Statistical Analysis Plan for DIVE-I study : Dopaminergic restauratIon controlled by intraVEntriculaire administration.

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This document is written according to Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. (1)

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Protocol Version	SAP version no.	Section number changed	Description of and reason for change	Date
7.0	1.0	NA	First SAP version signed	16/05/2023
7.0	2.0	5.1 Outcome definitions 5.1.2 Phase II Secondary outcomes Exploratory outcomes	Revised the change after data-blind review (22/04/2023): Moving exploratory as secondary outcome: 'Fluctuation dyskinesia score' Adding secondary outcome:'Time in good autonomy' Move secondary as exploratory outcome : 'Clinical global impression of patient and investigator', 'the 50th percentile of the available	28/05/2024

		5.2 Analysis methods	bradykinesia score', 'the 50th percentile of the available dyskinesia score' All analysis for phase II party of study are revised regarding the limited number of sample size (n=9) by comparison to the planned sample size (n=20). Primary outcome efficacy analysis will be performed a non-parametric paired test, and by reported a case-report descriptive analysis. All secondary and exploratory quantitative outcomes will be analyzed using descriptive analysis without statistical test.	

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Protocol title: Dopaminergic restauratIon controlled by intraVEntriculaire administration

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List of Abbreviations

Abbreviations	Label
AIMS	Abnormal Involuntary Movement Score
BKS	Bradykinesia score
CGI	Clinical Global Impression
CI	Confidence limit
DKS	Dyskinesia score
DRS	Dyskinesia rating scale
ECG	Electrocardiogram
eCRF	Electronic case report form
ECMP	Echelle comportemental Maladie de Parkinson (behaviour scale for Parkinson's disease)
FDS	Fluctuation and dyskinesia score
GKC	Global Kinetics Corporation
HVA	Homovanillic acid
ICV	Intracerebroventricular
LARS	Lille Apathy rating scale
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating
MRI	Magnetic resonance imaging
MOCA	Montreal Cognitive Assessment
NPI	Neuropsychiatry Inventory
PAS	Parkinson Anxiety Scale
PDQ39	Parkinson's Disease Questionnaire
PKG	Parkinson KinetoGraph
PTI	Percentage of time of immobility
PTO	Percent Time Over target
PTT	Percentage of time with a tremor

1 INTRODUCTION

1.1 Background and rational

Parkinson's disease is characterized by cerebral dopamine depletion. Dopamine cannot be administered orally. On the model of the insulin pump in diabetes, we want to restore the natural circadian cycle of dopamine at the cerebral level by administering it at the intra-ventricular level. This is done according to the classic neurosurgical intervention of ventricular bypass by implanting a delivery system by a fine catheter connected subcutaneously to a high-tech pump placed at the intra-abdominal level already on the market. The adjustment of the pump by telemetry makes it possible to adapt hour by hour the exact need of each patient. The objective of bi-monthly filling avoids oral intake of L-dopa every two to three hours, ensuring perfect ergonomics. This therapeutic concept has already been carried out in two patients in 1984 and 1989, revealing very good tolerance and efficacy. At that time the patients treated were fragile with dementia and psychosis and no precautions were taken for the deleterious auto-oxidation of dopamine; however, tolerance was good and efficacy was clearly reported. However, this was not pursued for fear of the deleterious oxidation of dopamine, the wrong indication (too advanced patients with dementia and severe hallucinations) and above all responsible for an exhaustion of the effect (tachyphylaxis). The exhaustion being due to the wrong indication, to a constant dose (instead of respecting the circadian rhythm of dopamine) and especially to the oxidation of the latter.

Given the need to perform a brief neurosurgical intervention (30 to 60 minutes, similar to ventricular bypass but with rigorous intraoperative identification using preoperative MRI) with the installation of a medical device, we carry out a proof-of-concept study in three phases: a first safety phase (phase I) with administration of intracerebroventricular dopamine (intervention) according to a very careful slow titration protocol including one patient at a time up, a second efficacy phase II study using a cross-over design, and a long term follow-up phase of patients treated with intervention. This three-phases strategy will make it possible to guarantee the precautionary principle by progressively exposing the fewest patients while then allowing patients who undergo this intervention to benefit from this therapeutic procedure while providing the first reliable data on safety and efficacy.

1.2 Research hypothesis

The hypothesis of phase I trial is that, in Parkinson's disease in the stage of severe motor and non-motor complications related to L-dopa, the administration of intracerebroventricular dopamine is safe regarding the occurrence of serious adverse event. The hypothesis of phase II trial is that, in Parkinson's disease in the stage of severe motor and non-motor complications related to L-dopa, there is an increase in the Percent Time Over target (PTO) in the intervention phase (A-dopamine intracerebroventricular) by comparison to the control phase (usual optimized oral medical treatment). The hypothesis of long-term follow-up phase trial is the maintenance of efficacy on motor and non-motor complications.

1.3 Study Objectives

Phase I study:

The primary objective is to determine the feasibility and the safety of administration of intracerebroventricular (ICV) dopamine.

Phase II study:

The primary objective is to determine the efficacy (superiority) of administration of intracerebroventricular (ICV) dopamine in combination of oral L-dopa at optimized dose versus usual optimized oral medical treatment in combination with ICV Placebo for improving PTO in patients with Parkinson's disease in the stage of severe motor and non-motor complications related to L-dopa.

Secondary objectives are:

1) to assess the efficacy of administration of ICV dopamine in combination of oral L-dopa at optimized dose versus usual optimized oral medical treatment in combination with ICV Placebo on:

- motor aspects
- cognitive-behavioural aspects: drowsiness, anxiety, depression, apathy, sleep, hallucinations cognition and psychiatric assessment
- quality of life
- general condition

2) To assess the tolerance of administration of intracerebroventricular dopamine versus usual optimized oral medical treatment alone

3) To assess the psychiatric tolerance of administration of intracerebroventricular dopamine versus usual optimized oral medical treatment alone

Long term follow-up study:

The primary objective is to assess the maintenance of efficacy of long-term continuous administration of intracerebroventricular dopamine on motor control and non-motor complications.

Secondary objectives are

1) To assess the maintenance of efficacy on:

- motor aspects
- cognitive-behavioural aspects: drowsiness, anxiety, depression, apathy, sleep, hallucinations cognition and psychiatric assessment
- quality of life
- general condition

2) To assess the maintenance of tolerance of intracerebroventricular dopamine administration

2 TRIALS METHODS

2.1 Trial design

DIVE-1 is a proof of concept study with three phases:

- a first safety phase (phase I) with administration of intracerebroventricular dopamine (intervention) according to a very careful slow titration protocol.
- a second efficacy phase II study (including patients enrolled in phase I who reached the titration objective without complications) using a randomized 2x2 cross-over design with administration of intracerebroventricular dopamine as intervention condition and usual optimized oral medical treatment alone as control condition
- a long-term follow-up phase of ICV dopamine administration restricted to patients enrolled in phase II study.

Each study phase is fully detailed in study protocol, according to study flow provided in figure 1.

Briefly, in first safety phase I, a slow titration of intracerebroventricular dopamine administration including one to one (namely, the second patient will be included after the end of titration period of the first patient, and so on) and with an independent Monitoring Committee who will review all adverse events.

The following go no go safety rule is applied to go to phase II:

1) for the first 5 patients, if no or at most one serious and unexpected adverse events (apart from the rare surgical risks of haemorrhage and infection with no impact in vital and functional prognosis of the patient) is observed, 15 other patients may be included and phase II will be start.

2) If two or more serious or unexpected adverse events (apart from the rare surgical risks of haemorrhage and infection with no impact in vital and functional prognosis of the patient) occur in first five patients, only 5 new patients could be included, and the following rule will be proposed to the independent Monitoring Committee:

- if no or at most one of serious and unexpected adverse events among the 5 new patients, 10 other patients will be included in phase I and phase II can be started

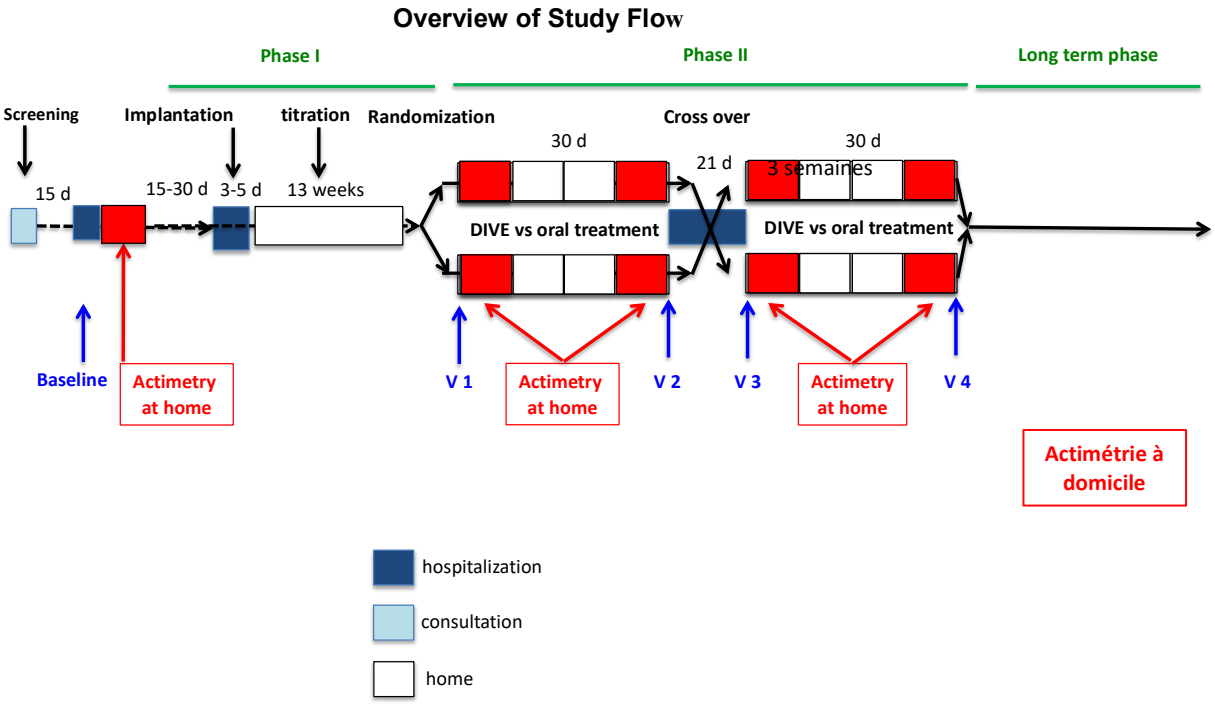
- if two or more serious or unexpected adverse events among the 5 new patients, the Independent Monitoring Committee could decide to stop the study.

During phase I, Independent Monitoring Committee will be aware for each unexpected adverse events one patient at a time up and can propose to stop the study at any time.

In second efficacy phase II, 20 patients will be enrolled after terminating the titration phase I without complications and randomized in two groups according to cross-over design of 2 treatment periods of 4 weeks separated by a therapeutic switch carried out in the hospital. The previous treatment will be stopped at the end of period 1 and replaced by the new treatment, after 3 weeks of washout. During the 2 treatment periods and washout period, the patients will be treated by oral L-dopa at optimized dose. In summary, patients will be randomized into two groups according to the following treatment sequences:

- group 1 (n=10): period 1(ICV dopamine treatment + oral L-dopa at optimized dose) vs. period 2 (oral treatment at optimized dose + ICV Placebo treatment)
- group 2 (n=10): period 1: (oral treatment optimized + ICV Placebo treatment) vs. period 2 (ICV dopamine treatment + oral L-dopa at optimized dose)

At the end of phase II, all patients are invited to continue to use ICV dopamine treatment over the long term with the dose that allows satisfactory motor control (less than 1 hour of moderate or severe off per day and less than half an hour of dyskinesia) with or without a minimal residual dose of oral dopaminergic therapy.



2.2 Randomisation

For the phase II part of the DIVE-1 study, patients are randomized in 2 treatment sequences according to a balanced plan (1:1) by using a randomization list generated by computer and provided by an independent statistician of CHU of LILLE. The randomization list will be implemented into the eCRF developed with Clinsight software. Patients will be randomized as soon as possible after having completed the phase I part of study (patients reached, at this time, a balanced titration established within 9 weeks).

2.3 Sample size

Full details of the sample size are described within the clinical trial protocol and was determined according to the phase II part of study. We planned to dispose to 20 patients analysable (who completed the two-treatment sequence in phase II without major protocol deviations) to have a power >80% to detect, with a two-sided test at 0.05 significance level, an absolute decrease in PTO of 10% in intervention period compared to control period, by assuming a standard deviation of 15% and a correlation of 0.5 between the repeated measures.

The sample size was revised in 23 February 2023 following an amendment regarding the ability of central pharmacy of Lille university hospital to ensure the weekly production of experimental treatment in safe condition for a maximum of 12 patients. Regarding the proof of concept phase II study, the number of 12 patients was considered acceptable to provide first evidences of efficacy (by interpreting effect size on primary outcome and by a detailed descriptive analysis of changes in secondary outcomes in each period). During the data blind review, only 9 patients have available complete data on primary outcome and could be analysed.

2.4 Framework

Primary and secondary comparative objectives of phase II part of DIVE-1 trial are tested for superiority in favour of intervention versus control treatment period. For phase I study, none statistical tests will be done and only descriptive analysis with go no go rule for safety will be done. For long term follow-up phase, intra-patient comparisons will be done to assess the maintenance efficacy and safety.

2.5 Statistical interim analyses and stopping guidance

No statistical interim analysis was planned. Stopping guidance for safety (go no go rule with evaluation by an independent Monitoring Committee) is detailed in study protocol and in section 2.1.

2.6 Timing of analysis

Final analysis for phase II is planned to take place in June 2024 after the database is cleaned and locked according to data management plan. The first main report/publication of the DIVE-1 trial will be prepared at the same time.

2.7 Timing of outcome assessments

The time points at which outcomes are measured is provided in table 1. Full detail of the schedule of the study visits are described within the clinical trial protocol.

Table 1. The schedule of follow-up study visits

		SC	Baseline	Implantation /titration	V1 (randomization phase II)	V2	V3	V4	Visites at long term every 6 months (1)
Possible delay		*/*	*+2 weeks*	*+1 months*	*+1 week*	*+1 week*	*+1 week*	*+1 week*	*+/- 2 weeks*
Checking inclusion and non-inclusion criteria		x							
Informing the patient		x							
Signing of consent		x							
Randomisation			x		x				
Socio-demographic data (age, socio-cultural level), previous and current associated medical and psychiatric disorders		x							
Medical check-up Clinical examination		x	x	x	x	x	x	x	x
	Weight, height, BP with orthostatic hypotension test, ECG, temperature, respiratory rate	x	x	x	x	x	x	x	x
	Collection of concomitant treatments	x	x	x	x	x	x	x	x
Psychiatric assessment			x		x	x	x		x
Chest X-ray, cardiac ultrasound			x						
Covid-19 test before surgery (if required by Covid-19 pandemic health measures)			x						
Implantation neurosurgical procedure				x					
Post-operative CT scan				x					
Monitoring of therapeutic adaptation (in hospital and then at home by daily calls)				x					
Standard biological work-up			x	x	x	x	x	x	x
FSH and LH tests (for all women)									
β-HCG assay (for women of childbearing age only)			x	x	x	x	x	x	
Continuous actimetry measurement (PKG)					x	x	x	x	
Acute L-dopa administration test (MDS UPDRS part III, video dyskinesia scales)			x						
MDS UPDRS part III, video dyskinesia scales in On Drug condition (either oral L-dopa or brain dopamine)					x	x	x	x	x
MDS-UPDRS parts I, II and IV			x		x	x			x
MOCA					x	x	x	x	x
Neuropsychological examination (cognition and behaviour) : NPI, PAS, LARS, ECMP			x		x	x	x	x	x
Clinical Global Impression (CGI) physician			x		x	x	x	x	x
Auto-questionnaires : CGI patient, échelle de Schwab et England, échelle d'Epworth, de Parkinson's Disease Sleep Scale, PDQ39			x		x	x			x
patient diary (periods 1 et 2)					x	x	x	x	x
Brain MRI			x				x	x	

	SC	Baseline	Implantation /titration	V1 (randomization phase II)	V2	V3	V4	Visites at long term every 6 months (1)
Possible delay	*/*	*+2 weeks*	*+1 months*	*+1 week*	*+1 week*	*+1 week*	*+1 week*	*+/- 2 weeks*
Exploratory criteria: pharmacogenetic and biobanking		**x**						
Exploratory criteria: Biology (oxidised metabolites of dopamine)		**x**	**x**		**x**	**x**	**x**	
Adverse events	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**

3 STATISTICAL PRINCIPLES

3.1 Confidence intervals and p-values

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level.

No statistical comparisons will be done for secondary objectives, only a descriptive analysis will be performed and we will report standardized differences between active and control period as effect sizes. All confidence intervals (CIs) presented will be 95%CI and 2-sided.

3.2 Adherence and Protocol Deviations

Patient's adherence during phase II part was evaluated by the volume of ICV Dopamine (placebo) before each refill and compared to the planned volume. For the oral L-dopa regimen, the adherence will be evaluated by the judgment of clinician regarding the optimized dose. Deviation in adherence will be defined as a one ml difference for ICV Dopamine (placebo) and as a modification of more than 20% of planned dose for the oral L-dopa regimen.

Protocol deviations will be identified and classified as major or minor in blind reviews before the database freezing. Major deviations will include unexpected treatment modification (dose, duration) of dopamine or oral treatment. The number and % of patients with major and minor protocol deviations will be provided, with details of the type of deviation. No formal statistical comparison will be done.

3.3 Analysis population

For phase I study, all included patients who have been operated, whatever they received or not a dose of study treatment, will be considered in analysis as a safety population.

For the phase II study, regarding the proof of concept, the efficacy population will include all randomized patients, who completed the two-treatment period with available primary endpoint —and without major protocol deviation. All patients randomized and excluded from the efficacy population will be described with the reason of exclusion. The safety population of phase II study will include all randomized patients who receive ICV dopamine (or placebo).

For the long-term phase part of study, all patients having received ICV dopamine for at least 6 months after end of the phase II part will included in the analysis population of long-term phase part of DIVE-1 study.

4 TRIAL POPULATION

4.1 Screening data

The overall recruitment period will be provided in months. The number of screened patients, number of patients included in each phase of DIVE-1 study, with the reason for non-inclusion will be reported according to flow diagram (figure 1).

4.2 Eligibility

The trial inclusion and exclusion criteria are full detailed in clinical trial protocol. The number of ineligible patients screened and not included will be provided according to flow diagram (figure 1).

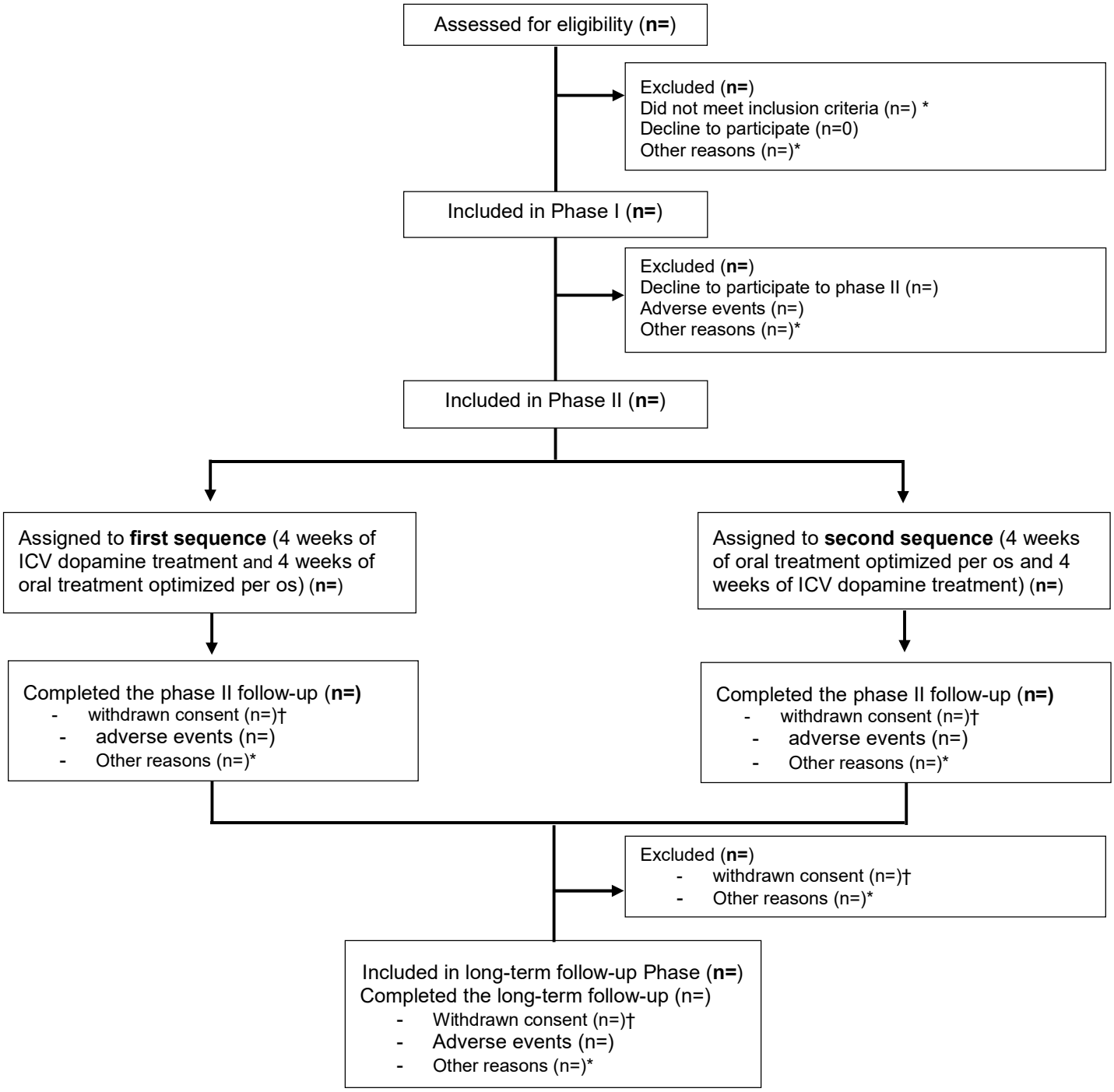
4.3 Withdrawal/Follow-up-level of withdrawal

The level of withdrawal will be tabulate and classified as:

- Withdrawn consent from follow-up but allow data to be used until the date of consent withdraw
- Withdrawn consent from follow-up and did not allow data to be used until the date of consent withdrawal
- Withdrawal due to lost to follow-up
- Withdrawal due to investigator decisions

The timing of withdrawal and reasons for withdrawal will be provided according to flow diagram (figure 1).

Figure 1. Flow of participation in the DIVE-1 study.



* Reasons will be provided. † Level of consent withdrawal will be provided

4.4 Baseline patient characteristics

Detail of baseline characteristics are reported in table 2, for each population analysis according to the study phases. Quantitative variables will be expressed as median (range values) and categorical variables will be expressed as frequencies and percentages. The number of missing data will be also reported. No formal statistical comparisons will be done.

Table 2.1. Baseline characteristics of patients included in safety Phase I part (titration of ICV dopamine)

Age (years)
Sex
Body mass index (kg/m^2)
Disease duration since the first symptoms (years)
Disease duration since diagnosis (years)
Duration of L-dopa (years)
Duration of motor fluctuations (years)
Duration of dyskinesia (years)
Hoehn & Yahr of symptoms progression
Schwab & England activities of daily living
MDS-UPDRS total score of handicap
MDS-UPDRS motor handicap, part III (Off drug)
MDS-UPDRS motor handicap, part III (On drug)
L-Dopa sensitivity (%)
LEDD (mg)

Table 2.2. Baseline characteristics of patients included in efficacy Phase II part (cross-over design)

	Overall	**First sequence of treatment**	**Second sequence of treatment**
Age (years)			
Sex			
Body mass index (kg/m^2)			
Disease duration since the first symptoms (years)			
Disease duration since diagnosis (years)			
Duration of L-dopa (years)			
Duration of motor fluctuations (years)			
Duration of dyskinesia (years)			
Hoehn & Yahr of symptoms progression			
Schwab & England activities of daily living			
MDS-UPDRS total score of handicap			
MDS-UPDRS motor handicap, part III (On drug)			
MOCA			
L-Dopa sensitivity (%)			
LEDD (mg)			

Table 2.2. Baseline characteristics of patients included in long-term follow-up phase (maintenance of ICV dopamine efficacy)

Age (years)
Sex
Body mass index (kg/m^2)
Disease duration since the first symptoms (years)
Disease duration since diagnosis (years)
Duration of L-dopa (years)
Duration of motor fluctuations (years)
Duration of motor dyskinesia (years)
Hoehn & Yahr of symptoms progression
Schwab & England activities of daily living
MDS-UPDRS total score of handicap
MDS-UPDRS motor handicap, part III (On drug)
MOCA
L-Dopa sensitivity (%)
LEDD (mg)

5 Analysis

Data analysis will be performed by an academic statistician from Biostatistics Department of University of Lille (France) under the responsibility of Elodie Drumez.

5.1 Outcome definitions

5.1.1. Phase I

Primary outcome: Feasibility of DIVE treatment (ICV dopamine administration) assessed in term of safety evaluated by occurrence of any adverse effects, assessed by an independent monitoring committed to decide whether to continue or stop the treatment.

The following complications will be considered for safety evaluation:

- Serious infection involving the vital prognosis of the patient
- Serious haemorrhage involving the vital and functional prognosis of the patient
- Frank worsening of the motor and/or non-motor symptoms of Parkinson's disease in a sudden or rapid manner over a month (i.e. more than double the points of classic aggravation over 3 months or more than 6 points of the total MDS UPDRS score over a month with the optimal dose of A-dopamine: best on condition)
- Neurological deficit apart from symptoms of Parkinson's disease
- Status epilepticus
- Death during the postoperative period
- Any modification of following parameters (blood pressure, pulse, ECG blood and urinary levels of dopamine and its metabolites (HVA and 5-cysteinyl-dopamine)) after stopping the titration

5.1.2. Phase II

Primary outcome:

Percent Time Over target (PTO) assessed by actimetry (from first and last recording weeks of each study period) with the Parkinson KinetoGraph (PKG) system from the Global Kinetics Corporation (GKC) laboratory. The PTO is the sum of the PTO for bradykinesia and for dyskinesia. The over target bradykinesia is the percentage of time the subject was bradykinetic. This is the proportion of time in bradykinesia score (BKS) severity level 3 or above (% of 2-min periods with >BKS 26) after removing artifacts. Higher values represent more epochs that the subject was severely bradykinetic. The

percentage over target dyskinesia is the percentage of time the subject was dyskinetic during the recording period between 9 am and 6 pm (% of 2-min periods with dyskinesia score (DKS) >10 above target).

Secondary outcomes of efficacy:

- Other validated actimetry criteria calculated every 2 minutes throughout the first and last recording weeks of each study period.
  - The PTO bradykinesia
  - The PTO dyskinesia
  - Fluctuation Dyskinesia score (estimating the amount of variability in relation to optimal control, i.e. insufficient control (bradykinesia) or overdose (dyskinesia); expected benefit with a reduction in %)
- Patient diary measures during the first and last weeks of each study period.
  - Time in good autonomy is expressed in % is the percentage of time in On state or with slight dyskinesia or slight off.
  - Time in perfect control is expressed in % or in hours (h) and represents the time in On state without dyskinesia
  - Time in “on” time without troublesome dyskinesia is expressed in % and represents the Time On with or without slight dyskinesia
  - Time in “on” time without dyskinesia and/or with slight dyskinesia and/or with slight bradykinesia is expressed in %
  - Time in dyskinesia is expressed in % and represents the time with slight, moderate or severe dyskinesia
  - Time in severe dyskinesia (%)
  - Time in severe bradykinesia = Time in severe off (%)
- Clinical criteria at end of study treatment period (V2 for first sequence treatment and V4 for second sequence treatment)
  - MDS-UPDRS part IV

- Dyskinesia rating scale (DRS) score
- The abnormal Involuntary Movement Score (AIMS)
- MDS-UPDRS parts II (on periods) III (on drug)

Secondary outcomes of safety:

- MDS-UPDRS parts I
- Epworth Sleepiness Scale and Parkinson's Disease Sleep Scale
- Cognitive measures (MOCA, NPI, PAS, LARS and ECMP)
- Psychiatric tolerance: a score from a simple questioning on the disorders (no thymic, anxious, psychotic decompensation).
- Frequency of adverse events during the 4 weeks of treatment period reported by the patient and/or noted by the investigator according to clinical examination, ECG, blood pressure, pulse and biological assessment (standard biology, biological iron assessment, blood and urinary levels of dopamine and its metabolites (HVA) and variations in weight, temperature, and blood pressure on the orthostatic hypotension test.

Exploratory outcomes:

- Actimetry criteria
  - The 50th percentile of the available bradykinesia score (BKS) (50 percentile: normal value =18.6)
  - The 50th percentile of the available dyskinesia score (DKS) (50 percentile: normal value = 4.3)
  - The percentage of time of immobility (PTI), which represents the absence of movement during recording
  - Percentage of time with a tremor (PTT)
- Clinical criteria at end of study treatment period (V2 for first sequence treatment and V4 for second sequence treatment)
  - PDQ39 score
  - Schwab and England scale score
- Biological modification between the two periods of treatment

- blood and urine determinations of dopamine, and its metabolites HVA and 5-cysteinyl-dopamine after 2 hours of treatment in the morning on an empty stomach (either 2 hours after the first oral treatment or 2 hours after the first daytime dose of A-dopamine)
- markers of oxidative stress (MDA, 4-HNE, 8 oxoDG)
- markers of axonal destruction (light chain filaments) in blood

- Pharmacogenetic parameters of dopamine metabolism (DaT, COMT, MAO, DDC, ceruloplasmin) which may influence the response to L-dopa on the reduction of dyskinesia and off period

5.1.3 Long term follow-up phase

Primary outcome:

- Percentage in “on” time without dyskinesia and with or without slight bradykinesia

Secondary outcomes of efficacy:

- Patient diary measures
  - Time in good autonomy is expressed in % is the percentage of time in On state or with slight dyskinesia or slight off.
  - Time in perfect control is expressed in % or in hours (h) and represents the time in On state without dyskinesia
  - Time in “on” time without troublesome dyskinesia is expressed in % and represents the Time On with or without slight dyskinesia
  - Time in “on” time without dyskinesia and/or with slight dyskinesia and/or with slight bradykinesia is expressed in %
  - Time in dyskinesia is expressed in % and represents the time with slight, moderate or severe dyskinesia
  - Time in severe dyskinesia (%)
  - Time in severe bradykinesia = Time in severe off (%)
- Clinical criteria at end of study treatment period (V2 for first sequence treatment and V4 for second sequence treatment)
  - MDS-UPDRS parts II, III and IV

- The abnormal Involuntary Movement Score (AIMS) and the Dyskinesia rating scale (DRS) score

Secondary outcomes of safety:

- MDS-UPDRS parts I
- Epworth Sleepiness Scale and Parkinson's Disease Sleep Scale
- Cognitive measures (MOCA, NPI, PAS, LARS and ECMP)
- Psychiatric tolerance: a score from a simple questioning on the disorders (no thymic, anxious, psychotic decompensation).
- Frequency of adverse events during the 4 weeks of treatment period reported by the patient and/or noted by the investigator according to clinical examination, ECG, blood pressure, pulse and biological assessment (standard biology, biological iron assessment, blood and urinary levels of dopamine and its metabolites (HVA and 5-cysteinyl-dopamine) and variations in weight, temperature, and blood pressure on the orthostatic hypotension test.

Exploratory outcomes:

- Clinical criteria at end of study treatment period (V2 for first sequence treatment and V4 for second sequence treatment)
  - PDQ39 score
  - Schwab and England scale score

5.2 Analysis methods

5.2.1 Phase I

A case-report analysis will be done for phase I part of DIVE-1 study, with the following safety go no go rule: 1) In no or at most one serious and unexpected adverse events (apart from the rare surgical risks of haemorrhage and infection with no impact in vital and functional prognosis of the patient) in the first five patients, 15 other patients may be included in Phase I and the phase II will be start.

2) If two or more serious or unexpected adverse events (apart from the rare surgical risks of haemorrhage and infection with no impact in vital and functional prognosis of the patient) occur in first five patients, only 5 new patients could be included, and the following rule will be proposed to the independent Monitoring Committee to start the phase II:

- in the no or at most one serious and unexpected adverse events in the 5 new patients, 10 other patients may be included in Phase I and phase II will be start.

- if two or more serious or unexpected adverse events, the Independent Monitoring Committee could decide to stop the study without start the phase II trial.

5.2.2 Phase II

The phase II part of study follow a cross-over randomized design in 2 treatment sequences including **E**xperimental (ICV dopamine treatment) and **S**tandard (oral dopamine treatment optimized per os) treatments.

We will used to define the statistical methods the following notations:

3) a sequence noted E-S to define the patient's group which received ICV dopamine in first period following by oral dopamine in second period,
4) a sequence S-E to define the patient's group which received oral dopamine in first period following by ICV dopamine in second period.
5) E1 designates the value of the endpoint in the first period for the experimental treatment.
6) S1 designates the value of the endpoint in the first period for the standard treatment.
7) E2 designates the value of the endpoint in the second period for the experimental treatment.
8) S2 designates the value of the endpoint in the second period for the standard treatment.

Primary outcome:

A case-report descriptive analysis will be done by reporting individual values of primary outcome according to the two periods as well as by using spaghetti plots showing the individual change from control to experimental period (by indicating the sequence of treatment). We also reported the mean, median and range values for control and experimental period. To assess the treatment effect (experimental vs. standard treatment) on primary outcome, we will use a Wilcoxon 'signed rank test. We will also report the standardized differences (Hedges'g) calculated from the within-patient's differences (E1-S2 and E2-S1) as effect size (calculated on rank transformed data).

Secondary outcomes:

For secondary and exploratory quantitative outcomes, only a descriptive analysis will be done by reporting the mean, median and range values as well as plotting the values using spaghetti plots showing the change from control to experimental period (by indicated the sequence of treatment using dedicated colors). We will also report the standardized differences (Hedges'g) calculated from the within-patient's differences (E1-S2 and E2-S1) as effect size (calculated on rank transformed data). The frequency of adverse events during the 4 weeks of treatment period will be reported in each treatment group without statistical comparison.

5.2.3 Long term follow-up

Primary outcome:

The percentage in "on" time without dyskinesia and with or without slight bradykinesia during a 7 day consecutive period (assessed using patient diary) between the last available follow-up and the evaluation during the treatment period of phase II part of DIVE will be done using a linear mixed model including phase (phase II vs. long term follow-up), and delay from phase II evaluation to long-term follow-up evaluation as fixed effects and patients as random effects to account the within intra-patients correlation. In cases of deviation to normality of model residuals, the difference between the phase II evaluation to long-term follow-up evaluation between the two evaluations by using a Wilcoxon-rank signed test.

Secondary outcomes:

The same methods described to analyse the primary outcome of long-term follow-up phase will be used to analyse secondary and exploratory quantitative outcomes.

The frequency of adverse events from end of phase II trial to the last available follow-up will be reported.

5.3 Subgroup analyses

None.

5.4 Missing data

No imputation, only cases available analysis will be done.

5.5 Sensitivity analyses

None.

5.6 Additional analyses

No additional analyses will be done.

5.7 Statistical software

Data will be analysed using the SAS software (Version 9.4. SAS Institute Inc, Cary, NC, USA). Other package such as R software may be used if necessary.