk factor.	The same as for standard PD.	None.
Metabolic disturbances due to glucose absorption	Glucose based PD results in significant amounts of glucose being absorbed 50-150 g daily. This may contribute to weight gain and lipid abnormalities in PD patients.	The same as for standard PD.	The baseline CAPD prescription (2.27% glucose dwells) is replaced by 1.36% glucose dwells. Glucose absorption is expected to be comparable with the Carry Life® UF system and the standard CAPD prescription.
Hyperglycemia	In diabetic patients, peritoneal glucose absorption results in poorer glycemic control and adjustment of or initiation of blood glucose lowering medication may be needed. While data are limited one study indicate that 8% of non-diabetic patients become diabetic	The same as for standard PD.	The patients' standard PD treatment is modified so that the subject's weekly glucose exposure will be comparable when the Carry Life® UF system is used. Blood glucose levels will be frequently measured during the in-clinic phase of the study.

Anticipated adverse device effect	Frequency in standard PD treatment	Estimated relative risk for Carry Life® UF vs standard PD treatment	Carry Life® UF risk mitigations
	after start of PD therapy (8).		Diabetic subjects will monitor and manage their blood glucose levels according to their standard diabetes management. After starting to use the Carry Life® UF device at home, blood glucose levels will be evaluated daily by the clinic for at least three days until judged clinically stable and thereafter weekly.
Altered concentrations of electrolytes in blood	>10% of patients treated with hourly exchanges of hypertonic PD solution develops hypernatremia due to sodium retention. 10-30% of PD patients have hypokalemia, which may be due to PD removal of potassium, glucose absorption, or other reasons not related to PD. Insufficient calcium removal is common in PD. Low-calcium PD solutions are available to increase calcium removal during PD.	Same as for standard PD.	Concentration of electrolytes in blood will be measured at start of study (Visit 1) and after each study arm.
Peritoneal protein loss	6-8 g of protein are lost daily by PD, which may result in a decrease in serum albumin.	Same as standard PD.	None.
Hemodynamic instability due to increased peritoneal UF	This is a rare adverse event of standard PD.	As Carry Life® UF is intended to increase UF rates, compared to standard PD treatment the risk for hemodynamic instability may be increased. No issues of hemodynamic instability have been observed during previous clinical investigations with the Carry Life® UF device, also at higher glucose doses.	The risk during the clinical investigation is mitigated by the design of the investigation: the glucose dosage during the in-clinic phase starts at the lowest dose and symptoms of hemodynamic instability will be monitored. Subjects will not be allowed to continue in the study if they experience a systolic blood pressure below 100 mmHg during the in-clinic treatment phase of the

Anticipated adverse device effect	Frequency in standard PD treatment	Estimated relative risk for Carry Life® UF vs standard PD treatment	Carry Life® UF risk mitigations
			study or generates a UF rate higher than 20 ml/lg body weight/5-hour treatment. A systolic blood pressure below 100 mmHg and clinical signs of dehydration are used as exclusion criteria in the study.
Increased intraperitoneal pressure due to increased UF	This is a rare occurrence in APD and is mitigated by performing a complete drainage mid treatment.	Comparable to APD treatment.	The subjects will for the Carry Life® UF treatments use the same fill volume as in their standard PD treatment. Hourly drainage is performed during the study sessions, thereby reducing the risk for increased intraperitoneal pressure and there is a complete peritoneal drain at the end of the 5-hour treatment session. The subject will not be allowed to continue the study if a UF rate higher than 20 ml/kg body weight/5-hour treatment occurs during the in-clinic phase.
Blood concentration of dialyzable drugs can be reduced	This is a known adverse effect and adjustment to medications are performed accordingly.	Comparable to other PD therapies.	None.
Shoulder or abdominal pain due to infusion of air in the peritoneal cavity	Pneumoperitoneum is not uncommon in CAPD patients and the main reason is user error during the PD bag exchange.	Comparable to CAPD treatment.	The Carry Life® UF treatment cannot be started if priming, which removes the air from the line set before use, has not been performed.

The anticipated adverse device effects which are particularly relevant when using the Carry Life® UF device are related to the therapeutic mode of action (enhancing UF volumes by maintaining a stable IP glucose concentration).

The possible anticipated adverse events and their mitigation are:

- That increased UF volumes may result in hemodynamic instability such as hypotension during Carry Life® UF study sessions. Mitigation: Blood pressure and generated UF rate will be assessed according to a pre-defined procedure during the in-clinic treatment phase. Blood pressure and heart rate will be measured before and after the Carry Life® UF study sessions and additionally if clinically indicated. If the patient becomes hemodynamically instable during the Carry Life® UF study session, the session will be discontinued, and the patient returned to their normal treatment.
- That glucose absorption may increase the blood glucose levels. Mitigation: Blood glucose levels will be monitored during the in-clinic visits and blood glucose will be regularly monitored in diabetic patient during the home treatment phase of the study.
- That the IP volume is increased due to the enhanced UF. During the Carry Life® UF study sessions there will be hourly drains of the IP volume, and additional drains can be performed at any time if the patient experiences discomfort.

4.4 RESIDUAL RISKS ASSOCIATED WITH THE DEVICE

A risk analysis of the Carry Life® UF system has been performed according to ISO 14971:2019 and is available in Appendix C of the IB. The Carry Life® UF system complies to identified applicable regulatory standards and the risk analysis shows that the usage of the Carry Life® UF does not entail unacceptable risks.

The residual risks associated with the device have been reduced to an acceptable level or as a low level as reasonably possible. Further mitigation will not improve safety. The risk level for contamination is comparable to conventional PD therapies. From a general risk-benefit perspective, the risk posed by the clinical investigation performed by the Carry Life® UF system is acceptable and comparable to standard methods of PD.

4.5 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL INVESTIGATION AND MITIGATION

Risks associated with participation in the clinical investigation have been evaluated according to ISO 14971:2019. Risks with the clinical investigation are similar to standard CAPD treatment including hyper-or hypovolemia, hyper-or hypo glycemia, as well as risk associated with blood sampling. Risks of additional blood sampling, PET/CAPD dwell during in-clinic phase, and Carry Life UF® treatments in clinic, will be performed by healthcare professionals at the PD clinic according to routine clinical procedures. Risks associated with Carry Life UF® treatments at home during the home treatment phase will be mitigated by PD patients being trained in aseptic technique and on the Carry Life UF® treatment, furthermore a study nurse shall be present during the preparation and initiation of the first at home treatment. Diabetic patients on insulin frequently monitor blood glucose levels according to their regular diabetes management and are familiar with early symptoms of hypo-/hyper-glycemia and how to manage this.

Refer to Table 6 for a list of adverse effects associated with PD compared to the Carry Life® UF system and their study mitigations.

4.6 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

A concomitant therapy is any drug or substance administered between the time the patient has has been enrolled and the completion of the follow-up/end of the clinical investigation. Adjustments to medication regimes can be performed at the discretion of the Investigator and should be documented in the electronic case report form (eCRF) (assessments/evaluations) and medical records. Blood concentration of dialysable drugs can be reduced by PD but no change is expected when introducing the Carry Life® UF system as the amount of PD fluid used will not be changed during the study. Glucose has no known drug interaction with the Carry Life® UF system.

4.7 BENEFIT TO RISK RATIONALE

Based on the above assessments of the benefits and risks with the Carry Life® UF system, it can be concluded that the benefits exceed the risks for patients included in the clinical investigation and may significantly benefit future PD patients. The risks associated with the study treatment are the same as the risks associated with standard PD therapies.

5 OBJECTIVES OF THE CLINICAL INVESTIGATION

5.1 OBJECTIVES

5.1.1 Primary objective

The primary objective of the clinical investigation is:

- To demonstrate that a 5-hour Carry Life® UF treatment at home results in an increased UF volume compared to a 5-hour 2.27% glucose CAPD dwell in adult CAPD patients.

5.1.2 Secondary objectives

The secondary objectives of the clinical evaluation are:

- To evaluate the overall safety of the Carry Life® UF system used by the patient at home as measured by rates of adverse events (AEs) and serious adverse events (SAEs) in adult CAPD patients.
- To demonstrate that treatment with the Carry Life® UF system at home results in increased sodium removal compared to a 2.27% glucose CAPD dwell in adult CAPD patients.
- To demonstrate that treatment with the Carry Life® UF system at home results in a more glucose efficient peritoneal fluid removal compared to a 2.27% glucose CAPD dwell in adult CAPD patients.
- To evaluate if the peak glucose concentration during a Carry Life® UF treatment is lower than the glucose concentration of a 2.27% glucose PD solution.

5.1.3 Exploratory objectives

The exploratory objectives of the clinical evaluation are:

- Evaluation of peritoneal urea and creatinine removal.
- Evaluation of overall weekly UF based on the patient diary.

5.2 HYPOTHESES TO BE ACCEPTED OR REJECTED BY STATISTICAL DATA FROM THE CLINICAL INVESTIGATION

Primary endpoint hypothesis

The UF volume achieved with the Carry Life® UF system is superior compared to the UF volume achieved with CAPD using a 2.27% glucose PD solution during a 5-hour treatment.

Hypothesis:

: $H0: \mu_d \leq \delta$

$H1: \mu_d > \delta$

Where μ_d is the average paired difference in UF volume and δ is the superiority margin of 250 ml.

Where H_0 is rejected if the following is true:

$$\frac{(\hat{\epsilon} - \delta)}{\frac{\hat{\sigma}_m}{\sqrt{2n}}} < t_{\alpha,2n-2}$$

Secondary endpoint hypotheses

Peritoneal sodium removal: The peritoneal sodium removal achieved with the Carry Life® UF system is larger than the peritoneal sodium removal achieved with CAPD using a 2.27% glucose PD solution during a 5-hour treatment.

Hypothesis:

H0: $\mu_{CL} \leq \mu_{CAPD}$

H1: $\mu_{CL} > \mu_{CAPD}$

Where μ_{CL} is the average paired Carry Life® UF peritoneal sodium removal and μ_{CAPD} is the average paired CAPD peritoneal sodium removal.

Glucose UF efficiency: The glucose UF efficiency (ml UF volume / g glucose absorbed) achieved with the Carry Life® UF system is higher than the glucose UF efficiency achieved with CAPD using a 2.27% glucose PD solution during a 5-hour treatment.

Hypothesis:

H0: $\mu_{CL} \leq \mu_{CAPD}$

H1: $\mu_{CL} > \mu_{CAPD}$

Where μ_{CL} is the average paired Carry Life® UF glucose UF efficiency and μ_{CAPD} is the average paired CAPD glucose UF efficiency.

Peak dialysate glucose concentration:

H0: $Peak_{CL}$ dialysate glucose concentration $\geq$ 2.27%

H1: $Peak_{CL}$ dialysate glucose concentration < 2.27%

Where $peak_{CL}$ is the highest measured dialysate glucose concentration during the Carry Life® UF treatment (T1h to T5h).

AEs and SAEs:

There is no statistical test for the safety endpoint. The AEs will be tabulated and described in detail.

5.3 CLAIMS OF PERFORMANCE OF THE DEVICE

Claims and intended performance of the investigational device to be verified include:

- A larger UF volume can be obtained compared to a standard 2.27% glucose CAPD dwell.
- A larger sodium removal can be obtained compared to a standard 2.27% glucose CAPD dwell.
- The device maintains the intraperitoneal glucose concentration throughout the treatment.
- The glucose concentration is maintained below 2.27% i.e., below the glucose concentration of a medium strength glucose PD solution.
- The system prevents increases in intraperitoneal volume by hourly drainage of approximately 180 ml of dialysate.
- The glucose UF efficiency (ml UF / g glucose absorbed) is improved compared to a standard 2.27% glucose CAPD dwell.

5.4 RISKS AND ANTICIPATED ADVERSE DEVICE EFFECTS TO BE ASSESSED

Anticipated adverse device effects are contained in Section 4.3 and the specific adverse device effects for evaluation are as follows:

- Adverse device effects associated with excessive UF volumes:
  - Hypotension.
  - Weight reduction below target weight.
  - Other clinical symptoms of dehydration.
  - Reduced residual renal function.
  - Changes in blood chemistry (electrolytes, glucose, albumin, parathyroid hormone [PTH]).
- Adverse device effects associated with glucose absorption/inadequate diabetes medication:
  - Hyperglycemia.
  - Hypoglycemia.

6 DESIGN OF THE CLINICAL INVESTIGATION

6.1 GENERAL

The clinical investigation is a pre-market, prospective, multicenter, randomized, crossover study in adult subjects with ESKD treated with CAPD.

The study consists of the following five phases:

1. Inclusion phase.
2. In-clinic treatment phase for dose determination and safety evaluation.
3. Randomization phase.
4. Transition to home phase.
5. Home treatment phase for efficacy and safety evaluation.

Patients need to use the Baxter PD system and have a PD prescription of at least one 2.27% glucose day dwell of 1.5-2 L to be included in the study. There is an optional run-in phase during the inclusion phase in order for the patient to meet the PD prescription inclusion criteria. Throughout the study, the subject will use the fill volume they normally use, both for the standard PD prescription and for the Carry Life® UF treatments. However, for the PET a 2 L fill volume will be used.

The in-clinic phase consists of one 2.27% CAPD dwell (PET) and two Carry Life® UF treatments (one at 11 g/h glucose and one at 15 g/h glucose). The Carry Life® UF treatments will be used for a safety evaluation, and based on the UF volumes achieved, the Carry Life® UF glucose dose for the home treatment phase will be determined.

After completion of the in-clinic phase, subjects will be randomized to start the home treatment phase either with the control treatment arm or with the Carry Life® UF treatment arm. Subjects in the control arm will continue their standard CAPD treatment. In the Carry Life® UF arm, one 2.27% glucose CAPD dwells per day will at three days of the week be replaced by a Carry Life® UF treatment. During the remaining four days of the week, one 2.27% glucose CAPD dwell will be replaced with a 1.36% glucose CAPD dwell.

The Carry Life UF system will be used during Mondays, Wednesdays and Fridays, instead of a 2.27% glucose dwell. The time of the day when the Carry Life® UF system will be used does not need to be at the same the same time of the day as the 2.27% glucose dwell. The time of the day when the Carry Life UF system will be used, may differ on different days based on the subject's schedule.

At four (4) efficacy evaluation days during the home treatment phase (two per arm), there will be a careful recording of the solution volumes used (PD solution and glucose solution), volumes drained, and samples will be taken from the drain bags after treatment. The subject, together with the responsible physician, will determine during which days and during what time of the day the efficacy evaluation treatments (the 2.27% glucose dwell during the control arm and the Carry Life® UF treatment during the Carry Life® UF arm) will be performed. For each subject all efficacy evaluation treatments shall be performed on the same day of the week and on the same time of the day. A 2.27% glucose dwell will be the comparator dwell during the control arm. In order to perform the comparator dwell and the Carry Life UF treatment during at the same time of day, the physician may

need to modify the order and duration of the CAPD day dwells during the efficacy evaluation days in the control arm home phase of the study.

AEs, SAEs, and Carry Life® UF device malfunctions will be collected throughout the study. A nurse at each participating clinic who has undergone education and training necessary for thorough AE collection will be responsible for the recording of AEs (i.e., education in good clinical practice [GCP] will be required and training with respect to the eCRF for AE reporting). In case of an AE or device malfunction in the home treatment phase, the subject will be instructed to immediately contact the clinic. Furthermore, the clinic will contact the subject weekly and specifically ask about the occurrence of any AE or Carry Life® UF device malfunction.

The patient's participation will be approximately 12 weeks. The actual time mainly depends on how frequent the three in-clinic visits are scheduled, how many training sessions are required, and the scheduling of the training visits. The study schedule will include 8 to 13 visits dependent on the individual device training requirements. Only the in-clinic visits and the visits during the home treatment phase have been assigned a specific visit number:

1. Inclusion phase – Screening & consent – Visit 1.
2. In-clinic treatment phase for dose determination efficacy and safety evaluation – Visits 2–4 (approximately 2 weeks).
3. Randomization phase – No visit.
4. Transition to home treatment phase – Visit T1 to T7 (2–7 visits, approximately 1 week).
5. Home treatment phase for efficacy and safety evaluation – Visit 5 and 6 (8 weeks; 4 weeks in the control arm and 4 weeks in the treatment arm).

The subject will be followed up for one week for new or continuing AEs after the end-of-study visit. The follow-up will be in the form of a phone call or a physical meeting as determined by the investigator.

There will be at least one day in between treatment during the in-clinic phase of the study.
Any changes in medications or PD prescriptions will be recorded during the study. If changes to diuretic prescription or PD prescription are made, the reason for the change will be documented. If a study participant discontinues the study the reason for this will be documented in detail.

A flow diagram of the study design is shown in Figure 1 and Figure 2. Table 1 outlines the schedule of activities at each study visit.

6.2 DESCRIPTION OF CLINICAL INVESTIGATION PHASES

6.2.1 Inclusion phase (Visit 1)

Following approval by the ethics committee and any required competent authority, the subject will be screened for study eligibility and a signed informed consent will be obtained.

Once the patient has signed the approved ICF and has met all the inclusion and no exclusion criteria, the subject will be considered eligible to be enrolled in the study.

If the subject does not meet the PD prescription requirement, the subject may consent to participate in the study and to a change of PD prescription in order to meet the requirement. A run-in period of at least two weeks with a PD prescription that meets the inclusion criteria will then be performed.

After the run-in period physician will review the eligibility of the patient to continue the study and complete the inclusion of the patient (enrolment point) ***or*** alternatively exclude the patient from the study. The exclusion of the patient will be recorded as a screening failure and will not be further followed up in the study.

Patient demographics, medical history, concomitant medications, baseline PD prescription and 24-hour UF volume will be recorded. A screening log will be maintained at each study site containing limited non-identifiable information.

During the inclusion phase the subject will, together with the responsible physician, decide during what day of the week and what time of the day the efficacy evaluation treatments will be performed. All efficacy evaluation treatments should be performed the same day of the week and the same time of the day. In order to perform the 2.27% glucose comparator dwell and the Carry Life® UF treatment at the same time of day, the physician may need to modify the order and duration of the CAPD day dwells during the efficacy evaluation days in the control arm of the home treatment phase of the study.

6.2.2 In-clinic treatment phase for dose determination and safety evaluation

The in-clinic treatment phase will be used to determine the Carry Life® UF dose to be used during the home treatment phase and to enable a safety assessment of the Carry Life® UF glucose dose before using the Carry Life® UF device at home. The in-clinic treatment phase will consist of one 2.27% glucose, 4-hour dwell (PET), and two 5-hour Carry Life® UF treatments (one at 11 g/h glucose and one at 15 g/h glucose). The PET may be performed in the patient's home if the clinic has experience of this practice and a procedure for performing PET at home.

The subjects will use their regular PD prescription the night before each visit, and the PD fluid will be drained at the clinic in the morning before the start of the study treatment. However, the night before the PET, patients who use an icodextrin PD solution overnight will replace the icodextrin solution with a 2.27% glucose solution.

There will be at least one day in between the treatments during the in-clinic treatment phase.

The time and type of breakfast before the in-clinic treatments will be recorded. Any food and fluid intake, as well as urinary output during the visits will be recorded. The subject will be allowed to have a light meal with low glucose content (avoiding sugary carbohydrates) and will only be allowed to drink water and beverages without sugar. Diabetic subjects will record the time for diabetic medications taken before and during the treatment.

AEs, SAEs, and Carry Life® UF device malfunctions will be recorded.

After each in-clinic treatment, the physician may modify the subject's PD prescription for the reminder of the day according to clinical judgement and standard clinical practice to enable adequate fluid removal.

Visit 2 (2.27% glucose PET)

- The day before Visit 2, a 24-hour urine collection will be initiated, unless the patient is anuric (<100 ml urine volume/24 hours), and analyzed according to Table 1.
- Patients with an icodextrin prescription for the overnight dwell will replace the icodextrin PD solution with a 2.27% glucose PD solution the night before the PET.
- A 4-hour PET with 2 L, 2.27% glucose PD solution will be performed and the dialysate will be analyzed according to Table 1.
- Blood samples will be taken before treatment for analysis of study base line blood chemistry according to Table 1.
- Venous blood samples for blood glucose measurement will be taken before treatment, at 30 min, at 1 hour and then hourly until the fourth hour (end of treatment) via a peripheral intravenous cannula. If it is not possible to cannulate a subject, samples shall be taken by venipuncture before treatment, at 1 hour and 4 hours.
- Body weight, blood pressure and heart rate will be measured before and after the treatment.

Visit 3-4 (Carry Life® UF treatments)

- A 5-hour Carry Life® UF treatments will be performed (Visit 3 using the 11 g/h glucose dose and Visit 4 using the 15 g/h glucose dose).
- A 1.36% glucose PD solution, 1.5–2 L according to the subject's standard prescription will be used for the initial fill and automatic drains will be performed hourly, which means that approximately 180 ml of dialysate will be removed by the system and transferred into a drain bag every hour. The dialysate will be analyzed according to Table 1.
- Venous blood samples for glucose measurement will be taken before treatment, at 30 min, at 1 hour and then hourly until the fifth hour (end of the treatment) via a peripheral intravenous cannula. If it is not possible to cannulate a subject, samples shall be taken by venipuncture before treatment, at 1 hour and 5 hours.
- Body weight, blood pressure and heart rate will be measured before and after the treatments. In addition, blood pressure will be measured in case of clinical symptoms suggestive of hypotension such as lightheadedness, dizziness, feeling faint, tiredness or weakness, change of consciousness e.g., drowsiness, nausea, and cold and clammy skin.

Subjects will be withdrawn from the rest of the study if they:

1. Experience a systolic blood pressure < 100 mmHg where the hypotension is deemed to be caused by hypovolemia due to excessive peritoneal UF.
2. Generate an UF rate higher than 20 ml/kg body weight/treatment.

If the 11 g/h glucose dose Carry Life® UF treatment results in a UF volume of 1.0 L or greater, the 15 g/h glucose Carry Life® UF treatment will not be performed.

Based on the UF volume obtained from the Carry Life® UF treatments the Carry Life® UF dose prescription for the home treatment phase will be determined according to the following criteria:

1. The 15 g/h glucose dose will only be used if both of the following conditions are met:
   - The treatment with the 11 g/h glucose dose achieved a UF volume of less than 1.0 L.
   - The treatment with the 15 g/h glucose dose achieved a UF volume 25% greater than the treatment with the 11 g/h glucose dose.
2. In all other cases the 11 g/h glucose dose will be used.

For example:

- The 11 g/h glucose dose gave a UF volume of 500 ml and 15 g/h glucose dose gave a UF volume of 700 ml UF (40% greater than the 11 g/h glucose dose) à the 15 g/h the Carry Life® UF glucose dose shall be used.
- The 11 g/h glucose dose gave a UF of 500 ml and 15 g/h dose gave a UF of 620 ml (24% greater) à the 11 g/h Carry Life® UF glucose dose shall be used.
- The 11 g/h glucose dose gave a UF volume of 1000 ml à the 11 g/h Carry Life® UF glucose dose shall be used.

Before continuing to the randomization phase, the responsible physician will review the blood chemistry and blood glucose data generated during the in-clinic treatment phase, as well as and the occurrence of a systolic blood pressure of < 100 mmHg or, an UF rate exceeding 20 ml/kg body weight/treatment and confirm that the subject can proceed to the next phase of the study.

Identification of efficacy evaluation days: The patient, together with the physician, will confirm the scheduling of the four efficacy evaluation days which will take place during week 2 and week 4 of each study arm in the home treatment phase. For each patient, the efficacy evaluation days should be scheduled on the same day of the week, a Monday, Wednesday or Friday and the same time of the day.

6.2.3 Randomization phase

After completing the in-clinic treatment phase, subjects who will be prescribed the Carry Life® UF 11 g/h glucose dose will be randomized with an equal ratio into Group A (starting with the control arm) and Group C (starting with the Carry Life® UF arm). Subjects who will be prescribed the Carry Life® UF 15 g/h glucose dose will be randomized with an equal ratio into Group B (starting with the control arm) and Group D (starting with the Carry Life® UF arm) (refer to Figure 1). The randomization is being done to reduce any potential for bias based on subjects starting in the treatment or control arms.

6.2.4 Transition to home phase

The subjects (and their caregivers, in case the subject has a caregiver who normally performs the PD treatment for the subject) will undergo daily training on the Carry Life® UF device, for 2-5 days, to ensure that the user can operate the device safely and autonomously.

Before allowing the subject to proceed to the Carry Life® UF home treatment phase, the patient/caregiver will be evaluated and has to pass a Carry Life® UF system competency test (Attachment A), which has to be signed by the responsible training nurse. Each training session will be documented.

If the patient/caregiver does not pass the device competency assessment, two additional training sessions may be performed and the device competency assessment repeated. If the subject/caregiver still does not pass the device competency assessment the subject will be excluded from the home treatment phase of the study. The number of subjects who do not pass the device competency assessment will be documented and reported.

AEs, SAEs, and Carry Life® UF device malfunctions will be recorded.

6.2.5 Home treatment phase for efficacy and safety evaluation

Subjects randomized to Group A and Group B will start the home treatment phase in the control arm with their standard CAPD prescription. Subjects randomized to Group C and Group D will start the home treatment phase in the Carry Life® UF treatment arm. After four weeks the subject will cross-over to the other arm.

In the control arm subjects will use their regular CAPD prescription. In the Carry Life® UF arm, on Mondays, Wednesdays and Fridays, the subject will replace a 2.27% glucose dwells with the Carry Life® UF treatments at the determined glucose dose (11 g/h or 15 g/h). Each Carry Life UF treatment may be performed at a time of the day that suits the subject. The remaining four days of the week, one 2.27% glucose dwell will be replaced by a 1.36% glucose dwell. Both arms of the home treatment phase will start the same day of the week, either on a Wednesday or a Friday.

The week prior to starting home treatment with the Carry Life® UF device, subjects will undergo training on the device and an assessment of their device competency will be performed, as described in Section 6.2.4.

The Carry Life® UF device will be incorporated in the subject's CAPD regimen as follows:

- The preceding CAPD dwell will be ended with a complete peritoneal drain.
- The Carry Life® UF treatment starts with a fill of 1.36% glucose PD solution, 1.5-2 L, according to the subject's standard CAPD procedure.
- After the fill, the Carry Life® UF device will be connected to the catheter extension set according to the IFU, and the Carry Life® UF treatment will be started.
- After five hours the Carry Life® UF treatment will end, the device will be disconnected and the peritoneal fluid will be drained. The subjects will then continue with their standard CAPD prescription.

A clinical professional will be present for the first Carry Life® UF treatment at home to oversee the Carry Life® UF system set-up.

During the home treatment phase of the study, the subject will record body weight, blood pressure and heart rate daily in a patient diary (Table 1). Furthermore, the glucose concentration of the PD solutions that are used will be recorded daily, together with the PD fill and drain volumes.

Diabetic subjects will monitor and manage their blood glucose levels in accordance with their normal practice. After initiating Carry Life® UF treatments, blood glucose levels, measured as part of the

subject's standard diabetes management, will be evaluated daily by the clinic for at least three days, until judged clinically stable. Thereafter, blood glucose levels will be evaluated weekly by the clinic.

At the start of the second and third week of each study arm of the home treatment phase a nurse will contact the subject to check on clinical status, AEs, and Carry Life® UF device malfunctions. The clinical follow-up will include data on body weight and blood pressure, as well as a clinical assessment of volume status and clinical symptoms. These evaluations will also be performed at the end-of study arm visits.

Based on the clinical assessments throughout the study, the responsible physician will adjust the subject's PD prescription in order to maintain an adequate fluid balance according to clinical judgement and standard clinical practice. In the control arm, the glucose concentration of the PD dwells may be adjusted as required.

If a reduced peritoneal fluid removal is deemed necessary during the Carry Life® UF arm, the change in prescription shall be performed in the following order.

1. Reduce the glucose concentration of the CAPD dwells.
2. Reduce the frequency of the Carry Life® UF treatments.

When a Carry Life® UF treatment is removed from the prescription, a 2.27% glucose or a 1.36% glucose CAPD dwell will replace the Carry Life® UF treatment based on the clinical judgement of the responsible physician.

The Carry Life® UF treatment should be performed at least twice per week. If the subject requires a Carry Life® UF treatment frequency fewer than two days per week to avoid hypovolemia, the subject will be withdrawn from the study.

If an increased peritoneal fluid removal is deemed necessary during the Carry Life® UF arm, the change in prescription shall be performed in the following order:

1. Re-introduce the 2.27% glucose CAPD dwells that were reduced to 1.36% glucose (one at the time at a frequency indicated by the subject's clinical status).
2. When all 2.27% glucose dwells have been re-introduced, one additional Carry Life® UF treatment will be added weekly until the fluid removal is deemed sufficient. The added Carry Life® UF treatment will always replace a 2.27% glucose CAPD dwell.

All changes to the subject´s PD prescription will be documented and the reason for the change specified.

The subject should immediately contact the clinic if they have any questions or concerns about their clinical status or the study in general. If there are any concerns about the subject's clinical status that cannot be resolved by phone, the subject should always be brought to the clinic for a clinical assessment.

The subject will be instructed to record all clinical symptoms (AEs) and all technical issues (device malfunctions) with the Carry Life® UF system during the home treatment phase on forms which are part of a patient diary and provided to the subject before starting the home treatment phase. The

subject will be instructed to immediately contact the clinic if any clinical symptoms or technical issues with the Carry Life® UF system occur. The means of contacting the clinic will be provided.

Efficacy evaluation days: The efficacy evaluation days will be performed during week 2 and week 4 of each study arm during the home treatment phase, on the day (a Monday, Wednesday or Friday) and time of the day agreed. If an immediate change in a subject's prescription is required, affecting the planned efficacy evaluation day, the efficacy evaluation treatment will be postponed 2-3 days. Such occurrences will be recorded in the eCRF and indicated in the study report.

During the efficacy evaluation days the dialysate drained from the comparator 2.27% glucose dwell (control) and from the Carry Life® UF treatment will be collected by a research assistant for endpoint evaluation and analyzed according to Table 1. The 2.27% glucose control dwell will be 5 hours i.e., the same duration as the Carry Life® UF treatment.

Visit 5–6

The day after the completion of each arm (control and Carry Life® UF), the subject will visit the clinic for data collection according to Table 1. The Carry Life® UF end-of-arm visit will be performed the day after the last Carry Life® UF treatment. The end-of-arm visits should be planned to be performed on the same day of the week, e.g., for a subject who started the study arms on a Wednesday, the last treatment of the arm will be on a Monday and the end-of-arm visits will be on a Tuesday. Starting two days before the end-of-arm visits, a 24-hour urine sample will be collected, unless the subject is anuric (< 100 ml urine volume/24 hours), and analyzed according to Table 1. Visit 6 will be the completion of the study for the subject. Upon completion of the study, subjects who had their PD prescription adjusted to enable entry into the study have the option of returning to their previous prescription.

Subjects who prematurely end the study will undergo an end-of-study visit.

6.2.6 Description of measures to minimize or avoid bias

The Sponsor will avoid improper influence on any parties participating in, or contributing to, the clinical investigation or the induction thereof. The selection and treatment of participants and evaluation of clinical investigation data are potential sources of bias. Methods that are incorporated within the clinical investigation design to minimize potential bias include, but are not limited to, screening participants to confirm eligibility with defined inclusion/exclusion criteria prior to enrolment; maintaining a log of all participants screened and enrolled; collecting demographics, medical history, and medications at baseline to later assess possible characteristics that may influence endpoints; standardizing data collection requirements and clinical investigation procedures; using standardized training materials for all study personnel; and by conducting regular monitoring visits to verify adherence to the CIP and source data.

As the clinical investigation involves the use of a medical device it is not possible to blind the investigational staff or the patients. Randomizing the order of the study arms in this cross-over study will minimize the risk that a general disease progress affects the outcome.

The UF volume result may be biased if the peritoneal drain is performed in different subject positions during the drain. During the efficacy evaluation days the subject will be instructed to perform the study drains in the sitting position.

The UF volume is determined by the length of the treatment. Both the control dwell and the Carry Life® UF dwells during the efficacy evaluation days therefore should be of similar duration. In a standard CAPD dwell, maximum UF occurs after around 2 hours after which it slowly decreases as there will be a net fluid absorption when the osmotic pressure gets too low.[23] The treatment time for both the control and the Carry Life® UF treatment is defined as the time between the end of peritoneal fill and the start of the peritoneal drain. For the control dwell, the subject will be instructed to start the peritoneal drain 5 hours after the end of the peritoneal fill. Both start time and end time will be recorded. For the Carry Life® UF There will be a short delay between the end of fill and start of treatment of the Carry Life® UF device for connection and priming of the system. The Carry Life® UF treatment automatically stops 5 hours 0/+15 min after the start of treatment. The Carry Life® UF treatment therefore is expected to be up to 20 min longer than the control dwell. This bias is in favor of the control dwell as a longer control dwell after a 5-hour dwell time would result in an equal or lower UF volume.

6.2.7 Endpoints

6.2.7.1 Primary endpoint

The primary endpoint has been defined to address the primary objective; to demonstrate that Carry Life® treatment at home results in an increased UF volume compared to a 2.27% glucose CAPD dwell.

Primary endpoint:
UF volume during 5-hour treatments at home (Carry Life® UF treatment vs. a 2.27% glucose CAPD dwell).

Rationale for the primary endpoint:
Carry Life® UF has been developed to address inadequate fluid management in PD patients which has been associated with increased morbidity, mortality, and technique failure.

6.2.7.2 Secondary endpoints

- AE and SAE rates.
- Peritoneal sodium removal.
- Glucose UF efficiency.
- Peak dialysate glucose concentration.

Rationale for the secondary endpoints:

- The Carry Life® UF system should be as safe to use as standard PD methods.
- Higher peritoneal sodium removal has been associated with increased survival.[12]
- Glucose absorption in PD is associated with metabolic syndrome and increased body weight. An increased glucose efficiency means that a required UF volume may be achieved with a reduced glucose uptake.

- Hypertonic PD solutions are associated with peritoneal membrane deterioration which reduces the UF capacity resulting on technique failure. A higher dialysate glucose concentration also leads to a higher glucose uptake rate. Carry Life® UF is expected to obtain a higher UF volume with a lower dialysate peak glucose concentration.

6.2.8 Methods and timing for assessing, recording, and analyzing of variables

The following clinical tests/assessments will be performed to assess the performance of the Carry Life® UF system (Table 7). The timing of the assessments in relation to the study visits is contained in Table 1.

Table 7. The tests methods, recording and analysis of variables

Test/assessment	Required measurements	Recording	Analysis	Source data
PD fill volume	Weight of full PD bags with or without outer wraps. Weight of plastic material (may be predetermined).	In-clinic visits, PET, and Carry Life® UF treatments: Home phase efficacy evaluations treatments (control and Carry Life® UF). All CAPD dwells and Carry Life® UF treatments during home phase.	Calculated by electronic data capture (EDC): The weight of full PD bags minus weight of the plastic material.	Work sheets for measured data and eCRF for calculated data.
Drained volume	Weight of drain bags. Weight of plastic material (may be predetermined)		Calculated by EDC: The sum of all volumes drained for each treatment, including all dialysate sample volumes. The drained volume in each drain bag is calculated as the weight of the drain bag minus the weight of the plastic material.	Work sheets for measured data and eCRF for calculated data.
Treatment time (hours)	Time for end of peritoneal fill and start of peritoneal drain.		Calculated by EDC: Time between “end of peritoneal fill” and “start of peritoneal drain”	Work sheets for measured data and eCRF for calculated data.
Glucose volume$_{exact}$	Weight of full glucose bag with or without outer wrap. Weight of used glucose bag. Weight of plastic material (may be predetermined)	Carry Life® UF in-clinic treatments and Carry Life® UF efficacy evaluation treatments (ml).	Calculated by EDC; Weight of full glucose bag minus weight of used glucose bag (g) divided by the density of the 50% glucose solution (1.2235 g/ml).	Work sheets for measured data and eCRF for calculated data.
Glucose volume$_{approx}$ for Carry Life® UF home treatments other than efficacy evaluation days (ml)	None, nominal volume for the 5 hour Carry Life® UF treatment at each dose 110 ml (11 g/h) and 150 ml (15 g/h) is used.	Daily during Carry Life® UF arm	N/A	eCRF (prescribed Carry Life UF glucose dose).

Test/assessment	Required measurements	Recording	Analysis	Source data
UF volume$_{exact}$ (ml)	PD fill volume. Glucose volume. Drained volume.	In-clinic visits, Home phase efficacy evaluations treatments	Calculated by EDC; Drained volume-PD fill volume - Glucose volume$_{exact.}$	Work sheets for measured data and eCRF for calculated data.
UF volume$_{approx.}$ (ml)	PD fill volume. Glucose volume. Drained volume.	All dwells/Carry Life® UF treatments during home phase.	Calculated by EDC; Drained volume-PD fill volume - Glucose volume$_{approx.}$	Work sheets/electronic patient-reported outcome measures (ePROM) for measured data and eCRF for calculated data.
UF rate (ml/kg body weight/treatment)	UF volume$_{exact.}$ Body weight before treatment.	In-clinic phase, Carry Life® UF treatments.	Calculated by EDC; UF volume$_{exact}$/Body weight before treatment.	Work sheets for measured data and eCRF for calculated data.
UF volume % increase	UF volume$_{exact}$	End of In-clinic phase	Calculated by EDC; ([UF volume$_{exact}$ Visit4/ UF volume $_{exact}$ Visit3]-1)*100	eCRF
Dose determination	UF volume % increase	End of In-clinic phase	Determined by EDC according to dose determination algorithm.	
Dialysate glucose concentration	Glucose concentration in drain samples	In-clinic phase, PET, and Carry Life® UF treatments: PET: T0, T1h, T2h, T4h Carry Life UF: T0, T1h, T2h, T3h, T4h, T5h, peritoneal drain	Laboratory analysis	Laboratory data
Peak dialysate glucose concentration	Glucose concentration in drain samples	In-clinic phase, Carry Life® UF treatments: T1h, T2h, T3h, T4h, T5h	Data analysis	N/A
PET	Sodium and creatinine concentration in dialysate.	PET, at T0, T1 and T2 T4	D/P creatinine Transfer type determined as D/P creatinine at 4h Low: 0.34-0.50 Low average: 0.50-0.65 High average: 0.65-0.81 High: 0.81-1.03 Sodium dip: Dialysate sodium: T1 minus T0	Laboratory data

Test/assessment	Required measurements	Recording	Analysis	Source data
Glucose absorption	PD fill volume. Glucose volume$_{exact.}$ Drain volumes (peritoneal drain + Carry life UF drain bag). Glucose concentration of drain volumes (peritoneal drain + Carry life UF drain bag).	In-clinic (Carry Life UF treatments) Home phase efficacy evaluations treatments (control and Carry Life® UF).	Sum of glucose added (PD fill volume (ml) * glucose concentration of PD solution (13.6 or 22.6 g/ml) + Glucose volume$_{exact}$ (ml) * 0.5 g/ml) minus the sum of glucose drained (peritoneal drain volumes * the glucose concentration of drain volumes (g/ml).	Work sheets for measured data, laboratory data and eCRF for calculated data.
Fluid intake and urine output.	Fluid intake volume and urine volume.	During the PET and Carry Life® UF study session.	For evaluation.	Worksheets
Body surface area (BSA)(m2)	Subject height and body weight.	V2 before treatment	(BSA according to Gehan and George = $0.0235\text{Body weight (kg)}^{0.51456}\text{Height (cm)}^{0.42246}$).	Worksheets for measured data and eCRF for calculated data
Urine clearance	24-h urine volume and 24-h urine sample for analysis of creatinine and urea.	Urine collection completed prior to V2, V5 and V6.	Calculated by EDC; Calculation of creatinine and urea clearance and residual renal function normalized to 1.73m^2 BSA. Urinary clearance (ml/min) of creatinine and urea is calculated using the following equation: $Cl = \frac{(U_S \cdot V_U)}{(P_S \cdot T)}$*1.73/BSA where U_S is the concentration of the substance in the 24-hour urine sample, V_U urine volume (ml), P_S is the concentration in plasma of the substance, and T total time for urine collection (min).	Worksheets and laboratory data
Residual renal function	Urine clearance of creatinine and urea	N/A	Calculated by EDC; ($Cl_{creatinine}$+Cl_{urea})/2	Worksheets and laboratory data, eCRF for calculated data. Laboratory data
Body weight change	Body weight.	Before and after the PD exchange in PET and Carry Life® UF study sessions and daily during the home phase	Body weight after minus body weight before.	Worksheet or eCRF (in case of electronic diary use during home phase)

Test/assessment	Required measurements	Recording	Analysis	Source data
Peritoneal creatinine and urea removal	Carry Life UF drain volume. Peritoneal drain volume. Concentrations of creatinine and urea in drain volumes.	In-clinic Carry Life® UF study sessions. Efficacy evaluation treatments during home phase.	Data analysis. The sum of removal in Carry Life® UF drain volume and the peritoneal drain.	Work sheets and Laboratory data
Blood chemistry: Na^+, K^+, Mg^{2+}, ionized Ca^{2+}, PO_4^{3-}, albumin, creatinine, urea and PTH	Concentration of solutes in blood samples.	At study start (before PET visit 2, and at end of each arm (V5 and V6).	Laboratory analysis.	Laboratory data.
Peritoneal solute removal Na^+, K^+, Ca^{2+}, PO_4^{3-}, albumin, creatinine and urea	PD fill volume. Concentration of each solute in the PD solution (known) Drain volumes (peritoneal drain + Carry life UF drain). Concentration of each solute in drain volumes (peritoneal drain + Carry life UF drain bag).	In-clinic, Carry Life UF treatments (V3 and V4) and during efficacy evaluation days during home phase	Data analysis. The difference between amount added in the PD solution (volume * concentration) and the sum of the amounts removed in drained fluid (volumes * concentrations)	Work sheets for measured data and eCRF for calculated data. Laboratory data
Vital signs	Blood pressure and heart rate (HR).	During visits to the clinic (before and after treatment). Blood pressure and heart rate daily by patient during home phase.	Monitoring of status and changes.	Worksheet or eCRF (in case of electronic diary use during home phase).

6.2.9 Equipment for assessing the clinical investigation variables

The measurement of the clinical variables in the clinical investigation will be performed with equipment used in clinical praxis, such as scales and blood pressure cuffs.

For the measurements performed at the clinic the same scale for PD solutions shall be used for all subjects, where possible. If possible, the calibration status of equipment used in-clinic for measuring the clinical investigation parameters will be documented at the initiation visit.

During the home treatment phase, subjects will use the same equipment as they normally use for their PD treatment (scales, and blood pressure cuff). A subject who does not have the required equipment at home will be provided with adequate equipment for the study. All measurements of PD bags and drain bags will be performed on desk scales, as hook scales are not deemed to be reliable.

The same body weight scale, PD bag scale and blood pressure cuff will used by each subject for the measurements at home to which means that small systematic measuring errors by the equipment will not have an impact on the outcome of the study.

Laboratories normally used by the clinics will be performing the laboratory analyses used for this clinical investigation. Blood and urine samples will be analyzed by the authorized laboratory at the clinical sites. One authorized laboratory will be used for analyses of all dialysate samples. Samples collected for laboratory analysis will only be saved for the duration required for the study.

6.2.10 Investigational device and comparator

The patient's exposure to the investigational device occurs during the Carry Life® UF treatments (two in the in-clinic treatment phase and approximately 12 during the home treatment phase). Each treatment with the device lasts for 5 hours which results in a total device exposure of 70 hours.

Table 8. Carry Life® UF treatments during the clinical investigation

Carry Life® UF treatments during study
14 treatments x 5-hour study sessions
Total = 70 hours

In total approximately 40 devices will be used in this clinical investigation across 6-12 sites. The patients will as far as possible use the same device during the clinical investigation.

If a subject finishes the Carry Life® UF arm of the study, the device may be cleaned according to Section 10.1.1 "Cleaning with spillage" in the IFU and then used by another subject. No comparator devices will be used in the investigation. A 2.27% glucose CAPD dwell will be the comparator.

6.2.11 Other materials/products required for the clinical investigation

Table 9. Products used in the clinical investigation

Product	Procedure
A permanent PD catheter	Available in situ and used to perform the subject's standard PD therapy.
A Baxter MiniCap extended life PD transfer set with twist clamp	The Baxter MiniCap extended life PD transfer set with twist clamp is part of the patient's standard PD treatment. Each transfer set is used normally used for several months before it is exchanged.
Standard Baxter 1.36%/1.5%* glucose PD solutions	Initial fill prior to starting the Carry Life® UF treatment and according to the patient's standard PD prescription during the study.
Standard Baxter 2.27%/2.5%* glucose PD solutions	Used for the PET treatment (Visit 2) and according to the patient's standard PD prescription during the study.
50% glucose (500 g per L) solution for infusion in the Freeflex bag (Fresenius Kabi)	Added to the PD solution by the Carry Life® UF system during treatments.
** 1.5% monohydrous glucose (Dianeal) is equivalent to 1.36% anhydrous glucose (Physioneal) and 2.5% monohydrous glucose (Dianeal) is equivalent to 2.27% anhydrous glucose (Physioneal).*	

6.2.11.1 Peritoneal dialysis catheter

A prerequisite for treatment with the Carry Life® UF device is that the patient has a permanent PD catheter, as access to the peritoneal cavity is required. Patients recruited to the clinical investigation will be stable on PD therapy and have a permanent PD catheter in situ. The type of catheter used by the patient is not critical. The Carry Life UF system has been verified using a flow restrictor simulating the combined flow resistance of the peritoneal catheter, transfer set and connector in accordance with IEC 60601-2-39:2018 (Particular requirements for basic safety and essential performance of peritoneal dialysis equipment).

6.2.11.2 A Baxter MiniCap extended life PD transfer set with twist clamp

The Carry Life UF system has been verified for use with a Baxter MiniCap extended life PD transfer set with twist clamp. The Carry Life UF system was connected to the Baxter MiniCap extended life PD transfer set with twist clamp also in the previous clinical investigations.

6.2.11.3 Baxter 1.36 % (1.5%) glucose PD solution for the Carry Life® UF study sessions

In the previous clinical investigation Tmed-007, the Carry Life UF system was used with a 1.36% glucose Baxter Physioneal PD solution. The justification for the choice of the 1.36 % glucose PD solution for the Carry Life® UF treatment is that the use of hypertonic glucose solution should be minimized. When starting with a 1.36% glucose PD solution for the Carry Life® UF treatment, the peritoneal membrane will be exposed to lower dialysate glucose concentration than when using a 2.27% glucose PD solution and the total glucose uptake with the Carry Life® UF treatment will be as low as possible.

In this study the subject will use the same Baxter PD solution that they already use for their standard PD prescription, Physioneal or Dianeal. Dianeal is not marketed in Sweden, but is available on the UK market. The 1.5% monohydruos glucose used in the Dianeal PD solution is equivalent to the 1.36% anhydrous glucose used in the Physioneal PD solution.

There are only small differences in the composition of the different PD solutions as seen in the Table 10 below. The buffer concentration is 35 mM or 40 mM, provided either as a combination of bicarbonate and lactate or only lactate. The calcium concentration varies between 1 mM and 1.75 mM between different solutions based. The lower calcium concentrations are used in order to obtain a larger peritoneal calcium removal in patients for whom that is indicated. The small difference in the PD solutions has no impact on the treatment with Carry Life UF.

Table 10. The composition of different Baxter low strength glucose PD solutions

	Physioneal 35	**Physioneal 40**	**Dianeal PD 2**	**Dianeal PD 4**	**Dianeal 1 mmol/L Calcium**
Glucose anhydrous (%)	1.36%	1.36%	-	-	-
Glucose H_2O (%)	-	-	1.5%*	1.5%*	1,5%
Sodium (mM)	132	132	132	132	132
Calcium (mM)	1.75	1.25	1.75	1.25	1
Magnesium (mM)	0.25	0.25	0.25	0.25	0.25
Chloride(mM)	101	95	96	96	96
Lactate (mM)	10	15	40	40	40
Bicarbonate (mM)	25	25	-	-	-

Osmolality (mOs)	345	344	346	345	344

** 1.5% Glucose monohydrate is equivalent to 1.36% anhydrous glucose.*

Subjects will use the same fill volume that they use for their standard CAPD prescription.

6.2.11.4 A 2.27 % (2.5%) glucose PD solution in

The subject will use a 2.27% Baxter PD solution according to their CAPD prescription during the study but not for the Carry Life® UF treatments.

6.2.11.5 The 50% glucose solution

The 50% glucose is a solution for infusion indicated for nutritional purposes and manufactured by Fresenius Kabi. The product is marketed in Sweden with authorization number 9590 and has the ATC-Code B05BA03. The glucose solution will have an additional label in English and Swedish, including the statement FOR CLINICAL TRIAL USE ONLY/ ENDAST FÖR KLINISK PRÖVNING/.

The 50% glucose solution is added during the Carry Life® UF treatment in order to maintain the glucose concentration in the dialysate, provided by the initial peritoneal fill of a 1.36% glucose PD solution. Glucose is the most commonly used osmotic agent in PD solutions, and the 50% glucose solution has the same intended use (peritoneal UF) and mechanism of action, acting as an osmotic agent, as the glucose in the PD solution. The same Fresenius-Kabi 50% glucose solution was used in the clinical investigation Tmed-007. The glucose solution has an interface to the line set and is compatible with the glucose spike of the Carry Life® UF line set.

6.3 SUBJECTS

6.3.1 Subject selection

The patients to be recruited in the clinical investigation have been on stable PD therapy for ESKD for at least three months and with a PD prescription of 2-4 CAPD dwells/day, unchanged for a minimum of two weeks, with at least one 1.5-2 L 2.27% glucose day dwell daily.

Should a change of the PD prescription be necessary for a subject to be eligible for the study, a run-in period of at least two weeks with the modified PD prescription should take place. The change in prescription will be made after assessment by the responsible physician to ensure that the new prescription is clinically comparable to the current prescription. Such a change will require the subject to consent to a change of PD prescription on the Patient Informed Consent Form.
After the run-in period physician will review the eligibility of the patient to continue the study and complete the inclusion of the patient (enrolment point) ***or*** alternatively exclude the patient from the study. The exclusion of the patient will be recorded as a screening failure and the subject will not be further followed up in the study.

If patients treated with PD therapies have regular clinical checkups the Investigator may either approach the patient during these visits or by other means. After the patient has signed the ICF they are allocated a specific study number, which is used in the investigation documents and consecutive number are allocated with continued inclusion at each site.

Approximately 25 patients will be enrolled in this clinical investigation with a goal of 19 completing the study per protocol. Patients will be enrolled across six (6) to twelve (12) European sites.

There will be a competitive enrolment without a minimum enrolment for each site.

All patients recruited in the clinical investigation shall be accounted for, including those who withdraw from the investigation. The total duration of the patient's participation is around 12 weeks depending upon when it is suitable for the patients to schedule the study visits. The total time for recruitment and study completion is estimated to be approximately 12 months (including an estimated 9-month enrolment period).

6.3.1.1 Inclusion criteria

1. Age ≥ 18 years.
2. Subjects with ESKD treated with PD for at least three (3) months.
3. A PD prescription of 2-4 CAPD dwells/day unchanged for a minimum of two (2) weeks, with at least one 1.5-2 L 2.27% glucose day dwell daily.
4. Subjects must be able to tolerate a 2 L PD fill volume for the PET.
5. Subjects using the Baxter PD system.
6. In the opinion of the Investigator, the subject has the capacity to learn how to use the Carry Life® UF system or has a caregiver who can do so.
7. Obtained written consent to participate in the study.

Exclusion criteria

1. A PD prescription including a regular 3.86% glucose day dwell.
2. An episode of peritonitis within the last three (3) months.
3. Serum potassium > 6 mmol/l within the last three (3) months.
4. Serum urea > 35 mmol/l within the last three (3) months.
5. Clinical signs of dehydration.
6. Systolic blood pressure < 100 mmHg within the last month.
7. Known diagnosis of clinically significant aortic stenosis.
8. Clinical condition of unstable diabetes.
9. Subjects with a life expectancy of < 6 months.
10. Evidence of any other diseases or medical conditions that may interfere with the planned treatment or affect participant compliance.
11. Participation in clinical trials, interfering with the present study, within the previous month.
12. Anticipated living donor kidney transplantation within six (6) months of screening.
13. Pregnant, breastfeeding, or women of childbearing potential who are not using an effective method of contraception (hormonal contraceptives or barrier contraceptive methods).

6.3.2 Criteria and procedures for subject withdrawal or discontinuation

6.3.2.1 Withdrawal of subjects from the clinical investigation

Subjects may withdraw from the clinical investigation for any reason and at any time, without the need to justify their decision and without further medical care being penalized. However, the Investigator should record the date and reason for the participant's withdrawal, if possible. The Investigator also has the right to withdraw participants at any time if it is in the participant's best interest. Subjects must be withdrawn from the clinical investigation for the following reasons:

- The patient withdraws consent.
- The patient is unwilling or unable to comply with the CIP.
- Lost to follow-up.

The subject must be permanently removed from the clinical investigation for the following medical reasons:

- The occurrence of peritonitis.
- The patient experiences a medical emergency that necessitates permanent discontinuation of the investigation.
- At the discretion of the Investigator for medical reasons or for noncompliance.

The reason for the withdrawal must be recorded in the medical records and in the CRF. If a subject is withdrawn from the study, an end-of study visit should be performed if possible. Any AE that is ongoing when the patient is withdrawn from the investigation shall be followed-up until the AE is resolved or the Investigator deems the AE stable and no further follow-up is required. The date when the Investigator considers one of these outcomes to have been fulfilled will be considered the last visit for the subject, and the outcome shall be recorded in the eCRF.

All data collected prior to the patient's withdrawal may be used in the analysis of the clinical investigation, with the patients consent.

6.3.2.2 Withdrawal of subjects from study treatment

A study treatment must be ended in case of the following reasons:

- The patient experiences a medical emergency that necessitates ending the treatment.
- At the discretion of the Investigator for medical reasons.

The reason for the withdrawal must be recorded in the medical records and in the eCRF and SAEs, SADE and USADE.

6.3.3 Procedures for replacing subject

Patients who withdraw or are withdrawn from the clinical investigation will be replaced if the desired number of patients has not been achieved. In this case other patients will be approached with regard to participation.

Participants who screen-fail may be replaced.

6.4 PROCEDURES

A description of the clinical investigation design is contained in Figure 1 and Figure 2. Table 1 details the schedule of activities at each visit.

6.4.1 Clinical investigation related procedures

<u>Visit 1: Screening and inclusion (-14–0 Days)</u>

The activities are mainly concerned with the collection of the informed consent and baseline data as follows:

1. Fulfillment of the Inclusion and exclusion criteria (enrolment point).

2. Demographics (year of birth, age, gender, ethnicity, height, and body weight).
3. Medical history (including, cause of ESKD, year of diagnosis of kidney disease, start of PD, start of ESKD therapy other than PD, if applicable, and comorbidities).
4. Concomitant medications.
5. Baseline PD prescription (volumes and glucose concentration for the day dwells, volume for the icodextrin and volume and glucose concentration for glucose-based night dwell, as applicable).
6. Fluid restriction.

Visits 2-4: In-clinic treatments (Week 1–2)

The in-clinic treatment visits will consist of:

1. Recording changes in concomitant medications.
2. Recording changes in fluid restriction.
3. Body weight, systolic and diastolic blood pressure, and heart rate will be measured before and after treatment. In addition, blood pressure will be measured in case of clinical symptoms suggestive of hypotension.
4. Food intake and fluid intake/urinary output.
5. Blood samples.
6. Dialysate samples.
7. PD bags used (the volume and glucose concentration of PD bags used for the PET and Carry Life® UF treatments will be recorded).
8. Fill and drain volumes (the PD bag and glucose bag will be weighed before treatment and the drain bag(s) after treatment for calculations of fill volume, drained volume and UF volume).
9. A baseline (Visit 2) 24-hour urine sample (urine volume and urine concentration of creatinine and urea collected for calculation of residual renal function).
10. Carry Life® UF safety assessment.
11. Transition to home evaluation.
12. AE, SAE, and device malfunction monitoring.

Device training visits (T1–T7; Week 3 Group C, D; Week 7 Group A, B)

The device training may be performed at the clinic or at the patients home as agreed between the clinic and the patient with a device competency assessment at the end of the transition to home phase.

The device training will further consist of:

1. Recording changes in concomitant medications
2. Recording changes in fluid restriction
3. AE, SAE, and device malfunction monitoring.

Home treatment phase (Week 3–6 Group A, B; Week 4–7 Group C, D; and Week 8–11)

The home treatment phase will consist of:

1. Recording changes in concomitant medications.
2. Recording changes in fluid restriction.
3. Body weight, systolic and diastolic blood pressure and heart rate measurements daily.
4. PD bags used (subjects will record volume and glucose concentration).
5. Fill and drain volumes (subjects will record fill and drain weights of all dwells)
6. 24-hour UF collection (end of arm).

7. Subject clinical evaluation (subjects will be contacted weekly for evaluation of body weight, blood pressure, volume status and clinical symptom).
8. AE, SAE, and device malfunction monitoring.
9. Four efficacy evaluation treatments 2nd and 4th week of each arm with collection of dialysate samples and weighing of the solutions bags (PD bag and glucose bag) and the drain bags.

Visit 5 (Week 6 Group A, B; Week 7 Group C, D)

Visit 5 will consist of:

1. Recoding changes in concomitant medications.
2. Recording changes in fluid restriction.
3. Body weight, systolic and diastolic blood pressure and heart rate measurements.
4. Blood samples.
5. 24-hour urine sample, (urine volume and sample).
6. AE, SAE, and device malfunction monitoring.

Visit 6/End-of-study visit (Week 11/After premature study exit)

Visit 6 will consist of the following:

1. Recoding changes in concomitant medications.
2. Recording changes in fluid restriction.
3. Body weight, systolic and diastolic blood pressure and heart rate Blood samples.
4. 24-hour urine sample, (urine volume and sample).
5. AE, SAE, and device malfunction monitoring.

6.4.2 Activities performed by sponsor representatives

A Triomed representative:

- May be on-site during the initial Carry Life® UF study sessions at the clinic to offer support with device related questions, but will not participate in procedures related to the investigation. The procedures involved in the clinical investigation will be performed by the clinical professionals at each respective site as described in Section 2.7.
- Will train the applicable personnel at each site in the Carry Life UF system.
- May train the patients/caregiver in the Carry Life® UF system (the clinic will be responsible for the device competency assessment)
- May oversee the first Carry Life UF treatment at home.
- May weigh solution bags and collect dialysate samples from the drainage bags during the efficacy evaluation treatments.

6.4.3 Foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results

The present study is designed as a controlled, randomized, multicenter, crossover study. The UF outcome in PD is dependent on the peritoneal transfer (transport) characteristics. In order to evaluate the results based on the subject's transport characteristic a PET is performed to determine the patient's transport type. To reduce the impact of interpatient variability the study is designed as a crossover study where each patient will generate results from both study arm. The difference between treatment will be assessed by a paired analysis.

The determined UF is dependent on the actual UF as well as the dialysate volume remaining in the peritoneal cavity from the preceding dwell and after the recorded dwell. In order to account for that variability, the performance endpoints will be based on the average from two treatments in each arm.

In order to determine correct UF during PD it is very important to determine exactly the volume that is instilled into and drained from the peritoneal cavity. To ensure that the weighing of the solution bags and drain bags is performed correctly, detailed written weighing procedures will be used. Furthermore, weighing will be performed by trained study personnel or a Triomed representative during the efficacy evaluation treatments.

The study is randomized for in what arm to start the study in order to account for possible disease progression, e.g., a decline in RRF over the course of the study.

6.5 MONITORING

Qualified monitors representing the sponsor will conduct monitoring activities according to the monitoring plan. The Investigator must permit clinical investigation related monitoring by providing direct access to source data and to the subject's medical records, as well as the Investigator Site File and storage location of the investigational device. The Sponsor, or its designee, is responsible for ensuring that the clinical investigation is adequately monitored. The purpose of monitoring is to ensure:

1. The rights and wellbeing of the subjects.
2. The clinical investigation data are accurate, complete, and verifiable from source documents.
3. The clinical investigation is compliant with the CIP, ICH-GCP, ISO 14155:2020 and regulatory requirements.

Due to the complexity of the clinical investigation monitoring will be performed on-site before, during and after the clinical investigation.
The activities involved with monitoring consist of:

1. Site initiation visit.
2. Routine Monitoring Visits regularly during the clinical investigation,
3. Close-out visit.

The site initiation visit is performed when all the documentation required to perform the clinical investigation have been obtained and compiled in the site investigation file, the study has been approved by the Ethics Committee and the Competent Authority and the Clinical Trial Agreement has been executed. The main purpose for the Site Initiation Visit is to ensure that the clinical investigation is conducted according to the CIP and in accordance with GCP and regulatory requirements.

The aspects of the clinical investigation that will be presented is including but not limited to:

- The function of the device and the IFU.
- Overall design for the clinical investigation.
- Presentation of the CIP and eCRF.
- The Initiation of the specific training required as described in Section 2.7.

During the clinical investigation the monitor will visit the investigation site at regular intervals as defined in the approved monitoring plan and as agreed with sponsor. During these visits the CRF's and supporting documentation related to the clinical investigation will be reviewed and any discrepancies or omissions will be resolved.

Reports of the monitoring visits will be submitted to the Sponsor representative for review. The monitoring report summarizes the significant findings, deviations, deficiencies, conclusions, and actions taken or recommended actions.

The monitoring visits must be conducted according to the appropriate Standard Operating Procedures (SOPs) based on ICH-GCP and EN ISO 14155:2020 guidelines to ensure adherence to the CIP, the quality of the data, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities. Representatives of the Sponsor and/or Regulatory agencies may visit the site to perform audits/inspections, including source data verification. The Investigator must permit access to source data during auditing and monitoring.

The documents generated for the clinical investigation will be traceable and identifiable by versions and corresponding dates. The essential documents for the clinical investigation contained in the ISF and TMF shall be securely stored both by the Investigator and the Sponsor.

Further information and details regarding monitoring arrangements can be found in the monitoring plan.

7 STATISTICAL CONSIDERATIONS

7.1.1 Sample size

The primary objective in the present study is to compare the UF volume obtained with the Carry Life® UF device, at the glucose dose determined by the UF volume obtained during the in-clinic phase of the study, and the UF volume obtained by a standard 2.27% glucose dwell of the same duration when performed by the patient at home. Carry Life® UF is intended as an intermittent treatment in order to provide an additional removal of fluid in patients whose UF need is not met be their standard PD regimen. A UF volume ≥ 250 ml greater with the Carry Life® UF treatment than with the 2.27% glucose CAPD dwell is considered a clinically relevant UF volume. Assuming three 5-hour treatments with Carry Life® UF per week this corresponds to an increase in fluid removal of 750 ml/week.

The sample size is calculated using the UF volume data from a previous pilot study (Tmed-007) on eight subjects, with the aim to demonstrate a superiority margin, delta (δ), of 250 ml. For each subject the delta (δ) UF volume between the control 2.27% CAPD dwell and the Carry Life® UF treatment (paired comparison) at either the 11 g/h or the 14 g/h glucose dose provided input to the sample size calculation. The glucose dose providing input was selected following the dose determination scheme described for the current study (refer to page 47). The difference between the Carry Life® UF and the control 2.27% CAPD dwell had a mean value of 574 ml and a standard deviation of 236 ml.

The sample size is estimated by

$$n = \frac{(z_\alpha + z_\beta)^2 \sigma_m^2}{2(\epsilon - \delta)^2}$$

where
ε = test - control
δ = superiority margin
σ_m = standard deviation of the paired differences

Set
Alpha = 0.025, Z_alpha = 1.96
Power = 0.80, Z_beta = 0.842
σ_m = 236
$\varepsilon = 574$
$\delta = 250$

Assuming a standard deviation of 236 ml, an expected difference of 574 ml and a superiority margin of 250 ml requires a sample size of 3 to obtain 80% power for the superiority test (α = 0.025) using a one sample superiority (one-sided) t-test sample size calculation.

We also consider a more extreme case where we assume a standard deviation of 1.4 times the previous standard deviation, or 330 ml. Further, we lower our assumed mean difference to 400 ml (about 0.7s below the previous observed value). With these assumptions (standard deviation of 330

ml, an expected difference of 400 ml, and a superiority margin of 250 ml) we require a sample size of 19 to obtain 80% power for the superiority test (α = 0.025).

The study size of 25 was selected based on the conservative sample size with additional subjects to account for possible dropouts.

7.1.2 Intent-to-treat and per protocol population

The intent-to-treat (ITT) population is defined as all the included patients.

Table 11. Definition of intention to treat and per protocol populations

Endpoint Description	Intent-to treat (ITT) population	Per protocol (PP) population
Primary Endpoint		
Primary endpoint (UF volume)	Subjects with data from one or more per protocol efficacy evaluation treatments in each study arm.	Subjects with two per protocol efficacy evaluations treatments performed on the planned efficacy evaluation day and dwell of the day in each study arm.
Secondary Endpoints		
Safety endpoint (AEs and SAEs)	All the included subjects.	All subjects who complete four week´s treatments in each study arm during the home treatment phase.
Peritoneal sodium removal and Glucose UF efficiency endpoints	Subjects with data from one or more per protocol efficacy evaluation treatments in each study arm.	Subjects with two per protocol efficacy evaluations treatments performed on the planned efficacy evaluation day and dwell of the day in each study arm.
Peak dialysate glucose concentration*	Subjects with in-clinic Carry Life UF per protocol treatments with one (1) to three (3) glucose dialysate results between T1h and T5h per glucose dose.	Subjects with in-clinic Carry Life UF treatments dialysate glucose samples from at least four (4) time points between T1h to T5h.

7.1.3 Safety population

The safety population is defined as all patients receiving at least one treatment with the Carry Life® UF system.

7.1.4 Per protocol treatments

Carry Life UF per protocol treatments are Carry Life UF treatments for which the Carry Life UF treatment with a treatment time of 5 ± 0.75 hours and a total stop time during treatment of at most 30 min.

CAPD per protocol treatments are CAPD treatments with a total treatment time of 5 ± 0.75 hours.

7.1.5 Randomization method

The randomization will occur after the in-clinic phase of the study, after the glucose dose the subject will use in the Carry Life® UF arm has been determined (refer to page 47 for a description of the dose determination). The randomization is being done to reduce any potential for bias based on subjects starting in the treatment or control arms. For each Carry Life® UF glucose dose (11 g/h and 15 g/h) the subjects will be randomized with an equal ratio (1:1) to start with either the control or the Carry Life® UF study arm. The randomization is based on block randomization using blocks of four, to ensure a balance between those who starts with control and those who starts with the Carry Life® UF arm. Subjects using the 11 g/h will be randomized to Group A or Group C. Subjects using the 15 g/h will be randomized to Group B or Group D. Group A and Group B will start with control. Group C and Group D will start with Carry Life UF. The randomization is a feature of the eCRF and will be manage centrally.

7.1.6 Statistical analysis of primary endpoint

The primary endpoint uses the UF measured per protocol at each efficacy evaluation treatment during the home treatment phase. Each subject is expected to have two efficacy evaluations per treatment arm. Subjects with one or more per protocol efficacy evaluations in each arm will be included in the primary endpoint analysis. The analysis will be performed for both the ITT and the PP population. Excluded subjects will be tabulated with narratives as to why they are missed efficacy evaluations.

For each subject, we use the mean UF_{CL} and the mean UF_{CAPD} for analysis. The mean difference (i.e., a paired comparison) between the UF achieved with the Carry Life® UF treatment and the UF achieved with the control CAPD dwell ($UF_{CL}(n) – UF_{CAPD}$) will be calculated (UFdiff(n)) with a 95% CI . A superiority (one sided t-test) test will be used to demonstrate that the Carry Life UF treatment is superior to the control with superiority margin of 250 ml. A superiority margin greater than 0 ml but less than 250 ml supports that the Carry Life® UF treatment increases UF as compared to the control, but at a level that may not be clinically significant.

For the primary endpoint analysis, the four groups (Group A, 11 g/h starting with control; Group B, 15 g/h starting with control, Group C, 11 g/h starting with Carry Life UF; Group D, 15 g/h starting with Carry Life UF) in the randomization scheme will be pooled. Control data generated from all four groups will be part of the control group and Carry Life UF data for both doses from all four groups will be part of the Carry Life UF group. This results in two final groups for primary endpoint analysis; control and Carry Life UF. Based on 1) prior pilot study results showing no significant difference between the doses and 2) our dose determination procedure, which assigns the glucose dose to be used by each subject based on the UF result in the in-clinic phase of the study, we expect the two Carry Life UF glucose dose groups to behave as a single population and be poolable for the purposes of the primary endpoint of the study. However, as part of our descriptive analysis, we intend to summarize the difference in UF volume between study arms for each Carry Life UF glucose dose as well as for different fill volumes.

The treatment performance for the primary objective will also be described based on demographic characteristics including age, gender, and ethnicity.

7.1.7 Statistical analysis of secondary endpoint

For the secondary endpoints no. 2 (peritoneal sodium removal) and no. 3 (glucose UF efficiency), each subject is expected to have two efficacy evaluations treatments per study arm. Subjects with one or more evaluation treatment in each arm will be included in the secondary endpoint analysis. For all secondary endpoints, excluded subjects will be tabulated with narratives as to why they are excluded. A subject may be excluded for one or more secondary endpoints, that is, exclusions are made independently for each endpoint.

7.1.7.1 AE and SAE rates

All safety events reported during the clinical investigation from either arm during the home treatment phase will add information to the safety dataset. Based on all safety data gathered during the study for the intent-to-treat (ITT) dataset, AE and SAE occurrences adjudicated to the Carry Life® UF treatment or the control treatment will be collected and summarized. The rates of AE and SAE and the rates of different types of AE and SAE during the Carry Life® UF treatment arm and during the control arm will be presented (events per day). Data for the home treatment phase per protocol (PP) data set and the in-clinic treatments will also be gathered and presented. The occurrence of AE and SAE for each Carry Life® UF glucose dose will be summarized.

7.1.7.2 Peritoneal sodium removal

Based on data gathered from the efficacy evaluation treatments during the home treatment phase of the study, peritoneal sodium removal will be calculated. For each patient the average sodium removal from the per protocol efficacy evaluation treatments in each arm will be used for the analysis. A paired comparison between sodium removal achieved with the Carry Life treatment ($NaRev_{CL}$) and sodium removal from the control CAPD dwell ($NaRev_{CAPD}$) will be conducted. The average paired difference and the associated 95% CI will be calculated. Further, a t-test will be used to demonstrate that the Carry Life® UF treatment has a larger peritoneal sodium removal than the control 2.27% CAPD dwell. The analysis will be performed for both the ITT and the PP population. The difference in peritoneal sodium removal for each Carry Life® UF glucose dose and each fill volume compared to the control CAPD dwell will be summarized.

7.1.7.3 Glucose ultrafiltration efficiency

Based on data gathered from the efficacy evaluation treatments during the home treatment phase of the study glucose ultrafiltration efficiency will be calculated. For each patient the average glucose UF efficiency (ml UF / g glucose absorbed) from the per protocol efficacy evaluation treatments in each arm will be used for the analysis. A paired comparison between the glucose UF efficiency achieved with the Carry Life® UF treatment ($GlucEff_{CL}$) and the control CAPD dwell ($GlucEff_{CAPD}$) per protocol treatments will be conducted. The average paired difference and the associated 95% CI will be calculated. Further, a t-test will be used to demonstrate that the Carry Life® UF treatment has a higher a glucose ultrafiltration efficiency than the control 2.27% CAPD dwell. The difference in glucose UF efficiency for each Carry Life® UF glucose dose and each fill volume compared to the control CAPD dwell will be summarized.

7.1.7.4 Peak dialysate concentration

During the in-clinic phase of the study the peak dialysate glucose concentration during the Carry Life® UF treatments will be determined from hourly dialysate sampling points, for each glucose dose. For this secondary endpoint, each subject is expected to have dialysate glucose data (T1h to T5h) from one in-clinic treatment at each Carry Life® UF glucose dose.

The average peak glucose dialysate concentration (in %; gram glucose per 100 ml fluid) for each glucose dose of the Carry Life® UF in-clinic treatments and the associated 95% CI will be calculated for the PP population. Further, a t-test will be used to demonstrate that the peak dialysate glucose concentration during the Carry Life® UF treatment is lower than 2.27%.
The peak glucose concentration at each fill volume will be summarized.

7.1.8 Statistical analysis of exploratory endpoints

A basic comparison peritoneal removal of creatinine and urea as well as of the weekly UF based on patient diary will be performed across the arms of the study.

7.1.9 Description and interference

Aggregated continuous data will be presented in terms of mean, median, standard deviation, minimum and maximum, and number of observations. Aggregated categorical data will be presented using frequency tables.

7.1.10 Missing values

Subjects who drop out of the study will be characterized and compared to those remaining in the study based on demographics and co-morbidities.

7.1.11 Additional summaries

All demographic and baseline characteristics captured in the CRF will be summarized for all populations included in the analysis (ITT and PP as defined for all endpoint analysis see 7.1.1) and those that are not, and descriptive statistics will be presented when applicable. The frequency and distribution of missing data for any characteristic will also be described.

7.1.12 Listings

All data captured in the study will be listed. This will include outcomes not included in the summaries such as concomitant medication and medical history.

8 DATA MANAGEMENT

8.1 PROCEDURES USED FOR DATA REVIEW

During the site initiation visit, training on the CIP and eCRF will be performed to ensure familiarity with the documents and eCRF completion of good quality. Data entries in the eCRF will be monitored during the clinical investigation against the source data and verified for accurateness and completeness. Data entered to the eCRF are subject to system-implemented edit-checks and additional manual checks by data management as per data management plan and data validation plan. Any queries generated regarding missing, inconsistent, or illogical data in the eCRF will be followed up by the site and verified by the monitor or data management. The eCRF is also reviewed for missing data early in the clinical study to reduce systematic data errors, allowing all required data to be captured. Any corrections made in the CRF will be tracked by the audit trail and the eCRF is signed by the Investigator at completion.

During the clinic visits data may be recorded in the patient file and on source data worksheets before entry into the eCRF. Blood and urine samples will be analyzed at the local laboratory used by the site and the result entered into the eCRF. For the dialysate samples, the study will use a central laboratory that perform all dialysate laboratory analyses. Dialysate data do not need to be analyzed until the end of the study and will not be entered into the eCRF. After review of all entered data was concluded, all queries have been resolved and all pages have been signed electronically by the principal investigators, the eCRF will be locked.

During the home treatment phase subjects will record clinical measurements and solution weights daily. Primarily, the subjects will enter the data (e.g., weight and blood pressure) into a mobile application. The data entered into the App will be transferred directly into the eCRF and there is no additional source documentation expected and thus these values are not subject to source data verification through the monitor. In case a subject does not use the App, but records data in a paper-based diary instead, the data are entered by dedicated site staff into eCRF and are subject for source data verification. However, in case of out of limit measurements the site is going to be alerted by means of a query and is going to follow-up with the patient to verify and discuss the entered data for any potential error. When copies of original source documents as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document. Copies of the source data shall remain at the clinical investigation site when the investigation is completed allowing an independent account of the investigation process.

The data from the eCRF will be managed in an EDC system. The EDC database will be programmed to use the input data from the eCRF to calculate output data including the endpoint measures (e.g., UF volume, peritoneal removal of the substances analyzed in the dialysate, and glucose efficiency). To be able to perform the calculation the following constants will be used:

- Glucose molecular weight: 180.16 g/mol.
- 50% glucose solution concentration: 0.5 g/ml.
- Density 50% glucose solution: 1.2235 g/ml.

Additionally plastic weights of solution bags and drain bags may be pre-weighed and used to calculate fill and drain volumes.

8.2 PROCEDURES FOR VERIFICATION, VALIDATION AND SECURING OF ELECTRONIC DATA SYSTEMS

An EDC system will be used in the clinical investigation. Refer to the data management plan for further details.

8.3 DATA RETENTION AND SPECIFIED PERIOD

The essential clinical investigation documents shall be stored both by the Investigator and Sponsor. The location of the archived documents will be defined and documented for both parties and retained for ten (10) years after the completion of the clinical investigation.

9 AMENDMENTS TO THE CIP

The CIP may require to be amended during the conduct of the clinical investigation. The rationale for the amendment must be justified and assessed as to whether it is a substantial or non-substantial amendment.[24] Amendments regarded as substantial are likely to have a significant impact on:

- The safety or physical or mental integrity of the clinical investigation participants, or,
- The scientific value of the clinical investigation.

Changes in previously approved documents are initiated by Triomed and agreed upon between the Sponsor and the Principal Investigator. Substantial amendments are submitted to the competent authorities and changes are implemented when approval is obtained. The clinical investigation documentation is updated as required and the CIP amendment log (ISF) signed by the Investigator. Triomed may at any time amend the CIP to eliminate immediate hazards to subjects. In this case the competent authority will be notified subsequently of the modifications.

10 DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

The Investigator shall conduct the clinical investigation according to and in compliance with the CIP agreed to by Triomed and approved by the competent authorities (CA). A deviation from the CIP, is a failure to comply with the information specified in the CIP.

The Investigator shall:

- Not implement any deviation from or change the CIP without prior agreement by the Sponsor or documented approval from the regulatory authority(ies) of an amendment, except where necessary to eliminate an immediate hazard(s) to participating patients.
- Promptly notify the Sponsor and document the reasons for the deviation and if appropriate proposed protocol amendment(s) to allow expedite reporting to the regulatory authority(ies).

During the clinical investigation the monitor will document and report deviations from the CIP, GCP and applicable regulations which will be reported to Triomed. The report should include a summary of what the monitor reviewed as described in Section 6.5. Accidental protocol deviations can happen at any time and must be adequately documented and reported to the Sponsor immediately. Frequently recurring deviations will require immediate action and could potentially be classified as a serious breach.

With finding of noncompliance to the CIP which significantly affect the patients and the scientific integrity of the clinical investigation, a root cause analysis will be performed, and appropriate corrective and preventive action taken. The Investigator will be informed in writing by Triomed of the corrective actions to be taken to avoid the reoccurrence of deviations and the corrective actions will be followed-up. If the Investigator/institution is persistently noncompliance despite corrective action by Triomed the Investigators participation in the clinical investigation will terminate. The termination of the clinical investigation due to noncompliance will be reported to the competent authorities by Triomed.

11 DEVICE ACCOUNTABILITY

The Carry Life UF system including the cycler, line set, carrying bag, storage bag, glucose solution, battery, battery charger and PD belt will only be used in the clinical investigation. The Sponsor and the Principal Investigator will keep records documenting the shipment (to and from the investigational site) and the location of all investigational devices and accessories beginning from shipment of investigational devices to the investigation sites until their return to Triomed or destruction, as applicable. The Principal Investigator will keep records documenting the hand-over or return of all investigational **devices** and accessories to/from the patient. This will be documented in the device accountability log which is contained in both the TMF and ISF and will be updated throughout the clinical investigation.

The device accountability log will include information on:

- The date of receipt and the quantities.
- Identification of each investigational device and accessory (batch number or serial number).
- Date on which the investigational device or accessory was returned and the date of return of unused, expired or malfunctioning investigational devices, and date of return of unused glucose solution.

The serial/batch numbers of the device, the line sets, and glucose solution, and the dates of use will also be documented in the patient specific eCRF page. The equipment required for the clinical investigation will be stored in a secure area at the participating sites according to the storing conditions as outlined in the respective IFUs. The monitor will verify the accountability process at each site during the site monitoring visits and at the close-out visit.

12 STATEMENTS OF COMPLIANCE

12.1 ETHICAL PRINCIPLES

To ensure the quality and integrity of research, this clinical investigation will be conducted according to the CIP, principles of ISO 14155:2020, EU medical device regulation (MDR) 2017/745, UK MDR 2002, the Declaration of Helsinki and its amendments, and any applicable national guidelines.

This study must be approved by the relevant competent authority and independent ethics committee (IEC) prior to enrolling participants into the study.

Any additional requirements imposed by the IEC or regulatory authority shall be followed, as appropriate.

Where applicable and consistent with local regulations and prior to consenting and enrolment of participant, the CIP, CIP amendments, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents must be submitted to an IEC and reviewed and approved by the IEC before the investigation is initiated. Any additional requirements imposed by the IEC or regulatory authority shall be followed, if appropriate. Consenting and enrolment of any patient will not start before written confirmation of approval from the relevant central or local IEC. All parties involved in the conduct of the clinical investigation shall share the responsibility for its ethical conduct in accordance with their respective roles.

12.2 INTERNATIONAL STANDARDS

The investigation will be performed in accordance with international standards and any regional or national regulations, as appropriate. Any additional requirements imposed by the IEC or regulatory authority shall be followed, if appropriate. The Carry Life® UF system complies with identified applicable regulatory standards, according to Appendix D in the IB.

12.3 START OF CLINICAL INVESTIGATION

Before the start of the clinical investigation, approval will be sought from the IEC and regulatory authority(ies) with regard to the CIP, IB, informed consent forms and other appropriate documents. Approval in writing by an IEC and regulatory authority(ies) shall be received before consenting and enrolment of any patient into the investigation. Substantial protocol amendments will be submitted by the Sponsor for review and approval by the regulatory authority(ies), and premature termination and the reasons for the decision to the regulatory authority(ies) and IEC.

12.4 ADDITIONAL REQUIREMENT BY EU OR REGULATORY AUTHORITY

All additional requirement imposed by EU or regulatory authorities shall be followed.

12.5 INSURANCE

Sponsor will maintain appropriate clinical study insurance coverage as required under applicable laws and regulations for the duration of the clinical investigation.

12.6 FINANCING

This clinical investigation will be financed by Triomed AB.

Investigators will provide the Sponsor with sufficient and accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and after completion of the study according to national regulations. All Investigators will be required to meet the requirements of applicable EU/UK regulation. Financial disclosures will be collected from all Investigators prior to their participation in the investigation.

The financial agreement between the Sponsor and the investigation sites/Investigators are addressed in a separate agreement.

All expenses arising in connection with the investigation, the remuneration of the Investigators for performance of the investigation, and the indemnification of the participants for their participation will be reimbursed in accordance with the respective contracts.

13 INFORMED CONSENT PROCESS

Prior to performing any clinical investigation activities, including screening tests and assessments, written informed consent will be obtained from subjects by signing the approved informed consent form.

During the informed consent process the Investigator shall:

1. Provide the background of the clinical investigation, the procedures involved, the risks and benefits and that participation is voluntary. Information shall be provided both verbally and in written form.
2. The patient must be given sufficient time for questions and to consider whether to participate in the clinical investigation.
3. It is the Investigators responsibility to ensure that the patient has understood the purpose of the clinical investigation before the ICF is signed.
4. A copy of the signed and dated consent form will be given to the patient, and participation shall be documented in the medical records.
5. The patient must be informed that they have the right to withdraw their consent at any time, without the need for justification and that future medical care will not be jeopardized
6. If the patient prematurely withdraws from the clinical investigation, make all reasonable effort to ascertain the reason.
4. During the clinical investigation the Investigator shall inform the patients in writing of new information that can significantly affect the patient's future health or medical care. In this case the patient has the right to re-evaluate their decision to participate, and a revised patient information and informed consent will be signed by both the Investigator and patient.
5. Provide adequate medical care for the participants during and after the investigation, in the event of adverse events and medical emergencies (Section 14.1).
6. The ICF will be retained in the ISF.

13.1 PATIENT CONFIDENTIALITY

Participant confidentiality and privacy are strictly held in trust by the participating Investigators, their staff, and the Sponsor. All health data collection is conducted in a manner compliant with General Data Protection Regulation (GDPR) in the European Union (EU) and applicable data privacy law. Therefore, the CIP, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

Confidentiality of data shall be observed by all parties involved in the clinical investigation at all times. All data shall be secured against unauthorized access and in general by:

- The patient's identification being depersonalized using a clinical investigation coded number.
- The data transferred to the Sponsor shall be in coded form.
- The privacy of the participants and confidentiality regarding information shall be preserved in reports and published data.

- The Principal Investigator will however provide direct access to source data during and after the clinical investigation for monitoring, audits, EC review and regulatory authority inspections.

The informed consent will also specify that collected data may be transferred (to either EEA countries and/or non-EEA countries). In accordance with the EU Data Protection Directive (95/46/EC), the data will not identify any patients taking part in the clinical investigation.

14 SAFETY

14.1 PATIENT SAFETY ASSESSMENTS DURING THE CARRY LIFE® UF STUDY SESSIONS

Foreseeable adverse events and anticipated adverse device effects are associated with excessive UF, increased IP volumes and abnormalities in plasma glucose and electrolytes and a complete description of the anticipated device effects and their mitigations can be found in Section 4.3.

14.1.1 Excessive UF volumes

During the Carry Life® UF study sessions, it is expected that greater UF rates will be achieved compared to standard PD regimes. A maximum total UF volume of ≥ 20 ml/kg body weight/treatment has therefore been set for the Carry Life® UF study sessions.

14.1.2 Clinical evaluation

Clinical symptoms indicative of fluid depletion due to excessive UF volumes shall be assessed during the in-clinic Carry Life® UF treatments. The blood pressure and heart rate are to be monitored before and after treatment and when clinically indicated.

If the systolic blood pressure is <100 mmHg during the Carry Life® UF treatments the patient will be excluded from the study.

The patient will also be excluded from the rest of the study if the Carry Life® UF rate is >20 ml/kg body weight/treatment.

It is at the discretion of the Investigator to discontinue the study session if or when they see fit. The Investigator shall treat the clinical symptoms which occur during the study sessions according to clinical praxis. The subject's clinical condition will be evaluated and documented in the CRF after the Carry Life® UF study session.

14.1.3 Increased IP volumes

Increased IP volumes is mitigated by the automatic hourly drains during the Carry Life® UF treatments and optional additional if the patient has symptoms related increased IP volumes.

14.1.4 Abnormalities in the plasma glucose and electrolyte

Patient with CKD have abnormal creatinine, urea, and electrolyte values such as potassium, despite adequate treatment for CKD. The results of the blood samples cannot be evaluated using normal values and ranges and will therefore be assessed and corrected by the Investigator according to clinical praxis. The P-glucose will also be assessed and corrected according to clinical praxis (diabetic patients). Baseline blood data will be taken during the 2nd visit and blood glucose will be taken regularly during the in-clinic visits. The baseline blood chemistry and blood glucose data during the treatment will be reviewed by the physician before allowing the subject to continue to the home phase of the study.

14.2 SAFETY DEFINITIONS

Throughout the course of the clinical investigation, vigilance must be maintained with regard to possible AEs and in the event of their occurrence the first concern is for the safety and well-being of the subjects.

When the ICF is signed, each subject must be informed and receive the names and telephone numbers of clinical investigation site staff for reporting AE's and medical emergencies.

Adverse events will be categorized according to EN ISO 14155:2020, Annex F, MDCG 2020-10/1 and/or national regulatory requirements.

14.2.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational device or the comparator.
NOTE 2: This definition includes events related to the procedures involved.
NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

14.2.2 Serious Adverse Events (SAE)

A serious adverse event is defined according to the following:

1. Death,
2. Serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
   - a life-threatening illness or injury, or
   - a permanent impairment of a body structure or a body function including chronic diseases, or
   - in-patient or prolonged hospitalization, or
   - medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,
3. Fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment.

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered a serious adverse event.

14.2.3 Device deficiencies

The definition of a device deficiency is an inadequacy of a medical device related to its identity, quality, durability, usability, reliability, safety, or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer including labelling.

14.2.4 Device deficiency with SADE potential

Device deficiencies that did not lead to an AE but could have led to a Serious Adverse Device Effect (SADE) if:

- suitable action had not been taken,
- if intervention had not been made, or
- if the circumstances had been less fortunate.

14.2.5 Adverse device effect (ADE)

An adverse device effect is an adverse event related to the use of an investigational medical device.

NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
NOTE 2: This includes any event that is a result from a use error or intentional abnormal use of the investigational medical device.

14.2.6 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

14.2.7 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity, or outcome has been previously identified in the risk analysis.

14.3 REPORTING OF SAFETY EVENTS

Investigators must report to the Sponsor, or its designee, all reportable safety events (SAE, Device Deficiencies with SAE potential, etc.) via the EDC system, immediately, but not later than three (3) days of first awareness.

For all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it, the Sponsor must report to the National Competent Authority (NCA) immediately, but not later two (2) calendar days after awareness of a new reportable event or of new information in relation with an already reportable event.

Any other reportable events or a new finding/update to it, must be reported by the Sponsor to the National CA immediately, but not later than seven (7) calendar days following the date of awareness by the Sponsor of the new reportable event or of new information in relation with an already reported event.

Refer to the below sections for further details.

14.4 IDENTIFICATION, RECORDING AND REPORTING ADVERSE EVENTS

14.4.1 Recording adverse events

The site must record every AE and observed device deficiencies (DD), together with a severity and causality assessment in the subject's medical notes and in the eCRF.

The collection of AEs and DDs can be achieved through discussion with the participant during visits, through review of the participant's medical records or via information obtained from relatives or other clinicians or support departments involved in the participant's care.

Documentation includes dates of event, treatment, resolution, assessment of seriousness, expectedness, causal relationship to device and/or clinical investigation procedure (*cf. 14.7 – Assessments of adverse events*).

The clinical course of each event shall be followed until resolution or stabilization. Any AE that is ongoing when the patient is withdrawn from the investigation shall be followed-up until the AE is resolved or the Clinical Investigator deems the AE stable and no further follow-up is required. The date when the Clinical Investigator considers one of these outcomes to have been fulfilled will be considered the last visit for the subject, and the outcome shall be recorded in the eCRF.

14.4.2 Safety monitoring

The Investigator is responsible for the identification of any AE and DD including SAE/SADE and USADE and their report to the Sponsor and designee via the eCRF.

The information may be transmitted verbally initially, but this information must be followed up with detailed written reports in the SAE/SADE form contained in the ISF. Written reports must be completed legibly, and include all relevant dates and descriptions required by the SAE/SADE form. The Investigator must review and sign all SAE/SADE reports. However, if the Investigator is not available at the time of completion of the initial SAE/SADE report then the site should not delay sending the initial report in order to comply with the regulatory timelines (listed below). If only limited data are initially available, a follow-up report is required. If new information including outcome becomes available, the follow-up information has to be documented.

Foreseeable adverse events and anticipated adverse device effects including their possible mitigation are contained in Section 4.3

Timelines:

Any AE/SAE/SADE that occur after the subject has been enrolled until study completion/ termination must be reported to the Sponsor **immediately, but not later than 3 calendar days** after investigational staff become aware of the event. All DDs involving any device component must be **reported within 24 hours** of staff become aware of the event to Triomed and the medical device handled according to Section 14.3.

Particular attention shall be given to the causality evaluation of USADE events. The occurrence of unanticipated serious adverse events related to the use of the device (USADE) could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand. All USADE must be reported to the Sponsor regardless of severity **within 24 hours.**

Table 12. Reporting information for SAE and SADE

Reporting Information for SAEs and DDs with SADE potential
Any **Serious Adverse Events** that occur between subject enrolment and the end of clinical investigation must be reported to the Sponsor or designee **immediately, but not later than 3 calendar days** after investigational staff become aware of the event.
EMERGENCY CONTACT DETAILS
AE reporting contact information hereafter may be used in lieu of reporting through the eCRF, should the system be down: carrylifeUF@iqvia.com
To report initial or follow-up information on a Serious Event, Fax or email a complete SAE/SADE or a DD form to the following: Monitor/Sponsor
The initial report shall contain at minimum: • Patient identification (M/F). • Age of patient at time of onset. • Time and date of medical event. • SAE/SADE classification. • Description of the event. • Specific treatment/action. • Device model and serial number. • Event Status. • Severity. • Relationship procedure (causality). • Relationship investigational device (causality). • Event outcome.
The Sponsor must receive a completed SAE/DD Form **within 3 calendar days of** the occurrence. Please use the form for "Serious Adverse Event (SAE)" and "Device Deficiency (DD)" as needed.

14.4.3 Isolation of the investigational device

The IFU provided with the Carry Life UF system describes how to identity and troubleshoot the alarm conditions. The patient will be instructed to contact the dialysis clinic if they need additional support. If the contact person at the clinic is not available, the patient may contact Triomed for technical support. The patients can always end treatment according to the instructions in the IFU.

If an alarm cannot be resolved by the patient, the cycler will be assessed by the clinic with support from Triomed. If the cycler is deemed functional the cycler will be returned to the patient. If the cycler issue cannot be solved, the patient will get a replacement cycler for the remaining duration of the study and the non-functional cycler will be returned to Triomed for further assessment.

Triomed technical support can be reached at the following phone number: +46(0)706560444.

If an DD causes an ADE that is defined as serious (SADE) or a DD that could have potentially led to a SADE (expected or unexpected) the Investigator must following the below procedures:

- Isolate the device as soon as possible; The device should not be discarded or repaired. The device shall be returned to the manufacturer. Detailed instructions on the return procedure will be provided by the sponsor to the investigator upon receipt of a DD notification.
- All material evidence i.e., parts removed, replaced, or withdrawn from use following an incident including relevant instructions, records and packaging materials or any other means of batch identification must be:
    - Clearly identified and labelled.

- Stored securely.

- Evidence should not be interfered with in any way, except for safety reasons or to prevent loss. Where relevant, a record of all readings, settings, positions of switches, valves, dials, gauges and indicators, along with any photographic evidence and eyewitness reports should be retained.

14.5 INVESTIGATORS REPORTING RESPONSIBILITIES

The Investigator's responsibilities regarding reporting of AE/ADE are as follows:

1. Record and monitor all safety events (AEs/SAEs/SADEs/USADEs) including DDs and DDs with SADE potential, regardless of the severity or relationship to clinical investigation treatment.
2. Ensure that safety events reported by the subject and/or caregiver, observed by the Investigator, or documented in medical records are also recorded on the adverse event eCRF, whether believed to be related or unrelated to the investigational device or procedure.
3. Determine the seriousness, severity, device and procedure relationship of each event.
4. Determine the onset and resolution date of each event.
5. Complete the eCRF as much as possible **immediately, but no later than 3 calendar days**.
6. Follow-up information must be actively pursued and the Sponsor informed **immediately but not later than 3 calendar days.**
7. All device deficiencies must be reported in the eCRF **within 24 hours** upon knowledge to Triomed.
8. Ensure all AE and SAE/SADE/USADE reports are supported by documentation in the patient's medical records.

14.6 SPONSORS REPORTING RESPONSIBILITIES

Triomed/Monitor responsibilities regarding the reporting of reportable events as described in Section 14.6.1 to the relevant National Competent Authorities and Ethics Committees are as follows:

1. Review the Investigator's assessment of:
   - 1.1 All AEs and determine and document in writing their seriousness, severity, and relationship to the investigational device;
   - 1.2 Review all device deficiencies and determine and document in writing whether they could have led to a SADE;
   - 1.3 In case of disagreement between the Sponsor and the Principal Investigator(s) on the above, the Sponsor shall communicate both opinions to concerned parties.
2. Ensure the reporting to the CAs/ECs of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or by the CAs/ECs.
3. For all reportable events where there is an imminent risk of death, serious injury, or serious illness, that requires prompt remedial action to safeguard other patients or users or,
4. The identification of new finding must be reported **immediately, but no later than** 2 calendar days after awareness by Sponsor of a new reportable event or of new information in relation to already reported events (reportable event section).
5. Any other reportable events as outlined in Section 14.3 or new finding/update to it must be reported immediately, but no later than 7 calendar days after the date of awareness by the Sponsor.

6. Triomed or designee will report events according to in the MDCG 2020-10/1 rev1 guidelines via the **MDCG 2020-10/2** reporting form that can be found here.
7. In case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether corrective or preventive action is required.

Where necessary to ensure timely reporting, the Sponsor (or designee) may submit an initial report that is incomplete followed up by a complete report as soon as additional information becomes available.

14.6.1 Reportable events to Competent Authorities (CAs) and Ethic committees (ECs)

The following events are considered reportable to the competent authorities in accordance with the MDR requirements (Regulation (EU) 2017/745), and the MDCG 2020-10 Guidance on safety reporting in clinical investigations shall be followed:

1. Any SAE that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible.
2. Any device deficiency that might have led to a SAE if:
   - Suitable action had not been taken or,
   - Intervention had not been made or,
   - If circumstances had been less fortunate.
3. New findings/updates in relation to already reported events in 1) and 2).

14.7 Assessments of Adverse Events

14.7.1 Severity assessment

An assessment of severity is required to determine if an event is at a severity not usually seen (i.e., that it is unanticipated). The Investigator should assess the severity for each AE according to the following criteria (Table 13).

Table 13. Assessment of severity

Severity of Event	
Mild	The AE does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance.
Moderate	The AE produces some impairment of function but not hazardous to health. It is uncomfortable and/or an embarrassment.
Severe	The AE produces significant impairment of functioning or incapacitation and/or it is a hazard to the patient.

14.7.1.1 Serious health threat

A serious health threat refers to a signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.

This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

14.7.1.2 Expected assessment

For all Adverse Device Effects (ADEs), the risk analysis in the CIP will be used by the Investigator as a basis for identifying anticipated/unanticipated ADEs characterized by their nature, incidence, severity, and outcome. The Investigator must document the version of the IB used on the SAE form and/or the DD if applicable.

The assessment of the anticipated nature of the event is important to determine the submission timelines of a reportable case.

ADEs will be reported by ticking the "yes" box for ADEs on the eCRF page for AEs/ADEs.
The procedures described for AEs above will be followed for documenting ADEs.

14.7.2 Causality assessments

The relationship between the use of the investigational medical device (including the medical/surgical procedure) and the occurrence of each AE shall be assessed and categorized. During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the IB, the CIP or the risk analysis report shall be consulted, as all the foreseeable SAEs and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other current illness or risk factors shall also be considered.

The assessment of the causality assessment of the event is important to determine the regulatory timelines and the reportability of a case to the relevant CAs/ECs.

The Sponsor and Investigator will distinguish between the SAE related to the investigational device and those related to the procedures (any procedures specific to the clinical investigation). An AE can be related both to procedures and the investigational device.

Complications caused by concomitant treatments are considered not related, as well as routine procedures if the said procedure would have been applied to the patients also in the absence of the investigational device use/application (standard of care).

Each SAE should be classified according to four different levels of causality. The Sponsor and Investigator will use the following definitions to assess the relationship of the SAE to the investigational device or procedure according to the following table (Table 14).

Table 14. Assessment of causality

Not Related	Relationship to the device, comparator or procedures can be excluded when: - the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device; - the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;

	- the event involves a body-site or an organ that cannot be affected by the device or procedure; - the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.
Possible	The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
Causal relationship	The serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational device or procedures have an effect on; - the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/ procedures and the serious adverse event

15 VULNERABLE POPULATION

The clinical investigation will not involve the inclusion of vulnerable populations unable to give consent freely.

16 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

16.1 END OF THE CLINICAL INVESTIGATION

The definition of the end of the clinical investigation is the last patient last visit.

16.2 SUSPENSION OF THE CLINICAL INVESTIGATION

Triomed may suspend or prematurely terminate the clinical investigation at the investigation site for significant and documented reasons. The Principal Investigator, EC, or regulatory authority may also suspend or prematurely terminate the participation of the investigational site for which they are responsible.

Conditions that warrant suspension or premature termination include but are not limited to:

- The suspicion of an unacceptable risk to the patients.
- New data regarding the risks/benefits of the therapy.
- Serious or repeated deviations by the Investigator of the CIP or GCP.
- When instructed by the EC or regulatory authorities.

NOTE: an earlier end of the clinical investigation, which is not based on grounds of safety, but on other grounds, such as faster recruitment than anticipated, is not considered as premature termination.

If suspicion of an unacceptable risk to subjects arises during the clinical investigation, Triomed shall suspend the clinical investigation while the risk is assessed. Triomed shall terminate the clinical investigation if an unacceptable risk is confirmed.

If suspension or premature termination occurs Triomed shall inform the responsible regulatory authorities within 15 days of the date of termination by submitting a 'Declaration of the End of a Clinical Trial'. The Principal Investigator and Sponsor shall keep each other informed of any communication received from either the EC or the regulatory authority.

NOTE: The usual lines of communication are Sponsor <-> Principal Investigator or Sponsor <-> EC, and Sponsor <-> regulatory authority.
NOTE: The timing and method of this communication will depend upon the circumstances and perceived risks.

With early termination Triomed shall remain responsible for providing resources to fulfil the obligations of the CIP and existing agreements for the follow-up of enrolled patients. Routine close-out activities shall be conducted to ensure that:

- The Principal Investigator's records are complete.
- All documents needed for the Sponsor's files are retrieved.
- The remaining clinical investigation materials are disposed of.
- Previously identified issues have been resolved and all parties are notified.

Triomed will also ensure that regulatory authorities are notified as applicable. The Principal Investigator shall promptly inform the enrolled patients of the suspension or premature termination of the clinical investigation if appropriate.

16.3 PROCEDURE FOR RESUMING THE CLINICAL INVESTIGATION AFTER TEMPORARY SUSPENSION

When the Sponsor concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, Triomed shall inform the Principal Investigators, the ECs, and the regulatory authority of the rationale and provide them with the relevant data supporting this decision.

NOTE: The usual lines of communication are Sponsor <-> Principal Investigator or Sponsor <-> EC, and Sponsor <-> regulatory authority.

Concurrence shall be obtained from the IECs and regulatory authorities before the clinical investigation resumes. If subjects have been informed of the suspension, the Principal Investigator shall inform them of the reasons for resumption.

17 PUBLICATION POLICY

The results of the clinical investigation will be documented in the Clinical Investigation Report (CIR), which will also be the case if the investigation is prematurely terminated. The report will be prepared by Triomed according to Annex D of ISO 14155:2020 and the Declaration of Helsinki and reviewed and signed by the Sponsor and Investigator's designated as signatory.

The results of the investigation may be submitted for publication, and publications and presentations. Triomed also has the right to use the clinical investigation results for registration and internal presentations and promotion. With publications of the results the EudraCT number will be used, demonstrating that the requirements of the international committee for medical journal editors (ICMJE) have been meet.

The clinical investigation will be registered in a publicly accessible database in accordance with the Declaration of Helsinki. Triomed will supply written information of the clinical investigation results to the Investigator, which will be distributed to the patients who participated.

For further information concerning publication please refer to the "Clinical Study and Investigation Agreement" in the ISF.

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19 SIGNED AGREEMENT OF THE CLINICAL INVESTIGATION PLAN

I have read the CIP "A clinical study with the Carry Life® UF system in continuous ambulatory peritoneal dialysis (CAPD) patients" (Study No.: Tmed-010; Version: 6.0; Date: Feb 08 2024) and agree to conduct the clinical investigation according to the CIP and the applicable ICH guidelines and GCP regulations and to inform all who assist in the conduct of this study of their responsibilities and obligations.

Sponsors Representative's Signature (Clinical Manager)	Date
Sponsors Representative's Name (Print)	
Investigator's Signature	Date
Investigator's Name (Print)	
Study Site (Print)	

20 ATTACHMENTS

20.1 ATTACHMENT A. PRINCIPAL INVESTIGATOR, COORDINATING INVESTIGATOR AND INVESTIGATION SITE(S)

20.2 ATTACHMENT B. CHECKLIST FOR ASSESSMENT OF CARRY LIFE® UF USER COMPETENCY

20.3 ATTACHMENT C. SETTING THE CARRY LIFE® UF GLUCOSE DOSE

20.4 ATTACHMENT D. THE PET PROCEDURE (VISIT 2)

20.5 ATTACHMENT E. WEIGHING AND SAMPLING PROCEDURE, VISITS 3 AND 4

20.6 ATTACHMENT F. WEIGHING AND SAMPLING PROCEDURE DURING THE EFFICACY EVALUATION TREATMENTS OF THE HOME PHASE