Clinical Study Protocol

Levodopa pharmacokinetics in patients with Parkinson's disease and symptom fluctuation: A phase I, open-label, randomized, multicentre, crossover study comparing intravenous and subcutaneous Infudopa with intestinal Duodopa

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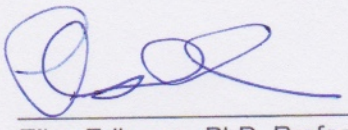
Sponsor:	Elias Eriksson, PhD, Professor Institution of Physiology and Neuroscience Sahlgrenska Academy, Gothenburg University Sweden Tel: +46 709 5 5 50 55 E-mail: elias.eriksson@neuro.gu.se
Principal Investigator(s):	Filip Bergquist, MD, PhD Department of Neurology Sahlgrenska University Hospital Gothenburg, Sweden Tel: +46 702 22 36 64 E-mail: filip.bergquist@gu.se
Monitor:	Gothia Forum

SIGNATURES OF AGREEMENT FOR IPO-001

Reviewed and Approved by:

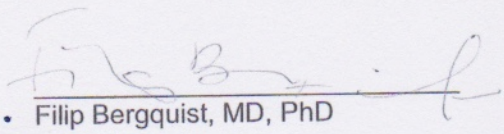
Sponsor:



Elias Eriksson, PhD, Professor

26 March 2019
Date

Coordinating Principal Investigator:



- Filip Bergquist, MD, PhD

26 March 2019
Date

LIST OF ABBREVIATIONS

Abbreviation	Explanation
3-OMD	3-O-methyldopa
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	alanine transaminase
AST	aspartate transaminase
AUC	Area Under the Curve
BK	Bradykinesia Score
BMI	Body Mass Index
CD	Carbidopa
CI	Confidence Interval
CK	creatine kinase
COMT	Cathecol-O-methyltransferase
COV	Coefficient of Variation
CSP	Clinical Study Protocol
DHPA	3,4-dihydroxypheylacetone
DK	Dyskinesia Score
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report From
EMA	European Medicines Agency
EU	European Union
FDS	Fluctuation Score
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
H&Y	Hoehn and Yahr
i.v.	Intravenous
IB	Investigator´s Brochure
ICF	Informed Consent Form
ISF	Investigator´s Study File
IVO	The Health and Social Care Inspectorate
LCIG	Levodopa-Carbidopa Intestinal Gel
LD	Levodopa
LLOQ	Lower Limit Of Quantification
MPA	Medicinal Products Agency
PD	Parkinson´s Disease
PE	Polyethylene
PK	Pharmacokinetics
PKG	Parkinson´s KinetiGraph
PTF	Peak-through fluctuation
PTT	Percent Time with Tremor
RBC	Red Blood Cell
s.c.	Subcutaneous
SAE	Serious Adverse Event
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TRS	Treatment Response Scale
UPDRS	Unified Parkinson´s Disease Rating Scale
VAS	Visual Analogue Scale
WBC	White Blood Cell

SYNOPSIS

Title: Levodopa pharmacokinetics in patients with Parkinson's disease and symptom fluctuation: A phase I, open-label, randomized, multicentre, crossover study comparing intravenous and subcutaneous Infudopa with intestinal Duodopa

Coordinating Investigator

Filip Bergquist, MD, PhD
Department of Neurology
Sahlgrenska University Hospital
Gothenburg, Sweden
Tel: +46 702 22 36 64
E-mail: filip.bergquist@gu.se

Study site(s) and number of subjects planned

Approximately 6 sites in Sweden will participate in the study. Five interim patients were completed 2nd Quarter 2018. Approximately 22 more patients aged 30 and above are to be enrolled in this study.

Study period		Phase of development
Date of first patient enrolled	2nd Quarter 2018	I
Estimated date of last patient completed	4th Quarter 2019	

Study design

IPO-001 is a prospective, randomized, 3-period cross-over, open-label multicentre trial comparing intravenous and subcutaneous Infudopa with intestinal Duodopa. The trial includes patients with Parkinson's disease who are on Duodopa treatment because of severe on-off manifestation when on oral levodopa. The patients will be identified and recruited at neurology clinics at university hospital clinical sites in Sweden, and travel from their living location to a clinical phase I site with full Good Clinical Practice (GCP) standard at the Sahlgrenska University Hospital in Gothenburg for the three treatment visits.

The subjects will be assessed at the phase I study clinic, where they during one treatment visit will receive Duodopa at optimal dosage for 16 hours, during another treatment visit will receive i.v. Infudopa at a rate estimated to yield corresponding serum levels of levodopa for the same duration, and at a third treatment visit will again receive the corresponding amount of levodopa but in the form of s.c. Infudopa. The study will hence have a cross-over design with a minimum of three days on Duodopa between the different treatment visits, where the order of treatments will be non-blinded but randomized.

Blood samples will be drawn according to a set schedule during the treatment visits, and subjects will be monitored for safety throughout the study, with focus on the local tolerability at the injection sites of i.v. and s.c. administration.

The duration of subject participation in the study is expected to be around 3-4 months from screening to final follow-up (with variation depending on subject´s availability between treatment visits), and the subject will be on study treatment for in total 3 days (3x16 hours).

Objectives

Primary objective is to:

- Demonstrate that Infudopa i.v. and s.c. yield steady state plasma concentrations of levodopa that are equivalent with those of Duodopa, and that the variability in plasma concentrations during the dosage interval is non-inferior to that obtained with Duodopa.

Secondary objectives are to:

- Evaluate the safety of the products with special focus on the local tolerability at the injection sites of i.v. and s.c. administration.

- Establish the bioavailability of levodopa and carbidopa given s.c. and as Duodopa compared to the i.v. administration.

- Compare other pharmacokinetic variables as well as motor function during treatment with s.c. and i.v. Infudopa versus Duodopa.

Investigational product, dosage and mode of administration

Infudopa will be supplied in three different bottles: 1. Infudopa Active containing 20 mg/mL levodopa and 2.5 mg/mL carbidopa, 2. Infudopa Buffer IntraV, and 3. Infudopa Buffer SubC, the two latter with no active ingredients. Product 1 will be combined with product 2 for i.v. infusion, and product 1 with product 3 for s.c. infusion. After online mixing by two infusion pumps, Infudopa will contain 10 mg/mL levodopa and 1.25 mg/mL carbidopa. Each single dose treatment in the 3 dose groups below will be given during 16 h.

Dosing will be based on the patient's *regular day time hourly dose-requirement of Duodopa*. This consists of the regular continuous Duodopa dose (mg) plus the average accumulated daily extradoses (mg) divided by the regular daily infusion time (h). The morning Duodopa bolus dose is for the study set to 110% of the *regular day time hourly dose-requirement of Duodopa*. Consequently the *pre-study daily Duodopa dose* is for this study defined as:

> The *regular day time hourly dose-requirement* × (16 h – morning bolus infusion time h) + 110% of the *regular day time hourly dose-requirement of Duodopa*.

Dose group 1. Infudopa i.v. infusion will be given through an indwelling catheter placed in the arm. The total Infudopa i.v. dose will be 81% of the subject's individual *pre-study daily Duodopa dose.* Infudopa i.v. will be administered as a morning bolus dose followed by continuous i.v. infusion up to 16 h. The morning bolus dose will be 110% of the hourly continuous dose. The morning dose will not exceed 24 mL after mixing, corresponding to 240 mg levodopa. The expected 16-h levodopa dosage will be in total 492 to 2900 mg. The maximum daily dose levodopa during i.v. administration is not allowed to exceed 3240 mg (equal to 81% of the maximum allowed daily dosage for Duodopa that is 4000 mg).

Dose group 2. A suitable split 2-needle infusion set will be placed laterally on the abdomen for the s.c. infusion of Infudopa. The total Infudopa s.c. dose will be 86% of the *pre-study daily Duodopa dose.* Infudopa s.c. will be administered as a morning bolus dose followed by continuous s.c. infusion up to 16 h. The morning bolus dose will be 155% of the hourly continuous dose. The morning dose will not exceed 30 mL after mixing, corresponding to 300 mg levodopa. The expected 16-h levodopa dosage will be in total 496 to 2950 mg. The maximum daily dose levodopa during s.c. administration is not allowed to exceed 3440 mg (equal to 86% of the maximum allowed daily dosage for Duodopa that is 4000 mg).

Dose group 3. Duodopa will be supplied in cassettes containing a gel with 20 mg/mL levodopa and 5 mg/mL carbidopa monohydrate, and be administered directly to the proximal small intestine via a PEG-J tube connected to a portable infusion pump. In dose group 3 the patient will receive the *pre-study daily Duodopa dose* administered as a morning bolus dose (110% of the continuous hourly dose) followed by continuous infusion up to 16 h. The morning dose will not exceed 15 mL, corresponding to 300 mg levodopa. The expected 16-h levodopa dosage will be in total 600 to 3160 mg. The maximum daily dose levodopa is not allowed to exceed 4000 mg.

Statistical methods

Statistical assessments of dosage normalized levodopa $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-}16}$, $AUC_{0\text{-}2}$, $AUC_{2\text{-}16}$, and $AUC_{8\text{-}16}$ by analysis of variance (ANOVA) will be made on the logarithmic values, with back-transformation to nominal values of point estimates and confidence interval (CI). These variables will also be tested with dosage un-normalized values. The terms to be used in the ANOVA model will be sequence, patient within sequence, period, and formulation (i.v. or s.c. Infudopa and Duodopa; test and reference, respectively).

The statistical method for testing relative dosage normalized levodopa bioavailability will be based on the 90% CI for the ratio of the population means (test/reference). These statistical tests will also be done with dosage un-normalized values. The acceptance range for AUC ratio of the 90% CI for levodopa will be 0.80 to 1.25. These tests will be performed for Infudopa i.v. or Infudopa s.c. vs. Duodopa comparison.

The COV (coefficient of variation or % standard deviation; SD) will be calculated for each individual for plasma concentration between 2 and 16 h by dividing the SD for each individual curve with the mean value of plasma concentration between 2 and 16 h. The mean value of plasma concentration will be calculated for each curve as $AUC_{2\text{-}16}/14$. Basic statistics for the COV will then be calculated per treatment group. The one-sided 90% CI of the intersubject COV will be calculated for Treatment 1 (i.v.) and Treatment 2 (s.c.) vs. Treatment 3 (Duodopa; reference) comparison, and for Treatment 1 (i.v. reference) vs. Treatment 2 (s.c.). It will also be tested with paired t-tests if there are significant differences in intersubject COV between treatments (i.v. vs. Duodopa, s.c. vs. i.v., and s.c. vs. Duodopa).

The level of significance will be p=0.05.

Safety will be summarized with the standard set of AE summary tables, and descriptive summary statistics of vital signs by visit and change from baseline. Local tolerability will be presented with descriptive summary statistics by visit and change from baseline.

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1. INTRODUCTION

1.1. Background and rationale for conducting the study

The critical importance of the brain neurotransmitter dopamine for the regulation of locomotion was first described by the 2000 Nobel laureate Arvid Carlsson. In patients with Parkinson's disease (PD), the characteristic motor symptoms, i.e., slowness of movement (bradykinesia), tremor and rigidity, are consequences of the progressive degeneration of neurons containing and releasing dopamine.

As the result of Carlsson's seminal discovery that administration of levodopa – a precursor to dopamine that (unlike dopamine) passes the blood brain barrier – restored locomotion in animals rendered immobile due to dopamine depletion, neurologist George Cotzias introduced per oral administration of levodopa as a treatment for Parkinson's disease in the late 60's. As yet, this remains the unchallenged first-line treatment of this disabling condition (Carlsson, 2002).

Levodopa is usually co-administered with a peripherally acting compound that inhibits the enzyme levodopa decarboxylase, which converts levodopa to dopamine. By reducing the peripheral decarboxylation of levodopa, the amount of levodopa that reach the brain is hereby enhanced and the side effects caused by dopamine outside of the brain minimized. One commonly used such peripheral levodopa decarboxylase inhibitor is carbidopa.

During the first few years of treatment with levodopa, patients usually experience symptom reductions that last for 6 hours or longer after drug intake. With time, however, symptom reduction to an increasing extent reflects the short half-life of levodopa in serum (60-90 minutes). Some patients also respond with drug-induced dyskinesias. The human suffering and societal costs caused by this unpredictable and disabling condition, usually referred to as the on-off syndrome, are immense (Lökk et al, 2012).

Inpatient studies, in which levodopa has been administered intravenously, have demonstrated that the on-off syndrome is partly caused by the marked variation in serum levodopa levels following per oral administration. Thus, when patients experiencing marked on-off symptoms on oral treatment are instead exposed to an infusion causing stable serum levels of levodopa, the fluctuations in motor function to a large extent disappear (Shoulson et al, 1975, and Quinn et al, 1984).

A logical approach to the on-off problem in outpatients would thus be to administer levodopa by a route of administration causing stable serum levels either by means of continuous subcutaneous administration (as used e.g. for insulin in patients with diabetes) or by continuous intravenous administration (as used e.g. for administration of chemotherapy to patients with cancer) using an infusion pump. However, no such formulation is yet approved by regulatory bodies for market access, the major obstacle having been to produce a levodopa solution with sufficient concentration and/or stability.

Levodopa–carbidopa intestinal gel (LCIG) is a carboxymethylcellulose aqueous gel delivered directly to the proximal small intestine via a percutaneous endoscopic gastrojejunostomy (PEG-J) tube connected to a portable infusion pump. Infusion of LCIG in the jejunum bypasses gastric emptying, helping to avoid the fluctuation in plasma levodopa levels. Daytime infusion of LCIG has demonstrated significantly improved motor symptoms and quality-of-life measures in advanced PD

patients compared to standard oral therapy (Wirdefeldt et al 2016). This formulation (under the name Duodopa®) has been approved in the European Union (EU) and several other countries on the indication "Treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results".

However, while clearly confirming that an even administration of levodopa is of considerable benefit to Parkinson patients with on-off symptomatology, the LCIG approach is marred by the need for surgery (for the insertion of the intestinal tube) and various possible complications following this, as well as by side effects such as abdominal pain. There are also reports of weight loss and polyneuropathy that are suspected to result from the intestinal continuous administration of levodopa-carbidopa gel. No doubt, much would be gained if the stable serum levels of levodopa produced by LCIG could instead be obtained by means of an s.c. pump not requiring surgery.

A neurologist at Linköping University Hospital (Nil Dizdar Segrell) succeeded in producing a physiologically acceptable levodopa solution in a concentration allowing for a continuous intravenous (i.v.) or subcutaneous (s.c.) administration of therapeutic doses to humans. Early experience of this strategy at the Linköping University Hospital confirms that both i.v. and s.c. administration of this solution results in stable serum levodopa levels and markedly improved motor functioning (Dizdar Segrell and co-workers, unpublished).

Based on the early work of Dizdar Segrell, researchers at Dizlin Medical Design AB, Pharm Assist Sweden AB, and University of Gothenburg, together with Dizdar Segrell, and in collaboration with Recipharm AB, have now produced a modified version of the original solution, Infudopa, containing even higher levels of levodopa as well as carbidopa. The aim of the present study will be to compare the pharmacokinetic profile of Infudopa administered i.v. and s.c. with that of LCIG administered enterally in parkinsonian patients with on-off complications, the tested hypothesis being that s.c. and i.v. administration of Infudopa will result in serum levels of levodopa at least as stable as those obtained by LCIG at clinically effective dosage. By showing this, we hope to expedite the clinical introduction of s.c. Infudopa as an alternative to LCIG for outpatients with Parkinson’s disease with on-off symptoms and/or of the introduction of i.v. Infudopa for the treatment of inpatients requiring a stabilisation of serum levodopa levels in order to be eligible for surgery.

1.2. Rationale for study design

The aim of this study is to alleviate the considerable human and societal burden caused by late stage Parkinson’s disease with on-off symptomatology by facilitating a prompt clinical introduction of s.c. (and/or i.v.) administration of Infudopa in Sweden and other countries. To this end, a moderately but adequately sized multi-centre study will be undertaken with the aim of confirming that i.v. or s.c. administration of Infudopa causes as stable serum levels of levodopa as does Duodopa, administrated enterally, which will serve as a control treatment. The study will also monitor the safety of these administrations, with focus on the local tolerability at the administration site, both during stay at the phase I ward and at follow-up.

Since the active ingredients of Infudopa are the same as in Duodopa, i.e. levodopa and carbidopa, and since it is already well established that the stable serum levels of levodopa obtained by

Duodopa is of marked benefit for patients with the on-off syndrome, showing that similar serum levels as those resulting from Duodopa may be obtained also by s.c. Infudopa might be sufficient for introducing s.c. Infudopa as a novel treatment of Parkinson's disease by means of a so-called hybrid application (EU regulation 726/2004). The primary aim of the planned study is hence not to show efficacy of Infudopa, which would be a much more costly endeavour, but to confirm that Infudopa is equal to Duodopa in causing stable serum levodopa levels at comparable steady-state levels of levodopa. Adverse effects during the one-day treatment and at follow-up will be recorded as well. For exploratory purposes, motor function during the one-day treatment with Dudopa. i.v. Infudopa, and s.c. Infudopa, respectively, will also be assessed. While it will not be possible to blind the study, motor function will be assessed by objectives measures, i.e. by video recording rated by an observer blind to treatment in combination with automatic measurement of motor function using a wrist worn device (Parkinson's KinetiGraph) (Grifftiths et al, 2012).

Short-term injections or infusions of i.v. Infudopa would be highly valuable in clinical situations when oral levodopa treatment temporarily is not working. Of note is that many patients with disabling late stage Parkinson's disease with on-off symptomatology are at present denied surgery for various disorders since they are not believed to be able to cope with the intervention and/or rehabilitation because of their poor motor condition. While the main purpose of this study, as discussed above, is to expedite the process of introducing long-term s.c. Infudopa for outpatients with the on-off syndrome, the introduction of i.v. Infudopa to in-patients may also meet a considerable unmet medical need by making it possible to conduct surgery, sometimes lifesaving, on this group of patients. Such treatment can be short-term and based individually on the patients need pre- intra- or postoperatively and can be given as slow injections of also low dosages. If successful, the trial presented in this application may thus make it possible to introduce this strategy to surgery-warranting patients with Parkinson's disease in Sweden and elsewhere shortly. In addition, in case unforeseen problems should arise regarding the s.c. administration, i.v. Infudopa administered at a continuous basis by means of a subclavian port-a-cath may turn out to be a feasible strategy for outpatients.

Based on statistical power analyses of primary efficacy variables (section 8.1), the required number of subjects is estimated to be 24. It is suggested to include 28 subjects into the study in order to compensate for 4 possible drop-outs.

1.3. Rationale for doses

Laboratory studies have shown that the stability of the ready-to-use Infudopa solution is relatively short when the pH of the solution is kept at 3-6, i.e. at a pH interval considered not to cause skin complications. A new administration system was hence developed, having two infusion pumps working at the same speed, each with a 50 to 60 mL syringe, one containing a solution of Infudopa Active, the other a solution of Infudopa Buffer IntraV (for i.v. administration) or Infudopa Buffer SubC (for s.c. administration). Each pump has a short infusion line to a mixing connector (a Y-connector). After the Y-connector there is a single infusion line of approximately 150 cm ending in a fine pore filter. From this filter there is finally a short infusion line with one or two catheters for administration to the patient. The concentration of levodopa at the catheter outlet to the patient will be 10 mg/mL with a carbidopa concentration of 1.25 mg/mL (ratio 8:1) for patients needing mid to high dosage of levodopa. For further details on the infusion pump system, refer to Appendix A.

A PD patient in late stage on Duodopa treatment needs on average about 1000 to 1600 mg levodopa per day (with carbidopa intraintestinally in a 4:1 ratio; Olanow et al. 2014, and Nyholm et al. 2013), and it is calculated that this would be equivalent to about 750 to 1200 mg by i.v. route (with carbidopa i.v. in a 8:1 ratio). This i.v. dose would correspond to a 75 to 120 mL volume of Infudopa infusion. A pharmacokinetic study in patients comparing the i.v. with the s.c. route of a levodopa solution similar to Infudopa administered during 6 h has shown that the absorption following s.c. administration is delayed by 2 to 3 h compared to that following i.v. administration, and that the area under the unbound concentration vs. time curve (AUC) of the s.c. formulation is approximately 50% of that of the i.v. formulation until infusion is stopped. Whereas plasma levels following termination of the i.v. administration levels off rapidly, they are more sustained (about 2 h) following s.c. administration; hence the s.c. formulation could be considered as completely absorbed if calculated from AUC and elimination from the biophase for a longer time period (with extrapolation to infinity) (Dizlin, data on file).

There is no documentation available showing the levodopa bioavailability for Duodopa vs. the i.v route. Based on the needed dosages of a levodopa solution administered i.v. to patients previously treated with Duodopa at the Linköping University Hospital, it may be estimated that Duodopa administered enterally is about 75% bioavailable as compared to i.v. administration. Experience from patients following s.c. administration at the same center suggests that equal doses of s.c. and Duodopa administrations can be used (Dizlin, data onfile). This suggested that the bioavailability of s.c. formulation may be in the range 75-100% when considering a complete dosage interval of a day. The dosage calculations for s.c. administration when starting the trial was hence based on the assumption of a 75% bioavailability. Analysis of data from the first 5 interim analysis patients, however, revealed that the absolute bioavailability of Infudopa s.c. is 100% vs. the i.v. standard, i.e. higher than expected (Clinical Study Interim Report 2019-01-15). Also Duodopa had a slightly higher absolute bioavailablity than the previous estimation (82% vs. i.v.). The ratio between LCIG and s.c. Infudopa levodopa bioavailability based on AUC 0-infinity was 0.78 and based on AUC 0-16 h 0.86. The AUC 0-16h was regarded as the most relevant variable for dose adjustment, because this is the time interval when the patient needs the optimal effect. Hence it was decided, that for the second part of the trial the dosage of Infudopa s.c. will be based on the assumption of an 86% bioavailability of Duodopa as compared to Infudopa s.c..

The aim of the present study will be to compare the pharmacokinetic and safety profile of Infudopa administered i.v. and s.c. with Duodopa administered enterally in patients with late stage Parkinson’s disease.

1.4. Risk/Benefit evaluation

Patients with fluctuating Parkinson’s disease, displaying on-off reactions to levodopa treatment, are usually severely disabled; this fairly common condition hence constitutes a major cause of poor life quality and is also, since these patients usually require intense care, associated with large societal costs. Any progress in this area should hence aid to meet a large unmet medical need.

The aim of this project, i.e. to facilitate the implementation of a novel treatment with the potential of markedly enhancing life quality and functioning of these patients within a foreseeable future, should not be regarded as overly optimistic. Thus, since

i) we already know that we are able to produce a concentrated solution of levodopa,

ii) we have good reasons to assume that s.c. administration of this solution will result in stable serum levels of levodopa, and
iii) previous studies regarding Duodopa have confirmed beyond doubt that producing stable serum levels of levodopa is indeed an effective way to improve motor functioning in patients displaying the on-off syndrome,

It is in fact not unlikely that s.c. Infudopa will turn out to be a major step forward with respect to the treatment of late stage Parkinson's disease. Moreover, albeit the decision of the authorities when assessing novel treatments for potential marketing may be difficult to predict, there are good reasons to believe that s.c. Infudopa, provided that the trial here presented is undertaken and successful, may reach patients in need within a relatively short future.

Also, as discussed above, today many patients with fluctuating Parkinson's disease are denied surgery such as orthopaedic surgery. The introduction of i.v. Infudopa for inpatients requiring a stabilisation of their motor functioning in order to cope with various forms of surgery (and the following rehabilitation), which might also be a consequence of this study, hence also must be regarded as an achievement of considerable clinical significance.

There is no reason to believe that Infudopa would exhibit any additional systemic adverse reactions than those described for other levodopa/carbidopa products, as summarised in the product information for Duodopa (see Investigator's Brochure). Duodenal administration of Duodopa has, however, a high risk of device- and procedure-related adverse reactions, such as postoperative wound infection, excessive granulation tissue, and incision site erythema, each reaction affecting more than 10% of patients (see Investigator's Brochure).

There is a potential risk of local adverse reactions at the administration site following Infudopa, however, local tolerance study in rabbits indicate that this risk should be low, and the reaction only short-term and not severe. However, the interim analysis of 5 patients showed that s.c. administration was associated with hematoma and transient and moderate pain or discomfort. Based on literature data, it was concluded that this was most likely due to the relatively high osmolarity caused by the high citrate concentration of the solution. Thus, when the trial starts again, a new buffer composition named Infudopa Buffer SubC, with a citrate concentration of only 20% of the previous one, will be used for the s.c. administration.

The half-life in plasma is short for levodopa, meaning that a lowering in pump rates following all routes of studied administration will quickly adjust down the levels of levodopa in plasma should, for example, dyskinesia occur. The clinical study is conducted at a phase I centre with intense monitoring of the patients that further reduces the risks. Please also refer to section 6.2 in the clinical study protocol for study dose and study design rationales. Data from the interim analysis have also given information allowing a fine tuning of the dosages.
When the study starts again, there will be a new interim analysis of pharmacokinetics (PK) and safety data after 4 of 18 (or 22 considering also possible compensatory patients) completed patients, after which a monitoring committee will meet to discuss the results and conclude if the study should continue, be modified with respect to design or discontinued. Evaluation will include blood PK samples, inspection of local dermal area/scoring including photos, and adverse events.

At high concentrations, citrate impairs coagulation. The levels of citrate (as well as those of phosphate) in Infudopa are, however, so low that no significant influence on systemic coagulation

even at maximal doses is to be expected, and also no other adverse effects of either citrate or phosphate. Nevertheless, safety laboratory analyses have been included in the study to monitor any possible effects on coagulation, by analysing total and ionized calcium and magnesium in serum, and blood base excess.

Hence, relevant precautions have been taken to minimize the risks and discomforts of patients participating in the study. This includes thorough information to the staff at the phase 1 unit where the trial will be conducted regarding the correct administration of the study product and the dose adjustments based on the clinical outcome (dyskinesia or on/off effect) that will aim to mitigate any adverse reactions.

In summary, it may be concluded that the risks for participating PD patients is low, and is outweighed by the profound benefit that a new s.c. and i.v. administration route would present to PD patients. Hence, the risk/benefit ratio for the clinical study is clearly beneficial.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary objective

- To demonstrate that doseadjusted Infudopa s.c. yield steady state plasma concentrations of levodopa that are equivalent with those of Duodopa, that the variability in plasma concentrations during the dosage interval is non-inferior to that obtained with Duodopa., and to establish the absolute bioavailability of levodopa when given as Infudopa s.c. or Duodopa as compared to Infudopa i.v.

2.2. Secondary objectives

- To evaluate the safety of the products with special focus on the local tolerability at the injection sites of i.v. and s.c. administration
- To establish the bioavailability of carbidopa given s.c. and as Duodopa compared to the i.v. administration
- Compare other pharmacokinetic variables as well as motor function during treatment with s.c. and i.v. Infudopa versus Duodopa

3. STUDY DESIGN AND PROCEDURES

3.1. Overall study design and flow chart

This is a prospective, randomized, 3-period cross-over, open-label multicentre trial. Patients fulfilling all of the inclusion and none of the exclusion criteria will be randomized to one of the three treatment arms. There have been 5 interim patients already studied. Enrolment upon restart of the study will be continued until the required sample size is achieved (18 subjects in total entering the second part of the study, giving in total 23 subjects in the study). Once informed consent is

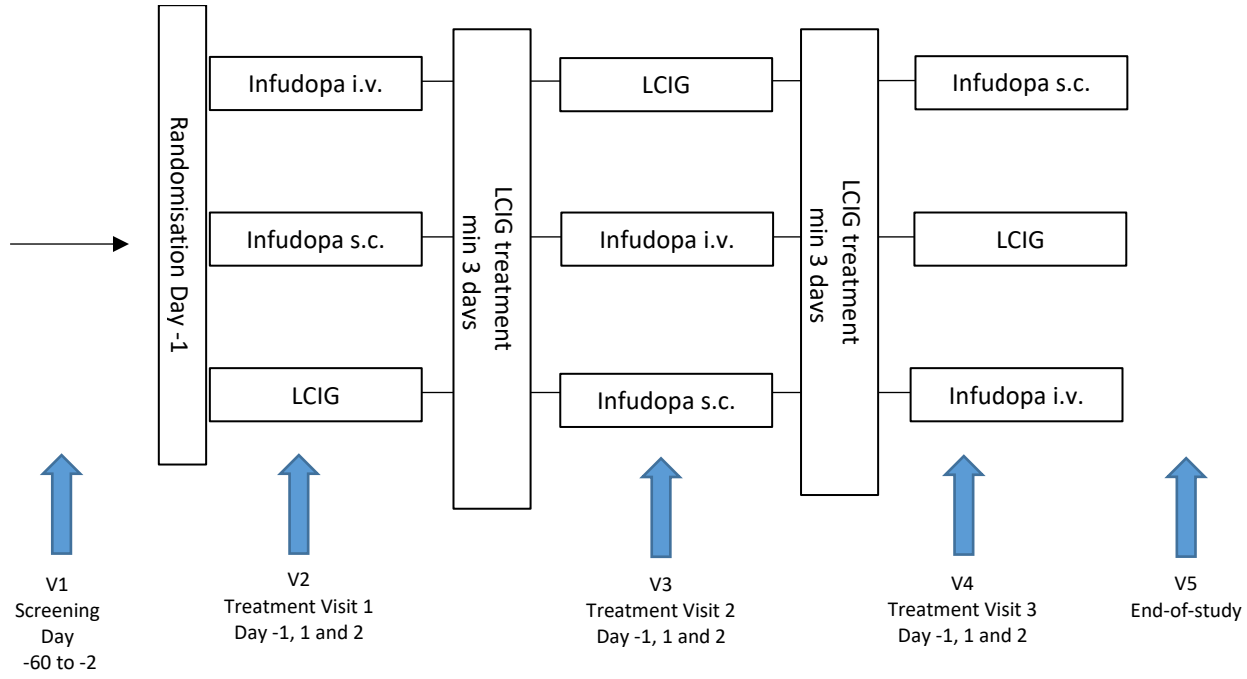
obtained, screening data will be collected to determine each patient's eligibility for study participation.

The duration of subject participation in the study is expected to be around 3-4 months from screening to final follow-up (with variation depending on subject´s availability between treatment visits), and the subject will be on study treatment for in total 3 days.

Patients with Parkinson's disease who are on Duodopa treatment because of severe on- off manifestation when on oral levodopa will be identified and recruited by experienced neurologists at neurology clinics at university hospital clinical sites in Sweden. Patients will travel from their living location to a clinical phase I site with full Good Clinical Practice (GCP) standard at the Sahlgrenska University Hospital in Gothenburg for the three treatment visits.

The subjects will be assessed at the phase I study clinic, where they during one treatment visit will receive Duodopa at optimal dosage for 16 hours, during another treatment visit will receive i.v. Infudopa at a concentration estimated to yield corresponding serum levels of levodopa for the same duration, and at a third treatment visit will again receive the corresponding amount of levodopa but in the form of s.c. Infudopa. The study will hence have a cross-over design with a minimum of three days on Duodopa between the different treatment visits, where the order of treatments will be non-blinded but randomized.

Figure 1 Study design



3.2. Study visits

Table 1 lists all of the assessments and indicates with an "X" the visits when they are performed. Table 2 lists the assessments during the treatment visits in more detail. All the obtained data must be supported in the subject's medical records (or equivalent), i.e. source documentation.

Subjects who for any reason discontinue study drug before completing the study should be scheduled for an End-of-Study visit as soon as possible, at which time all of the assessments listed for the End-of-Study visit will be performed.

Table 1. Assessment schedule, Study

Procedure	**Scree-ning**	**Treatment Visit 1**			**Return to Duodopa 1**	**Treatment Visit 2**			**Return to Duodopa 2**	**Treatment Visit 3**			**Return to Duodopa 3**	**Infudopa s.c. Follow-Up Visit**	**End-of-Study Visit**
Day within study period	**-60 to -2**	**-1**	**1**	**2**	**3 days minimum**	**-1**	**1**	**2**	**3 days minimum**	**-1**	**1**	**2**	**3-5**	**30 days after Infudopa s.c. Day 2 (+/- 5 days)**	**30 days after V4, Day 2[3] (+/- 5 days)**
Visit	**1**	**2**				**3**				**4**				**F-U[2]**	**5**
In house confine-ment		**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**			
Informed consent	X														
Demography & Medical History	X														
Physical examination	X														X
12-lead ECG	X														
Vital signs	X	X	X			X	X			X	X				X
Height, weight	X														
Previous / concomitant treatment	X	X				X				X					X
Use of per protocol drugs during levodopa nighttime withdrawal		X	X	X		X	X	X		X	X	X			
Pregnancy test (for females)	X	X				X				X					
Laboratory tests	X[9]		X	X			X	X			X	X			X

In-/exclusion criteria	X	X				X[1]				X[1]					
Randomi-zation		X													
Treatments			X				X				X				
Inspection of local dermal area/scoring		X	X	X		X	X	X		X	X	X		X	X
Photo of local dermal area		X[4]		X		X[4]		X		X[4]		X		X[4]	X[4]
Blood PK samples[5]			X	X			X	X			X	X			
Adverse Events	X[6]	X	X	X	X[7]	X	X	X	X[7]	X	X	X	X[7]	X	X
Study completion form															X
Efficacy measure-ments (video, PKG)			X	X[8]			X	X[8]			X	X[8]			

[1] At the discretion of the Investigator, the subjects could continue the study if any deviation to the inclusion/exclusion criteria is not clinically relevant and should not alter study integrity.

[2]Infudopa s.c. follow-up visit should be performed 30 days after the end of the Infudopa s.c. treatment visit. It can be done as part of the End-of-Study visit if applicable, otherwise as a separate visit at the local site.

[3]End-of-Study visit should be performed as soon as possible if the subject is prematurely withdrawn from the study.

[4]Photo will always be taken at day -1 and day 2 of each treatment visit, but only to document any abnormalities at the Infudopa s.c. follow-up visit and the End-of-Study visit.

[5]See Section Study Procedures, Drug levels and pharmacokinetic assessments, for schedule of blood collection.

[6]SAEs must be collected from time of informed consent. AEs from time of study drug administration.

[7]Phone call on Day 3 and 5 (acceptable to adjust for week end and call the next week day if applicable) after treatment visit 1, 2, and 3, respectively.

[8]PKG up to morning of Day 2

[9]Prothrombin complex (PTK-INR), Activated Partial Thromoplasmin Time (APTT), HIV and Hepatit B and C only applicable at the screening visit

Table 2. Assessment schedule, Treatment Visits

Day within visit	**-1**	**1**																								
Time point (h)	**after noon**	**Pre dose**	**0**	**15 min**	**30 min**	**1**	**1,5**	**2**	**2,5**	**3**	**3,5**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**12**	**14**	**16**	**16,5**	**17**	**17,5**	**18**	**23**	**24**
Vital Signs	X	X																									
Pregnancy Test (for females)	X																										
Randomization[1]	X																										
In-/exclusion criteria[2]	X																										
Previous / concomitant treatment	X																										
Use of per protocol drugs for levodopa abstinence	X	X																			X	X	X	X	X	X	X
Treatment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Inspection of local dermal area/scoring	X							X								X					X						X
Photo of local dermal area	X																										X
Food[8]							X					X				X			X								X
Adverse Events[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
Video recording[6]		X					X						X	X	X					X[6]							
PKG		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood PK samples[9]			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Laboratory Tests[7]																											X[7]

Laboratory Tests[10]		X[10]			X[10]				X[10]							X[10]										X[10]

[1]Randomization, only at Treatment Visit 1

[2]At the discretion of the Investigator, at treatment visit 2 and 3, the subjects could continue the study if any deviation to the inclusion/exclusion criteria is not clinically relevant and should not alter study integrity.

[4]Adverse Events collected throughout the study as described in section 7.

[5]Including question at day 2 about subject´s experience during the treatment day.

[6]Starting 15 (±5) min after the blood PK sampling. Assessment at 14 h can be omitted for practical reasons (exact reason documented in the eCRF).

[7]Laboratory tests on Day 2 only at the third Treatment Visit (according to Table 1).

[8]Low-protein snack is allowed between meals if needed

[9]PK sampling should be prioritised at time points when more than one procedure is scheduled at the same time point

[10]This time point samples only for total and ionized calcium and magnesium in serum, and blood base excess.

Visit 1, Screening visit (day -60 to -2):
The subject will receive information about the study. After the informed consent document has been dated and signed, both by the subject and the investigator, and the subject has been provided with a copy of the subject information and a copy of the signed informed consent form, screening information will be obtained.
The subject will be allocated a unique subject number.

The procedures to be undertaken are shown in Table 1, and results entered into the electronic Case Report Form (eCRF).

The visit will take approximately 90 minutes.

Visit 2, 3 and 4, (day -1 to 2 in each treatment visit)
Within 60 days after the screening visit, eligible subjects fulfilling all inclusion criteria and none of the exclusion criteria will be asked to come to the phase I unit in Gothenburg for the first treatment visit on Day -1 of treatment visit 1. It will be adequate for subjects to arrive at the phase I unit in the afternoon for procedures according to Day -1 of treatment visit 1. Randomization of subjects will be made on Day -1 of treatment visit 1.

At Day -1 in treatment visit 2 and 3 subjects will also be admitted to the clinical site. The procedures to be undertaken are shown in Table 1 and 2.

No Duodopa or oral levodopa–carbidopa or levodopa-benserazide tablets will be allowed later than 7 h prior to the start of the infusion on the day of pharmacokinetic assessments (i.e. last dose approximately 23.00 the night before).

Prior to the pharmacokinetic sampling, subjects will be fasted overnight (starting from 22:00 on the previous day). On the pharmacokinetic assessment day, subjects will receive the same standardized, low protein meals at the following approximate times relative to starting infusion: breakfast (1.5 h, +/-15 min), lunch (4 h, +/-30 min), dinner (8 h, +/- 30 min), and evening meal (12 h, +/- 30 min). Water will be allowed ad libitum. After the end of blood sampling, before leaving the clinic, they will be served breakfast.

At day 1 of the treatment visits, drug administration will start early in the morning and continue for 16h. Whole blood samples will be collected via an indwelling catheter or by direct venous puncture during the visit immediately prior to the initiation of treatment in the morning and at the following time points after the initiation of infusion (0h):

Table 3. PK sampling details

PK sample	Time window for sampling
Pre-administration	- 30 to 0 min
15 min	+/- 1 min
30 min	+/-1 min
1 h	+/- 5 min
1.5 h	+/- 5 min
2 h	+/- 5 min
2.5 h	+/- 5 min

3 h	+/- 5 min
3.5 h	+/- 5 min
4 h	+/- 5 min
5 h	+/- 10 min
6 h	+/- 10 min
7 h	+/- 10 min
8 h	+/- 10 min
10 h	+/- 10 min
12 h	+/- 10 min
14 h	+/- 10 min
16 h	+/- 10 min
16,5 h	+/- 10 min
17 h	+/- 10 min
17,5 h	+/- 10 min
18 h	+/- 10 min
23 h	+/- 15 min
24 h (for patients on Duodopa treatment, the PEG tube should be flushed at 24 h, after the PK sample has been taken)	+/- 15 min

A video recording of the subject will be made for subsequent assessment of motor function. During Day 1, subjects will be video recorded for 1 to 2 minutes pre-dose and after start of medication according to Table 2. The video recordings will be made just after any blood sampling. The video sequences will subsequently be assessed by two blinded, independent neurologists as secondary efficacy variable (see 3.3.8 Video Recordings). Blinding of the assessing neurologists will be obtained by having the subjects equipped with dummy infusion lines, so that the actual treatment arm could not be judged from the video sequences.

Moreover, a Parkinson's KinetiGraph (PKG; Global Kinetics Corporation, Melbourne, Australia) for collection of efficacy data (Griffiths et al, 2012) will be used. The PKG automatically collects accelerometry data from spontaneous wrist movements and scores the degree of bradykinesia and dyskinesia as well as detects tremor (see 3.3.9 Parkinson's KinetiGraph).

Adverse event monitoring and inspection of local dermal area including scoring will be undertaken as shown in Table 1 and 2. The local tolerability will be assessed and photographs subsequently evaluated by a dermatologist (see 3.3.6 Inspection of local dermal area/scoring including photos).

Subjects will leave the clinical site in the morning on Day 2 after initiating their standard treatment and having breakfast.

Return to Duodopa treatment between Visit 2-3 and Visit 3-4
It is required that the subjects return to Duodopa treatment for a period of minimum 3 days between Treatment Visit 2 and Treatment Visit 3, and between Treatment Visit 3 and Treatment Visit 4, respectively.

There will be telephone follow-ups of the subject from the site in Gothenburg on the day after (Day 3) and 3 days after (Day 5) treatment visit 1, 2 and 3, and, if needed, a visit at the local clinic for follow-up if there are possible adverse events that have to be assessed/followed up during these periods. If needed, additional telephone follow-ups will be made.

Infudopa s.c Follow-Up visit
Approximately 30 days (+/- 5 days) after the end of the treatment visit where the subject was randomized to receive Infudopa s.c., the subject will visit the local Investigator for a follow-up inspection of the local dermal area. The visit will include an inspection of local dermal area/scoring, with photos if anything abnormal is identified.
This visit can be done at the same time as the End-of-Study visit, or be combined with a treatment visit if applicable, but will otherwise be performed as an individual visit 30 days after the s.c. treatment.

End-of-Study visit, Visit 5
An End-of-Study visit will be performed by the local Investigator approximately 30 days after the end of the third treatment visit (Table 1). If a subject is prematurely withdrawn from the study, an End-of-Study visit will be performed as soon as possible following the decision to withdraw. The visit will include an inspection of local dermal area/scoring, with photos if anything abnormal is identified.

3.3. Study Assessments

3.3.1. Demography and Medical History

Recording of demographic data will be done at the screening visit (Visit 1) and include date of birth, race and gender. Medical History will be recorded as judged relevant by the Investigator.

3.3.2. Physical Examination

Physical examinations will be performed at screening (Visit 1) and at the End-of-Study visit. The complete physical examination will include an assessment of the following:

- General appearance
- Examination of abdominal skin (including area around stoma) and skin on upper extremities
- Neurological (reflexes and sensory screening for vibration and pin prick in extremities)
- Body Mass Index (BMI), measure and record height (cm) and weight (kg) (only at screening)

Physical examination data to be recorded on the eCRF will include:

- Normal/abnormal
- Description of any abnormalities

3.3.3. 12-lead electrocardiogram (ECG)

A standard resting 12-lead ECG will be obtained at screening (Visit 1). ECG will be recorded after the subject has been lying down for 10 minutes. From the ECG, normal/abnormal/abnormal specification and clinical significance of the abnormality will be recorded.

3.3.4. Vital signs

Vital signs will be measured at screening (Visit 1), at day -1 and 1 during each treatment visit, and at the End-of-Study visit. Vital signs consist of sitting pulse and sitting blood pressure, and will be measured after the subject has been seated for at least 5 minutes.

Pulse and blood pressure will be determined while the subject is seated using a generally accepted method.

3.3.5. Previous and concomitant treatment

Previous medication will be recorded as part of the medical history during the screening visit, as judged relevant by the Investigator. Concomitant medication during the study will be asked about and recorded in the eCRF at screening (Visit 1), and at day -1 during each treatment visit, and at the End-of-Study visit.

3.3.6. Use of permitted drugs during night time levodopa abstinence

Concomitant treatment with dopamine agonists as per the subject's regular medication schedule is allowed throughout treatment visits. The patient is however not allowed to use any levodopa-containing drug other than the IMPs between 23:00 on Day-1 and the reinstatement of Duodopa-treatment in the morning of Day 2 of treatment visits. During this time levodopa-abstinence symptoms like Restless Leg Syndrome (RLS), and Parkinson OFF-symptoms can be treated with paracetamol, oxazepam and short acting dopamine agonists like pramipexol, ropinirol or temporarily worn rotigotine patches. Temporary use of the following drugs during night time levodopa abstinence must be noted in the eCRF (dose and time of administration): paracetamol, oxazepam, pramipexol, ropinirol, rotigotine, but should not be noted as change of concomitant medication.

3.3.7. Inspection of local dermal area/scoring including photos

Inspection of local dermal area, including adverse event scoring, and photos will be performed at the site in Gothenburg at day -1 and day 2 during the treatment visits. The same assessments will be made at the Infudopa s.c. follow-up visit and the End-of-Study visit by the local Investigator.
In addition to visual inspection and photo documentation of the skin area the area will be assessed for increased subcutaneous consistency, tenderness and pruritus (itching). Pain, tenderness and itching, respectively, will be rated by the subject using a horizontal 10 cm visual analogue scale (VAS) (Furue et al, 2013 and Younger et al, 2009). In the event of any occurrence of noduli or increased subcutaneous consistency, it will be photographed, and then the approximate borders will be delineated on the skin with a pen and photographed.

Photos will always be taken at day -1 and day 2 of each treatment visit according to provided instructions, and to document any abnormalities at the Infudopa s.c. follow-up visit, and at the End-of-Study visit. Photos of the skin area will be taken using a dark background behind the subject.

Perpendicular artificial lighting will be used and the subject will be asked to relax muscles. The subject will be photographed in dorsal recumbent position on all occasions. A 10 cm paper ruler tag will be placed at on the skin at the side of the infusion site and the full length of the ruler included in view. The subjects face or other identifiable features will not be included.

The photos will be assessed and scored according to the Draize Score (refer to Appendix B) by two blinded and independent dermatologists, and photos will be randomized between time, subjects and treatments for the assessment. The assessors will be trained before the study, and the order of the photos will be broken when all assessments are finalized. Estimation of area of the affected skin will be made, using the above-mentioned ruler as a calibration unit.

Adverse events involving the skin will be evaluated by study personnel when prompted by the subject and at the pre-defined time points. At the pre-defined time points any occurrence of the following pre-defined symptoms will be assessed and severity rated: erythema, discoloration, pain, pruritus, subcutaneous nodulus or tenderness. Predefined infusion related **adverse events** involving the infusion sites are: Acute transient infusion site reaction, Continuous infusion site reaction and delayed infusion site reaction which when appropriate can be described with other terms listed under the class “General disorders and administration site conditions” - “Infusion site reactions” or “General disorders and administration site conditions” - “Implant and catheter site reactions” See:
http://bioportal.bioontology.org/ontologies/MEDDRA/?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FMEDDRA%2F10018065.
When appropriate, free text terms can be used.

3.3.8. Laboratory Assessments

Blood and urine samples will be taken at the times indicated in the assessment tables (Table 1 and 2). The following samples will be collected and variables measured (see 6.3.2 for total volume):

- Clinical chemistry (calcium, phosphate, total bilirubin, alkaline phosphatase, urea, urate, chloride, creatinine, total protein, albumin, aspartate transaminase (AST), alanine transaminase (ALT), sodium, potassium, creatine kinase (CK), homocysteine, prothrombin complex (PTK-INR), activated partial thromoplasmin time (APTT))
- HIV and hepatit B and C
- Haematology (haemoglobin, platelet count, haematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials)
- Total and ionized calcium and magnesium in serum, and blood base excess
- Urinalysis (pH, ketones, glucose, proteins, blood), urine pregnancy test, − 10 mL midstream.
- Blood PK samples; Levodopa (LD), carbidopa (CD), and 3-O-methyldopa (3-OMD)

Blood and urine samples (except for PK samples) will be analysed at the site or at the local hospital laboratory according to routine procedures, and then destroyed.

Laboratory values outside the reference limits suspected to be of any clinical significance will be re-checked, but without further recording in the eCRF. Subjects in whom the suspected clinical significance is confirmed at the repeated sampling will either not be included or, if already included, will be followed until normalization or for as long as the Investigator considers necessary.

The PK blood samples will be stored at −20°C until shipment to laboratory for analysis.

Details for biological sample handling will be specified in a study specific Laboratory Manual.

Levodopa, carbidopa, and 3-OMD will be analysed at a certified laboratory with Good Laboratory Practice (GLP) standard, and the bioanalytical method should be fully validated according to European Medicines Agency (EMA) Guideline on bioanalytical method validation (July 2011, EMAE/CHMP/EWP/192217/2009). The lower limit of quantification (LLOQ) will be at least 15 ng/mL for plasma of both active ingredients levodopa and carbidopa. Separate bioanalytical study plan will be prepared and approved before study sample analysis.

3.3.9. Video recordings

Each of the video sequences to be recorded on Day 1 will contain the following tasks: finger tapping, leg agility, alternating hand movements, arising from a chair, and walking (at least 3 m). Assessments of the video sequences will be made by two senior neurologists after the study. The order of the recordings will be randomized between time, subjects and treatments. All video recordings will be installed on two laptop computers together with a rating form for the items described below. The assessors will be trained before the study, using video recordings from previous studies. The order of the video sequences will be broken when all assessments are finalized.

The operational definitions of the motor examination part of the Unified Parkinson´s Disease Rating Scale (UPDRS) (Fahn et al, 1987) will be used for finger tapping (item 23), rapid alternating movements of hands (item 25), leg agility (item 26), arising from chair (item 27), gait (item 29), and bradykinesia (item 31). These items are considered to be the most relevant and convenient for the brief recordings. Dyskinesias will be observed on the video recordings, and reported using the definitions of the Modified Dyskinesia Scale (Goetz et al. 1994).

A Treatment Response Scale (TRS) (Nyholm et al, 2005) will be used for a global assessment of clinical response. The TRS ranges from -3 (severe “off”) to +3 (“on” with severe dyskinesia), where 0 is “on” without any dyskinesias.

A composite secondary efficacy variable will be the percentage of TRS ratings within the interval -1 to +2 that is, a clinically desirable, functional “on” state accepting mild parkinsonism and not more than moderate dyskinesia, and percentage of ratings within the intervals -3 to -2 (severe to moderate “off”) and +3 (“on” with severe dyskinesia).. Interrater reliability will be assessed using percentage agreement between the raters and κ (kappa) coefficients. Kappa coefficients between 0.60 and 0.80 are considered “good” and coefficients higher than 0.80 “very good.”

3.3.10. Parkinson's KinetiGraph

Parkinson Kinetigraph recordings will be obtained from the wrist on the subjects most disease affected side. Recordings will start in the morning of day 1 of each treatment visit and continue for up to 24h or until the subject leaves the trial site on day 2. The accelerometer data will be uploaded and proprietary algorithms (Global Kinetics Corporation, Melbourne, Australia) will be used to calculate the 25th, 50th and 75th percentiles of a bradykinesia score (BK) and a dyskinesia score (DK) over the time-period 09-18 as well as +1h to +16h from pump start. Tremor episodes consisting of at least 10 seconds meeting the operational tremor criteria defined by Braybrook et al (2016) will be recorded and the percent of time with ongoing tremor between 9-18 as well as +1h to +16h after pump start will be calculated. The interquartile ranges of BK and DK will be used to calculate a fluctuation score (FDS) for the measured time periods. Other outcomes will be median BK, DK, FDS scores as well as percent time with tremor in the normal daytime period (9-18) as well as the entire infusion period following the first hour after treatment start.

4. STUDY POPULATION

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1. Inclusion criteria

For inclusion in the study, patients should fulfill the following criteria:

1. Signed informed consent
2. Male or female patients at least 30 years old
3. Patients with advanced Parkinson's disease who are already on LCIG (Duodopa®) for at least 30 days, on a stable treatment regimen of 600 mg to 4000 mg levodopa per day, and with approximately 16- or 24-h Duodopa infusion regimens
4. Patients with a Hoehn and Yahr (H&Y) score of ≤ 3 on Duodopa treatment (including concomitant medication)
5. Body mass index range from 18.0 to 35.0 kg/m^2
6. Patients in general good health, as judged by the Investigator, and as determined by vital signs, medical history, physical examination, ECG, and laboratory tests
7. Females of childbearing potential must have a negative pregnancy test prior to randomization and must be willing to use a highly effective contraceptive measure during relevant systemic exposure to the investigational drug and the first menstrual cycle after treatment cessation (see section 7.3).
8. Males must be willing to refrain from fathering a child, including sperm donation, during the study and 3 months following the last dose.

4.2. Exclusion criteria

Patients must not enter the study if any of the following criteria are fulfilled:

1. Simultaneous participation in any other clinical drug trial
2. Clinically significant abnormal laboratory data at baseline or any abnormal laboratory value that could interfere with the study assessments

3. Patients with current serious symptomatic CNS-lesions, neurological, psychiatric, or behavioral disorders other than Parkinson's disease (e.g. major stroke, epilepsy, substance use disorder, previous neurosurgery including DBS) and that may interfere with the conduct or interpretation of the study
4. History or presence of any condition that can interfere with absorption, distribution, metabolism, or excretion of study drug (not including the percutaneous endoscopic gastrojejunostomy tube needed for Duodopa administration)
5. Patients on medication with warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, monoamine oxidase-A inhibitors and alpha-methyldopa (within the last 60 days); selegiline, catechol-O-methyltransferase (COMT) inhibitors other than a single daily dose of entacaponeparenteral ergots, anticholinergics, methylphenidate, amphetamine, isoprenaline, adrenaline, dobutamide, reserpine, or other drugs with known dopamine receptor antagonistic effect (within the last 30 days); and iron salts (within the last 7 days), or any other treatment that could affect the metabolism of levodopa
6. Patients who use antineoplastic chemotherapy or biological immunosuppressants (within the last 5 years), and drugs known to increase risks for cardiac toxicity, Torsade de Pointes, sudden death or prolonged QT interval (within five elimination half-lives before baseline and for the duration of the study)

4.3. Restrictions

Not applicable

4.4. Subject enrolment and randomization

Subject eligibility will be established before *enrolment*. Subjects will be *enrolled and randomized* strictly sequentially, as subjects are eligible *for randomization*. If a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study.

Identified potential study subjects will be given thorough information regarding the study, both orally and in writing, by a physician. After the subject has been given the opportunity to ask any question regarding the study they will be asked to consent to study participation. If they do, they will sign the informed consent form.

At screening (before randomization): subjects will be assigned a unique subject identification (enrolment number).

At randomization, all eligible subjects will be given a randomization number that assigns them to one of the treatment groups. The randomization numbers are sequentially allocated to the subjects in the order of randomization. Each subject will receive only that treatment regimen which is labelled with the randomization number allocated to him/her.

If the subject fails to be randomized for any reason, the subject's identification and the reason for not being randomized will be entered into the eCRF. Note: The enrolment number is different from the randomization number.

Randomization will be performed with random assignment of treatment groups in the specified ratio of 1:1:1.

Subjects discontinuing treatment prematurely will not be replaced.

According to the recommendations given in the ICH E9 Guideline "Statistical Principles for Clinical Trials" (CPMP, 1998), the used block length is specified in a separate document, which is withheld from the study centre.

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the subject should be discontinued as soon as the error or incorrectness is evident, and returned to pre-study treatment, i.e. Duodopa.

4.5. Discontinuation and withdrawal of subjects

Subjects are free to discontinue their participation in the study at any time without prejudice to further treatment. The subjects may be withdrawn from the study at the discretion of the investigator due to safety concerns or if judged non-compliant with study procedures. In either case, serious adverse events will be followed up. Other reasons for discontinuing a subject are incorrect enrolment and subjects lost to follow-up.

4.5.1. Premature termination of the study

The Investigator may terminate the study prematurely for any reasonable cause.

Furthermore, the Board of the Interim Study Analysis may terminate the study prematurely for any reasonable cause. It is also possible that the Board may suggest changes to the study design and procedures that will be implemented for the rest of the study. When such changes are implemented, they should be documented in an amendment to the study. If such an amendment is regarded as a major change, it should be approved by the Ethics Committee (EC) and Medicinal Products Agency (MPA).

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- If MPA obtains information that raises doubts about the safety or scientific validity of the clinical study, MPA can suspend or prohibit the study.

If the trial is prematurely terminated or suspended, the investigator should promptly inform the subjects and ensure appropriate therapy and follow-up. Furthermore, EC and MPA will be informed promptly.

5. STUDY TREATMENTS

5.1. Identity of investigational medicinal products

Table 4. Product identity

Medical product (substance)	Dose, strength, route of administration	Manufacturer	Provided by
LCIG (Duodopa®) for treatment 3	Supplied in cassettes containing 100 mL of gel (20 mg/mL levodopa and 5 mg/mL carbidopa monohydrate) for intraintestinal administration	Fresenius Kabi Norge AS, Halden, Norway	Requisition from the pharmacy
Infudopa Active for treatment 1 and 2	Supplied in bottles containing 50 mL of solution (20 mg/mL levodopa and 2.5 mg/mL carbidopa) for i.v. or s.c. administration	Recipharm, Solna, Sweden	Manufacturer
Infudopa Buffer IntraV for treatment 1	Supplied in bottles containing 50 mL of solution	Recipharm, Solna, Sweden	Manufacturer
Infudopa Buffer SubC for treatment 2	Supplied in bottles containing 50 mL of solution	Unimedic, Matfors, Sweden	Manufacturer

5.1.1. Doses and treatment regimens

All dosing during the study will be based on the patient's *regular day time hourly dose-requirement of Duodopa*. This consists of the regular continuous Duodopa dose (mg), plus the average accumulated daily extradoses (mg) divided by the regular daily infusion time (h). The morning Duodopa bolus dose is for the study set to 110% of the *regular day time hourly dose-requirement of Duodopa*. Consequently the *pre-study daily Duodopa dose* is for this study defined as:

> The *regular day time hourly dose-requirement* × (16 h – morning bolus infusion time h) + 110% of the *regular day time hourly dose-requirement of Duodopa*.

The total dose per day will be the sum of two components: morning bolus dose, and continuous (maintenance) dose given over a 16-h period. The combined i.v. infusion of Infudopa Active with Infudopa Buffer IntraV will be named Infudopa IntraV, and the combined s.c. infusion of Infudopa Active with Infudopa Buffer SubC will be named Infudopa SubC. In the following text doses and treatments apply to subjects in the second phase of the study (n=18). Before the start of this phase, it was decided that the bolus doses should be determined by a fixed percentage of the continuous hourly dose. The percentage chosen was for Infudopa IntraV 110%, for Infudopa SubC 155%, and for LCIG 110%. If clinically justified in the individual patient, the bolus dose may be adjusted, maintaining the relation 1 : 1.4 : 1 between the bolus doses for the different administration modes i.v : s.c : intestinal. The total dose is adjusted for the relative bioavailability based on AUC during the 0-16 h dosage interval vs. LCIG that was found in the interim study (ratio LCIG/Infudopa IntraV = 0.81; ratio LCIG/Infudopa SubC = 0.86).

Treatments will comprise the following therapy, where treatment 1 and 2 are considered investigational, and treatment 3 reference therapy:

1. Infudopa IntraV, at 81% of the subject's individual *pre-study daily Duodopa dose*, will be delivered over a 16-h period and administered as a continuous fixed infusion rate preceded by a morning bolus dose. The i.v. morning bolus is 110% of the hourly continuous dose delivered at the rate of 60 ml/h (mixed volume rate Infudopa Active + Infudopa Buffer IntraV). The morning dose will not exceed 24 mL, corresponding to 240 mg levodopa. The maximum daily dose levodopa during i.v. administration is not allowed to exceed 3240mg (equal to 81% of the maximum allowed daily dosage for Duodopa that is 4000 mg). Detailed dosing limits for intravenously administered Infudopa Active are given in Table 5. Infudopa Buffer IntraV must always be delivered at equal infusion rate and to equal volumes as Infudopa Active.

Infudopa IntraV will be supplied in 2 different bottles for online mixing by 2 infusion pumps: A. Infudopa Active containing 20 mg/mL levodopa and 2.5 mg/mL carbidopa, and B. Infudopa Buffer IntraV with no active ingredients. After online mixing Infudopa will contain 10 mg/mL levodopa and 1.25 mg/mL carbidopa. SPACE Infusion Pump System (B. Braun Melsungen AB, Melsungen, Germany), or similar, will be used for the i.v. infusion, which will be given through an indwelling catheter placed in the arm.

Table 5. Dose Group 1, Infudopa i.v.

Group 1: Infudopa i.v.	**Infusion rate Infudopa Active (mL/h)***		**Volume Infudopa Active (mL)***		**Dose levodopa (mg)**	
	Min	**Max**	**Min**	**Max**	**Min**	**Max**
Morning bolus	30		1.6	10 (≤12)	32	200 (≤240)
Maintenance for up to16 h	1.4	8.1	23	135	460	2700
Total	-	-	24.6	145 (162)	492	2900 (3240)

*) The infusion rate and volume of the Infudopa Active and Infudopa Buffer IntraV mix are twice the values in the table. Levels in parenthesis should not be exceeded.

2. Infudopa SubC in 86% of the the subject's individual *pre-study daily Duodopa dose* will be delivered over a 16-h period and administered as a continuous fixed infusion rate preceded by a morning bolus dose. The s.c. morning bolus is 155% of the hourly continuous dose delivered at the rate of 80 ml/h (mixed volume rate Infudopa Active + Infudopa Buffer SubC). The morning dose will not exceed 30 mL, corresponding to 300 mg levodopa. The maximum daily dose levodopa during s.c. administration is not allowed to exceed 3440mg (equal to 86% of the maximum allowed daily dosage for Duodopa that is 4000 mg). Detailed dosing limits for subcutaneously administered Infudopa Active are given in Table 6. Infudopa Buffer SubC must always be delivered at equal infusion rate and to equal volumes as Infudopa Active.

Infudopa SubC will be supplied in 2 different bottles for online mixing by 2 infusion pumps as described under 1. above. After online mixing Infudopa will contain 10 mg/mL levodopa and 1.25 mg/mL carbidopa. The same SPACE Infusion Pump System as mentioned under 1. above will be used. Two suitable infusion needles (for example a Cleo 90^{TM} infusion needle, Smiths Medical,

Minnesota, USA) will be placed laterally on each side of the the abdomen for s.c. infusion of levodopa.

Table 6. Dose Group 2, Infudopa s.c.

Group 2: Infudopa s.c.	Infusion rate Infudopa Active (mL/h)*		Volume Infudopa Active (mL)*		Dose levodopa (mg)	
	Min	Max	Min	Max	Min	Max
Morning bolus	40		2.3	12.5 (≤15)	46	250 (≤300)
Maintenance (up to16 h)	1.5	8.6	22.5	135	450	2700
Total	-	-	24.8	147.5 (172)	496	2950 (3440)

*) The infusion rate and volume of the Infudopa Active and Infudopa Buffer SubC mix is twice the values in the table. Levels in parenthesis should not be exceeded.

3. The *pre-study daily Duodopa dose* (Duodopa; AbbVie/Abbott Laboratories, Abbott Park, Illinois, USA) will be delivered over a 16-h period and administered as a continuous fixed infusion rate preceded by a morning bolus dose. The morning bolus is 110% of the hourly continuous dose delivered at the rate of 40 ml/h. The morning dose will not exceed 15 mL, corresponding to 300 mg levodopa. The maximum daily dose levodopa is not allowed to exceed 4000mg. Detailed dosing limits for Duodopa are given in Table 7.

Duodopa will be supplied in cassettes containing 100 mL of gel (20 mg/mL levodopa and 5 mg/mL carbidopa monohydrate), and be administered with a portable infusion pump (CADD-Legacy® Duodopa, Smiths Medical, Minnesota, USA).

Table 7. Dose Group 3, Duodopa

Group 3: Duodopa	Speed Duodopa (mL/h)		Volume Duodopa (mL)		Dose levodopa (mg)	
	Min	Max	Min	Max	Min	Max
Morning bolus	40		2	10 (≤15)	40	200 (≤300)
Maintenance (up to16 h)	1.8	10	28	148	560	2960
Total	-	-	30	158 (200)	600	3160 (4000)

Levels in parenthesis should not be exceeded.

5.1.2. Dose adjustments during treatment and temporary interruptions of infusion

No extra LCIG infusion doses will be allowed (extra bolus doses are not possible to provide with the Infudopa pump system).

A movement disorder specialist will be present during the first 4 hours of treatment to clinically evaluate the efficacy of the given treatment and to adjust doses to avoid problematic under- or overtreatment. After the first 4 h the movement disorder specialist is available as needed for the

rest of the infusion period. If the subject experiences mild and easily endurable Off-symptoms or symptoms of overtreatment the infusion rate will not be changed. Non-levodopa containing medication such as benzodiazepines or paracetamol can be used as determined appropriate by the investigator. If a subject treated with Infudopa after the first hour of treatment is uncomfortably "OFF" by comparison to what he/she experiences with the regular treatment with Duodopa, the investigator can increase the infusion rate of Infudopa by 10-20%. Such increases may be repeated once in the following 2 h and on maximum two further occasions during the following treatment period. If the subject develops severe symptoms of overtreatment, such as uncomfortable dyskinesia, disturbing nausea, symptomatic hypotension or hallucinations, the infusion will be stopped for 10 minutes, reduced to minimum flow 1.4 mL/h for 20 minutes and then resumed at an infusion rate 20% lower than the preceding. The decision to stop infusion can be taken by the investigator or a study nurse who must immediately contact the investigator for further advice. A temporary stop of infusion may be repeated every second hour until symptoms are manageable or uncomfortable hypokinesia develops. All changes in infusion rates will be recorded.

The subcutaneous maintenance infusion rate (maximum ca 17 mL/h mixed solution) is much lower than what is safely used for subcutaneous fluid hydration (60-70 mL/h). During the morning bolus a higher infusion rate (80 mL/h) will be used for up to 25 minutes (maximum 30 minutes). To avoid discomfort, the administration will be split to two subcutaneous infusion sites at each side of the abdomen. If despite this there is subject-reported subcutaneous oedema or pain in the infusion area, the infusion can be moved to another infusion site on the abdomen. If pain develops also at this site, the infusion must stop and the investigator must be contacted immediately. The infusion must also be stopped immediately if the subject develops signs of an allergic reaction in the infusion area (rapid development of itching or urticarial efflorescence) or in other parts of the body, in particular face and airways. Infusion must be stopped immediately at the occurrence of severe systemic events including but not restricted to: respiratory distress, chest pain, abdominal pain or impaired consciousness. The decision to interrupt infusion in the above cases can be made by a study nurse who will immediately contact a study physician and/or the investigator.

Oral levodopa–carbidopa or levodopa-benserazide will not be allowed until the last pharmacokinetic sample has been collected. If rescue medication is needed after the cessation of infusion, other non-levodopa and non-carbidopa medication will be used, for example benzodiazepines. If oral levodopa or carbidopa medication despite this is required prior to the last pharmacokinetic sample, a final blood sample will be taken prior to administration of oral drug.

Those subjects who receive infusion for more than 16 h/day prior to study start will have their pumps turned off after 16 h of infusion.

5.1.3. Return to previous treatment

After collection of the last pharmacokinetic sample, subjects will resume their original levodopa–carbidopa regimens (i.e. Duodopa treatment). If the treatment must be interrupted due to adverse events during the infusion period the subject will revert to his/her previous continuous treatment with Duodopa within approximately one hour or as judged appropriate by the investigator.

5.1.4. Dosing groups

Subjects will for practical reasons be admitted to the phase I unit in Gothenburg for the treatment visits in groups of up to three subjects. When more than one subject is treated at the same

occasion, dosing will for safety reasons be initiated with approximately 10-30 minutes in between each subject.

5.1.5. Labelling

Infudopa Active and Infudopa Buffer IntraV will be packed and labelled at Recipharm, Infudopa Buffer SubC will be packed and labelled at Unimedic, and Duodopa will be packed and labelled at Tamro, according to current EU Good Manufacturing Practice (GMP) guidelines for pharmaceuticals.

Each infusion vial/cassette will be labelled with study code, dosage form, strength, quantity, dosage instructions, name of investigator, expiry date, storage instruction, “for clinical study use only”, address and telephone number to sponsor/investigator.

5.1.6. Storage and handling

All study medication should be kept separately from other medications at the study site, and in a secure place under appropriate storage conditions as specified on the pack label and handled according to the manufacturer’s instructions. Expiry dates for investigational products are according to label.

The study medication should be stored in a fridge (2°C–8°C). The temperature of the fridge will be monitored each week and recorded in a temperature log.
It is the investigator’s responsibility to establish a system for handling the study drugs to ensure that it is correctly received and recorded and only dispensed to subjects in accordance with this protocol and manufacturer instruction.

5.1.7. Drug accountability and treatment compliance

The medication provided for this study is for use only as directed in the protocol. All unused drugs will be accounted for and destroyed appropriately by study site personnel. The study personnel will account for all drugs dispensed. At the end of the trial, it must be possible to reconcile delivery records with records of usage and returned stocks.

5.1.8. Medical device equipment

Two infusion pumps, each having a 50 to 60 mL syringe (Figure 2) have UV-protected polyethylene (PE) infusion lining to a mixing connector (a Y-connector). After the Y-connector there is a single UV-protected infusion line (approx. length 150 cm) ending in a fine pore filter (Figure 3). An exit line after the filter is connected to a cannula, suitable for s.c. or i.v. administration. Both pumps are driven with the same speed and are started at the same time. The system is always primed with the solutions by starting with a high speed (40 mL/h) until a small aliquot comes out from the cannula (this priming can be automatically set).

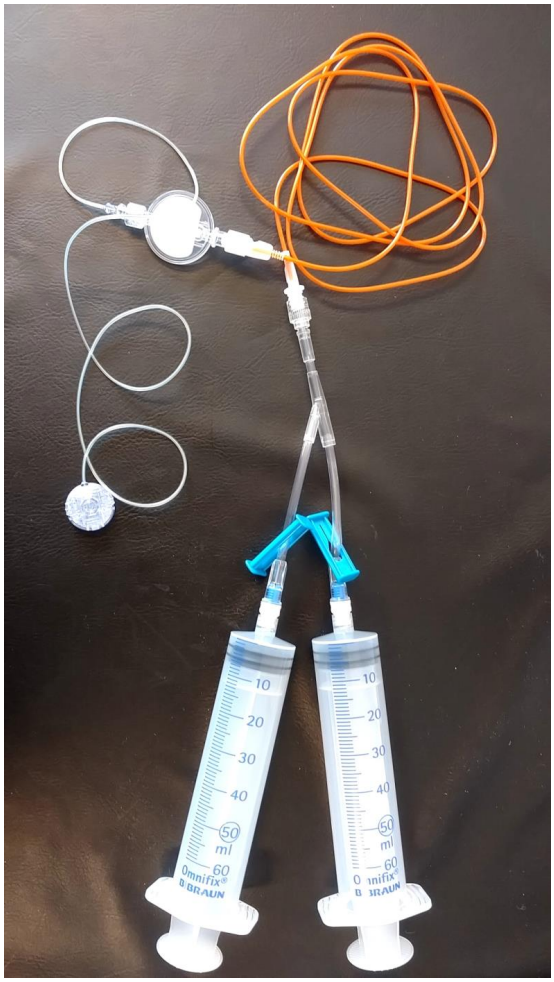
The system has been extensively tested in laboratory experiments by following the levels of levodopa and carbidopa including a breakdown product of carbidopa (DHPA) and physical stability measures. The results show that Infudopa fulfils demands of a pharmaceutical product, also during in-use conditions. Infudopa is protected worldwide by approved patents and patent applications.

Figure 2, A and B

A: The syringe filled with (1): Infudopa Active or (2) Infudopa Buffer IntraV (i.v. administration) or Infudopa Buffer SubC (s.c. administration)

B: Two loaded syringes are started with the same speed, at the same time. See how infusion line set is connected in Figure 3.

Figure 3. Set-up of the syringes, Y-connector, long UV-protected infusion line (to reach from Y-connector to bed/chair), 0.2 µM sterile filter (white colour), which then is connected to another type of Y-connector with two short infusion lines with two cannulas for s.c. (only one shown here) or i.v. injection to the subject. The two B Braun Infusomat Space syringe pumps (not shown) drive the two syringes at the same speed.



5.1.8.1. Specification of equipment

All medical device equipment is CE-marked.

The following medical device equipment will be used in the study:

- B Braun Mini-Spike Green filter, ref 4550242,
- 50 mL syringe B Braun Omnifix Luer Lock Solo, ref 4617509F,
- Carefusion SmartSite Extension Set (Y-connector), ref 20061E7D
- B Braun Original Perfusor Line 150 cm (UV-protect), ref 8723017,
- B Braun Sterifix 0.2 µm filter, ref 4099354, (at s.c. administration can also B Braun Intrapur 1.2 µm filter, ref 4099850, be used),
- BD Venflon 20G 1.0 x 32 mm catheter, ref 391452 with suitable extension line, for i.v administration or Infucare Cleo 90 needle, ref 2021-08, for s.c. administration
- Infucare Y-set (ref. 210580) with 3 Luer Lock connections for 2 Infucare Cleo 90 needles

Other CE-marked medical device equipment distal to the filter may be used and should in these cases be noted in the eCRF.

5.1.8.2. Setting up the administration system and selecting dosage rates on pumps

A detailed instruction in Swedish is available for connection the different parts of the system, priming the system, and setting pump rates (see Appendix A).

5.2. Concomitant medication

Medications that are considered necessary for the subject's safety and well-being may be given at the discretion of the investigators unless not specified in the exclusion criteria. Concomitant medication will be recorded in the eCRF. Regarding administration of Duodopa, refer to the Summary of Product Characteristics (Investigator´s Brochure, section 10 Appendix - reference safety information (RSI)). Drugs given during study specific Duodopa abstinence and listed in the protocol for that purpose do not have to be entered as concomitant medication, but each administration is recorded in the eCRF.

6. STUDY MEASUREMENTS AND VARIABLES

6.1. Primary variable(s)

The steady-state plasma concentration of levodopa, the area under plasma concentration versus time curve (AUC), and the coefficient of variation (COV) for plasma concentrations during the dosage interval in the subjects are the primary efficacy variables of the study. Also refer to Table 8.

6.2. Secondary variable(s)

Adverse events and vital signs documentation, local tolerability scores at the injection site, and laboratory assessments will be secondary variables to evaluate the safety of the study medication with special aim on the local tolerability at the injection sites of i.v. and s.c. administration.

Bioavailability based on the area under plasma concentration versus time curve (AUC) will establish the bioavailability of levodopa and carbidopa given s.c. and as Duodopa compared to the i.v. administration.

The third secondary objective of the study is to compare the efficacy and other pharmacokinetics during a treatment day of s.c. and i.v. Infudopa versus Duodopa, and supporting variables will be video recordings, PKG, and other pharmacokinetic variables, including the peak to trough fluctuation (PTF), than those mentioned as primary variables (refer to section 8.3 for the pharmacokinetic variables).

Evaluation of video recordings will include the secondary efficacy variables percentage of ratings within the interval -1 to +1, that is, a clinically desirable, functional "on" state accepting mild parkinsonism or mild dyskinesia, and percentage of ratings within the intervals -3 to -2 (severe to moderate "off") and +2 to +3 ("on" with moderate to severe dyskinesia). In everyday practice, most subjects prefer being dyskinetic before being "off." However, severe choreatic dyskinesia may be incapacitating and painful. Therefore, a secondary analysis of the interval -1 to +2, including moderate dyskinesia, will also be used.

The PKG measures median BK, median DK, FDS and percent time with tremor (PTT) will be evaluated for both normal active daytime (9-18, which is the most commonly reported measure) and for the full treatment time except the first hour.

6.3. Biological sampling procedures

6.3.1. Handling, storage and destruction of biological samples

Blood samples will be saved in an IVO registered biobank at Sahlgrenska University Hospital (number 890) according to the biobank act (Biobankslagen SFS 2002:297). All samples will be coded/pseudonymized. Samples will be saved for twenty years and will be used to address the study questions. Subjects will be informed that they can leave the study without any explanation at any time and that they can request that the samples should be destroyed or become anonymized. The samples may become analysed outside EU/EES. Only study responsible persons will have access to collected samples. Disclosure of samples for purposes not described in the project can be done only with the permission of the affected ethics committee.

6.3.2. Total volume of blood per subject

The total volume of blood taken from each subject during the study is maximum 450 mL.

7. SAFETY

7.1. Definitions

7.1.1. Adverse event (AE)

An Adverse Event is any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. The terms “infusion site reaction” and “catheter site reaction” are used as predefined skin AE when there is a possible or most likely relation to the locally infused drug or the implanted catheter. More specific terms (like “infusion site pain” or “infusion site erythema”) can be used when such symptoms occur in isolation, whereas “reaction” is the preferred description of combinations of symptoms which follow a similar time course.

Causality

The investigator is responsible for determining whether there is a causal relationship between an AE and the use of a medicinal product.
All AEs are categorized either as unrelated, possibly related or related, as defined below:

- **Unrelated**: the AE is not reasonable in relation to the use of the medicinal product, or another cause can itself explain the occurrence of the event.
- **Possibly related**: the AE may be explained by the medicinal product and the onset is reasonable in relation to the use of the medicinal product, however there is insufficient information to determine the likelihood of this possibility.

- **Related**: the AE is most likely explained by the medicinal product and the onset is reasonable in relation to the use of the medicinal product.

Severity
In addition to assessing the relationship of the administration of the investigational product(s) to adverse events, an assessment is required of the intensity (severity) of the event. The following over-all classifications should be used:

- **Mild:** An adverse event which is relatively mild and transient in nature, but can be an annoyance, and does not interfere with normal activities.
- **Moderate:** An adverse event which may be uncomfortable but is not hazardous to health. It may be sufficiently discomforting to interfere with normal activities but does not completely prevent them.
- **Severe:** An adverse event which is incapacitating and/or it is a hazard to the subject.

7.1.2. Adverse drug reaction (ADR)

An ADR is a noxious and unintended response to a medicinal product related to any dose administrated. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
The definition covers also medication errors and uses outside what is foreseen in the protocol, including overdose, misuse and abuse of the product.

7.1.3. Serious adverse event (SAE)

Any untoward medical occurrence or effect that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether an event is 'serious' and if expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events should also usually be considered SAEs.

7.1.4. Suspected unexpected serious adverse reaction (SUSAR)

A SUSAR is a serious adverse reaction of which nature or severity is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product)

7.2. Reporting

7.2.1. Adverse event

All AEs occurring during the trial that are observed by the Investigator or reported by the subject, will be recorded by the study personnel on the eCRF, whether or not attributed to trial medication. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication and action taken. Follow-up information should be provided as necessary.

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

7.2.2. Adverse drug reaction

AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

7.2.3. Serious adverse event

All SAEs irrespective of relationship to study treatment (other than those defined in the protocol as not requiring reporting) must be reported on the SAE Reporting Form. The completed SAE Report Form should be sent via e-mail, within 24 hours from the Investigator's knowledge of the event, to the Safety Monitor at Pharm Assist Sweden AB, pharmacovigilance@pharmassist.se.

Deaths and **Life-threatening SAEs** should be **immediately reported** to pharmacovigilance@pharmassist.se.
If a verification of receipt has not been received within one working day, the SAE Report Form should be sent again.

Any SAE occurring after study completion and that is assessed by the Investigator as related to study treatment, should be reported to the Sponsor regardless of the length of time that has passed since study completion.

The SAE Report Form should be filled out as completely as possible at the time of the initial report. As a minimum, the initial SAE Report Form should contain the following information:

- Subject identification (subject identification code)
- Study identification
- Treatment specification
- Diagnosis or symptoms
- Time specification for the SAE
- Causality assessment
- Reporter identification

Any follow-up information received on SAEs should be forwarded within 1 (one) business day of its receipt. If the follow-up information changes the Investigator's assessment of causality, this should also be noted on the follow-up SAE Report Form.

Evaluation of relationship between the treatment and the SAE is to be made both by the Investigator and by the Sponsors's Medical Expert. If any of the parties decides that the SAE is related to the study product, the reaction is defined as a SUSAR and must be reported to the EudraVigilance database by Safety Monitor at Pharm Assist.

7.2.4. Suspected unexpected serious adverse reaction

All SUSARs will be reported by Safety Monitor at Pharm Assist to the relevant Competent Authority and to EudraVigilance data base as applicable. For fatal and life-threatening SUSARs, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

7.2.5. Annual safety report

A safety report will be completed by Safety Monitor at Pharm Assist once a year and sent to the relevant Competent Authority and the Ethics Committee. The document will define the time period reported and summarize all occurred serious medical events (SAEs). The safety report should also always include a summary assessment of the safety of subjects that are still included in the trial and whether the benefit-risk assessment changed since the study was approved.

The Safety Monitor will establish and maintain a safety database, covering all SAEs in the study.

7.3. Procedures in case of pregnancy

Females of child-bearing potential are not allowed to be included in this study unless they use highly effective contraceptive measures. Contraceptive measures must be maintained during treatment and during the first menstrual cycle after relevant systemic exposure, which for the sake of this study is defined as the first 24h after cessation of treatment with Infudopa. The following contraceptive methods are considered highly effective: combined estrogen-progesterone hormonal contraceptives (oral, vaginal or transdermal), progesterone only hormonal contraceptives (oral, injected or implanted), intrauterine device with or without hormone releasing properties, bilateral tubal occlusion, vasectomized partner or sexual abstinence. Male subjects must refrain from fathering a child, including sperm donation, during the study and 3 months following the last dose. If the Investigator receives information that a pregnancy has occurred during the study (including pregnancy in the partner of a male subject) despite these restrictions, Safety Monitor at Pharm Assist should be informed and a specific Pregnancy Report Form completed.

7.3.1. Maternal exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs Safety Monitor at Pharm Assist within 1 day ie, immediately but no later than 24 hours when he or she becomes aware of it.
The same timelines apply when outcome information is available.

7.3.2. Paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose. If a subject's partner becomes pregnant during the course of the study, investigational product should be discontinued immediately.
Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be followed up and documented. To capture information about a pregnancy from the partner of a male subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome; the male subject should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 3 months after the last dose should be followed up and documented.
If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs Safety Monitor at Pharm Assist within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.
The same timelines apply when outcome information is available.

8. STATISTICS

8.1. Sample size calculation

Sample size determinations are based on the primary pharmacokinetic variable from a similar study (Nyholm et al, 2013) regarding 16-hour intestinal infusion of Dudopa in advanced Parkinson's disease patients. Data from the 5 interim analysis patients are also used. A standard t-test model with continuity correction has been used (Microsoft Excel program, Pharm Assist Sweden AB). Z-alpha level was 1.96 and Z-beta level was 0.84 for equivalence testing of 90% CI of 0.80 to 1.25, and Z-alpha level was 1.65 and Z-beta level was 0.84 for non-inferiority testing of 90% CI of 0.80 to 1.25.

The test suggests that 14 subjects are appropriate for the test of dose-normalized AUC 0 to infinity of levodopa. This number of subjects is valid both based on the Nyholm et al. 2013 data for LCIG (COV 24.5%), and the data in the interim study (COV 17.0% allowing as a safety margin for a 40% higher COV, 23.8%, giving n=14).

For the non-inferiority test of intersubject coefficient of variation (COV) the sample size estimation suggests 18 subjects to be included.

Based both on the levodopa dose-adjusted AUC 0 to infinity and the intersubject COV it is planned that 22 subjects will be recruited to the study, also allowing for 4 drop-outs.

8.2. Statistical analysis

Statistical assessments of dosage normalized levodopa $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}16}$, $AUC_{0\text{-}2}$, $AUC_{2\text{-}16}$, and $AUC_{8\text{-}16}$ by analysis of variance (ANOVA) will be made on the logarithmic values, with back-transformation to nominal values of point estimates and confidence interval (CI). These variables will also be tested with dosage un-normalized values. The terms to be used in the ANOVA model will be sequence, patient within sequence, period, and formulation (i.v. or s.c. Infudopa and Duodopa; test and reference, respectively).

The statistical method for testing relative dosage normalized levodopa bioavailability will be based on the 90% CI for the ratio of the population means (test/reference). These statistical tests will also be done with dosage un-normalized values. The acceptance range for AUC ratio of the 90% CI for levodopa will be 0.80 to 1.25. These tests will be performed for Treatment 1 (i.v.) and Treatment 2 (s.c.) vs. Treatment 3 (Duodopa; reference) comparison, and for Treatment 1 (i.v. reference) vs. Treatment 2 (s.c.).

For each individual will be calculated the COV (coefficient of variation or % standard deviation; SD) for plasma concentration between 2 and 16 h by dividing the SD for each individual curve with the mean value of plasma concentration between 2 and 16 h. The mean value of plasma concentration will be calculated for each curve as $AUC_{2\text{-}16}/14$. Basic statistics for the COV will then be calculated per treatment group. The one-sided 90% CI of the intersubject COV will be calculated for Treatment 1 (i.v.) and Treatment 2 (s.c.) vs. Treatment 3 (Duodopa; reference) comparison, and for Treatment 1 (i.v. reference) vs. Treatment 2 (s.c.). It will also be tested with paired t-tests if there are significant differences in intersubject COV between treatments (i.v. vs. Duodopa, s.c. vs. i.v., and s.c. vs. Duodopa).

The level of significance will be p=0.05.

Safety will be summarized with the standard set of AE summary tables, and descriptive summary statistics of vital signs by visit and change from baseline.

The local tolerability will be documented with photographs, which will be evaluated by a dermatologist. Pre-defined local tolerability AEs will be documented by the investigator, and tenderness and pruritus with VAS by the subjects. Local tolerability will be presented with descriptive summary statistics of these variables by visit and change from baseline.

8.3. Pharmacokinetic analysis

The population for PK analysis will be all subjects with analysable PK parameters for at least 2 treatment visits during Day 1 and 2. Levodopa and carbidopaplasma profiles over time and PK parameter values will be summarized by regimen with descriptive statistics and graphically for Day 1 and 2.

The major pharmacokinetic variables, that will be calculated for levodopa (LD), carbidopa (CD), and 3-OMD are found in Table 8 below.

Table 8. Pharmacokinetic variables estimated during Day 1 to 2

Parameter	Description/derivation	Substance
C_{max}	The maximum observed concentration; obtained directly from the plasma concentration vs. time data	LD, CD, 3-OMD
t_{max}	The time of the maximum observed plasma concentration.	LD, CD, 3-OMD
C_{min}	The minimum (or trough) plasma concentration during the 2-16 h dosing interval, directly obtained from the experimental data of plasma concentration versus time, without interpolation	LD, CD, 3-OMD
AUC_{0-16}	The area under the plasma concentration versus time curve, calculated from time 0 to 16 hours, computed using the log-linear trapezoidal rule (method of the lin-up log down trapezoidal rule).	LD, CD, 3-OMD
AUC_{2-16}	The area under the plasma concentration versus time curve, calculated from time 2 to 16 hours, computed using the log-linear trapezoidal rule (method of the lin-up log down trapezoidal rule).	LD, CD
AUC_{0-2}	The area under the plasma concentration versus time curve, calculated from time 0 to 2 hours, computed using the log-linear trapezoidal rule (method of the lin-up log down trapezoidal rule). This represents the time period during the dosage interval when early onset of plasma concentrations are most representative.	LD, CD
AUC_{8-16}	The area under the plasma concentration versus time curve, calculated from time 8 to 16 hours, computed using the log-linear trapezoidal rule (method of the lin-up log down trapezoidal rule). This represents the time period during the dosage interval when apparent steady-state conditions of plasma concentration will be reached.	LD, CD
C_{last}	Last determinable plasma concentration	LD, CD, 3-OMD
AUC_{0-last}	The area under the plasma concentration versus time curve, calculated from time 0 to the last quantifiable plasma concentration (C_{last}), computed using the log-linear trapezoidal rule (method of the lin-up log down trapezoidal rule).	LD, CD, 3-OMD
$t_{½}$	Elimination half-life determined from the terminal slope of the log-linear curve	LD, CD
AUC_{0-inf}	The area under the plasma concentration versus time curve, calculated from time 0 to infinity, computed using the log-linear trapezoidal rule (method of the lin-up log down trapezoidal rule) including the rest AUC from the last quantifiable sampling point up to infinity (calculated using C_{last} and the elimination slope).	LD, CD
C_{av}	The average plasma concentration at the steady-state = $AUC_{8-16}/8$	LD, CD
PTF	The peak-trough fluctuation = $(C_{max}-C_{min})*14/AUC_{2-16}$	LD, CD

PK variables will be calculated based on the actual sampling times rather than the scheduled sampling times.

If there is a baseline plasma concentration of levodopa and carbidopa that is >LLOQ this concentration value will be subtracted from the actual plasma concentration value at baseline, and subsequent concentration values assuming an elimination of the substances that is in accordance with the subject's own elimination rate (calculated from 16 h and up). This will be made until the so calculated subtraction value is insignificant (i.e. < LLOQ). No such baseline correction will be made for 3-OMD.

Bioavailability will be calculated in the cross-over design on dosage normalized levodopa and carbidopa $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}16}$, $AUC_{0\text{-}2}$, and $AUC_{8\text{-}16}$ for test versus reference by using the logarithmic values, with back-transformation to nominal values of point estimates (cf. Section 8.2).

8.4. Interim analysis

There has been an interim analysis of first 5 subjects in the study (Clinical Study Interim Report 2019-01-15). There will be a new interim analysis of PK and safety data after 4 completed subjects after the study has re-started. The number of 4 subjects for the interim analysis is because it will allow for reasonably adequate mean values of numerical variables and frequencies of distribution of binominal variables, including reasonable estimates of confidence intervals. The following data will be included in the interim analysis (see Table 1 and 2):

- Blood PK samples
- Inspection of local dermal area/scoring incl. photos
- Adverse events

A Board of the Interim Study Analysis will meet to discuss the results and conclude if the study should continue or not.

The possible outcomes the Board will evaluate, and the basis for the decisions are:

1. Are the plasma levels of LD following s.c. and i.v. too high or too low as compared to Duodopa at any time during the treatment, so a dosage adjustment is necessary?
Decision rules:
- If the deviation from Duodopa is of a magnitude that is deemed clinically important, appropriate changes in the dosing protocol in the study will be considered.
- If the deviation from Duodopa at steady-state is larger than established limits for bioequivalence (80% - 125%), the appropriate changes in the dosing protocol will be made.

2. Is the local and systemic tolerance acceptable?
Decision rule:
If adverse events have occurred which, according to the committee, can be attributed to the study drug and make it ethically unjustifiable to pursue the trial, the trial will be stopped. However, the trial can continue after the appropriate changes have been made if it can be convincingly demonstrated that changes in the protocol, e.g. a change of infusion rate, infusion system, an increase in the number of subcutaneous infusion sites or other feasible actions, will mitigate the risk for further adverse events.

In case the dosage regimen is changed, or other major change is made to the Clinical Study Protocol (CSP) an amendment must be submitted to MPA and EC.

Only descriptive summary statistics will be performed. There will be no statistical hypothesis testing.

The members of the Board of the Interim Study Analysis are presented in Appendix C.

9. DATA MANAGEMENT

9.1. Recording of data

The investigator will ensure that all data collected in the study are recorded in a timely manner according to any instructions provided.

An electronic CRF will be used for data collection. The investigator will ensure that the data are recorded in the CRF as specified in the study protocol and in accordance with the instructions provided. The investigator ensures the accuracy, completeness and timeliness of the data recorded. The investigator will sign the completed CRF. A copy of the completed CRF will be archived at the study site.

9.1.1. Source data

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information in the eCRF must be traceable to these source documents in the subject's file. The investigator must ensure that all source documents are accessible for monitoring. Data not requiring a written or electronic record will be defined before study start and will be recorded directly into the eCRFs, which will be documented as being the source data. In this study, inclusion and exclusion criteria has been identified as data where the eCRF may be the source. The investigator must also keep a copy of the signed informed consent form.

9.2. Data storage and management

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification. All raw data, a copy of the completed CRF, original protocol with amendments and the final report will be stored for a minimum period of ten years after termination of the trial, in accordance with Swedish regulation/law (Chapter 10, 3 § in LVFS 2011:19).

A Study Monitor will review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are issued electronically. Designated investigator site staff is required to respond to the query and confirm or correct the data.

At the conclusion of the study, the occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and available for data analysis.

9.3. Study timetable and end of study

The end of the study is defined as "the last Visit of the last subject undergoing the study."
The study started in 2nd Quarter 2018 and 5 interim patients were completed in the same Quarter.
The study will re-start in 2nd Quarter of 2019 and to end by 4th Quarter 2019.
The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. The Sponsor may also terminate the entire study prematurely if concerns for safety arise.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Monitoring

A study monitor will be appointed by the Sponsor. The monitor will be appropriately trained and informed about the nature of the study, subject written information, GCP and applicable regulatory requirements. The monitor's qualifications will be documented.

The monitor will have regular contacts with the clinic to verify informed consents of participating subjects, to confirm that facilities remain acceptable, that the investigational team is adhering to the protocol, and that data are being accurately recorded in the CRFs and that therapy accountability is being carried out. The monitor will also ensure source data verification (comparison of the data in the CRF with the medical records and other source data). The extent and practical arrangements of monitoring will be defined in a monitoring plan.

10.2. Audits and inspections

Authorized representatives of the sponsor, a regulatory authority or an Ethics Committee may perform audits or inspection at the centre, including source data verification. The investigator must ensure that all source documents are accessible for auditing and inspection. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed and accurately reported according to the protocol, GCP and any applicable regulatory requirements.

11. ETHICS

The study will be performed in accordance with the protocol, with the latest version of the Declaration of Helsinki, with Good Clinical Practice (ICH-GCP E6(R1) and applicable regulatory requirements.

11.1. Ethics committee

The final study protocol, including the final version of the Informed Consent Form and other information given to subjects e.g. advertisements, must be approved or given a favourable opinion in writing by an Ethics Committee (EC) as appropriate. The Principal Investigator is responsible for informing the EC of any amendment to the protocol, in accordance with local requirements. Progress reports and notifications of any serious and unexpected adverse drug reactions will be provided to the EC according to local regulations and guidelines.

11.2. Informed consent

The Principal Investigator at each centre will ensure that the subject is given full and adequate oral and written information about the nature, purpose and possible risks and benefits of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The original, signed Informed Consent Form (ICF) must be stored in the Investigator's Study File (ISF). A copy of the signed ICF must be given to the subject.

If a protocol amendment requires a change to the ICF, the EC must approve modifications that lead to a revised ICF before the revised form is used.

11.3. Subject data protection

The Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorize the collection, use and disclosure of their study data by the investigator and by those persons who need that information for the purposes of the study.
The Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by the Sponsor will be identified by *Subject ID*.
The Informed Consent Form will also explain that for data verification purposes, authorized representatives of the sponsor, a regulatory authority or an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

11.4. Insurances

The study subjects are covered by the Swedish Patient Injury Act and the Pharmaceutical Insurance (http://lff.se/).

12. PROTOCOL DEVIATIONS AND AMENDMENTS

Modifications to the signed protocol are only possible through approved protocol amendments and with the agreement of all responsible persons. Details of non-substantial amendments are to be clearly noted in the amended protocol. In case of a substantial protocol amendment, the concerned Ethics Committee and Competent Authority must be informed and should be asked for its opinion/approval prior implementation of amended protocol, as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The Investigator must not implement any deviation from, or change to the protocol, without discussion with, and agreement by the Sponsor and prior review and documented approval/favourable opinion of the amendment from the relevant ethics committee and competent authority, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study (e.g. change in monitor(s), change of telephone numbers).

13. REPORT AND PUBLICATIONS

After completion of the study, the results will be analysed and a clinical study report will be prepared and submitted to the regulatory authorities. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

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APPENDIX A. INFUSION PUMP SYSTEM

Beskrivning av pumpsystemets uppkoppling

2017-11-10, rev. 2019-02-05
Pharm Assist Sweden AB
Mats Ehrnebo

1. Plocka fram:
   - två B Braun Mini-Spike Green filter, ref 4550242,
   - två 50 ml sprutor B Braun Omnifix Luer Lock Solo, ref 4617509F,
   - en Carefusion SmartSite Extension Set (Y-koppling), ref 20061E7D
   - en B Braun Original Perfusor Line slang 150 cm (UV-protect), ref 8723017,
   - ett B Braun Sterifix 0.2 µm filter, ref 4099354, (vid s.c. administrering kan även B Braun Intrapur 1.2 µm filter, ref 4099850, användas),
   - en BD Venflo 20G, ref 391452, med lämplig förlängning till filtret för i.v administrering eller två Infucare Cleo 90 kanyl, ref 2021-08, för s.c. administrering,
   - Om s.c. administrering, en Infucare Y-koppling, ref. 210580, som i ena änden kopplas till B. Braun Steritix filtret och i andra änden till de två Infucare Cleo 90 kanylerna
   - Vid **i.v.** administrering: en **Infudopa Buffer IntraV** (50 ml) och en **Infudopa Active** (50 ml). Dessa ska **nå rumstemperatur.**
   - Vid **s.c.** administrering: en **Infudopa BufferSubC** (50 ml) och en **Infudopa Active** (50 ml). Dessa ska **nå rumstemperatur.**

   Bilder på dessa komponenter finns sist i dokumentet.

2. Fyllning av spruta med **Infudopa Buffer IntraV** (50 ml) alternativt **Infudopa Buffer SubC** (50 ml):
   - Avlägsna cappen som försluter glasvialen på 50 ml (vit flip-off).
   - Öppna ytterförpackningen som sprutan ligger i.
   - Tryck ner sprutkolven i botten på sprutan, så att all luft är tömd.
   - Montera en Mini-Spike på sprutan, tag av det gröna skyddshöljet.
   - Penetrera gummiproppen på vialen 50 ml med spetsen på Mini-Spiken. Vänd vialen och sprutan upp och ned och sug upp all produkt i sprutan.
   - Tag av Mini-Spiken när all produkt har sugits upp med sprutan.
   - Avlägsna eventuella luftbubblor i sprutan genom att knacka försiktigt på sprutan så att luftbubblorna hamnar vid mynningen på sprutan. Tryck ut luften.

3. Montering av **Infudopa Buffer** (50 ml) alternativt **Infudopa Buffer SubC-sprutan** på **Y-kopplingen**:

- Öppna ytterförpackningen som Y-kopplingen ligger i. Montera den ena porten på Y-kopplingen till den fyllda Infudopa Buffer SubC-sprutan. Detta görs genom att sprutans spets sticks in i den blå gummidelen på Y-kopplingen och vrids tills den sitter fast.

4. Montering av **Infudopa Buffer** IntrV (50 ml) alternativt **Infudopa Buffer SubC-sprutan i pumpen**:
    - Öppna luckan till den ena pumpen genom att böja denna framåt.
    - Drag ut det beigea handtaget rakt ut och vrid det sedan ett kvarts varv medsols. Handtaget låses i detta läge. Släpp handtaget.
    - Nu kan sprutan monteras i pumpen. Lägg sprutan på plats så att sprutans handtag är riktat uppåt, och ligger innanför den gröna delen på pumpens arm (se bild nedan).

    - För tillbaka handtaget på pumpen genom att dra detta utåt och vrida det ett kvarts varv motsols. Stäng luckan. Var noga med att slangen till Y-kopplingen inte kläms av luckan.
    - Displayen visar texten: ”*Välj spruta. B Braun OMNIFIX 50*”. Bekräfta genom att trycka på pilen till vänster.
    - Pumpen justeras nu och låses efter sprutan.
5. Fyllning av spruta med **Infudopa Active** (50 ml):
    - Avlägsna cappen som försluter glasvialen med Infudopa Active-lösning (vit flip-off).
    - Öppna ytterförpackningen som sprutan ligger i.
    - Tryck ner sprutkolven i botten på sprutan, så att all luft är tömd.
    - Montera en Mini-Spike på sprutan, tag av det gröna skyddshöljet.
    - Penetrera gummiproppen på vialen med spetsen på Mini-Spiken. Vänd vialen och sprutan upp och ned och sug upp all produkt i sprutan.
    - Tag av Mini-Spiken när all produkt har sugits upp med sprutan.

Avlägsna eventuella luftbubblor i sprutan genom att knacka försiktigt på sprutan så att luftbubblorna hamnar vid mynningen på sprutan. Tryck ut luften.

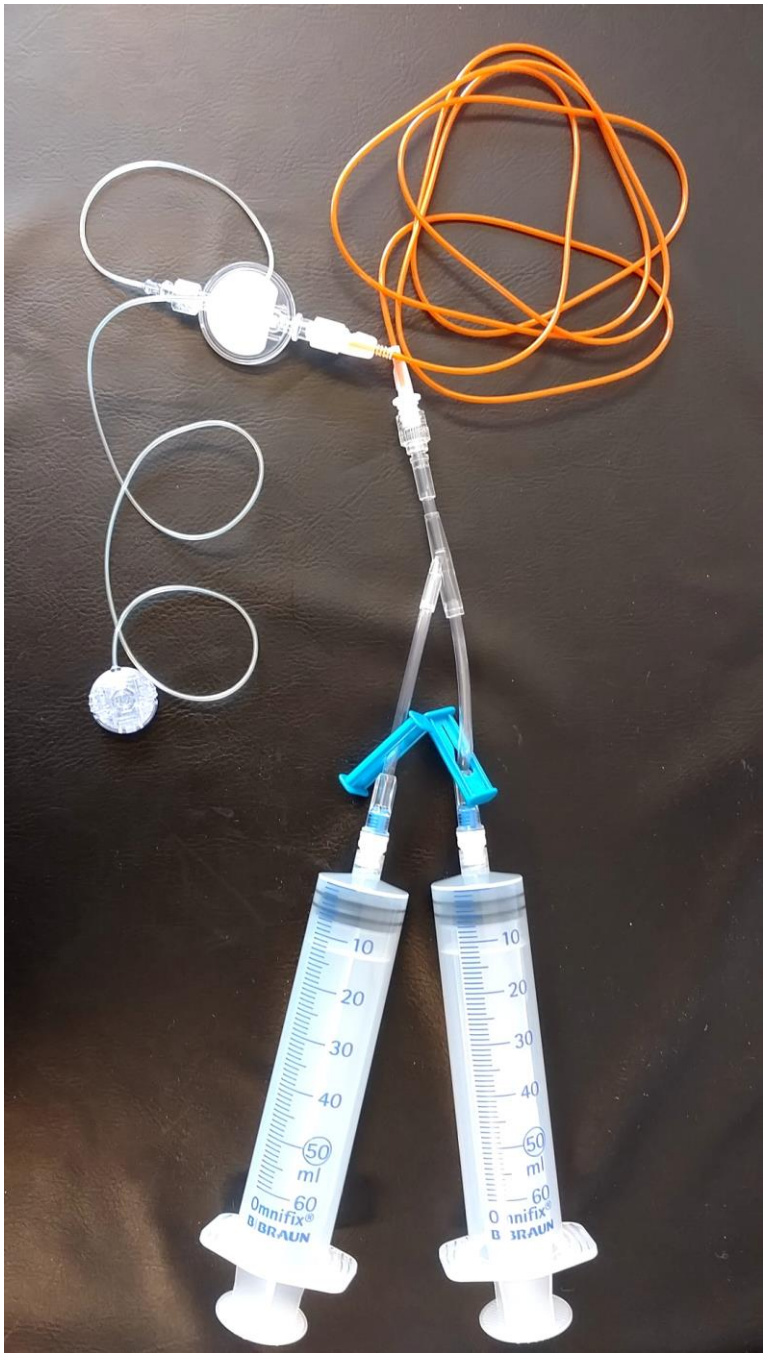
6. Montering av **Infudopa Active-sprutan** på **Y-kopplingen**:
    - Montera den lediga porten på Y-kopplingen till den fyllda Infudopa Active-sprutan. Detta görs genom att sprutans spets sticks in i den blå gummidelen på Y-kopplingen och vrids tills den sitter fast.
7. Montering av **Infudopa Active-sprutan** i pumpen (B Braun Infusomat Space Line):
    - Öppna luckan till den andra pumpen genom att böja denna framåt.
    - Drag ut det beigea handtaget rakt ut och vrid det sedan ett kvarts varv medsols. Handtaget låses i detta läge. Släpp handtaget.
    - Nu kan sprutan monteras i pumpen. Lägg sprutan på plats så att sprutans handtag är riktat uppåt, och ligger innanför den gröna delen på pumpens arm.
    - För tillbaka handtaget på pumpen genom att dra detta utåt och vrida det ett kvarts varv motsols. Stäng luckan. Var noga med att slangen till Y-kopplingen inte kläms av luckan.
    - Displayen visar texten: ”Välj spruta. B.Braun OMNIFIX 50”. Bekräfta genom att trycka på pilen till vänster.
    - Pumpen justeras nu och låses efter sprutan. Du har nu två kompletta pumpar monterade, se bild nedan:

8. Montering av infusionssystemet
    - Öppna ytterförpackningen till slangen. Tag bort de vita plasthylsorna på båda sidorna av slangen. Anslut slangen till Y-kopplingen genom att trycka in Y-kopplingens anslutningsport till slangens anslutningsport. Detta fungerar endast åt ett håll, slangen kan inte monteras åt fel håll.

- Öppna ytterförpackningen till filtret. Tag bort de vita plasthylsorna på båda sidorna om filtret. Anslut slangen till filtret genom att trycka in slangens anslutningsport till filtrets anslutningsport.

- Vid intravenös behandling ansluts den andra öppningen av filtret till den kopplingsslang som skall sitta mellan filter och perifer venkateter.
  Vid subkutan behandling ansluts den andra öppningen av filtret till den andra typen av Y-koppling för de två s.c. kanylerna. De två s.c. infusionskanylerna ansluts sedan till Y-kopplingen.

- Ordningen på infusionsystements komponenter skall vara:
  För i.v. SPRUTA – Y-KOPPLING – SLANG – FILTER – INFUSIONSSET.
  För s.c. SPRUTA – Y-KOPPLING – SLANG – FILTER – Y-KOPPLING – TVÅ INFUSIONSSET.
  Se bild nedan, som har ett s.c. infusionsset anslutet. Vid två s.c. kanyler sitter i stället en Y-koppling efter filtret:



9. Efter att sprutorna har monterats visar displayen rubriken ”*Huvudmeny*”. I denna är ”*Flöde*” markerat. Tryck på pilen åt vänster. Flödet ställs in med piltangenterna och bekräftas genom att trycka ”OK”. Gör detta får båda pumparna. Normalfallet är att de första 3 ml skall pumpas fram med flödeshastigheten 40 ml/h (tar 4,5 min). Båda pumparna skall då vara inställda på 40 ml/h.

10. Starta båda pumpsystemen samtidigt genom att trycka in Start/Stop. Displayen visar nu att pumparna är startade.

11. Kassera de första 0,5-1 ml som kommer ut från infusionsslangen.

12. Stoppa pumparna samtidigt genom att trycka på Start/Stop på båda pumparna samtidigt.

13. Ändra pumphastigheten på båda pumparna till önskad infusionshastighet enligt den individuella doseringsanvisning som finns i protokollet. Båda pumparna skall alltid gå med samma hastighet.

14. Anslut infusionsslang till fungerande perifer venkateter (kontrollerad genom spolning med fysiologisk koksaltlösning) eller tidigare placerad subkutan kateter.

15. Starta pumpen

16. Träna på att **snabbt göra momenten 2-9 ovan**, ex. med fys. koksaltlösning. Från moment 2 till att pumparna startas i moment 9 **bör det ta 3-5 min**, och **aldrig mer än 10 min**. Detta gäller även när man för en patient måste skifta till 2 nya sprutor med Infudopa Buffer IntraV alt. Infudopa Buffer SubC och Infudopa Active.

17. Avsluta infusionen **utan sprutbyte**:

    - Vid avslut av infusionen skall **båda pumparna stoppas samtidigt**. Det görs genom att trycka in Start/Stop.

    - Ta bort kanylen från patienten och följ separata råd kring deapplicering av subkutan och intravenös kateter.

    - Öppna luckan till den ena pumpen. Stäng den igen. På displayen visas ”*Sprutbyte*”. Bekräfta genom att trycka på pilen uppåt.

    - Sprutorna avlägsnas nu på samma sätt som de monterades: genom att dra ut det beigea handtaget och vrida det ett kvarts varv medsols. Nu är sprutan löskopplad och kan avlägsnas från pumpen.

    - Gör samma sak för båda pumparna.

    - Sprita av utrustningen.

18. Fortsätta infusionen **med sprutbyte**:

    - Förbered i god tid innan sprutbyte genom att plocka fram:
      - två B Braun Mini-Spike Green filter,
      - två 50 ml sprutor B.Braun Omnifix,
      - för i.v. en **Infudopa Buffer IntraV** (50 ml) alt. för s.c. **Infudopa Buffer SubC** (50 ml) och en **Infudopa Active** (50 ml). Dessa ska **nå rumstemperatur.**

    - Även vid detta temporära stopp av infusionen skall **båda pumparna stoppas samtidigt**. Det görs genom att trycka in Start/Stop.

    - Öppna luckan till den ena pumpen. Stäng den igen. På displayen visas ”*Sprutbyte*”. Bekräfta genom att trycka på pilen uppåt.

- Sprutorna avlägsnas nu på samma sätt som de monterades: genom att dra ut det beigea handtaget och vrida det ett kvarts varv medsols. Nu är sprutan löskopplad och kan avlägsnas från pumpen.
- Gör samma sak för båda pumparna.
- Följ punkt 2 ovan: ”Fyllning av spruta med **Infudopa Buffer IntraV** (50 ml) alternativt **Infudopa Buffer SubC** (50 ml)”, och punkt 3 ovan: ”Montering av **Infudopa Buffer IntraV-** (50 ml) alternativt **Infudopa Buffer SubC-sprutan** på **Y-kopplingen”**, efter att först ha avlägsnat gamla sprutan från Y-kopplingen. Det är viktigt att tillse att inga luftbubblor finns. Fortsätt med punkt 4 ovan: ”Montering av **Infudopa Buffer IntraV-** (50 ml) alternativt **Infudopa Buffer SubC-sprutan i pumpen**.
- Följ punkt 5 ovan: ”Fyllning av spruta med **Infudopa Active** (50 ml)”, och punkt 6 ovan: ”Montering av **Infudopa Active-sprutan** på **Y-kopplingen**”, efter att först ha avlägsnat gamla sprutan från Y-kopplingen. Det är viktigt att tillse att inga luftbubblor finns. Fortsätt med punkt 7 ovan: ”Montering av **Infudopa Active-sprutan** i pumpen”
- Efter att sprutorna har monterats visar displayen rubriken ”*Huvudmeny*”. I denna är ”*Flöde*” markerat. Tryck på pilen åt vänster. Flödet ställs in med piltangenterna och bekräftas genom att trycka ”OK”. I normalfallet ska man fortsätta med samma hastighet som innan byte av sprutor. Gör detta för båda pumparna.
- Starta båda pumpsystemen samtidigt genom att trycka in Start/Stop. Displayen visar nu att pumparna är startade.
- Avsluta infusionen: Följ punkt 16 ovan.

19. Byta infusionkateter:

- Om venkateter slutar fungera kopplas infusionsslangen bort men pumparna får fortsätta gå och lösningen slaskas. Anteckna i eCRF den volym som slaskas.
- Sätt ny perifer venkateter och kontrollera att den fungerar.
- Stanna pumparna och anslut infusionsslangen till fungerande kateter.
- Starta pumparna.
- Om byte av subkutan infusionsplats skall ske sätts först nya subkutana katetrar.
- Stanna pumparna och koppla genast över Y-kopplingen till de nya subkutana katetrarna.
- Starta pumparna.

Viktigt:

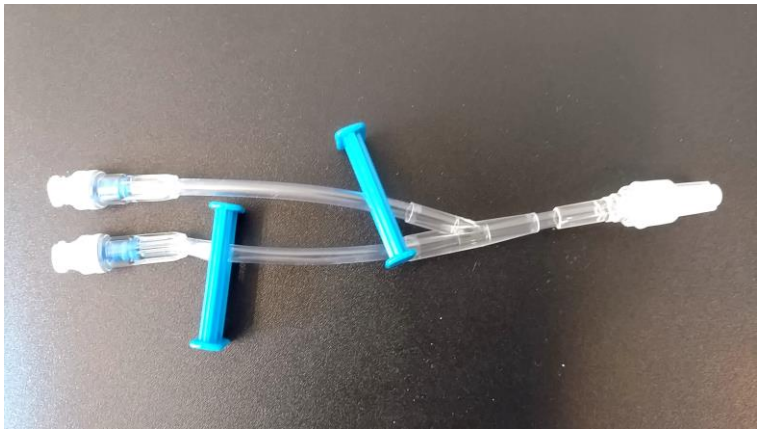
1. Om en pump stannar larmar den. Ansvarig personal ska då omgående stoppa även andra pumpen och inleda felsökning. Informera även patienten om vikten av att personal tillkallas om alarm ljuder från pumpen. Efter åtgärdande av fel startas pumparna samtidigt igen.
2. Om infusionen stannar under mer än 10 minuter måste infusionssetet kopplas bort från subkutan eller intravenös kateter och all slang distalt om y-kopplingen spolas ur med koksaltslösning och åter fyllas med Infudopa.
3. Arbeta aseptiskt med all inkoppling av pumpar, infusionset och lösningar.

Bilder på produkterna:

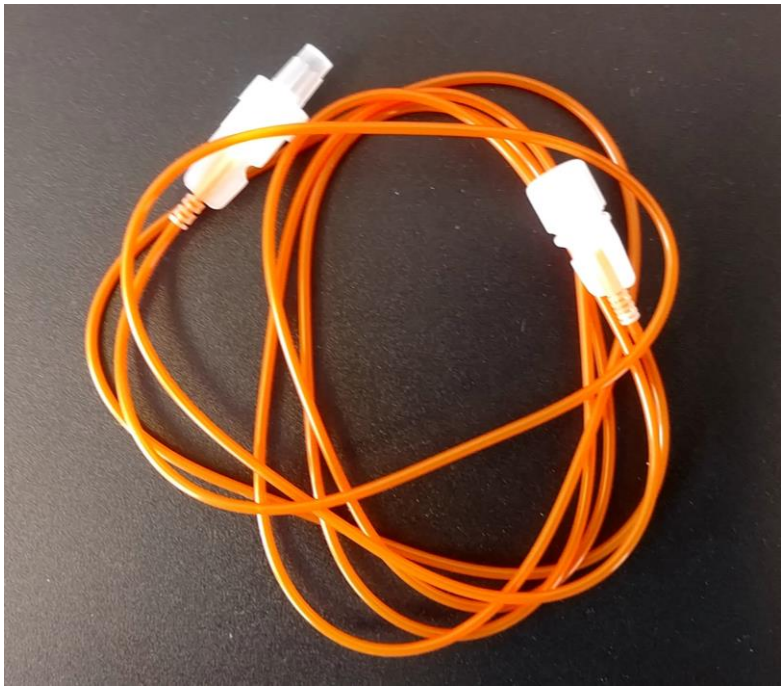
B Braun Mini-Spike filter, ref 4550242:

50 ml spruta B Braun Omnifix Luer Lock Solo, ref 4617509F:

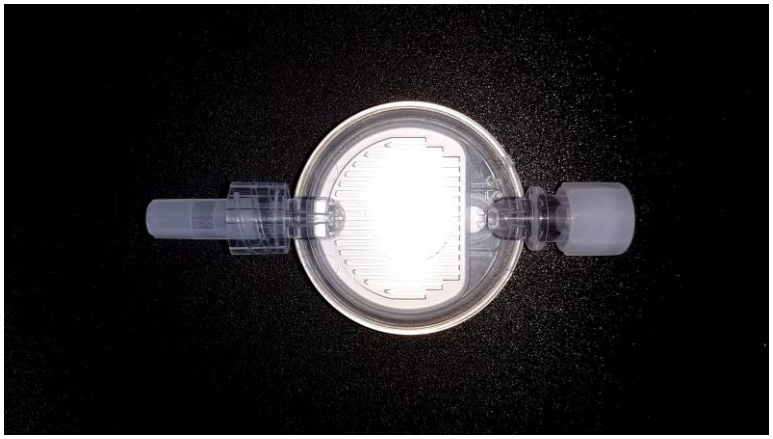
Carefusion SmartSite Extension Set (Y-koppling), ref 20061E7D:



B Braun Original Perfusor Line slang 150 cm (UV-protect), ref 8723017:

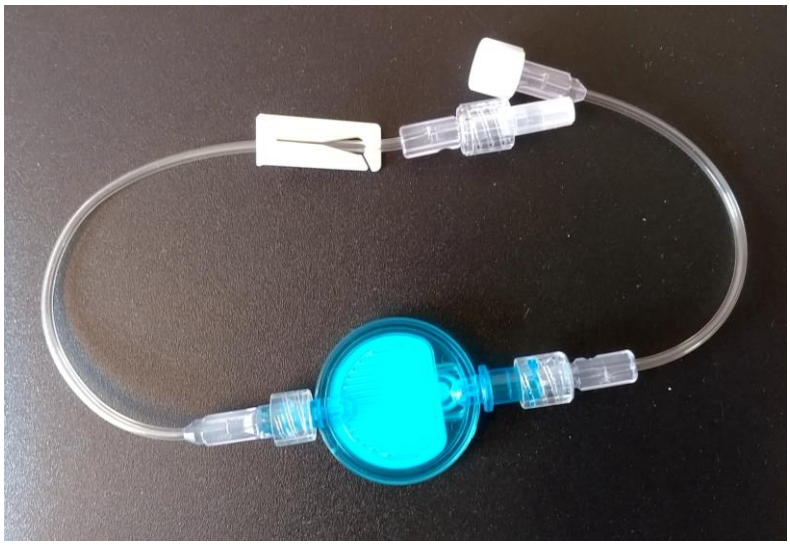


B Braun Sterifix 0.2 µm filter, ref 4099354:



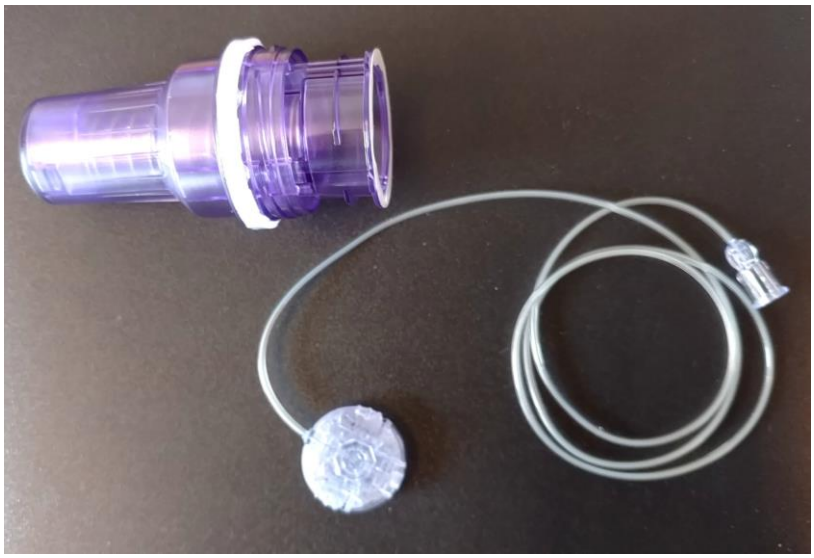
3-way connection for splitting line into 2 s.c. Cleo catheters (Infucare 21 05 80)

B Braun Intrapur 1.2 µm filter, ref 4099850:



BD Venflon 20G 1.0 × 32 mm kanyl, ref 391452 (färgkod rosa), för i.v administrering, tillsammans med lämplig förlängning till filtret:

Infucare Cleo 90 kanyl, ref 2021-08, för s.c. administrering:



Infudopa Buffer IntraV (50 ml), **Infudopa Buffer SubC** (50 ml) och **Infudopa Active** (50 ml), här utan etiketter:

APPENDIX B. EVALUATION OF LOCAL TISSUE REACTIONS IN TISSUE IRRITATION STUDIES - DRAIZE SCORE

Pharm Assist Sweden AB
Mats Ehrnebo
2017-06-05

Skin Reaction	Value
Erythema and eschar formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Necrosis (death of tissue)	+N
Eschar (sloughing or scab formation)	+E
Edema formation	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised ~1 mm)	3
Severe edema (raised more than 1 mm*)	4
Total possible score for primary irritation	**8**

From:
Irritation and Local Tissue Tolerance in Pharmaceutical Safety Assessment
Drug Safety Evaluation: Edition 3
Shayne Cox Gad, 1 December 2016
John Wiley & Sons

*Modified from reference that has the addition: “and extending beyond the area of exposure”

APPENDIX C. MEMBERS OF THE BOARD OF THE INTERIM STUDY ANALYSIS

Filip Bergquist, MD, PhD
Department of Neurology
Sahlgrenska University Hospital
Gothenburg, Sweden
Tel: +46 702 22 36 64
E-mail: filip.bergquist@gu.se

Dag Nyholm, Docent
Institution of Neuroscience, Neurology
Uppsala University Hospital (Akademiska Sjukhuset)
Uppsala, Sweden
Tel: +46 18 611 5038
E-mail: dag.nyholm@neuro.uu.se

Mats Ehrnebo, Ph.D., M.Pharm.Sci
Pharm Assist Sweden AB
Uppsala, Sweden
Tel: +46-70-6421501
E-mail: mats.ehrnebo@pharmassist.se

Elias Eriksson, PhD, Professor
Institution of Physiology and Neuroscience
Sahlgrenska Academy, Gothenburg University
Sweden
Tel: +46 709 55 50 55
E-mail: elias.eriksson@neuro.gu.se