Evaluation of the safety and efficacy of Continuous Dopaminergic Stimulation by intracerebroventricular administration of anaerobically preserved dopamine in Parkinson's disease in the motor fluctuation stage : Single-center pilot study

SHORT TITLE: DIVE-I

(Dopaminergic restauratIon controlled by intraVEntricular administration)

Code number assigned by the promoter	**2018_49**
EudraCT no.	**2020-000155-12**
Research Involving the Human Person (RIPH)	**Category 1 research: Interventional research**
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N° Current version/ Date :	Version 9.2 of 10/08/2023

PROTOCOL UPDATE HISTORY

VERSION	DATE	REASON(S) FOR MODIFICATION
1.0	11/01/2020	Initial version
1.1	19/02/2020	Response to ANSM's comments (parts 2 and 3)
1.2	02/03/2020	Response to ANSM's comments (part 1)
2.0	01/04/2020	Response to ANSM comments - Re-submission
3.0	28/10/2020	Substantial modification n°1
4.0	17/03/2021	Substantial amendment no. 2
5.0	22/07/2021	Substantial modification no. 3
5.1	15/09/2021	Response to ANSM's comments
5.2	25/10/2021	Response to CPP's comments
6.0	16/11/2021	Substantial amendment no. 4
7.0	02/04/2022	Substantial modification n°5
7.1	31/05/2022	Modifications following the suspensive opinion of CPP Nord-Ouest 2 (meeting of May 19, 2022) And to exchanges dated 05/20/22 with Ms Camille **Schurtz**, Head of the Early Trials and Therapeutic Innovations Unit (PEPIThe) at ANSM. Request from ANSM for substantial modification no. 6 for this version of the protocol
8	10/10/2022	Substantial change to the dispensing of experimental treatment at the end of phase 2 and the patient's entry into the long-term follow-up phase at home by a care provider
9	23/02/2023	- Clarification of participation termination criteria - Reducing the number of subjects to be included - Modification of diary and actimetry assessment frequency - Mention of the drafting and transmission to ANSM of a report describing all safety and clinical data from the first 5 patients treated in phases 1 and 2. - Clarification of abbreviation use "EIG".

9.1	19/04/2023	Replies to ANSM's interim letter dated 13/04/2023 - Cancellation of Modification of diary and actimetry assessment frequency in version 9 - Amendment to study participation termination criteria and early termination Addition of procedure for non-stop treatment of a patient with a life-threatening condition - The long-term follow-up phase of the protocol will end when the last treated patient in the study reaches the end of his life. his last visit of Phase II (Visit 3).
9.2	10/08/2023	Responses to ANSM interim letters dated 27/07/2023 - Follow-up extended to 06/30/2024

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PROTOCOL SIGNATURE PAGE

Developer code: 2018_49
Long title: Evaluation of the safety and efficacy of continuous dopaminergic stimulation by intracerebroventricular administration of anaerobically preserved dopamine in Parkinson's disease at the motor fluctuation stage: Single-center pilot study.
Short title: DIVE-I (Dopaminergic restauratIon by intraVEntricular administration)
Version no. and date: Version 9.2 of 10/08/2023

L'investigateur principal et le promoteur s'engagent à réaliser cette étude selon le protocole, les règles et les recommandations des bonnes pratiques cliniques internationales et selon les dispositions législatives et réglementaires applicables à la recherche.

		DATE	SIGNATURE
PROMOTEUR PAR DELEGATION	**CHU de Lille** **M. Renan TARGHETTA**	10/08/2023	

SIGNATURE OF PRINCIPAL INVESTIGATOR

I have read all the pages of this protocol, for which the Lille University Hospital is the promoter by delegation from In Brain Pharma, and I confirm that it contains all the information required to conduct the trial.
I undertake to carry out the trial in compliance with the protocol and the terms and conditions defined therein, as well as any amendments thereto that may be sent to me by the sponsor. I undertake to conduct this protocol in accordance with Good Clinical Practice, the Public Health Law of August 9, 2004 and the implementing decree of November 16, 2016, and in particular by providing information and obtaining written consent from patients prior to any protocol selection procedure.
I undertake to ensure that investigators and other qualified members of my team have access to copies of this protocol and documents relating to the conduct of the trial to enable them to work in compliance with the provisions set out in these documents.
I have been informed that my personal data will be processed automatically for the purpose of setting up and carrying out the research. This information may be transferred outside the European Union. In accordance with the provisions of the amended law on data processing, data files and individual liberties, and the European regulation on the protection of personal data (2016/679), I have the right to access and rectify my personal information with the promoter.

		DATE	SIGNATURE
INVESTOR PRINCIPAL **ESTABLISHMENT**	**Prof. Caroline MOREAU** **Lille University Hospital Neurology and Movement Pathology Department**	**10/08/2023**	

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AIMS	Abnormal Involuntary Movement Score
ANSM	Agence Nationale de Sécurité du Médicament
ARC	Clinical Research Associate
BKS	Bradykinesia Score
CGI	Clinical Global Impression
CHU	University Hospital
CNIL	Commission Nationale de l'Informatique et des Libertés (French Data Protection Authority)
COMT	Catecholamine-O-MethylTransferase
CPK	Creatine PhosphoKinase
CPP	Comité de Protection des Personnes
CRF/eCRF	Case Report Form/electronic Case Report Form
CSI	Independent Supervisory Board
DaT	Dopamine Transporter
DDC	DOPA-DeCarboxylase
DIVE	Dopaminergic restauratIon controlled by intraVEntricular administration
DKS	DysKinesia Score
DRS	Dyskinesia Rating Scale
ECG	ElectroCardioGram
ECMP	Behavioral assessment in Parkinson's disease
EI	Undesirable Event
EIG	Serious Adverse Event
FDA	Food and Drug Administration
MSDS	Fluctuation Dyskinesia Score
FSH	Follicle-stimulating hormone
HVA	Homovanillic acid
ICV	IntraCerebroVentricular
MRI	Magnetic Resonance Imaging
CSF	Cerebrospinal fluid
LH	Luteinizing Hormone
MAO	Monoamine oxidase
MDA	MalonDiAldehyde
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MINI	Mini International Neuropsychiatric Interview
MOCA	Montreal Cognitive Assessment
NPI	Neuropsychiatric Inventory
NOT	Parkinson Anxiety Scale
PDQ-39	Parkinson's Disease Questionnaire - 39 items
PKG	Parkinson KinetoGraph
PTA	Percentage of Time Above Target
PTI	Percent Time Immobile
PTT	Percent Time Tremor
CPR	Summary of Product Features
RGPD	General Data Protection Regulation
TA	Blood Pressure
TCA	Activated partial thromboplastin time
TP	Prothrombin levels

FULL SYNOPSIS IN FRENCH

Parkinson's disease is characterized by a cerebral depletion of dopamine. Dopamine cannot be administered orally. Following the example of the insulin pump in diabetes, we aim to restore the natural circadian cycle of dopamine in the brain by administering it intra-ventricularly. This is achieved using the classic neurosurgical procedure of ventricular shunting, by implanting a delivery system via a fine catheter connected subcutaneously to a high-tech intra-abdominal pump already on the market. The pump's telemetric regulation enables it to adapt to the exact needs of each patient, hour by hour. The aim of the bi-monthly filling system is to avoid the need to take L-dopa orally every two to three hours, thus ensuring perfect ergonomics. This therapeutic concept has already been applied to two patients in 1984 and 1989, with excellent tolerance and efficacy. At the time, the patients treated were frail, with dementia and psychosis, and no precautions had been taken against the deleterious auto-oxidation of dopamine; nevertheless, tolerance was good and efficacy clearly reported. However, this was not pursued for fear of deleterious dopamine oxidation, misdirection (patients too advanced with dementia and severe hallucinations) and, above all, exhaustion of the effect (tachyphylaxis). Exhaustion is due to poor indication, constant dosage (instead of respecting dopamine's circadian rhythm) and, above all, oxidation.

We have overcome this obstacle by preparing and storing dopamine anaerobically (A-dopamine), including in the pump. This makes it possible to administer natural dopamine without preservatives. We have demonstrated and defined feasibility, efficacy and tolerability in 3 Parkinson's models (7-day MPTP mouse, 1-day 6-OH-Dopamine rat, 2-month dose-ranging MPTP monkey).

Given the need to perform a brief neurosurgical procedure (30 to 60 minutes, similar to ventricular bypass, but with rigorous intraoperative mapping using preoperative MRI) with the insertion of a medical device, we are carrying out a two-phase proof-of-concept study and a long-term follow-up phase: a first phase (phase I) of safety with administration according to a very cautious slow titration protocol, including one patient at a time up to five patients. Then, we propose to request authorization from the Independent Monitoring Committee to continue the inclusion of the remaining 7 patients, to enable us to carry out a randomized, single-blind, cross-over study of two 1-month periods with 2 groups: Intracerebroventricular A-dopamine versus optimized usual oral medical treatment. This two-phase strategy will make it possible to guarantee the precautionary principle by progressively exposing the fewest number of patients, while at the same time enabling patients who undergo this procedure to benefit from it, while providing the first reliable data on safety and efficacy. A report describing all the safety and clinical data from the first 5 patients treated in phases 1 and 2 will be drawn up and sent to the ANSM. The main objective is to evaluate the safety (phase I) and efficacy on motor and non-motor complications (phase II) of continuous diurnal intracerebroventricular administration of A-dopamine on a maximum of 12 patients treated.

At the end of phase 2, and subject to the patient's agreement, the patient will be offered to continue to benefit from DIVE treatment during a long-term follow-up phase until the date of the last phase 2 visit of the last patient included, estimated at 06/30/2024.
During this phase, a follow-up visit in consultation and in association with the patient's usual care will take place every 6 months until the date of the last phase 2 visit of the last patient included.

During this phase, for the well-being of patients and to make their daily lives easier, the promoter calls on a homecare provider to fill the pump in the patient's home.

The conditions of the care provider's intervention are defined in this protocol.

In this context, dispensing of the experimental treatment remains the responsibility of the principal investigator and the Lille University Hospital's in-house pharmacy.

The sponsor undertakes to provide the necessary logistical support for the transport of the patient's experimental treatment and to pay for its transport.

As with other treatments such as the apomorphine pump or Duodopa®, the dose can be moderated according to the patient's needs and the progression of the disease. Filling will take place every 7 to 15 days at Lille University Hospital during phase II. The time between 2 fillings can be adapted to the patient's therapeutic needs and wishes.

The Sponsor, InBrainPharma, undertakes to do everything in its power, within the limits of the regulations and its financial resources, to extend the long-term follow-up phase in order to ensure continuity of treatment until marketing authorization is granted.

It does not seem ethical to propose surgery for acute treatment. It also seems essential to obtain reliable initial safety and efficacy data in order to judge whether or not to pursue development. The target population is Parkinsonian patients at the stage of severe L-dopa-related complications (fluctuation and dyskinesias), with a major impact on autonomy and quality of life. These are patients who require invasive second-line treatment (deep brain stimulation, gastrostomy with Duodopa® system) after an unsuccessful trial of less invasive second-line treatment with an apomorphine pump. Patients will have the choice between a validated but less ergonomic invasive treatment (gastrostomy with Duodopa® system with externalized pump or deep brain stimulation with two deep electrodes and continued oral treatment) or the present experimental treatment, the aim of which is greater ergonomics (everything is inside the body, with no need for oral treatment every 2 to 3 hours, but transcutaneous filling every 15 days).

Theoretical duration: 3 years and 9 months

PROMOTER BY DELEGATION	CHU de Lille - Direction de la Recherche et de l'Innovation 1 avenue Oscar Lambret 59037 LILLE Cedex
FINANCIER / PROMOTER	INBRAIN PHARMA
TITLE	Evaluation of the safety and efficacy of Continuous Dopaminergic Stimulation by intracerebroventricular administration of anaerobically preserved dopamine in Parkinson's disease at the stage of motor fluctuations: Single-center pilot study
SHORT TITLE	**DIVE-I (Dopaminergic restauratIon controlled by intraVEntricular administration)**
PRINCIPAL INVESTIGATOR	**Pr MOREAU Caroline**, *PU-PH, RPPS N° : 10002296704* Neurology, Université Lille, CHU Lille Neurology Department Hôpital R. Salengro CHRU de Lille - University of Lille - INSERM U1171
Scientific Manager	**Pr DEVOS David**, *PU-PH, RPPS N°: 10002296704* Medical Pharmacology Université Lille, CHU Lille Service de Pharmacologie Médicale Faculté de Médecine de Lille Pole Recherche ; 1 place de Verdun 59000 Lille University of Lille - Lille University Hospital - INSERM U1171
NUMBER OF CENTERS	1
CONCEPT	Prospective, monocentric, randomized, controlled, open-label, cross-over study of two 1-month periods and a long-term follow-up period with 2 groups: Intracerebroventricular A-dopamine versus optimized oral medical treatment in parkinsonian patients at the stage of severe motor complications (fluctuations and dyskinesias) associated with oral L-dopa. A-dopamine is an anaerobically preserved dopamine to avoid auto-oxidation and the use of preservatives. Once delivered into the cerebrospinal fluid, this dopamine acts like conventional dopamine. This therapeutic concept has been validated in three animal models of Parkinson's disease: the acute MPTP-intoxicated mouse treated for 7 days with A-dopamine, the unilaterally 6-hydroxydopamine-injured rat treated for 1 month with A-dopamine, and the chronic MPTP-intoxicated monkey treated for 1 to 2 months with A-dopamine. In addition, two advanced patients had already been treated with non-anaerobic intracerebroventricular administration of dopamine in 1984 and 1989. At that time, the patients treated were frail, with dementia and psychosis, and no precautions had been taken for the deleterious auto-oxidation of dopamine; nevertheless, tolerance was good and efficacy clearly reported. This treatment had not been developed because the concept of dopaminergic stimulation was not known until some fifteen years after the introduction of L-dopa. Moreover, the authors were afraid of dopamine oxidation. This risk is now under control. Technically, the anaerobic dopamine is contained in a high-tech pump, already on the market, implanted in the abdominal region and connected to a subcutaneous catheter to the right ventricular frontal horn. The surgical procedure is well known, as it takes around 30 to 60 minutes to perform for hydrocephalus requiring ventricular shunting. The equipment (pumps and catheters) is used for thousands of patients who benefit from the procedure. intrathecal administration of baclofen or analgesics. Adapting the equipment to intraventricular administration just requires a little more time.

	The same catheter can be used for long lengths, so there are no particular technical problems. The pumps can be precisely adjusted by telemetry to ensure continuous, personalized administration, as is the case with baclofen, for example. In the long term, bi-monthly transcutaneous filling will eliminate the need for patients to take oral L-dopa every 2 to 3 hours, thus ensuring maximum ergonomics. For the well-being of patients and to make their day-to-day lives easier, the sponsor is using a homecare provider to fill the pump in the patient's home at the end of phase 2, when the patient begins his or her long-term follow-up phase. It should be noted that the experimental treatment will be transported in accordance with the temperature and environmental conditions specified by the sponsor, and in compliance with the RGPD. The conditions of the care provider's intervention are defined in this protocol. Intracerebroventricular administration has been used in numerous therapeutic trials (e.g. administration of growth factors), antiepileptic).
ETHICAL CONSIDERATIONS	For ethical reasons, it does not appear feasible to perform a neurosurgical pump placement procedure with intracerebroventricular dopamine administration in healthy subjects. Likewise, it does not appear feasible to perform this procedure on Parkinson's patients for administration lasting only a few hours or days. What's more, a very significant symptomatic therapeutic benefit is logically expected, and this is likely to encourage patients to ask to benefit from this innovation in the longer term. As was the case for deep brain stimulation in Parkinson's disease or Duodopa®. Implanted patients have retained their treatment over the long term. However, this long-term approach requires A first validation of safety, followed by a second validation of efficacy compared with the reference oral treatment.
EXPERIMENTAL DESIGN	Our aim is to restore the natural circadian cycle of dopamine in the brain by administering it intra-ventricularly. Two patients have already been treated in the 80s, with very reassuring safety data despite the absence of precautions against dopamine oxidation. To take account of ethical considerations and patient care, the protocol will be carried out sequentially to provide initial safety data, followed by efficacy data on motor fluctuations. - **Feasibility and safety phase 1 :** Initiation of treatment in 5 patients with : - Collection of all adverse events and especially serious and unexpected adverse events reviewed by an Independent Monitoring Committee (IMC) after the A-dopamine dose titration phase: o In the absence of serious unexpected adverse events. (apart from the rare surgical risks of haemorrhage and infection which do not jeopardize the patient's vital and functional prognosis, see section 7.1.2), other patients may be included o If two or more serious and unexpected adverse events occur, after consultation with the Supervisory Committee

Independent, only 5 new patients could be included.
  - Then, in the absence of serious unexpected adverse events, other patients could be included.
  - If two new serious and unexpected adverse events occur, the Independent Monitoring Committee may decide to stop the study. This decision to stop the study if at least 4/10 patients experience serious adverse events will serve as a clear follow-up rule for the ISC. However, this decision may be modulated according to the severity and diversity of adverse events impacting the well-being of patients, and whether they are totally unexpected or become predictable and manageable. (A list of expected rare adverse reactions has been drawn up for the surgical procedure, the dopamine and the medical device, in addition to the investigator's brochure, the investigational drug file and the medical device file. (see section 7.1.2)).

- Monitor blood pressure, pulse and ECG after each dose increase and change in concentration.
- Blood and urine tests for dopamine and its metabolites (HVA and 5-cysteinyl-dopamine) once a week, with a change in dose and concentration.

Any change in these parameters would lead to discontinuation of titration until resolution of the abnormality and a cardiological opinion. In the event of persistent abnormality, a new cardiological opinion would be sought, together with the opinion of the Independent Monitoring Committee (IMC), to decide whether or not to continue treatment.

- **Validation and effectiveness phase 2**

Continuous administration of dopamine should prevent the highly deleterious fluctuations in motor control induced by treatment with oral L-dopa, which has a half-life of 2 to 3 hours. Two patients have already been treated in the 80s, with data showing efficacy on fluctuations. This is a proof-of-concept, prospective, monocentric, randomized, controlled study involving a maximum of 12 patients treated according to a cross-over design of 2 4-week periods separated by an in-hospital therapeutic switch. The previous treatment will be stopped at the end of period 1 and replaced by the new treatment, without discontinuity and progressively, so that the patient is always treated. After stabilization, and in the absence of adverse effects, the patient will return home and begin period 2 assessments one week later, in order to eliminate any residual effects of the first treatment. Patients will be randomized into two groups according to the following treatment sequences:

- group 1 (n= 6) :
  - period 1 dopamine treatment ICV
  - period 2 optimized oral treatment

	- group 2 (n= 6) :
	  o period 1 optimized oral treatment
	  o period 2 dopamine treatment ICV
	
	- **Long-term follow-up :**
	
	For the well-being of patients and to make their daily lives easier, the sponsor calls on a homecare provider to fill the pump in the patient's home at the end of phase 2, when the patient begins his or her long-term follow-up phase.
	The conditions of the care provider's intervention are defined in this protocol.
	
	Follow-up visits every 6 months with :
	o MDS UPDRS part III in On Drug, dyskinesia scales (Abnormal Involuntary Movement Score (AIMS) and Dyskinesia Rating Scale (DRS)) in On Drug
	o Tolerance assessment: general clinical examination, tolerance of product administered
	o Biology: standard biological workup and 24-hour urine test
	o Questionnaires: MDS-UPDRS parts I, II, and IV, patient CGI and physician CGI, Schwab and England scale, Epworth scale, Parkinson's Disease Sleep Scale, PDQ39
	o Cognitive examination: MOCA, NPI, PAS, LARS, ECMP
	o Psychiatric examination
	o 7-day actimetry-free diary
	
	This long-term follow-up phase of the protocol will end when the last treated patient in the study reaches the last visit of Phase II (Visit 3).
	
	Estimated date of last patient last visit: 30/06/2024

OBJECTIVES	**<u>Main objective of phase 1</u> :** Evaluate the feasibility and safety of dopamine ICV administration by recording adverse events, including the absence of serious unexpected adverse events. **<u>Main objective of phase 2:</u>** To evaluate the efficacy on motor and non-motor complications of continuous diurnal intracerebroventricular administration of A-dopamine using the telemetry-controlled intra-abdominal pump delivery system compared with optimized oral medical treatment (usual treatment). A-dopamine is a dopamine that is formed, preserved and administered anaerobically to avoid degradation by dopamine auto-oxidation. A-dopamine is therefore a classic dopamine, i.e. without preservatives or excipients, which enters the central nervous system from the ventricular system, in particular the 3ème ventricle adjacent to the striatum, the nucleus whose dopaminergic content is deficient in Parkinson's disease. DIVE compensates for this deficit in a continuous and circadian fashion.

	Main objective of the long-term follow-up phase: Evaluate the maintenance of efficacy on motor and non-motor complications of continuous diurnal intracerebroventricular administration of A- dopamine over the long term **Secondary objectives of phase 2 :** **Evaluate the efficacy of DIVE compared with the reference treatment on :** - motor aspects (MDS-UPDRS part III) - cognitive-behavioral aspects: sleepiness, anxiety, depression, apathy, sleep, hallucinations and cognition (MDS- UPDRS parts I, II, and IV, Epworth Sleepiness Scale, Parkinson's Disease Sleep Scale, MOCA, NPI, PAS, LARS, ECMP) - quality of life (PDQ39) - general condition (Clinical Global Impression (CGI) patient (assessment of condition and assessment of improvement), CGI physician (assessment of condition and assessment of improvement), Schwab and England scale) - tolerability: assessment of the tolerability of DIVE compared with oral treatment - psychiatric status (consultation without scales to assess DIVE's psychiatric tolerance, in particular the absence of thymic, anxious or psychotic decompensation, etc.) **Secondary objectives of the long-term follow-up phase:** Evaluate the continued efficacy on motor and non-motor complications and safety of continuous diurnal intracerebroventricular administration of A-dopamine over the long term. - motor aspects (MDS-UPDRS part III) - cognitive-behavioral aspects: sleepiness, anxiety, depression, apathy, sleep, hallucinations and cognition (MDS- UPDRS parts I, II, and IV, Epworth Sleepiness Scale, Parkinson's Disease Sleep Scale, MOCA, NPI, PAS, LARS, ECMP) - quality of life (PDQ39) - general condition (Clinical Global Impression (CGI) patient (assessment of condition and assessment of improvement), CGI physician (assessment of condition and assessment of improvement), Schwab and England scale) - tolerability: assessment of the tolerability of DIVE compared with oral treatment - psychiatric status (consultation without scales to assess DIVE's psychiatric tolerance, in particular the absence of thymic, anxious or psychotic decompensation, etc.) **Phase 2 Exploratory Objectives**: Study of parameters with theranostic biomarker value to help anticipate the safety and benefit of DIVE for future trials: - Blood measurements of dopamine and its metabolites at the end of each period (1 and 2) 2 hours after dopamine or L-Dopa administration has begun - Pharmacogenetic parameters of dopamine metabolism (single blood test at baseline visit (V0)) - **Exploratory objectives for the long-term follow-up phase:** - Blood tests for dopamine and its metabolites and at the end of the test of each period (1 and 2) 2 hours after the start of dopamine or L-Dopa administration

EVALUATION CRITERIA	Phase 1 primary endpoint

	Assessment of the feasibility of DIVE treatment with : • Collection of adverse events, particularly serious and unexpected adverse events, reviewed by an Independent Monitoring Committee, during the dopamine dose titration phase. In particular, the following complications will be investigated: - Severe, life-threatening infection - Severe hemorrhage threatening the patient's vital and functional prognosis - Sharp or rapid worsening of motor and/or non-motor symptoms of Parkinson's disease over one month (i.e. more than double the classical worsening points over 3 months or more than 6 points of the total MDS UPDRS score over one month with the optimal dose of A-dopamine: best on condition). - Neurological deficits other than Parkinson's disease symptoms - Status epilepticus - Deaths in the post-operative period - No positive effect of dopamine at all • Monitor blood pressure, pulse and ECG after each dose increase and change in concentration. • Blood and urine tests for dopamine and its metabolites HVA and 5-cysteinyl-dopamine once a week, with a change in dose and concentration. Rule: adverse events will be analyzed throughout the study. Only one patient will be included at a time during the surgery phase, post-surgery monitoring and up to the maximum possible titration. All safety data will be analyzed by an Independent Monitoring Committee (IMC). The safety data from the first 5 patients will be analyzed before authorizing or not the inclusion of new patients in phase 1. A report describing all the safety and clinical data from the first 5 patients treated in phases 1 and 2 will also be drawn up and sent to the ANSM. We expect no changes in blood pressure, pulse rate or ECG associated with increased doses of A-dopamine. We do not expect any increase in blood or urine levels of dopamine and its metabolites HVA and 5-cysteinyl-dopamine associated with dose-escalation of A-dopamine. Any change in these parameters would lead to discontinuation of titration until resolution of the abnormality and cardiological advice. In the event of persistent abnormality, a new cardiological opinion would be sought, together with the opinion of the Independent Monitoring Committee (IMC), to decide whether to continue or stop treatment. **Phase 2 primary endpoint :** **- Percentage of time off = slowed down and/or blocked = Percentage of Time Over Target (PTO)** by actimetry with the Parkinson KinetoGraph (PKG) system from Global Kinetics Corporation (GKC). PTA is the proportion of time over the nycthemeral period when the subject's recording shows a bradykinesia score (motor slowing or even blocking) greater than or equal to 26 (BKS≥26). The PTA does not include periods of immobility, removal of the actimeter and sleep. This parameter therefore makes i t possible to integrate periods of insufficient motor control through treatment (Farzanehfar et al., 2018). The average of the two recordings

	performed during the first and fourth weeks of each treatment period. This is **an objective criterion measured blindly by a third party**. **Primary endpoint for long-term follow-up :** The number of hours with either perfect or slightly slower control on the 7-day diary. It will be compared with that obtained in phase 2 to demonstrate the maintenance of long-term efficacy control. **Secondary endpoints :** - **The other validated actimetry criteria** (Farzanehfar et al., 2018; expert conference: Odin et al., 2018) **will analyze motor control:** - ***OS1: BKS*** (bradykinesia score): the bradykinesia score, calculated every 2 minutes throughout the recording period. The median BKS value is correlated with the bradykinesia disability score measured clinically by the UPDRS Part III score. - ***OS2: DKS*** (dyskinesia score): the dyskinesia score is calculated every two minutes throughout the recording period. The median DKS value is correlated with the dyskinesia score measured clinically by the modified Abnormal Involuntary Movement Score. - ***OS3: PTI*** **(**Percent Time Immobile): the percentage of time spent motionless, which represents the absence of movement during the 2-minute recording and is correlated with sleep in polysomnography. - ***OS4: FDS*** (Fluctuation Dyskinesia Score): fluctuations and dyskinesias score estimating the amount of variability in relation to optimal control, i.e. insufficient control (bradykinesia) or overdose (dyskinesias). - ***OS5: PTT*** (Percent Time Tremor): the percentage of time with tremor during the 2-minute recording. Tremor is considered present if it exceeds 1%. For all these criteria, the two recordings made during the first and fourth weeks of each treatment period will be averaged. Other clinical criteria: - ***OS6: MDS UPDRS part III*** - ***OS7: Patient diary***: We will measure OFF and ON times with and without overdosing and their severity on the motor diary completed by the patient at home during the first and fourth week of each treatment period. The percentage of time spent "on" corresponding to a satisfactory "unblocked" state, with no dyskinesias (involuntary overdosage movements) or mild dyskinesias or mild blockages rated on an ON/OFF diary (blockages and moderate and severe dyskinesias should be avoided). - ***OS8: Dyskinesia scales*** (Abnormal Involuntary Movement Score (AIMS) and Dyskinesia rating scale (DRS)) - ***OS9 (9-1-9-10)****:* MDS-UPDRS parts I, II, and IV, Epworth Sleepiness Scale, Parkinson's Disease Sleep Scale, MOCA, NPI, PAS, LARS, ECMP - ***OS10****:* PDQ39 self-questionnaire - ***OS11-1-3****:* Clinical Global Impression (CGI) patient (assessment of condition and evaluation of improvement), CGI physician (assessment of condition and evaluation of improvement), CGI physician (assessment of condition and evaluation of improvement), CGI physician (assessment of condition and evaluation of improvement). improvement assessment), Schwab and England scale

	- ***OS12:*** Frequency of adverse events reported by the patient and/or observed by the physician on clinical examination, ECG, blood pressure, pulse and laboratory tests (standard biology, biological iron assay, blood and urine assays for dopamine and its metabolites HVA and 5-cysteinyl-dopamine) and changes in weight, temperature and blood pressure on orthostatic hypotension test. - ***OS13:*** Psychiatric tolerance (no thymic, anxious or psychotic decompensation, etc.) assessed by means of a simple interview with a psychologist about the disorders experienced over the past month. **Secondary endpoints in the long-term follow-up phase** The same endpoints as in phase 2 will be studied, with the exception of actimetry: OS6-OS13 **Exploratory criteria**: - Biology: blood and urine assays for dopamine, its metabolites HVA, and 5-cysteinyl-dopamine in conjunction with markers of oxidative stress (MDA, 4-HNE, 8 oxoDG) and axonal destruction (filament light chain) in blood after 2 h of treatment in the morning on an empty stomach (either 2 h after the first dose of oral treatment, or 2 h after the first diurnal dose of A-dopamine). - Pharmacogenetic parameters of dopamine metabolism (DaT, COMT, MAO, DDC, ceruleoplasmin) **Exploratory criteria for the long-term follow-up phase :** Biology: blood and urine determinations of dopamine, its metabolites HVA, and 5-cysteinyl-dopamine in conjunction with markers of oxidative stress (MDA, 4-HNE, 8 oxoDG) and axonal destruction (filament light chain) in blood after 2 h of treatment in the morning on an empty stomach (either 2 h after the first dose of oral treatment, or 2 h after the first dose of oral treatment). diurnal dose of A-dopamine)
INCLUSION CRITERIA	- Parkinson's disease at the stage of L-dopa-induced severe motor and non-motor complications - Men or women over 18 - Parkinson's disease according to MDS criteria - Severe motor complications including motor fluctuations with at least 2 hours of Off and 1 hour of dyskinesias uncontrolled by optimized oral drug therapy (i.e. at least 5 doses of L-dopa and the addition or trial of a dopaminergic agonist (if tolerated) per os or by apomorphine pump). - The patient meets the criteria for a second-line invasive treatment such as deep brain stimulation (subthalamic or medial pallidum) or intrajejunal administration of levodopa gel (Duodopa®). - Patients with a contraindication or who prefer this invasive therapeutic alternative to the other two existing and validated treatments (subthalamic stimulation or Duodopa®) because of its advantages: lower theoretical risk of intracerebroventricular delivery compared with subthalamic stimulation and better ergonomics than Duodopa® but with the disadvantage of a benefit not yet demonstrated). - Social security - Able to provide free and informed consent to participate in research

	- Patient willing to comply with all study procedures and duration - Patient not considering not of modifying his style of lifestyle (nutritionally, physically and socially) during his study participation
NON-INCLUSION CRITERIA	- Over 75 years of age - Subjects not receiving at least 5 doses per day of oral dopaminergic therapy - Subject without a prior trial of an apomorphine pump (of lower risk); apomorphine pump treatment being a failure or a contraindication or refused by the patient - Psychiatric history using the semi-structured psychiatric interview with DSM IV MINI: decompensated bipolar illness, psychotic state, current severe depression. Dysthymia and an isolated history of depression are not exclusion criteria. - Patient with parkinsonian dementia (DSM IV and MDS criteria and MOCA score < or equal to 22) - Isolated patient, defined as the absence of a caregiver present at least 3 hours/day in the patient's home. - History of a fall in the last 6 months and/or a score >1 on items 2.12 (Walking and balance) and/or 3.12 (Postural stability) of the MDS-UPDRS scale - Presence of another serious pathology threatening short- or medium-term vital prognosis, malnourished or cachectic patient. - Hemostasis disorders - Cardiac rhythm disorders and/or heart failure not controlled by treatment - Uncontrolled blood pressure release - Breastfeeding and pregnancy - Women of childbearing age without effective contraception - Contraindication to general anaesthesia - Taking treatments containing guanethidine or its relatives, or non-selective and selective monoamine oxidase A inhibitors (iproniazid, moclobemide, toloxatone) - Neurosurgical contraindication (severe cerebral atrophy, brain tumor, infarction or other cerebral pathology, CSF flow disorder) - Contraindication to abdominal placement of a subcutaneous pump and catheter that impairs healing and transcutaneous filling (e.g. major obesity, skin pathology, etc.). - Contraindication to MRI (pacemaker, claustrophobia, etc.) and/or intolerance to gadolinium - Active infectious pathology (including Covid-19 infection) - Immunologically deficient pathology likely to promote superinfection of equipment - Patients under guardianship or trusteeship - Patient already participating in another therapeutic trial using an investigational drug or in an exclusion period
EXPERIMENTAL DRUG	**During safety phase 1**: An initial hospital titration will be carried out with a maximum daily increase of 20 mg (1.11 mg/h over 18 h) up to a first maximum level of 100 mg (5.55 mg/h), then titration will continue on an outpatient basis under real-life conditions, with a weekly increase of 20 mg (1.11 mg/h over 18 h) which may be repeated 2ème times a week, i.e. a maximum of 40 mg/week. until the dose required for satisfactory motor control is reached, with or without a minimal residual dose of oral dopaminergic treatment.

	The minimum effective dose is planned between 10 and 18 mg/h, i.e. between 180 and 324 mg per day (5 a.m.-11 p.m.). This titration plan is considered to be maximal: if there is any doubt about efficacy and/or tolerance, titration should be stopped for a few days (1 to 3 days) to avoid a cumulative effect and allow precise definition of the minimum effective dose. If efficacy is equivalent to oral intake, the dose will not be increased any further. **During phase 2 efficacy and tolerance testing**: A-dopamine will be administered for 30 days at the minimum dose, with the option of retaining a residual dose of oral treatment if deemed necessary by the investigator and for patient comfort. During the other 30-day period of the phase 2 cross-over design, the optimized oral treatment will be resumed and the A-dopamine will be removed from the pump and replaced by anaerobic saline. **During the long-term follow-up phase** At the end of phase 2, A-dopamine will be maintained over the long term at a dose which allows satisfactory motor control (less than 1 h of moderate or severe offending per day and less than half an hour of dyskinesia), with or without a minimal residual dose of oral dopaminergic treatment (50 mg of L-dopa every 2 to 3 h). To achieve the ideal therapeutic solution, i.e. no more oral treatment at all, and therefore no more Off, requires a very slow and steady increase in A-dopamine, starting at doses of 10 mg/h, to avoid being limited by the undesirable effects of drowsiness and nausea. In fact, as with apomorphine (less well tolerated), good control is achieved with high doses when this is done. This can advantageously be achieved during this phase with a very slow, moderate increase in A-dopamine. For the well-being of patients and to make their daily lives easier, the sponsor calls on a homecare provider to fill the pump in the patient's home at the end of phase 2, when the patient begins his or her long-term follow-up phase. The conditions of the care provider's intervention are defined in this protocol.
NUMBER OF PARTICIPANTS	Inclusion of one patient at a time in phase 1, then after 5 patients, validation and inclusion of a minimum of 7 other patients, for a maximum of 12 subjects treated, depending on the capacity of Lille University Hospital's central pharmacy. which cannot treat more than 12 patients with a weekly refill.
INVESTIGATION PROCEDURE AND DIFFERENCES FROM STANDARD CARE	Subjects will be included during a consultation at the CIC, after information, informed consent, verification of inclusion and non-inclusion criteria, history and concomitant treatments, previous and current psychiatric disorders or symptoms, and MoCA test. **Baseline visit V0 (neurology hospitalization, day 15):** Visit to evaluate the indication for second-line DIVE therapy. : • Full medical check-up (clinical examination, ECG, biology and chest X-ray) • Biological collection • Acute L-dopa administration test (MDS-UPDRS part III, video dyskinesia scales) • MDS-UPDRS total

- Physician (CGI-physician) and patient (PDQ- 39, CGI-patient, Schwab and England scale, Epworth scale, Parkinson's Disease Sleep Scale) questionnaires
- Neuropsychological examination (NPI, PAS, LARS, ECMP)
- Brain MRI

Neurosurgical implantation procedure (maximum D15-J30 from baseline)

An anesthetic check-up is carried out a few days before the operation, with an outpatient cardiac ultrasound. A Covid-19 test is performed prior to the operation, if required by health measures relating to the Covid-19 pandemic. If there are no symptoms suggestive of Covid-19 and the test is negative, the patient is hospitalized the day before the operation. The procedure for implanting the catheter in the right frontal horn near Monro's interventricular foramen will be carried out by stereotaxis, with direct mapping on brain MRI using the O Arm system, and catheter placement by Renishaw's Neuro Mate robot by Prof. Nicolas Reyns and Dr. Gustavo Touzet, using the same stereotactic procedure as for the implantation of two deep stimulation electrodes. However, the procedure for implanting the catheter in the frontal horn is simpler in terms of location than the subthalamic nucleus, because the ventricular target is larger (10 mm) and there is no need for intra-target somatotopy. In fact, the subthalamic stimulation electrode must be positioned in the posterior and lateral part of the subthalamic nucleus (posterior and lateral part of a grain of rice). Estimated locating time is 30 to 60 minutes for the ventricle. The catheter is attached to the right frontal bone of the skull using Medtronic's stim lock® system, then tunnelled under the skin to connect to the pump implanted in the abdominal region and attached to the rectus abdominis muscle. The skin suture is made laterally to the pump, i.e. at a distance from the filling ports. When implanted, the pump will contain 20 mL of anaerobic saline and will be programmed in the OR.

Phase 1 study and titration

- **In hospital** (for 10 days)

- D1 to D5: ***post-operative monitoring*** in neurosurgery, modelled on post-implantation monitoring for deep brain stimulation.
- Postoperative CT scan within 48 hours to verify absence of hematoma
- Rigorous monitoring to ensure there are no adverse effects (hematoma, infection, equipment malfunction (see section 7.1.2)).

- D6: ***transcutaneous filling of the pump with A-dopamine,*** if general condition and abdominal skin condition allow. In the event of slower healing, the patient may be discharged from hospital until D15 to D30, before returning to the hospital to perform the first A-dopamine filling and begin titration. During this period, the pump will be filled with anaerobic saline and the oral treatment will be maintained.

- D6-J10 (maximum): ***initial hospital titration***

- Daily titration of 20 mg (1.11 mg/hr over 18 hrs) up to an initial maximum of 100 mg (5.55 mg/hr)
- Daily monitoring of blood pressure, pulse and ECG after each daily dose increase and change in concentration
- Blood and urine tests for dopamine and its metabolites HVA and 5-cysteinyl-dopamine before and at the end of hospital titration

    - **Return home and continuation of therapeutic adaptation** (for 13 weeks)

- Continued adaptation of the best minimal effective dose under real-life conditions. Depending on tolerability and efficacy, a slow weekly titration will be continued in maximum increments of 20 mg (1.11 mg/h over 18 hours), which may be repeated 2ème times a week, i.e. a maximum of 40 mg/week.
- Monitoring for adverse events (daily telephone calls)
- The patient will be reviewed weekly in consultation for changes in pump output via telemetry and monitoring of neurological, psychiatric and cardiovascular safety (pulse, blood pressure, ECG).
- Blood and urine determination of dopamine and its metabolites HVA and 5-cysteinyl-dopamine once a week, with a change in dose and concentration.
- The pump is refilled every 15 days or every week as required to ensure and control the quality of the A-dopamine.

For the patient's comfort, oral treatment should be maintained during titration to avoid transient motor aggravation. As soon as the first positive effects are felt, the oral treatment is gradually reduced, while cerebral dopamine is cautiously increased.
The flow rate is set exclusively by telemetry. When the

patient is titrated and satisfied, he or she moves on to phase

2.

Times are indicative and may vary depending on the subject's state of health and feedback from the study.

Phase 2 study

- **Follow-up visit V1: Phase 2 baseline** (one-day hospitalization in Neurology)
    - Randomization
    - Change of therapy if the patient is randomized to group 2 (oral treatment) by an unblinded third-party neurologist. The patient will be monitored in hospital during the change of therapy.
    - MDS UPDRS part III in On Drug, dyskinesia scales (Abnormal Involuntary Movement Score (AIMS) and Dyskinesia Rating Scale (DRS)) in On Drug

	○ Tolerance assessment: general clinical examination, collection of surgical complications, tolerance of product administered ○ Biology: standard biological workup ○ Questionnaires: MDS-UPDRS parts I, II, and IV, patient CGI and physician CGI, Schwab and England scale, Epworth scale, Parkinson's Disease Sleep Scale, PDQ39 ○ Cognitive examination: MOCA, NPI, PAS, LARS, ECMP At the end of the V1 visit, the patient returns home for 4 weeks with : ○ Measurement of actimetry (PKG) during weeks 1 and 4 ○ Motor diary completed by the patient during the first and fourth weeks. If the patient is randomized to group 1 (period 1: dopamine ICV treatment), he or she will be seen again at the hospital 15 days after the V1 visit, for transcutaneous pump filling by a nurse. Tolerance will be assessed at this time, with blood pressure, pulse and ECG monitored. • **Follow-up visit V2: End of period 1** (one-day hospitalization in Neurology, 4 weeks after V1) ○ MDS UPDRS part III in On Drug, dyskinesia scales (Abnormal Involuntary Movement Score (AIMS) and Dyskinesia Rating Scale (DRS)) in On Drug ○ Tolerance assessment: general clinical examination, collection of surgical complications, tolerance of product administered ○ Biology: standard workup and specific biology (oxidized dopamine metabolites) ○ Questionnaires: MDS-UPDRS parts I, II, and IV, patient CGI and physician CGI, Schwab and England scale, Epworth scale, Parkinson's Disease Sleep Scale, PDQ39 ○ Cognitive examination: MOCA, NPI, PAS, LARS, ECMP ○ Psychiatric assessment • Change of therapy (oral treatment or cerebral dopamine) by a non-blinded third-party neurologist, at the end of the visit and under close medical supervision. - if the patient is randomized to group 1 (period 1: ICV dopamine treatment), the dopamine will be removed from the pump and replaced by anaerobic saline. At the same time, the optimized oral treatment will be resumed at the usual doses. - if the patient is randomized to group 2 (period 1: optimized oral treatment per os), the therapeutic change will consist of a progressive increase in cerebral dopamine and a concomitant reduction in oral treatment, with dopamine being reintroduced over a 24-hour period in hospital. Patient to return home if no effect during these 24 hours, then titration is carried out over 15 days. In order not to induce any difference between the 2 cross-over

A 15-day period will also be observed for the transition from dopamine to oral treatment.

This corresponds to the time needed to eliminate any potential residual effects of the treatment administered in period 1.

Thus, at the patient's home, 3 weeks after the end of visit 2 (i.e. 1 week after the 15-day titration period), the second 4-week period begins with :

- Measurement of actimetry (PKG) during weeks 1 and 4
- Motor diary completed by the patient during the first and fourth weeks.

If the patient is randomized to group 2 (period 2: dopamine ICV treatment), he or she will be seen again at the hospital 15 days after the V2 visit, for transcutaneous pump filling by a nurse. On this occasion, a tolerance evaluation will be carried out, with monitoring of blood pressure, pulse and ECG.

- **Follow-up visit V3: End of period 2** (one-day hospitalization in Neurology, 4 weeks after V2)
  - MDS UPDRS part III in On Drug, dyskinesia scales (Abnormal Involuntary Movement Score (AIMS) and Dyskinesia Rating Scale (DRS)) in On Drug
  - Tolerance assessment: general clinical examination, collection of surgical complications, tolerance of administered product
  - Biology: standard workup and specific biology (oxidized dopamine metabolites)
  - Questionnaires: MDS-UPDRS parts I, II, and IV, patient CGI and physician CGI, Schwab and England scale, Epworth scale, Parkinson's Disease Sleep Scale, PDQ39
  - Cognitive examination: MOCA, NPI, PAS, LARS, ECMP
  - Psychiatric assessment

Long-term follow-up phase

- Consultation visits every 6 months after V3:
  - MDS UPDRS part III in On Drug, dyskinesia scales (Abnormal Involuntary Movement Score (AIMS) and Dyskinesia Rating Scale (DRS)) in On Drug
  - Tolerance assessment: general clinical examination, tolerance of product administered
  - Biology: standard biological workup and 24-hour urine test
  - Questionnaires: MDS-UPDRS parts I, II, and IV, patient CGI and physician CGI, Schwab and England scale, Epworth scale, Parkinson's Disease Sleep Scale, PDQ39
  - Cognitive examination: MOCA, NPI, PAS, LARS, ECMP
  - Psychiatric examination
  - 7-day actimetry-free diary

For the well-being of patients and to make their daily lives easier, the sponsor calls on a homecare provider to fill the pump in the patient's home at the end of phase 2, when the patient
begins its long-term follow-up phase.

	The conditions of the care provider's intervention are defined in this protocol.
BENEFIT ASSESSMENT AND RISKS RELATED TO SEARCH	*Expected benefits :* This therapeutic concept has previously been validated in three models Parkinson's disease *in vivo* animals: mice intoxicated acutely and monkeys chronically intoxicated with MPTP, rats unilaterally injured at the 6 hydroxydopamine (Laloux et al., 2016; Moreau et al., in revision in Mov Disorders). After treatment with A-dopamine, motor function was restored to 100%. A powerful neuroprotective effect was even observed in the of MPTP mice. Two patients with advanced Parkinson's disease have already been treated by intracerebroventricular administration of anaerobic dopamine in 1984 and 1989. Tolerance was judged to be excellent. Similarly, the efficacy on motricity reached the same level as oral administration of L-dopa. However, at that time, the pathophysiology of Parkinson's disease was not as well known as it is today. In particular definition of dementia and parkinsonian psychosis were not and both patients were already clearly at a stage of dementia with hallucinations that reappeared on dopamine as with L-dopa. Similarly, the need not to maintain a constant flow rate but to differentiate a high dose day and weak at night only became known with the more recent experience of apomorphine and duodopa pumps. We therefore expect the absence of tachyphylaxis by following the restoration of the circadian rhythm. Finally, the technological level of pumps at the time was inferior to that of current pumps, which may account for a more efficient administration with doses less suited to the patient's condition. Despite these major limitations, the two authors conclude that "this treatment has been well tolerated for several months (including 10 months in one patient) and looks promising if dopamine oxidation can be controlled". They feared oxidation of dopamine due to tachyphylaxis observed and because preclinical publications have clearly demonstrated (DeYebenes et al., 1987). This oxidation of dopamine is now controlled with anaerobic dopamine. The only undesirable effects reported were rhinorrhea, yawning and a very brief facial flush during the start of infusion. The expected benefits are a major reduction in complications motor and non-motor, thanks to the concept of restoring stimulation continuous and circadian dopaminergic activity. Improved ergonomics use is also expected in comparison with the apomorphine pump and Duodopa® , since the pump is inside the body, as is the case with for the thousands of young patients with pump-treated spasticity or severe pain treated with morphine. The benefits compared to deep brain stimulation will be no worsening of axial motor skills (dysarthria and walking) and absence of behavioral worsening (impulsivity, suicidal risk, etc.), apathy and depression) sometimes secondary to subthalamic stimulation and/or reduction in dopaminergic treatment oral. Similarly, the risks of surgery and neurosurgery will be reduced. than subthalamic stimulation, as the surgical procedure is less time-consuming. that of a simple cerebrospinal fluid shunt such as a

	hydrocephalic neonates and demented patients with a history of dementia. hydrocephalus at normal pressure. Unlike implantation deep brain, the introduction of DIVE requires the shallow delivery material, frontal cortex to reach the

	ventricular horn, considerably limiting the risk o f deep hemorrhage. *Foreseeable risks :* In order to limit risks, management will be multidisciplinary at the Clinical Investigation Center and the Neurology and Neurosurgery Department, which have experience of Parkinson's surgery since 1997. Intracerebroventricular administration of treatment is not yet highly developed, but trials have already been carried out (Paul et al., 2015 with administration of PDGF-BB growth factor in Parkinson's disease; see review for neurodegenerative diseases Ruozi et al., 2012; Tovar-Y-Romo et al., 2014) and the risks are well known thanks to the data from these trials, the data from the first two patients treated with dopamine (Venna *et al.*, 1984; Horne *et al.*, 1989) and above all the thousands of patients treated with baclofen and morphine. - With regard to the risk of equipment malfunction, all risks have been the subject of training and the implementation of a procedure consisting in shutting down the pump, completely removing the dopamine from the pump and catheter, administering an anaerobic saline solution and resuming conventional oral treatment during the repair period. - For safety reasons, no MRI will be performed on the pump during the 2-month study period. In the event of an emergency MRI for a comorbidity unrelated to the disease or treatment, a procedure for stopping and draining the pump has been planned. - Intraoperative anesthetic risks - Extra-dural or sub-dural bleeding risk - Infectious risks on equipment - Side effects of dopamine at the central level (See experimental drug file) - Risks associated with preoperative MRI using Gadolinium-based contrast medium - Risks associated with blood sampling - Risks associated with cardiac echography - Risks associated with CT scanning
PERIOD OF PROHIBITION OF SIMULTANEOUS PARTICIPATION, PERIOD OF EXCLUSION	The research subject may not participate in another study for the duration of his or her participation and for one month following the last visit. i.e. : Period during which simultaneous participation is prohibited: for the entire duration of the patient's participation in the study (i.e. phases 1 and 2 and during long-term follow-up). Exclusion period: 1 month after last long-term visit
JUSTIFICATION FOR SETTING UP OR NOT SETTING UP AN INDEPENDENT SUPERVISORY COMMITTEE	In view of the study's objective, an Independent Monitoring Committee (IMC) is to be set up. The ISC members identified for the study are responsible for protecting the safety of study participants, evaluating t h e safety and efficacy of all study procedures, and ensuring the smooth running and overall conduct of the study. It will be composed of two neurologists and a neurosurgeon. This committee will serve as an independent advisory group to the principal investigator, and the sponsor is required to provide recommendations on the continuation and discontinuation of the study. The ISC will : • Analyze patient safety by assessing the benefit/risk balance and other factors that may influence study results;

	• Take into account factors external to the study, such as scientific or therapeutic developments that may have an impact on the safety of participants or on the ethics of the study; • Ensure the relevance of the study throughout its duration; • Review documentation concerning serious adverse events and safety reports and make recommendations regarding the safety of study participants; • Make recommendations on continuation, suspension, discontinuation or other modifications to the study based on accumulated experience, including observed beneficial or adverse effects, to the principal investigator and study sponsor. This committee is responsible for identifying any factors that could influence the overall conduct of the study. The ISC will be informed immediately of any serious adverse event. All safety information will be transmitted after each patient's inclusion. By default, the ISC will meet every six months to analyze the benefit/risk balance. The ISC may adapt the frequency of meetings according to safety data. Phase 1 in particular: One patient will be included at a time. The safety data from the first 5 patients will be analyzed before authorizing or not the continuation of inclusions. a. In the absence of serious and unexpected adverse events after the first 5 patients (apart from the rare surgical risks of bleeding and infection of mild to moderate consequences, i.e. not life-threatening or functionally compromising), the remaining ~~15~~ patients can be included. b. In the event of two or more serious and unexpected adverse events, only 5 new patients may be included, on the advice of the Independent Monitoring Committee. i. Then, in the absence of serious unexpected adverse events, the remaining ~~10~~ patients could be included. ii. If two new serious and unexpected adverse events occur, the Independent Monitoring Committee may decide to stop the study. This decision to stop the study if at least 4/10 patients experience serious adverse events will serve as a clear follow-up rule for the ISC. However, this may be modulated according to the severity and diversity of the effects impacting the well-being of individuals, and whether they are totally unexpected or become predictable and manageable. (A list of expected rare adverse events has been drawn up for the surgical procedure, the dopamine and the medical device, in addition to the investigator's brochure, the investigational drug file and the medical device file. The data collected will be used to draw up and submit to the ANSM a descriptive report of all safety and clinical data from the first 5 patients treated in France. phase 1 and 2.
STATISTICAL ANALYSIS	All statistical analyses will be carried out independently by CHU's methodology, biostatistics and data management unit (UMBD). As this is a proof-of-concept study, analyses will be carried out on analyzable subjects (complete-case analyses). To meet the main objective, the treatment effect will be evaluated by a linear mixed model including treatment, period and treatment*period interaction as fixed effects and a random effect

	patient to account for correlation between repeated measurements. If the carryover effect (interaction) is significant, the treatment effect will be estimated using only data from period 1 as in a parallel design (Student's t-test); otherwise, the treatment effect will be estimated using only data from period 2 as in a parallel design (Student's t-test). will be estimated by a linear mixed model with treatment and period as fixed effects.
DURATION OF STUDY	The duration of active patient participation for periods 1 and 2 is seven months, including four months under treatment (three months of titration and one month of efficacy study in phase 2). However, for phase 1, these times are indicative and may vary significantly depending on the patient's state of health and feedback from experience. The long-term follow-up phase of the protocol will end when the last treated patient in the study reaches the last visit of Phase II (Visit 3). Length of inclusion period: 27 months Theoretical duration of research: 3 years and 9 months Estimated date of last visit last patient: 30/06/2024 Data analysis time: 6 months

1 RATIONAL SCIENTIFIC

Parkinson's disease, linked to the degeneration of dopaminergic neurons in the nigro-striatal pathway, is the second most common neurodegenerative disease, affecting 6,500,000 patients worldwide and 1-2% of the population over 65. The disease manifests itself through a triad of motor symptoms (akinesia, tremors, rigidity and postural instability at a more advanced stage) and numerous non-motor signs (depression, anxiety, apathy, cognitive disorders, pain). Most of these signs are linked to dopamine depletion in the striatum. As a result, most symptomatic treatments are based on dopamine compensation. L-Dopa is a dopamine precursor which, unlike dopamine, crosses the digestive and blood-brain barriers (BBB). As only 5-10% of L-Dopa passes the BBB, DOPA decarboxylase inhibitors are co-administered. **However, this treatment leads to very disabling motor complications in 50% of patients after 5 years and 80% after 10 years.** This is due to the very short half-life of L-Dopa. In addition, the progressive degeneration of the substantia nigra (source of dopamine) can no longer ensure dopamine storage, making the patient directly dependent on per os administrations. In addition, systemic exposure to inhibitors can have side effects (adverse reactions: nausea, vomiting, tachycardia, arterial hypotension, malaise, pollakiuria... and exacerbation of oxidative stress).

There are three treatment options for L-dopa-related motor complications:

- **Subcutaneous infusion of a dopamine agonist (apomorphine)** is effective, improving L-dopa-related motor complications by over 50% and quality of life at 6 months (Drapier et al., 2016), but the risk/benefit balance of apomorphine is less favorable than L-dopa. Indeed, this dopaminergic agonist is less well tolerated (somnolence, orthostatic hypotension, confusion, psychosis, addictive behavior). Its efficacy remains limited compared with L-dopa, and it is very often necessary to continue the per os administration of L-dopa in combination, which leads to a resumption of complications. The tolerability and efficacy of dopaminergic agonists are limited and inferior to L-dopa. Here too, systemic exposure to L-dopa and agonists can have side effects. Finally, the ergonomics of the system (external pump) are poor, as the pump is externalized with a catheter connected to a needle and the need to prick the skin daily leading to skin nodules. A nurse, and sometimes patients themselves, have to prepare the product with dilutions on a daily basis. In France, around 1,500 patients are implanted each year.

- **Deep brain stimulation (subthalamic and medial pallidal nuclei),** which involves implanting two electrodes in the subthalamic nuclei and, more rarely, in the medial pallidal nuclei, is highly effective, often reducing motor complications by over 80%. On the other hand, neurosurgical intervention is delicate (requiring neurosurgical expertise) and risky (deep cerebral hematoma and worsening axial and cognitive disorders in advanced patients), limiting the number of operable patients. In particular, it cannot treat elderly patients with dementia, depression or severe walking difficulties. Given its invasive nature, it cannot be proposed for patients with little fluctuation. Some 700 to 800 patients undergo surgery every year, out of a total population of 15,000 implanted in France, i.e. 10% of all Parkinson's sufferers. What's more, this treatment only treats the problem of motor fluctuations, and does not remedy the many non-motor dopamine-dependent symptoms. On the contrary, in some cases, it is said to aggravate psycho-behavioural disorders (apathy, suicide, cognitive problems) as well as axial disorders (speech, walking and falls), either by direct action or by concomitant reduction in L-dopa. In addition, patients remain on reduced doses of oral L-dopa and thus return to fluctuating levels after 5 to 10 years.

- **Intraduodeno-jejunal delivery of L-Dopa gel** is a little-used technique, reserved for a few very advanced patients. Its indications could be very broad, given its high efficacy, with a 75% reduction in motor complications. However, it has very poor ergonomics, with a gastrostomy that can give rise to digestive complications and a heavy external pump (9 × 19 cm, weight 500 g) with a long

externalized and visible catheter. Only around a hundred patients are implanted each year in France, with 240 patients currently equipped.

The need: We need to develop a new symptomatic treatment for L-dopa-related complications that offers a better risk/benefit balance. Ideally, the missing dopamine could be continuously and appropriately compensated for directly in the brain.

The DIVE (for IntracerebroVEntricular Dopamine) **concept** consists in administering dopamine in anaerobic conditions and intracerebroventricularly (ICV) to Parkinson's disease patients at the stage of severe complications of oral treatment, i.e. after 5 to 10 years of progression. Dopamine produced under anaerobic conditions (sealed ampoule) is stored in a pump implanted subcutaneously in the abdominal region, to which a fine catheter tunnelled under the skin is connected, enabling dopamine to be distributed locally to the cerebral ventricles, avoiding peripheral side effects (figure 1B). The 20-mL pump is filled through the skin every 15 days. Compared with current treatments and those currently under development**, DIVE technology should offer improved ergonomics. In** fact, the intra-abdominal pump is said to offer a better quality of life than externalized pumps and numerous oral doses of treatment. If DIVE technology is effective, it will replace all oral treatments and avoid the need for externalized pumps. The neurosurgical procedure for installing this system is routine and similar to that for cerebrospinal fluid diversion in hydrocephalic newborns and elderly demented patients. The surgical risk is therefore very low, and much lower than that of deep brain stimulation, which is so popular with Parkinson's patients at the complication stage. Small, more superficial hematomas are to be expected, and therefore do not carry the same vital and functional risk as the deep hematomas caused by the insertion of electrodes deep in the brain.

Thanks to the anaerobic pump settings already marketed and implanted in over 300,000 patients (such as Medtronic's Synchromed II or Flowonix's Prometra or Tricumed's Siromedes Figure 1A, Table 1), ***dopamine deficiency is compensated for continuously, while respecting the natural circadian rhythm***. **DIVE should therefore treat all dopasensitive motor and non-motor symptoms compared with brain stimulation.** ***The pump's telemetry system will enable immediate reactivity to the treatment, enabling the dopamine dose to be finely and rapidly adjusted (flow rate, time range, etc.) for maximum benefit without side effects***. Furthermore, **the ability to administer the deficient neurotransmitter in a continuous, circadian manner (respecting the day/night rhythm) with the minimum effective dose, adapted to the evolving needs of each patient, would have a positive impact on quality of life in relation to the progression of the disease.**

The concept is similar to the continuous administration of insulin to a diabetic to compensate for his or her deficit throughout the day.

The DIVE project therefore targets patients after 5-10 years of evolution who present complications of fluctuations in effect to L-Dopa treatment and who are candidates for Deep Brain Stimulation (DBS).

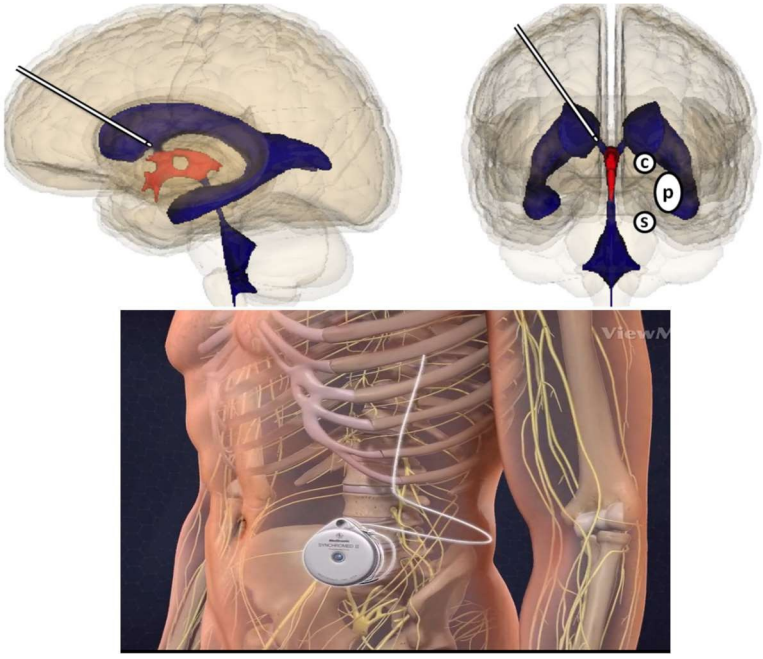

Figure 1: Implantation of the catheter in the frontal horn in near blue, at the entrance to the 3ème ventricle, a medial structure that adjoins the structures of the dopaminergic nigro-striatal pathway (S: substantia nigra, P: putamen and C: caudate nucleus; the last two forming the striatum, which is depleted in dopamine in Parkinson's disease). Below: subcutaneous implantation in the abdominal region of the pump (useful volume 20 mL).

	Product	Indication
Commercial	Intrathecal administration of baclofen	Treatment of severe spasticity in cerebral palsy and post-traumatic spinal cord injury or secondary to multiple sclerosis
	Intrathecal administration of analgesics	Treatment of severe chronic pain refractory to drugs systemically administered opiate or non-opiate treatments
Clinical Trial	ICV administration of PDGF-BB	Treatment of Parkinson's disease
	ICV administration of VEGF	ALS treatment
Pre-clinical	ICV administration of anti-Amyloid antibodies	Treating Alzheimer's disease
	Intraparenchymal delivery of Si RNA	Treatment of Huntington's disease

Table 1. Current and future uses of pumps (such as Medtronic's Synchromed II, Flowonix's Prometra or Tricumed's Siromedes).

	Treatment of symptoms engines	Treatment of non engines	Ergonomics	Invasiveness	No adverse effects peripheral	Absence of peripheral L-Dopa
DIVE	Yes	Yes	Good	Yes	Yes	Yes or very low
Apomorphine	Yes	Yes	Wrong	No	No	No
Duodopa	Yes	Yes	Wrong	Yes	No	No
Brain stimulation deep	yes	No	Good	Yes	Yes	No

Table 2: Comparison of the three main second-line treatments with DIVE technology.

2 OBJECTIVES OF THE STUDY

2.1 Objective main

Main objective of phase 1 :
Evaluate the feasibility and safety o f dopamine ICV administration by recording adverse events, including the absence of serious unexpected adverse events.

Main objective of phase 2:
To assess the efficacy on motor and non-motor complications of continuous diurnal intracerebroventricular administration of A-dopamine using the telemetry-controlled intra-abdominal pump delivery system compared with optimized oral medical treatment (usual treatment).
A-dopamine is a dopamine that is formed, preserved and administered anaerobically to avoid degradation by dopamine auto-oxidation. A-dopamine is therefore a classic dopamine, i.e. without preservatives or excipients, which enters the central nervous system from the ventricular system, in particular the 3ème ventricle adjacent to the striatum, the nucleus whose dopaminergic content is deficient in Parkinson's disease. DIVE compensates for this deficit in a continuous and circadian fashion.

Main objective of the long-term follow-up phase
Evaluate the maintenance of efficacy on motor and non-motor complications of continuous diurnal intracerebroventricular administration of A-dopamine over the long term.

2.2 Secondary objectives of phase 2

Evaluate the efficacy of DIVE compared with the reference treatment on :
- motor aspects (MDS-UPDRS part III)
- cognitive-behavioral aspects: sleepiness, anxiety, depression, apathy, sleep, hallucinations and cognition (MDS-UPDRS parts I, II, and IV, Epworth Sleepiness Scale, Parkinson's Disease Sleep Scale, MOCA, NPI, PAS, LARS, ECMP)
- quality of life (PDQ39)
- general condition (Clinical Global Impression (CGI) patient (assessment of condition and assessment of improvement), CGI physician (assessment of condition and assessment of improvement), Schwab and England scale)
- tolerability: assessment of the tolerability of DIVE compared with oral treatment
- psychiatric status (consultation without scales to assess DIVE's psychiatric tolerance, in particular the absence of thymic, anxious or psychotic decompensation, etc.)

2.3 Secondary objectives of the long-term follow-up phase

Evaluate the continued efficacy on motor and non-motor complications and safety of continuous diurnal intracerebroventricular administration of A-dopamine over the long term.
- motor aspects (MDS-UPDRS part III)
- cognitive-behavioral aspects: sleepiness, anxiety, depression, apathy, sleep, hallucinations and cognition (MDS-UPDRS parts I, II, and IV, Epworth Sleepiness Scale, Parkinson's Disease Sleep Scale, MOCA, NPI, PAS, LARS, ECMP)
- quality of life (PDQ39)
- general condition (Clinical Global Impression (CGI) patient (assessment of condition and assessment of improvement), CGI physician (assessment of condition and assessment of improvement), Schwab and England scale)
- tolerability: assessment of the tolerability of DIVE compared with oral treatment
- psychiatric status (consultation without scales to assess DIVE's psychiatric tolerance, in particular the absence of thymic, anxious or psychotic decompensation, etc.)

2.4 Exploratory objectives for phase 2

Study of parameters with theranostic biomarker value to help anticipate the safety and benefit of DIVE for future trials:
- Blood measurements of dopamine and its metabolites at the end of each period (1 and 2) 2 hours after the start of

dopamine or L-Dopa administration
- Pharmacogenetic parameters of dopamine metabolism (single blood sample at baseline visit (V0))

2.5 Exploratory objectives for the long-term follow-up phase

Blood measurements of dopamine and its metabolites at the end of each period (1 and 2) 2 hours after dopamine or L-Dopa administration has begun

3 EVALUATION CRITERIA

3.1 Evaluation criteria for the main objective

3.1.1 *Primary endpoint of phase 1*

Assessment of the feasibility of DIVE treatment with :

- Collection of adverse events, particularly serious and unexpected adverse events, reviewed by an Independent Monitoring Committee (IMC), during the dopamine dose titration phase. In particular, the following complications will be investigated:
  - Severe, life-threatening infection
  - Severe hemorrhage threatening the patient's vital and functional prognosis
  - Sharp or rapid worsening of motor and/or non-motor symptoms of Parkinson's disease over one month (i.e. more than double the classical worsening points over 3 months or more than 6 points of the total MDS UPDRS score over one month with the optimal dose of A-dopamine: best on condition).
  - Neurological deficits other than Parkinson's disease symptoms
  - Status epilepticus
  - Deaths in the post-operative period
  - No positive effect of dopamine at all
- Monitor blood pressure, pulse and ECG after each dose increase and change in concentration.
- Blood and urine tests for dopamine and its metabolites (HVA and 5-cysteinyl-dopamine) once a week, with a change in dose and concentration.

Rule: adverse events will be analyzed throughout the study. Only one patient will be included at a time during the surgery phase, post-surgery monitoring and up to the maximum possible titration. All safety data will be analyzed by an Independent Monitoring Committee (IMC). Safety data from the first 5 patients will be analyzed before authorizing or not the continuation of new patient inclusions in phase 1.
A report describing all the safety and clinical data from the first 5 patients treated in phases 1 and 2 will also be drawn up and sent to the ANSM.
We expect no changes in blood pressure, pulse rate or ECG associated with increased doses of A-dopamine. We do not expect any increase in blood and urine levels of dopamine and its metabolites (HVA and 5-cysteinyl-dopamine) associated with increasing the dose of A-dopamine. Any change in these parameters would lead to discontinuation of titration until resolution of the abnormality and cardiological advice. In the event of persistent abnormality, a new cardiological opinion would be sought, together with the opinion of the Independent Monitoring Committee (IMC), to decide whether to continue or discontinue treatment.

3.1.2 *Phase 2 primary endpoint :*

Percentage of time off = slowed down and/or blocked = Percentage of Time Over Target (PTO) by actimetry with the Parkinson KinetoGraph (PKG) system from Global Kinetics Corporation (GKC). PTA is the proportion of time over the nycthemeral period when the subject's recording shows a bradykinesia score (motor slowing or even blocking) greater than or equal to 26 (BKS≥26). The PTA does not include periods of immobility, removal of the actimeter and sleep. This parameter therefore makes it possible to integrate periods of insufficient motor control through treatment (Farzanehfar et al., 2018). The two recordings made during the first and fourth weeks of each treatment period will be averaged. This is **an objective criterion measured blindly by a third party**.

3.1.3 ***Primary endpoint of the long-term follow-up phase :***

The number of hours with either perfect or slightly slower control on the 7-day diary. It will be compared with that obtained in phase 2 to demonstrate the maintenance of long-term efficacy control.

3.2 Evaluation criteria for phase 2 secondary objectives :

Other validated actimetry criteria (Farzanehfar et al., 2018; expert conference: Odin et al., 2018)
analyze motor control :

- ***OS1: BKS*** (bradykinesia score): the bradykinesia score, calculated every 2 minutes throughout the recording period. The median BKS value is correlated with the bradykinesia disability score measured clinically by the UPDRS Part III score.
- ***OS2: DKS*** (dyskinesia score): the dyskinesia score is calculated every two minutes throughout the recording period. The median DKS value is correlated with the dyskinesia score measured clinically by the modified Abnormal Involuntary Movement Score.
- ***OS3: PTI*** **(**Percent Time Immobile): the percentage of time spent motionless, which represents the absence of movement during the 2-minute recording and is correlated with sleep in polysomnography.
- ***OS4: FDS*** (Fluctuation Dyskinesia Score): fluctuations and dyskinesias score estimating the amount of variability in relation to optimal control, i.e. insufficient control (bradykinesia) or overdose (dyskinesias).
- ***OS5: PTT*** (Percent Time Tremor): the percentage of time with tremor during the 2-minute recording. Tremor is considered present if it exceeds 1%.

For all these criteria, the two recordings made during the first and fourth weeks of each treatment period will be averaged.

Other clinical criteria:

- ***OS6: MDS UPDRS part III***
- ***OS7: Patient diary***: We will measure OFF and ON times with and without overdosing and their severity on the motor diary completed by the patient at home during the first and fourth week of each treatment period. The percentage of time spent "on" corresponds to a satisfactory "unblocked" state, without dyskinesias (involuntary movements caused by overdosing) or mild dyskinesias or mild blocking rated on an ON/OFF diary (blocking and moderate and severe dyskinesias should be avoided).
- ***OS8: Dyskinesia scales***: Abnormal Involuntary Movement Score (AIMS) and Dyskinesia rating scale (DRS)
- ***OS9 (9-1 to 9-10)****:* MDS-UPDRS parts I, II, and IV, Epworth Sleepiness Scale, Parkinson's Disease Sleep Scale, MOCA, NPI, PAS, LARS, ECMP
- ***OS10:*** PDQ39 self-questionnaire
- ***OS11 (11-1 to 11-3):*** Clinical Global Impression (CGI) patient (assessment of condition and assessment of improvement), CGI physician (assessment of condition and assessment of improvement), Schwab and England scale
- ***OS12:*** Frequency of adverse events reported by the patient and/or observed by the physician on clinical examination, ECG, blood pressure, pulse and laboratory tests (standard biology, biological iron assay, blood and urine assays for dopamine and its metabolites (HVA and 5-cysteinyl-dopamine) and variations in weight, temperature and blood pressure on orthostatic hypotension test.
- ***OS13:*** Psychiatric tolerance (no thymic, anxious or psychotic decompensation, etc.) assessed by means of a simple interview with a psychologist about the problems experienced over the past month.

3.3 Evaluation criteria for secondary objectives in the long-term follow-up phase :

- The same criteria as in phase 2 will be studied, with the exception of actimetry: OS6-OS13

3.4 Exploratory evaluation criteria

- Biology: blood and urine assays for dopamine, and its metabolites HVA and 5-cysteinyl-dopamine in conjunction with markers of oxidative stress (MDA, 4-HNE, 8 oxoDG) and axonal destruction (light chain filaments) in blood after 2 h of treatment in the morning on an empty stomach (either 2 h after the first dose of oral treatment, or 2 h after the first daytime dose of A-dopamine).
- Pharmacogenetic parameters of dopamine metabolism (DaT, COMT, MAO, DDC, ceruleoplasmin)

3.5 Exploratory criteria for the long-term follow-up phase:

Biology: blood and urine assays for dopamine, its metabolites HVA, and 5-cysteinyl-dopamine in conjunction with markers of oxidative stress (MDA, 4-HNE, 8 oxoDG) and axonal destruction (filament light chain) in blood after 2 h of treatment in the morning on an empty stomach (either 2 h after the first dose of oral treatment, or 2 h after the first diurnal dose of A-dopamine).

4 DESCRIPTION OF METHODOLOGY

4.1 experimental plan

Our aim is to restore the natural circadian cycle of dopamine in the brain by administering it intra-ventricularly. Two patients have already been treated in the 80s, with very reassuring safety data despite the absence of precautions against dopamine oxidation. To take account of ethical considerations and patient care, the protocol will be carried out sequentially to provide initial safety data, followed by efficacy data on motor fluctuations.

1) **Feasibility and safety phase 1 :**

Initiation of treatment in 5 patients with :

- Collection of all adverse events, especially serious and unexpected adverse events, reviewed by an Independent Monitoring Committee after the A-dopamine dose titration phase.
    a. In the absence of serious and unexpected adverse events (apart from the rare surgical risks of hemorrhage and infection which do not jeopardize the patient's vital and functional prognosis, see section 7.1.2), other patients may be included.
    b. In the event of two or more serious and unexpected adverse events, only 5 new patients may be included, on the advice of the Independent Monitoring Committee.
        i. Then, in the absence of unexpected serious adverse events, other patients could be included.
        ii. If two new serious and unexpected adverse events occur, the Independent Monitoring Committee may decide to stop the study. This decision to stop the study if at least 4 out of 10 patients experience serious adverse events will serve as a clear follow-up rule for the ISC. However, this decision may be modulated according to the severity and diversity of effects impacting the well-being of individuals, and whether they are totally unexpected or become predictable and manageable. (A list of expected rare adverse events has been drawn up (see section 7.1.2) for the surgical procedure, the dopamine and the medical device, in addition to the investigator's brochure, the investigational drug file and the medical device file).
- Monitor blood pressure, pulse and ECG after each dose increase and change in concentration.
- Blood and urine tests for dopamine and its metabolites (HVA and 5-cysteinyl-dopamine) once a week, with a change in dose and concentration.

A report describing all the safety and clinical data from the first 5 patients treated in phases 1 and 2 will also be drawn up and sent to the ANSM.

We expect no changes in blood pressure, pulse rate or ECG associated with increased doses of A-dopamine. We expect no increase in blood or urine levels of dopamine and its metabolites (HVA and 5-cysteinyl-dopamine) associated with dose-escalation of A-dopamine. Any change in these parameters should lead to discontinuation of titration until the abnormality is resolved, and cardiological advice sought. In the event of persistent abnormality, a new cardiological opinion would be sought, together with the opinion of the Independent Monitoring Committee (IMC), to decide whether to continue or discontinue treatment.

2) **Efficiency validation phase 2 :**

Continuous administration of dopamine should help avoid the highly deleterious fluctuations in motor control induced by treatment with oral L-dopa, which has a half-life of 2 to 3 hours. Two patients have already been

treated in the 80's with efficacy data on fluctuations. This is a proof-of-concept, prospective, single-center, randomized, controlled study involving a maximum of 12 patients treated according to a cross-over design of 2 4-week periods separated by an in-hospital therapeutic switch. The previous treatment will be stopped at the end of period 1 and replaced by the new treatment, without discontinuity and progressively, so that the patient is always treated. After stabilization, and in the absence of adverse effects, the patient will return home and begin period 2 assessments one week later, in order to eliminate any residual effects of the first treatment.

Patients will be randomized into two groups according to the following treatment sequences:

- group 1 (n=10) :
  - period 1: dopamine treatment ICV
  - period 2: optimized oral treatment
- group 2 (n=10) :
  - period 1: optimized oral treatment
  - period 2: ICV dopamine treatment

3) Long-term follow-up :

At the end of phase 2, A-dopamine will be maintained over the long term at the dose that enables satisfactory motor control (less than 1 h 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 treatment (50 mg of L-dopa every 2 to 3 h). To achieve the ideal therapeutic solution, i.e. no more oral treatment at all, and therefore no more Off, requires a very slow, steady increase in A-dopamine starting at doses of 10 mg/h, to avoid being limited by the adverse effects of drowsiness and nausea. In fact, as with apomorphine (less well tolerated), good control is achieved with high doses when this is done. This can advantageously be achieved during this phase with a very slow, moderate increase in A-dopamine.

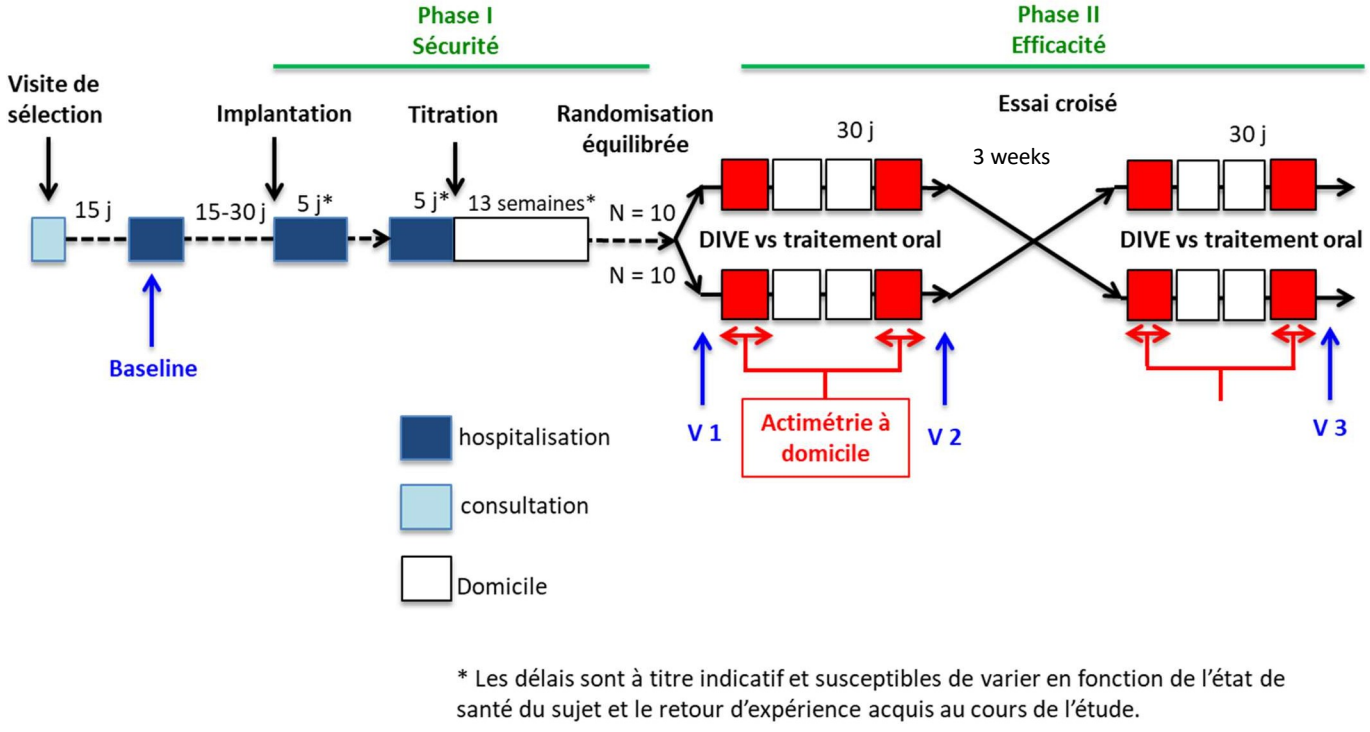

Figure 1: experimental design

Concerned about the well-being of patients, the promoter is proposing to dispense the experimental treatment at home via a service provider, in order to avoid weekly trips to the Lille University Hospital from the time they enter the long-term follow-up phase.

The service provider will be trained by the principal investigator in the nursing procedure for filling out the form, and will act in accordance with the French Data Protection Act of January 6, 1978.

Patients will be informed of this and will have the option of objecting to the transfer of their personal data to the healthcare provider. In this case, the data will be filled in at Lille University Hospital.

In this context, the delivery of A-Dopamine to the homes of included patients will be carried out under the following conditions:
- a prescription from the study investigators will be sent to the Lille CHU pharmacy, specifying the prescription for each patient.
- the healthcare provider will visit the Lille University Hospital pharmacy once a week to collect the number of treatments required for the week's planned dispensing, by mutual agreement between the sponsor, the principal investigator and the provider.
- Treatments will be temporarily stored for a maximum of 10 days on the provider's premises, in accordance with the sponsor's recommendations, for transport to the patient's home in the provider's vehicles equipped with temperature-controlled enclosures. Temperature records will be provided to the sponsor and principal investigator.
- The provider will contact the patient based on the information provided by the principal investigator in order to arrange a date for the home pump filling appointment. It should be noted that the provider's staff will be trained by the principal investigator in the nursing procedures involved in filling the pump.

At the end of each filling, the service provider undertakes to
- Send written report to principal investigator for validation
- Enter the data indicated by the sponsor in the study eCRF
- Take a photograph of the pump programmer before and after filling, and send it to the promoter and the CHU Lille team to enable them to validate the service rendered. This transmission will be carried out in accordance with current legal and regulatory obligations via a secure platform (CHU transfert).

The promoter, the CHU de Lille and the service provider undertake to act in accordance with the RGPD of the Act of January 06, 1978 relating to data processing, files and freedoms as amended and the principles laid down in the MR001 adapted by the CNIL (patient information, updates to information documents for patients to inform them of the sharing of their data with an additional recipient according to secure methods of transmission of personal data.

4.2 Measures taken to minimize bias

4.2.1 Randomization

Randomization of the 2 treatment sequences according to a balanced plan (1:1) will be carried out using a computer-generated randomization list supplied by LILLE University Hospital. It will be carried out at the start of phase 2 as soon as the patient is considered well-balanced (end of titration). Titration will last 9 weeks.

4.2.2 Setting blind

This is an open-label study, with the phase 2 primary endpoint (percentage of time off) measured in a blinded fashion by a third party using actimetrics. A third party will also analyze the phase 2 secondary endpoints on actimetry, clinical and paraclinical assessments. Another person will carry out therapeutic adaptation of the pump and oral treatments in cross-over.
This choice follows the model of what has been achieved for other so-called second-line treatments (apomorphine pump, Duodopa®, subthalamic stimulation). We want to compare DIVE with the best oral treatment, which must be optimized for each patient. This is an essential first step in validating

efficacy and tolerance. In addition, this will enable us to validate the ergonomic benefits compared with multiple oral treatments. Optimized oral treatment requires a combination of several oral treatments, varying from one subject to another (L-dopa, monoamine oxidase-B inhibitor, dopaminergic agonist, catechol-o-methyl transferase inhibitor, amantadine), which makes blinding impossible. There is the alternative of putting all patients solely on L-dopa versus placebo, but this does not correspond to the most effective therapeutic strategy for all patients. Many patients would be less well controlled.

4.2.3 Blind procedure

There is no double-blind procedure.

4.3 Number of subjects required

In all, a maximum of 12 treated patients can be recruited for this study, as the capacity of the central pharmacy at Lille University Hospital cannot handle the treatment of more than 12 patients with a weekly refill.
To calculate the number of subjects required, please refer to section 11.1 of the protocol.

5 ELIGIBILITY CRITERIA AND FOLLOW-UP PROCEDURES

5.1 Inclusion criteria

- Parkinson's disease at the stage of L-dopa-induced severe motor and non-motor complications
- Men or women over 18
- Parkinson's disease according to MDS criteria
- Severe motor complications including motor fluctuations with at least 2 hours of Off and 1 hour of dyskinesias uncontrolled by optimized oral drug therapy, i.e. with at least 5 doses of L- dopa and the addition or trial of a dopaminergic agonist (if tolerated) per os or by apomorphine pump
- The patient meets the criteria for a second-line invasive treatment such as deep brain stimulation (subthalamic or medial pallidum) or intrajejunal administration of levodopa gel (Duodopa®).
- Patients with a contraindication or who prefer this invasive therapeutic alternative to the other two existing and validated therapies (subthalamic stimulation or Duodopa®) because of its advantages: lower theoretical risk of intracerebroventricular delivery compared to subthalamic stimulation and better ergonomics than Duodopa®, but with the disadvantage of an as yet unproven benefit.
- Social security
- Able to provide free and informed consent to participate in research
- Patient willing to comply with all study procedures and duration
- Patient not planning to change lifestyle (nutritionally, physically or socially) during study participation

5.2 Non inclusion criteria

- Over 75 years of age
- Subjects not receiving at least 5 doses of oral dopathy per day
- Subject without a prior trial of an apomorphine pump (of lower risk); apomorphine pump treatment being a failure or a contraindication or refused by the patient
- Psychiatric history using the semi-structured psychiatric interview with DSM IV MINI: decompensated bipolar illness, psychotic state, current severe depression. Dysthymia and an isolated history of depression are not exclusion criteria.
- Patient with parkinsonian dementia (DSM IV and MDS criteria and MOCA score < or equal to 22)
- Isolated patient, defined as the absence of a caregiver present at least 3 hours/day in the patient's home.
- History of a fall in the last 6 months and/or a score >1 on items 2.12 (Walking and balance) and/or 3.12 (Postural stability) of the MDS-UPDRS scale
- Presence of another serious pathology with short- or m e d i u m - t e r m life-threatening consequences, malnutrition, cachectic.
- Hemostasis disorders

- Cardiac rhythm disorders and/or heart failure not controlled by treatment
- Uncontrolled blood pressure release
- Breastfeeding and pregnancy
- Women of childbearing age without effective contraception
- Contraindication to general anaesthesia
- Taking treatments containing guanethidine or related compounds or non-selective and selective monoamine oxidase A inhibitors (iproniazid, moclobemide, toloxatone)
- Neurosurgical contraindication (severe cerebral atrophy, brain tumor, infarction or other cerebral pathology, CSF flow disorder)
- Contraindication to abdominal placement of a subcutaneous pump and catheter that impairs healing and transcutaneous filling (e.g. major obesity, skin pathology, etc.).
- Contraindication to MRI (pacemaker, claustrophobia, etc.) and/or intolerance to gadolinium
- Active infectious pathology (including Covid-19)
- Immunologically deficient pathology likely to promote superinfection of equipment
- Patients under guardianship or trusteeship
- Patient already participating in another therapeutic trial using an investigational drug or in an exclusion period

5.3 Criteria for discontinuing study participation and early termination

Continuation of treatment is essentially dictated by the patient's desire for symptomatic benefit, supported by the investigating neurologist's assessment of this benefit, combined with a good tolerability profile, i.e. a favorable risk/constraint/benefit balance. Under these conditions, only the occurrence of a serious intercurrent event jeopardizing the therapeutic strategy should be considered. Many non-inclusion criteria were considered because of the need for neurosurgical intervention.

At any time, the subject may prematurely terminate his or her participation in the study, either at his or her own request or at the investigator's discretion, particularly in the following circumstances:

Criteria for discontinuing treatment if a new full neurosurgical procedure is required to change the catheter and pump

- Patient's wish to stop
- Presence of another serious pathology threatening short- or medium-term vital prognosis, malnourished or cachectic patient.
- Hemostasis disorders not controlled by treatment
- Cardiac rhythm disorders and/or heart failure not controlled by treatment
- Breastfeeding and pregnancy
- Women of childbearing age without effective contraception
- Contraindication to general anaesthesia
- Taking treatments containing guanethidine or related compounds or non-selective and selective monoamine oxidase A inhibitors (iproniazid, moclobemide, toloxatone)
- Neurosurgical contraindication (severe cerebral atrophy, brain tumor, infarction or other cerebral pathology, CSF flow disorder)
- Contraindication to abdominal placement of a subcutaneous pump and catheter that impairs healing and transcutaneous filling (e.g. major obesity, skin pathology, etc.).
- Contraindication to MRI (pacemaker, claustrophobia, etc.) and/or intolerance to gadolinium
- Active infectious pathology (including Covid-19)
- Immunologically deficient pathology likely to promote superinfection of equipment

Criteria for discontinuing treatment in the event of the need for an isolated pump change (pump lifespan between 5 and 8 years)

- Patient's wish to stop
- Presence of another serious pathology threatening short- or medium-term vital prognosis, malnutrition, cachecticity.
- Hemostasis disorders not controlled by treatment
- Cardiac rhythm disorders and/or heart failure not controlled by treatment
- Contraindication to general anaesthesia
- Taking treatments containing guanethidine or related compounds or non-selective and selective monoamine oxidase A inhibitors (iproniazid, moclobemide, toloxatone)
- Contraindication to abdominal placement of a subcutaneous pump and catheter that impairs healing and transcutaneous filling (e.g. major obesity, skin pathology, etc.).
- Active infectious pathology (including Covid-19)
- Immunologically deficient pathology likely to promote superinfection of equipment
- Breastfeeding and pregnancy
- Women of childbearing age without effective contraception.

Criteria for discontinuing treatment at any time

- Patient's wish to stop
- Occurrence of a serious pathology involving the short- or medium-term vital prognosis, and for which the administration of dopamine or the presence of the equipment is likely to aggravate the situation. (the occurrence of a serious pathology (cancer or pneumopathy...) for which the person's general condition is likely to worsen still further, with less effective control of Parkinsonian motor fluctuations, will not be grounds for discontinuation).
- Taking treatments containing guanethidine or related compounds or non-selective and selective monoamine oxidase A inhibitors (iproniazid, moclobemide, toloxatone)

Depending on the severity of the situation, the first emergency step is to replace the dopamine with saline and start the pump as soon as possible. Then, whether or not to remove the equipment will be discussed on a case-by-case basis. For example, if the patient is well and wishes to stop, the equipment will be removed. If the patient is at the end of his or her life, the equipment may not be removed, so as not to have to undergo an operation, whereas maintaining the equipment poses no problem. We already apply these rules with deep brain stimulation.

Withdrawal from a study, particularly in the event of a serious adverse event, may be decided by the competent administrative authority, the sponsor, the independent monitoring committee or the principal investigator, but also by an investigator or by the patient himself/herself, in accordance with regulations and as mentioned in the consent form. Patients will be seen in consultation for a check-up 15 days after stopping treatment, in order to monitor the adverse event.

Whatever the reason for the subject's withdrawal from the trial, it must be clearly mentioned in the observation book (date, description of the reason for the study stoppage, etc.), and the documents justifying it must be attached.

5.4 Ban on simultaneous participation and exclusion period

Research subjects may not take part in any other study for the duration of their participation and for one month following the last visit.

5.5 Pregnancy risk management in non- menopausal women

Following the recommendations of the Clinical Trials Facilitation Groups (CTFG), the term "menopausal woman" in the protocol corresponds to a confirmed state of menopause, i.e. no menstruation for 12 months without a pathological medical reason.

A high level of follicle-stimulating hormone (FSH) can be used to confirm a post-menopausal state in women not using hormonal contraception or hormone replacement therapy. However, in the absence of 12 months' amenorrhea, FSH measurement alone is insufficient.

5.5.1 Type of contraception required for protocol

Women of childbearing age participating in this study will be required to use at least one of the following methods of contraception:

- Combined hormonal contraception (estrogen-progestin) with ovulation inhibition:
  - oral
  - intra-vaginal
  - transdermal
- Microprogestogenic hormonal contraception with ovulation inhibition :
  - oral
  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormonal device
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (evaluated by investigator)

No contraception is required for male subjects.

5.5.2 Duration of contraception

Contraception should be maintained during treatment and until at least 5 half-lives have elapsed since the last dose.

5.5.3 Pregnancy tests

An FSH and LH assay is scheduled at the inclusion visit.
For women of childbearing age, a β-HCG blood test will be performed at the inclusion visit and at each follow-up visit.

5.5.4 For pregnancy

See section 9.5.1.4

6 RESEARCH

6.1 Feasibility and experience of teams

The study will be conducted as a single-center, multidisciplinary study at Lille University Hospital: patients will be included in the Clinical Investigation Center (CIC), in collaboration with the Neurology and Movement Pathology Department (Parkinson's disease reference center), the Functional Neurosurgery Department, the Medical Pharmacology Department and the central pharmacy. All investigators will ensure that the protocol is carried out according to good clinical practice. The neurology and neurosurgery departments have experience of Parkinson's disease surgery since 1997. Prof. Devos, scientific coordinator, has participated in 29 clinical trials, including 14 as coordinator and 14 multicenter trials.
UPARC, a mobile paramedical clinical research unit with extensive experience in decentralized clinical trials, will be responsible for pump filling in patients' homes during the long-term follow-up phase.

6.2 research

6.2.1 Selection / recruitment of patients

Patients will be selected from the active file of the Neurology and Movement Pathology Department, a referral center for Parkinson's disease, and possibly from referrals from hospital and private neurologists in the region.

6.2.2 Information and consent

Subjects will receive comprehensive oral and written information on the trial, the products administered, their adverse effects and the risks involved. A letter of information must be given to the subject by the investigator prior to inclusion in the study. Patients are given as much time as they feel is necessary to make their decision.
All subjects will be under medical supervision. They will be able to contact a team doctor at any time on the telephone number provided.

Signed informed consent will be obtained from each subject before entry into the study. No protocol-specific procedures may be performed without the patient's signed consent. The consent will be signed by the investigator or the physician representing him/her and the subject.

The information letter and consent form will be drawn up in 3 copies: one copy will be given to the subject, one copy will be kept by the investigator, who will send the last copy to the sponsor, in a sealed envelope (this envelope will be designed in such a way that it cannot be resealed after opening).

Patients will be informed of the sharing of their personal data with a homecare provider in order to fill the pump at home, via the information note and consent form they will receive.
They will have the rights guaranteed by the European Data Protection Regulation (right of access, information, rectification, erasure, limitation of processing, data portability, right to object, consent to the processing of personal data and right to revoke that consent.
Patients who do not wish to share their data with us will fill in their forms at the Lille University Hospital during the long-term follow-up phase.

6.2.3 Screening visit (CIC consultation, J0)

Subjects will be included during a consultation at the CIC, after information, informed consent and verification of inclusion and non-inclusion criteria.
A full medical history will be taken, documenting concomitant treatments and any associated medical and psychiatric disorders or symptoms, both past and present.
A MoCA test will also be carried out.

6.2.4 Baseline visit V0 (neurology hospitalization, J15)

Visit to assess the indication for second-line DIVE therapy.

- **Medical check-up**

- An initial clinical and neurological examination to ensure that the patient has no contraindications to neurosurgical intervention
- Pulse, blood pressure, standing up after 2 minutes and lying down after 10 minutes, temperature, respiratory rate
- 12-channel electrocardiogram
- Biological workup: CBC, PT, aPTT, group and rhesus in two determinations, ionogram, renal workup, liver workup, CRP and CPK, hemoglobin, serum iron, ferritinemia, transferrin, total binding capacity and transferrin saturation coefficient.
- FSH, LH (for all women) and βHCG assays (for women of childbearing age only)
- a chest X-ray.

- **Biological collection after 2 hours of treatment in the morning on an empty stomach:**

Exploration of pharmacogenetic parameters concerning :
- genetic polymorphisms in enzymatic (DaT, COMT, MAO, DDC) and non-enzymatic dopamine metabolism (iron auto-oxidation (ceruloplasmin))
- Determination of dopamine and its metabolites (HVA and 5-cysteinyl-dopamine) in blood and urine.
- Determination of markers of oxidative stress (MDA, 4-HNE, 8 oxoDG) and axonal destruction (light chain filaments)

- **Acute L-dopa administration test under rigorous, standardized conditions:** MDS-UPDRS part III, video dyskinesia scales

- **MDS-UPDRS total**

- **CGI- doctor**

- **Neuropsychological examination**: NPI, PAS, LARS, ECMP

- **Self-questionnaires:** PDQ-39 questionnaire, CGI-patient, Schwab and England scale, Epworth scale, Parkinson's Disease Sleep Scale

- **Brain MRI** to check for neurosurgical contraindications.
  We will perform a 3DT1 sequence with injection of gadoteric acid (Clariscan) for improved intraoperative vessel location when establishing the cortical catheter path. Clariscan is a macrocycle-structured gadolinium-based MRI contrast agent. It is administered at a dose of 0.1 mmol/kg (or 0.2 ml/kg). The macrocyclic nature of gadoteric acid exposes the patient to a low risk of systemic nephrogenic fibrosis, according to France's Haute Autorité de Santé.

6.2.5 Implantation neurosurgery (maximum J15-J30 from baseline)

An anesthetic check-up is carried out a few days before the operation, with an outpatient cardiac ultrasound. A Covid-19 test is carried out before the operation, if required by health measures relating to the Covid-19 pandemic. If there are no symptoms suggestive of Covid-19 and the test is negative, the patient is hospitalized the day before the operation.

The procedure to implant the catheter in the right frontal horn close to Monro's interventricular foramen will be carried out by stereotaxis with direct tracking on brain MRI using the O Arm system (https://www.medtronic.com/ca-fr/professionnels-de-la-sante/produits/neurologique/surgical-imaging-systems/o- arm.html) and catheter placement by Renishaw's Neuro Mate robot (https://www.renishaw.fr/fr/systeme-robotise- neuromate-pour-neurochirurgie-stereotaxique--10712) by Prof. Nicolas Reyns and Dr. Gustavo Touzet. This procedure allows a precision of 0.18 mm. After opening the skull with a pediatric-size trepanation, the dura mater is cauterized, then two needles are used to pierce the dura mater and allow transcortical passage up to 5 millimeters before the ventricular wall. The final portion of less than 5 millimeters of cortex, then passage of the ventricular wall, is performed directly with the catheter and its semi-rigid internal guide. This procedure eliminates the need for an external guide and limits the size of the intracortical passage to the diameter of the catheter.

The procedure will be carried out in the neurosurgical unit, which has experience of functional neurosurgery since the 1990s, and of deep brain stimulation in Parkinson's disease (internal pallidum in 1997 and subthalamic nucleus in 2000). Twenty to thirty Parkinson's patients are operated on each year at the Lille center. The procedure for implanting the catheter in the frontal horn follows the same stereotactic operating mode as that for implanting two deep stimulation electrodes. However, the procedure for implanting the catheter in the frontal horn is simpler in terms of registration than in the subthalamic nucleus, as the ventricular target is larger.

and without the need for intra-target somatotopy. In fact, the subthalamic stimulation electrode must be positioned in the posterior and lateral part of the subthalamic nucleus (posterior and lateral part of a grain of rice). Estimated locating time is 30 to 60 minutes for the ventricle. The catheter is attached to the right frontal bone of the skull using Medtronic's stim lock® system, then tunnelled under the skin to connect to the pump implanted in the abdominal region and attached to the rectus abdominis muscle.

During surgery and before the pump is implanted, it is rinsed with 20 ml of sterile saline in anaerobic conditions 4 times to remove residual air bubbles and ensure anaerobicity, then filled with 20 ml of sterile saline in anaerobic conditions. These solutions are delivered the same morning, without breaking the anaerobic chain, from the sterile complete anaerobic isolator located at the Lille University Hospital's central pharmacy to the neurosurgical unit. Indeed, it is not possible to maintain dopamine anaerobics during the procedure due to the air intake through the catheter. In the OR, pumps are rinsed and filled using 50ml bags of physiological saline. These bags are individually packaged by the CHU's in-house pharmacy in sterile, airtight packaging, to be kept in an anaerobic atmosphere until use. A closed system (Phaseal System, Becton Dickinson, New Jersey, USA) is used to preserve the anaerobic nature of the solution, in the same way as for dopamine filling. Rinsing of the pump and pump catheter access chamber requires the use of two devices: the Refill Kit (Flowonix (New Jersey, USA), Medizintechnik Promedt GmbH (Germany), Tricumed (Germany)) and the Catheter Access Kit (Flowonix, New Jersey, USA).

To ensure optimal operation of the entire system (pump and catheter) prior to skin closure, three checkpoints are performed:

- after rinsing and filling the pump with sterile, anaerobic saline, a bolus is performed (pump and catheter) in the pre-implantation phase to ensure that it is working properly;
- Once the catheter is placed subcutaneously, we collect 1 mL of CSF to check for continuity;
- the final check consists of removing 1 ml of saline from the catheter port after the catheter has been attached to the pump.

The skin suture is made laterally to the pump, i.e. at a distance from the filling ports (central filling port and lateral catheter port).

For safety reasons, the surgical phase should be separated from the dopamine treatment phase. On the same model, deep brain stimulation is implanted, followed by adaptation of the stimulation parameters over several months.

6.2.6 Phase 1 study and titration

- **In hospital** (for 10 days)
  - J1-J5: ***post-operative monitoring*** in neurosurgery, modelled on post-implantation monitoring for deep brain stimulation.
    - Postoperative CT scan within 48 hours to verify absence of hematoma
    - Rigorous monitoring to ensure there are no adverse effects (hematoma, infection, equipment malfunction (see section 7.1.2)).
  - D6: ***transcutaneous filling of the pump with A-dopamine,*** if general condition and abdominal skin condition allow. In the event of slower healing, the patient may be discharged from hospital until D15 to D30, before returning to the hospital to perform the first A-dopamine filling and begin titration. During this period, the pump will be filled with anaerobic saline and the oral treatment will be maintained.
  - D6-J10 (maximum): ***initial hospital titration***

- Daily titration of 20 mg (1.11 mg/hr over 18 hrs) up to an initial maximum of 100 mg (5.55 mg/hr)
- Daily monitoring of blood pressure, pulse and ECG after each daily dose increase and change in concentration
- Blood and urine tests for dopamine and its metabolites (HVA and 5-cysteinyl-dopamine) before and at the end of hospital titration.

- **Return home and continuation of therapeutic adaptation** (for 13 weeks)
  - Continued adaptation of the best minimal effective dose under real-life conditions. Depending on tolerability and efficacy, a slow weekly titration will be continued in maximum increments of 20 mg (1.11 mg/h over 18 hours), which may be repeated 2ème times a week, i.e. a maximum of 40 mg/week.
  - Monitoring for adverse events (daily telephone calls)
  - The patient will be reviewed weekly in consultation for changes in pump output via telemetry and monitoring of neurological, psychiatric and cardiovascular safety (pulse, blood pressure, ECG).
  - Blood and urine tests for dopamine and its metabolites (HVA and 5-cysteinyl dopamine) once a week, with a change in dose and concentration.
  - The pump is refilled every 15 days or every week as required to ensure and control A-dopamine quality.

For the patient's comfort, oral treatment should be maintained during titration to avoid transient motor aggravation. As soon as the first positive effects are felt, the oral treatment is gradually reduced, while cerebral dopamine is cautiously increased.
The flow rate is set exclusively by telemetry. When the patient

is titrated and satisfied, he or she moves on to phase 2.

These times are indicative and may vary depending on the subject's state of health and feedback from the study.

Maximum titration table :
Titration will be continued in the absence of adverse effects.
We propose an initial hospital titration with a maximum daily increase of 20 mg (1.11 mg/h) over the daytime period (5 a.m.-11 p.m.), as nocturnal needs are much less important and compatible with a slow titration, up to a first plateau at 5.55 mg/h (i.e. 100 mg/day). This is a maximum titration, and the patient may be discharged from hospital with a lower dose if his motor condition is deemed satisfactory.
Slow, cautious titration then continues on an outpatient basis, with a weekly increase of 20 mg (1.11 mg/h) which can be repeated 2ème times a week, i.e. up to a maximum of 40 mg/week, until the dose required for satisfactory motor control is reached, with or without a minimal residual dose of oral dopaminergic therapy. The advantage of this titration regimen is that the patient only has to return to hospital once a week for telemetric dose changes.
This will, of course, be adapted according to tolerance. If transient nausea, somnolence or any other undesirable effect occurs, the increase will be temporarily suspended, then titration will be resumed from the previous level or with a much slower increase of 0.25 mg/h.
A-dopamine is gradually titrated to the minimum effective dose needed to control dopaminergic motor symptoms with the same efficacy as oral L-dopa treatment, but on a continuous basis.

Day	Increase of 1 mg/h over 18h	18-hour diurnal dose (mg)	Night dose (mg)	TOTAL DOSE	Dose night/h (23h-5h) (mg/h)	Concentration (vials in mg/ml)	24-hour flow (ml/24h)	Daytime flow (ml/18h)	Night flow (ml/night)	Front volume	Volume after
Day 1	**1,11**	**20**	2	**22**	0,33	**50**	0,44	**0,4**	0,04	20	19,56
Day 2	**2,22**	**40**	2	**42**	0,33	**50**	0,84	**0,8**	0,04	19,56	18,72
Day 3	**3,33**	**60**	2	**62**	0,33	**50**	1,24	**1,2**	0,04	18,72	17,48
Day 4	**4,44**	**80**	5	**85**	0,83	**50**	1,7	**1,6**	0,1	17,48	15,78
Day 5	**5,56**	**100**	5	**105**	0,83	**50**	2,1	**2**	0,1	15,78	13,68
Saturday	**5,56**	**100**	5	**105**	0,83	**50**	2,1	**2**	0,1	13,68	11,58
Sunday	**5,56**	**100**	5	**105**	0,83	**50**	2,1	**2**	0,1	11,58	9,48
Week 1	**6,67**	**120**	5	**125**	0,83	**50**	2,5	**2,4**	0,1	9,48	6,98
Week 1	**6,67**	**120**	5	**125**	0,83	**50**	2,5	**2,4**	0,1	6,98	4,48
Week 1	**6,67**	**120**	5	**125**	0,83	**50**	2,5	**2,4**	0,1	4,48	1,98
Week 1	**7,78**	**140**	5	**145**	0,83	**100**	1,45	**1,4**	0,05	20	18,55
Week 1	**7,78**	**140**	5	**145**	0,83	**100**	1,45	**1,4**	0,05	18,55	17,1
Saturday	**7,78**	**140**	5	**145**	0,83	**100**	1,45	**1,4**	0,05	17,1	15,65
Sunday	**7,78**	**140**	5	**145**	0,83	**100**	1,45	**1,4**	0,05	15,65	14,2
Week 2	**8,89**	**160**	10	**170**	1,67	**100**	1,7	**1,6**	0,1	14,2	12,5
Week 2	**8,89**	**160**	10	**170**	1,67	**100**	1,7	**1,6**	0,1	12,5	10,8
Week 2	**8,89**	**160**	10	**170**	1,67	**100**	1,7	**1,6**	0,1	10,8	9,1
Week 2	**10**	**180**	10	**190**	1,67	**100**	1,9	**1,8**	0,1	9,1	7,2
Week 2	**10**	**180**	10	**190**	1,67	**100**	1,9	**1,8**	0,1	7,2	5,3
Saturday	**10**	**180**	10	**190**	1,67	**100**	1,9	**1,8**	0,1	5,3	3,4
Sunday	**10**	**180**	10	**190**	1,67	**100**	1,9	**1,8**	0,1	3,4	1,5
Week 3	**11,11**	**200**	10	**190**	1,67	**100**	1,9	**2**	0,1	20	18,1
Week 3	**11,11**	**200**	10	**210**	1,67	**100**	2,1	**2**	0,1	18,1	16
Week 3	**11,11**	**200**	10	**210**	1,67	**100**	2,1	**2**	0,1	16	13,9
Week 3	**11,11**	**200**	10	**210**	1,67	**100**	2,1	**2**	0,1	13,9	11,8
Week 3	**11,11**	**200**	10	**210**	1,67	**100**	2,1	**2**	0,1	11,8	9,7
Saturday	**11,11**	**200**	10	**210**	1,67	**100**	2,1	**2**	0,1	9,7	7,6
Sunday	**11,11**	**200**	10	**210**	1,67	**100**	2,1	**2**	0,1	7,6	5,5
Week 4	**12,22**	**220**	20	**240**	3,33	**100**	2,4	**2,2**	0,2	20	17,6
Week 4	**12,22**	**220**	20	**240**	3,33	**100**	2,4	**2,2**	0,2	17,6	15,2
Week 4	**12,22**	**220**	20	**240**	3,33	**100**	2,4	**2,2**	0,2	15,2	12,8
Week 4	**12,22**	**220**	20	**240**	3,33	**100**	2,4	**2,2**	0,2	12,8	10,4
Week 4	**12,22**	**220**	20	**240**	3,33	**100**	2,4	**2,2**	0,2	10,4	8
Saturday	**12,22**	**220**	20	**240**	3,33	**100**	2,4	**2,2**	0,2	8	5,6
Sunday	**12,22**	**220**	20	**240**	3,33	**100**	2,4	**2,2**	0,2	5,6	3,2

- If fully effective (i.e. oral treatment can b e stopped completely, with continuous symptom control and no fluctuation) □ **maintain the same dose of A-dopamine.**

- If partial efficacy (i.e. possibility of reducing oral treatment with better control of fluctuations) □ **continue to increase the dose of A-dopamine according to the titration schedule.**

- If dyskinesias appear or worsen **Stop increasing A-dopamine and gradually decrease until oral treatment is stopped. If this is not sufficient, reduce the dose of A-dopamine by returning to the previous well-tolerated level, with daily reassessment.**
- If no effect at all (i.e. same oral treatment and persistence of motor fluctuations) **continue increasing the dose of A-dopamine according to the titration schedule.**
- If restless nights (REM sleep behavior disorders) or insomnia or dyskinesias or motor restlessness on awakening or other hyperdopaminergic side effects (nausea) **reduce nocturnal dose by at least 25% and continue reducing gradually until resolution of these signs.**

6.2.7 Phase 2 study :

Phase II: efficacy and safety
30 days of A-dopamine treatment: maintenance of the minimum effective diurnal dose (theoretical dose between 180 mg and 324 mg/day).

A-dopamine will be administered for 30 days at the minimum effective dose, with the option of retaining a residual dose of oral treatment if deemed necessary by the investigator and for patient comfort. During the other 30-day period of the phase 2 cross-over design, the optimized oral treatment will be resumed and the A-dopamine will be removed from the pump and replaced by anaerobic saline.

➢ **Follow-up visit V1: Phase 2 baseline (**one-day neurology hospitalization)

- **Randomization :**

Patients entering phase 2 of the study will be randomized into one of 2 groups defining the order of cross-over:

- group 1 :
  - period 1 (4 weeks): ICV dopamine treatment
  - period 2 (4 weeks): optimized oral treatment
- group 2 :
  - period 1 (4 weeks): optimized oral treatment
  - period 2 (4 weeks): ICV dopamine treatment

- **Change of therapy if the patient is randomized to group 2 (oral treatment)** by an unblinded third-party neurologist. The patient will be monitored in hospital after the change in therapy.
- MDS UPDRS part III in On Drug, dyskinesia scales (Abnormal Involuntary Movement Score (AIMS) and Dyskinesia Rating Scale (DRS)) in On Drug
- **Tolerance assessment:** general clinical examination (weight, height, orthostatic hypotension test, temperature, respiratory rate, blood pressure, pulse, ECG), collection of surgical complications, tolerance of product administered.
- **Standard laboratory tests :**
  - Complete blood count, hemoglobin, PT, APTT, ionogram, kidney function tests, liver function tests, CRP and CPK
  - β-HCG assay (for women of childbearing age only)
- **Questionnaires:** MDS-UPDRS parts I, II, and IV, patient CGI (assessment of condition and assessment of improvement), physician CGI (assessment of condition and assessment of improvement), Schwab and England scale, Epworth scale, Parkinson's Disease Sleep Scale, PDQ39
- **Cognitive examination:** MOCA, NPI, PAS, LARS, ECMP

At the end of the V1 visit, the patient returns home for 4 weeks with :

- Measurement of actimetry (PKG) during weeks 1 and 4
- Motor diary completed by the patient during the first and fourth weeks.

If the patient is randomized to group 1 (period 1: dopamine ICV treatment), he or she will be seen again at the hospital 15 days after the V1 visit, for transcutaneous pump filling by a nurse. On this occasion, a tolerance evaluation will be carried out, with monitoring of blood pressure, pulse and ECG.

➢ **Follow-up visit V2: End of period 1** (one-day Neurology hospitalization, 4 weeks after V1)

- MDS UPDRS part III in On Drug, dyskinesia scales (Abnormal Involuntary Movement Score (AIMS) and Dyskinesia Rating Scale (DRS)) in On Drug
- **Tolerance assessment:** general clinical examination (weight, height, orthostatic hypotension test, temperature, respiratory rate, blood pressure, pulse, ECG), collection of surgical complications, tolerance of product administered.
- **Standard laboratory tests :**
  - blood count, hemoglobin, PT, APTT, ionogram, kidney function tests, liver function tests, CRP and CPK
  - β-HCG assay (for women of childbearing age only)
- **Specific biology:** blood and urine assays for dopamine and its metabolites (HVA, and 5- cysteinyl-dopamine) and markers of oxidative stress (MDA, 4-HNE, 8 oxoDG) and axonal destruction (light chain filaments) after 2 h of treatment in the morning on an empty stomach (either 2 h after the first dose of oral treatment, or 2 h after the first daytime dose of A-dopamine).
- **Questionnaires:** MDS-UPDRS parts I, II, and IV, patient CGI (assessment of condition and assessment of improvement), physician CGI (assessment of condition and assessment of improvement), Schwab and England scale, Epworth scale, Parkinson's Disease Sleep Scale, PDQ39
- **Cognitive examination:** MOCA, NPI, PAS, LARS, ECMP
- **Psychiatric evaluation:** consultation without scales to assess psychiatric disorders experienced during the last month of treatment
- **Change of therapy (oral treatment or cerebral dopamine)** by a non-blinded third-party neurologist, at the end of the visit and under close medical supervision.
  - if the patient is randomized to group 1 (period 1: ICV dopamine treatment), the dopamine will be removed from the pump and replaced by anaerobic saline. At the same time, the optimized oral treatment will be resumed at the usual doses.

  - if the patient is randomized to group 2 (period 1: optimized oral treatment per os), the therapeutic change will consist of a progressive increase in cerebral dopamine and a concomitant reduction in oral treatment, with dopamine being reintroduced over a 24-hour period in hospital.

  The patient will return home if there are no adverse effects, then titration will take place over 15 days. In order not to induce any difference between the 2 cross-overs, a 15-day period will also be observed for the transition from dopamine treatment to oral treatment.

  An additional week is then allowed to elapse, corresponding to the time needed to eliminate any potential residual effects of the treatment administered in period 1.

Thus, in the patient's home, 3 weeks after the end of visit 2 (i.e. 1 week after the 15-day titration period), the second 4-week period begins with :

- Measurement of actimetry (PKG) during weeks 1 and 4
- Motor diary completed by the patient during the first and fourth weeks.

If the patient is randomized to group 2 (period 2: dopamine ICV treatment), he or she will be seen again at the hospital 15 days after the V2 visit, for transcutaneous pump filling by a nurse. On this occasion, a tolerance evaluation will be carried out, with monitoring of blood pressure, pulse and ECG.

➢ **Follow-up visit V3: End of period 2** (one-day Neurology hospitalization, 5 weeks after V2)

- MDS UPDRS part III in On Drug, dyskinesia scales (Abnormal Involuntary Movement Score (AIMS) and Dyskinesia Rating Scale (DRS)) in On Drug
- **Tolerance assessment:** general clinical examination (weight, height, orthostatic hypotension test, temperature, respiratory rate, blood pressure, pulse, ECG), collection of surgical complications, tolerance of product administered.
- **Standard laboratory tests :**
  - blood count, hemoglobin, PT, APTT, ionogram, kidney function tests, liver function tests, CRP and CPK
  - β-HCG assay (for women of childbearing age only)
- **Specific biology:** blood and urine assays for dopamine and its metabolites (HVA, and 5- cysteinyl-dopamine) and markers of oxidative stress (MDA, 4-HNE, 8 oxoDG) and axonal destruction (light chain filaments) after 2 h of treatment in the morning on an empty stomach (either 2 h after the first dose of oral treatment, or 2 h after the first daytime dose of A-dopamine).
- **Questionnaires:** MDS-UPDRS parts I, II, and IV, patient CGI (assessment of condition and assessment of improvement), physician CGI (assessment of condition and assessment of improvement), Schwab and England scale, Epworth scale, Parkinson's Disease Sleep Scale, PDQ39
- **Cognitive examination:** MOCA, NPI, PAS, LARS, ECMP
- **Psychiatric evaluation:** consultation without scales to assess psychiatric disorders experienced during the last month of treatment

Treatments during cross-over

Patients will receive two one-month treatment phases in a randomized, open-label fashion, either with DIVE (A-dopamine) or with optimized oral treatment as usual. During the DIVE treatment phase, oral treatment may be maintained at a residual dose if deemed necessary by the investigator and for the patient's comfort. Conversely, if A-dopamine (DIVE) is discontinued during the month of oral treatment, the A-dopamine will be removed from the pump by transcutaneous injection and replaced in the pump by 20 ml of anaerobically prepared saline. The pump flow rate is maintained at 0.5 ml per day. Similarly, the catheter will be emptied and 1 ml of anaerobic saline injected transcutaneously into the catheter port.

➢ **Long-term follow-up phase**

Consultation visits every 6 months after V3 with :

- MDS UPDRS part III in On Drug, dyskinesia scales (Abnormal Involuntary Movement Score (AIMS) and Dyskinesia Rating Scale (DRS)) in On Drug
- Tolerance assessment: general clinical examination, tolerance of product administered
- Biology: standard biological workup and 24-hour urine test
- Questionnaires: MDS-UPDRS parts I, II, and IV, patient CGI and physician CGI, Schwab and England scale, Epworth scale, Parkinson's Disease Sleep Scale, PDQ39
- Cognitive examination: MOCA, NPI, PAS, LARS, ECMP
- Psychiatric examination
- 7-day actimetry-free diary

This long-term follow-up phase of the protocol will end when the last treated patient in the study reaches the last visit of Phase II (Visit 3). The estimated date of this last visit is 06/30/2024.

For the well-being of patients and to make their daily lives easier, the sponsor calls on a homecare provider to fill the pump in the patient's home at the end of phase 2, when the patient begins his or her long-term follow-up phase.

The Service Provider will collect the following data:

- Report serious or non-serious adverse reactions in the eCRF and fax them directly to pharmacovigilance.
- Dopamine treatment data (screenshot of programmer before and after filling and possible adjustment)

A post-filling screen copy to be sent to the investigating physician, the investigating CRA and the sponsor, to enable validation of the service rendered via a secure platform (Chutransfert).

The service provider undertakes to enter the data listed above into the study's eCRF at the end of each visit.

As part of good clinical practice, it may be necessary either to lower doses in the event of intolerance, or to slowly increase doses in the event of good tolerance and persistence of oral treatment. In the latter case, it may be appropriate to propose a slow increase in dose, as is done with the apomorphine pump, to allow further reduction of oral L-dopa and its complications. In the event of complete discontinuation of oral treatment, control could thus be optimal. Any psychotropic treatment requires slow titration, especially for higher doses. This will therefore be offered to all patients with good tolerance at the end of phase 2 cross-over.

Procedure in case of need for emergency pump shutdown (e.g.: need for emergency MRI for another medical reason)

To ensure that MRI can be carried out safely, the safety protocol established by Flowonix, and already routinely applied to all patients using Flowonix equipment, will be implemented. First, prior to imaging, the status and correct operation of the pump will be checked using the Prometra Programmer. Then, the pump will be switched off so that no more drug is delivered. Finally, the A-dopamine will be removed from the pump by transcutaneous puncture of the central port and catheter port, using the two kits provided for this purpose and accessible by the on-call team (the on-call supervisor has access to the neurology supervisor's office and to the office of the principal investigator, Prof. Moreau). The neurology and neurosurgery nurses have been trained in emptying and filling the pump, and all the neurologists on duty have been made particularly aware of the procedure required to perform an MRI.
The pump will be stopped. The MRI can then be carried out safely. At the end of imaging, the pump will be interrogated again to check that the MRI has not interfered with its programming. The pump's valves will be checked for proper functionality using a Refill Kit (Flowonix (New Jersey, USA), Medizintechnik Promedt GmbH (Germany), Tricumed (Germany)) (we'll need to verify that it's impossible to withdraw cerebrospinal fluid through the pump's central septum). Once these checks have been carried out, the pump reservoir can be filled in the usual way, and the pump reprogrammed to the required injection rate.

If, for any reason other than the need for imaging, for example, the interruption of the pump should last longer, the patient resumes oral dopaminergic treatment.
If the A-dopamine is removed and the pump stopped, the system is safe and can be reactivated in the following days according to the patient's medical needs.

Procedure in the event of an adverse reaction, technical problem or unavailability of A-dopamine requiring temporary discontinuation of DIVE treatment

In the event of an unexpected or voluntary pump shutdown, in the event of a suspected technical problem (catheter obstruction, disconnection or leak), or in the event of a suspected medical problem (suspected underdosing or abnormal overdosing, or patient's wish to stop DIVE treatment), A-dopamine will be removed from the pump by transcutaneous puncture of the central port and catheter port, using the two kits provided for this purpose and accessible by the on-call team (the on-call supervisor has access to the neurology supervisor's office and to the office of the principal investigator, Prof. Moreau). The neurology and neurosurgery nurses have been trained to empty and fill the pump. The pump will be shut down.

If the A-dopamine is removed and the pump stopped, the system is safe and can be reactivated in the following days, depending on the patient's medical needs. The system can then be replaced with 20 ml of anaerobically prepared saline. The pump flow rate should be maintained at 0.2 to 0.8 ml during the day and 0.1 to 0.5 ml at night (to enable refilling at D15). Similarly, the catheter will be emptied and 1 ml of anaerobic saline injected transcutaneously into the catheter port. This procedure should be carried out as soon as possible and ideally within 24 h (24-hour neurology and neurosurgery on-call, with one of the 4 neurologist investigators and 4 neurosurgeons trained in this procedure available on call). The patient resumes oral dopaminergic treatment.
The aim is to prevent the dopamine from stagnating in the catheter, particularly at the tip of the catheter in the cerebrospinal fluid, which has an oxygen partial pressure of 4.5% and could therefore lead to oxidation of the dopamine if it stagnates, with the formation of crystals that could obstruct the catheter and hamper restarting. On the other hand, the stability of A-dopamine in the pump poses no problem for more than a month. It may also be decided to reintroduce A-dopamine once the problem has been resolved.

Procedure in the event of permanent discontinuation of DIVE treatment (premature discharge or at the end of the study)

The same procedure as above will be applied for any premature study exit for whatever reason, or for study termination for patients not wishing to participate in the long-term follow-up phase. Initially, A-dopamine will be replaced by anaerobic saline at a pump rate of 1 ml day and night. The usual optimized oral treatment will be resumed. In addition, the patient will be offered several therapeutic strategies:
- return to optimized oral treatment. In this case, the neurosurgical procedure to remove the pump and catheter will be scheduled in the following days.
- subthalamic stimulation initially not chosen by the patient, but who could reconsider this choice. In this case, the neurosurgical procedure of removing the pump and catheter could be carried out, followed by bilateral implantation of the subthalamic stimulation using preoperative and intraoperative MRI scans. The pump can pass MRI if it is switched off and filled with saline.
- duodopa® treatment not initially chosen. Under these conditions, the pump and catheter would first be removed, followed by the gastroenterologist's intervention to perform the gastrostomy, with continuation of the usual management.

Procedure in the event of non-stop treatment for a patient with a vital prognosis

The CSI will be notified as soon as possible by the Vigilance Unit of the CHU de LILLE, of a decision to continue study treatment in a patient with a vital prognosis. In the meantime, the investigating team will make the best medical and ethical decision for the patient, in liaison with the medical team in charge of the life-threatening emergency. The therapeutic strategy will then be validated by the ISC, by return e-mail at the very least, or by a meeting organized on an exceptional basis.

6.3 Duration of research

- The duration of active patient participation for periods 1 and 2 is seven months, including four months under treatment (three months of titration and one month of efficacy study in phase 2). However, for phase 1, these times are indicative and may vary significantly depending on the patient's state of health and feedback from experience.
- The long-term follow-up phase of the protocol will end when the last treated patient in the study reaches the last visit of Phase II (Visit 3).
- Length of inclusion period: 27 months
- Theoretical duration of research: 3 years and 9 months (estimated LPLV: 30/06/2024)
- Data analysis time: 6 months

6.4 Flowchart from the study

		SC	Baseline	Location /titration	V1	V2	V3	Long-term visits every 6 months
	Possible delay	***/***	***+2 weeks***	***+1 month***	***+1 week***	***+1 week***	***+1 week***	***+/- 2 weeks***
Checking inclusion and non-inclusion criteria		x						
Patient information		x						
Signature of consent		x						
Randomization					x			
Socio-demographic data (age, socio-cultural level), associated past and present medical and psychiatric disorders		x						
Medical check-up	Clinical examination	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
	Collection of concomitant treatments	x	x	x	x	x	x	x
Psychiatric assessment		x				x	x	x
Chest X-ray, cardiac ultrasound			x					
Covid-19 test before surgery (if required by Covid-19 pandemic health measures)			x					
Neurosurgical implantation procedure				x				
Post-op CT scan				x				
Monitoring of therapeutic adaptation (in hospital, then at home through daily calls)				x				
Standard laboratory tests			x	x	x	x	x	x
Iron status: determination of serum iron, ferritinemia, transferrin, total binding capacity and transferrin saturation coefficient.			x					
FSH and LH assays (for all women)		x						
β-HCG assay (for women of childbearing age only)		x	x	x	x	x	x	
Continuous measurement of actimetry (PKG)					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 cerebral dopamine)					x	x	x	x
MDS-UPDRS parts I, II and IV			x		x	x	x	x
MOCA		x			x	x	x	x
Neuropsychological examination (cognition and behavior) : NPI, PAS, LARS, ECMP			x		x	x	x	x
Clinical Global Impression (CGI) doctor			x		x	x	x	x
Self-questionnaires: patient CGI, Schwab and England scale, Epworth scale, Parkinson's Disease Sleep Scale, PDQ39			x		x	x	x	x
Patient diary (periods 1 and 2)					x	x	x	x
Brain MRI with 3DT1 sequence with gadolinium			x					
Exploratory criteria: pharmacogenetics and biological collection			x					
Exploratory criteria: Biology (oxidized dopamine metabolites)			x	x		x	x	
Collection of AEs/EIGs		x	x	x	x	x	x	x

7 MEDICATION AT L'ÉTUDE

7.1 Name and description of investigational drug(s) (ME)

The study drug in the DIVE-I trial will be a solution of Dopamine Hydrochloride 10mg/mL (pH 4 solution) solubilized in 0.9% NaCl, and 50 mg/mL and 100 mg/mL (hyperosmolar pH 4 solutions) solubilized in PPI water. It is prepared in a sterile isolator under complete anaerobic conditions. The extremely low volume (< 4 mL over 24h, i.e. < 0.003 ml/min or < 0.0015 ml/30 sec, as the pump infuses every 30 seconds) of the drug administered in a cerebrospinal fluid volume averaging
150 ml in constant motion by the 70 heartbeats per minute instantly buffers hyperosmolarity and pH (as demonstrated in the monkey safety study and as documented in the drug file).

Clinical batches will be manufactured by the Lille University Hospital Central Pharmacy, under the coordination of Dr. Lannoy and Prof. Odou, in accordance with Good Preparation Practices.

Stability was assessed and confirmed over 3 months for the 10 mg/mL Dopamine Hydrochloride solution, and over 2 months for the 50 mg/mL and 100 mg/mL solutions in type I amber glass vials at 4° Celsius, and over one month at 37° Celsius in the Flowonix® PROMETRA II pumps used in the clinical trial, anaerobically after open-air filling with the closed system (PhaSeal System, Becton Dickinson, New Jersey, USA), the syringe of which was pre-filled with an inert gas.

Preparation of clinical batches of dopamine hydrochloride solution :

The solution is packaged in 20mL amber glass vials (the solution being photosensitive), corresponding to the capacity of the programmable implantable pump used during the DIVE-I trial. The clinical batches represent 45 vials, 25 of which are intended for administration to patients included in the clinical trial, the others being used for compliance testing or kept in a sample library. A 100ml sample of the solution will be taken prior to bottling, in order to control the bioburden of the raw material.

Solution preparation is carried out in an anaerobic atmosphere-controlled zone in a nitrogen isolator. All preparation is carried out under aseptic conditions, using sterile or autoclaved equipment. After weighing the required amount of dopamine and pouring it into a volumetric flask, the necessary quantity of 0.9% NaCl or PPI water (depending on the concentration of the solution) to obtain 1 liter of solution is added. The entire solution is transferred to a beaker for homogenization, and the necessary amount of HCL is added to obtain a pH 4 solution (except for the 100 mg/mL dopamine hydrochloride solution, which is already naturally at pH 4). The visual appearance of the solution is checked. The pH is checked using an electronic pH meter on a control bottle.

Once the solution has been formed, filling is also carried out in the isolator, in an anaerobic and aseptic atmosphere, using 20mL polypropylene syringes fitted with a 0.22 µm filter with a cellulose acetate membrane, enabling sterilizing filtration. Each vial, previously rinsed with ppi water and sterilized, is filled with 20mL of solution before being capped and crimped with an aluminum tear-off cap, previously sterilized in an autoclave.

Control of clinical batches of dopamine hydrochloride solution :

A bioburden test is carried out on the various components of the preparation whose sterility has not previously been tested: dopamine hydrochloride powder and HCL solution. This bioburden test will be carried out in accordance with the European Pharmacopoeia at the CBP (Centre de Biologie Pathologie) of Lille University Hospital. For further details on these bioburden tests, please refer to the document "Protocol and specifications for bioburden tests carried out on non-sterile components of dopamine hydrochloride solutions".

Various control tests are carried out after dopamine manufacture in accordance with the European Pharmacopoeia:

- Visual appearance of the solution,
- Identification of Dopamine Hydrochloride by HPLC-UV,
- 6-hydroxydopamine content is measured by HPLC-UV,
- Particle load control,
- Absorbance control,
- Osmolality control,
- pH measurement,
- Sterility and bacterial endotoxin control

For further details on the preparation of clinical batches, including preparation formulas, batch references and equipment used by the PUI, as well as test methodology and specifications, please refer to the documents "Protocol for the preparation of amber glass vials containing a solution of dopamine hydrochloride 10mg/mL diluted in NaCl 0,9% - Protocoles et spécifications des tests effectués sur les lots fabriqués" and "Protocole de préparation des flacons en verre ambré contenant une solution de chlorhydrate de dopamine à 50mg/mL diluée dans de l'eau PPI - Protocoles et spécification des tests effectués sur les lots fabriqués", all three attached to the investigational medicinal product file.

7.1.1 *Contraindications of dopamine*

There are no contraindications to the use of intracretbroventricular dopamine in Parkinson's patients, in compliance with the inclusion and non-inclusion criteria of this study (in particular, no patients with dementia or psychosis).

The contraindications to dopamine linked to its peripheral action are rarely, if ever, expected with central administration.

The main contraindications are

- Cardiac rhythm disorders and/or heart failure not controlled by treatment (in particular ventricular rhythm disorders)
- Uncontrolled blood pressure release

The theoretical peripheral interactions of dopamine are :

- Hallogen inhalation anesthetic gases (due to risk of ventricular rhythm disturbance)
- Guanethidine and related products (due to risk of increased blood pressure)
- Non-selective and selective monoamine oxidase A inhibitors: iproniazid, moclobemide, toloxatone (due to risk of increased blood pressure)

No anomalies of carcinogenesis, mutagenesis or effects on fertility are expected with this treatment. However, in principle, pregnancy and breast-feeding represent a contraindication in this study.

7.1.2 *Undesirable effects expected*

See Experimental drug file and Summary of data justifying the use and safety of the drug in research.

No cardiac arrhythmias or endocrine abnormalities have been reported (preclinical studies and two case reports). The authors report that high doses of dopamine (up to 45 mg) can be administered without serious adverse effects on vital functions. Dopamine administration did not damage the cerebroventricular wall.

Reference	Number of patients	Disease	Doses evaluated per day	Treatment time (months)	Undesirable effect
Venna *et al.*, 1984	Patient N°1	Parkinson's disease	40 µg to 16 mg	5 + 3	- Transient increase in blood pressure - Brief episodes of sneezing, yawning and flushing - Hallucination and confusion in a patient with pre-existing confusion and hallucinations at the same level as treatment with Oral L-dopa
Horne *et al.*, 1989	Patient N°2	Parkinson's disease	2.5 à 45 mg	7	Hallucination and confusion in a patient with pre-existing confusion and hallucinations at the same level as treatment with Oral L-dopa

Table: Adverse events reported in patients with Parkinson's disease Adverse events with dopamine

hydrochloride by venous infusion
Indication: shock after cardiac surgery, post-infectious vascular filling or after epidural or spinal anesthesia.
• Nausea and vomiting
• Heart rhythm disorders: tachyarrhythmia
• Peripheral vaso-constriction: hypertension and angina at high doses

Potential adverse effects of intracerebroventricular dopamine hydrochloride
Neurological and psychiatric effects
A-dopamine will enter the cerebrospinal fluid in the form of dopamine, as the cerebrospinal fluid is in a low aerobic atmosphere (4.5 to 6% oxygen). Dopamine is naturally present in the human brain. Only patients with a lack of dopamine will be treated (i.e. PD patients), with the aim of compensating for the lack of dopamine with the minimum effective dose. The effects observed in animals and humans were milder control of parkinsonian symptoms than oral treatment with L-dopa. Overdosage should result in dyskinesia. However, this was not observed with A-dopamine in mice, rats or monkeys. Dyskinesia with cerebral administration of dopamine was reported in one of two patients and is therefore likely to occur in a dose-dependent manner. Confusion and hallucinations have been reported in patients already experiencing confusion and hallucinations as symptoms of their dementia. These effects should not be observed in non-demented patients without prior confusion and hallucinations and treated with doses adapted to their motor handicap (i.e. without overdosing). Confusion, hallucinations, uncomfortable sensations and nausea could therefore represent warning signals of overdosage, leading to a reduction in dosage or even a transient cessation of pump output.
The adverse effect related to the central nervous system should be the same with no or fewer motor and non-motor fluctuations.
- Daytime sleepiness
- Nausea and vomiting (transient)
- Headache

The following adverse effects may be observed in patients with this condition, which may worsen on L-dopa and possibly on A-dopamine

- Impulse-control disorders (exceptional with L-dopa but frequent with dopamine agonists)
- Disorientation and confusion
- Extreme emotional states, particularly anxiety, but also excessive libido
- Vivid dreams or insomnia
- Auditory or visual hallucinations
- Sleepiness and narcolepsy
- Psychosis

Adverse reactions to intracerebroventricular dopamine hydrochloride should always be interpreted in terms of over- or under-dosing.
- Underdosing: resurgence of parkinsonian signs
Actions: increase the dosage or resume the associated oral treatment.
- Overdose: occurrence of malaise, nausea, vomiting, even hallucination or confusion with extreme doses
Actions: lower the dosage or even stop the pump after replacing the dopamine with anaerobic saline,
The highly symptomatic nature of dopamine, its very slow titration and the direct action of intracerebral administration should enable very rapid dose adaptation for minimum impact.

Peripheral effects are likely to be very limited and present only in the event of overdosage, as observed in monkeys with 10 times the minimum effective dose. Indeed, when overdosage was induced in monkeys, it was observed that dopamine was excreted from the cerebrospinal fluid and brain tissue into the venous system and then excreted in the urine, which turned black one hour after emission (see 4.4. Toxicology). The effects of dopamine administered by venous infusion vary according to dose.

The major peripheral risk is cardiac and vascular overdose. Dopamine should therefore be avoided in patients with severe, uncontrolled cardiac rhythm disorders (atrial fibrillation and flutter, ventricular tachycardia or fibrillation). However, the risk is likely to be much higher with peripheral administration of L-dopa, even when combined with a dopadecarboxylase inhibitor, which is the case for all patients with advanced PD.

Adverse effects related to peripheral organs should be absent or to a lesser degree.
- Orthostatic hypotension, especially if the dosage is too high
- Arrhythmias and other rhythm disorders, although exceptional
- Dysgeusia
- Constipation
- Gastrointestinal bleeding
- Disturbed breathing, which is not always harmful, and can actually benefit patients with upper airway obstruction
- Hair loss
- rash, itching,
- Non-specific visual and blood disorders
- Slight increase in transaminases

Undesirable effects associated with general anaesthesia
A preoperative assessment will be carried out to limit :
- risks of allergic reaction or intolerance to the anesthetic product
- Comorbid decompensation

Surgical side effects
- Extradural hematoma
- Subdural hematoma
- Intracerebral hematoma along catheter path to thalamus
Actions: These risks are classic and equivalent to those associated with the implantation of any neurosurgical equipment such as brain stimulation in Parkinson's patients.

These risks will be minimized by intraoperative MRI tracking to avoid vessels in the furrows (as for brain stimulation) and using the 3DT1 sequence with gadolinium. If there is any doubt, an additional scan will be performed in addition to the standard postoperative scan.
- Infection of equipment: catheter or pump
- Delayed healing (doubt of infection or low trophicity)
Actions: These risks are classic and equivalent to those associated with the implantation of any equipment such as brain stimulation. They lead to local disinfection and the prescription of antibiotics. If resolution is not rapid, the equipment is removed under antibiotic treatment.

Adverse reactions to percutaneous filling
- pain at the puncture site
- inflammation at the puncture site
- Wall hematoma
- Collected or uncollected wall infection
- subcutaneous collection of dopamine

Adverse reactions linked to* equipment *malfunction
Pump or catheter malfunction (see medical device file)
This will be manifested by loss of efficacy (underdosing) or overdosing (see adverse effects of dopamine) or pain or edema or inflammation in the abdomen or subcutaneous catheter pathway.

Adverse reactions associated with injection of Gadolinium contrast medium (MRI)
Headache, nausea and pain at the injection site. Anaphylactoid reactions are rare, occurring in about 0.03-0.1% of cases.

7.2 Dosage schedule and duration of treatment

Dosage is determined according to the principle of minimum effective dose and adapted to the patient's motor handicap, as with the apomorphine pump or Duodopa®. With these peripherally-administered treatments, the effect is usually felt after 30 minutes. Experience with these treatments has shown that the flow rate needs to be greater during the day than at night (by more than 50%) to respect the sinusoidal circadian cycle of dopamine as recorded in rats (Devos et al., 2009).
The first two cases treated in the 1980s with ICV dopamine appeared to be well controlled with doses of 8 to 45 mg/day. However, in the course of phase 1 titration in the first two patients included in this study, we found that the minimum effective dose of intracerebral A-dopamine was much higher than anticipated, at least 10 to 18 mg/h, which would correspond to a daily dose of 180 to 324 mg/day (calculated on the basis of the 18h daytime period, as nocturnal needs are much less important and compatible with slow titration).
In principle, the nocturnal dose should be reduced by 50-70% compared with the daytime dose, depending on the patient's symptoms and needs. The patient will be monitored during the initiation phase in hospital.

An initial hospital titration will be carried out with a maximum daily increase of 1 mg/h over the daytime period, corresponding to a maximum increase of 18 mg per day (calculated on the basis of the 18 hours (5 a.m.-11 p.m.) of the daytime period, as nocturnal needs are much less significant and compatible with slow titration), up to a first level of 5 mg/h (i.e. 90 mg/day). This is a maximum titration, and the patient may be discharged from hospital with a lower dose if his motor condition is deemed satisfactory.
Slow, cautious titration then continues on an outpatient basis, with a weekly increase of 1 mg/h, until the dose required for satisfactory control is reached, with or without a minimal residual dose of dopaminergic treatment. The advantage of this titration regimen is that the patient returns to hospital only once a week to perform the dose change by telemetry.

A-dopamine is gradually titrated to the minimum effective dose needed to control dopaminergic motor symptoms with the same efficacy as oral L-dopa treatment, but on a continuous basis.
The minimum effective dose is planned to be between 10 and 18 mg/h, i.e. between 180 and 324 mg per day (5 a.m.-11 p.m.).

This titration plan is considered to be maximal: if there is any doubt about efficacy and/or tolerance, titration should be stopped for a few days (1 to 3 days) to avoid a cumulative effect and allow precise definition of the minimum effective dose. If efficacy is equivalent to oral intake, the dose will not be increased any further.
For the patient's comfort, oral treatment should be maintained during the initial titration phase, to avoid transient motor aggravation. As soon as the effects are felt, the oral treatment will be gradually reduced, while cerebral dopamine is cautiously increased. This will be done in the same way as with the apomorphine pump, deep brain stimulation and Duodopa®. We hope to stop oral treatment altogether. The patient will then be maintained on the same daytime and night-time dose for the month of assessment.

7.3 Drug and medical device traceability, accounting and compliance monitoring

About the investigational drug :

Dispensing and traceability: treatments will be dispensed by the CHU Lille central pharmacy to the Neurology Department.

Prescription: The investigator will draw up a standard prescription for dispensing by the pharmacy. Dispensing covers the stability of the preparation (15 days).

Administration of treatment to the patient: At the time of the visit, after checking for tolerance and possible side effects, the nurse will transcutaneously inject the dopamine into the intra-abdominal pump in a sterile, anaerobic manner, following the usual procedures for baclofen filling. Volume and dose will be calculated to ensure a flow rate for 15 days of treatment.

Administration of treatment in the patient's home: During the long-term follow-up phase, treatments will be dispensed by the Lille CHU central pharmacy to the UPARC (Unité Paramédicale Ambulatoire de Recherche Clinique) service provider. Transport to the patient's place of residence will be ensured under treatment preservation conditions defined by the promoter. The pump will be refilled under the same conditions as in the neurology department. Unused treatments will be returned by the service provider to the Lille PUI.

Concerning the medical device :

Traceability
PROMETRA II pumps and accessories (Intrathecal Catheter, Refill Kit, Catheter Access Kit, programmer) will be sent by Flowonix (New Jersey, USA) to the central pharmacy of Lille University Hospital.

Refill Kits marketed by German companies Medizintechnik Promedt and Tricumed will also be sent directly to Lille University Hospital's central pharmacy.

Distribution will be carried out by the Lille University Hospital Central Pharmacy in the Neurosurgery Department on the day of surgery.

7.4 Drugs and treatments not authorized in the study

The following treatments will be prohibited for the duration of the study:

- Hallogen inhalation anesthetic gases (due to risk of ventricular rhythm disturbance)
- Guanethidine and related products (due to risk of increased blood pressure)
- Non-selective and selective monoamine oxidase A inhibitors: iproniazid, moclobemide, toloxatone (due to risk of increased blood pressure).

8 BIOLOGY

8.1 Location of analyses

The CIC/CRB of the CHU de LILLE will manage biological samples with a view to their subsequent analysis, as well as their storage and management in terms of referencing, storage, and traceability of inputs, outputs or incidents. These aspects of the CIC/CRB's activities are certified to ISO9001v2015 and NF-S-96900 standards.

The storage and centralization of biological products is coordinated by the CIC/CRB, using a biological sample management software system that enables rigorous traceability of each sample. This system uses specific barcode labels. This software, called Databiotec®, is located and managed by the CIC in Lille. Access is password-controlled. Each connection is logged, and access to the database is restricted according to a personal user profile. All movements and events linked to the existence of a sample (entries, exits, reintegration, cold chain incidents) are recorded and can be queried in the software.

This sample management and traceability software enables you to manage :

- the subject code number,
- sample labeling,
- tube contents,
- the tubes belong to a research protocol
- bank entry and exit dates,
- type of pathology,
- any problems encountered.

Each sample is uniquely identified: the sample belongs to one study and one subject. The sample is identified by a barcode. A barcode reader provides automatic access to all sample information. The method and conditions of sampling, the people involved, clinical information, additional examinations, contamination, quality, dangerousness and location of the sample are all recorded.

DataBiotec® provides a precise description of all types of storage equipment (containers), specifying :

- storage elements: floors, drawers, racks, boxes, wells
- location management: occupied, reserved, available

It integrates the creation of configurable sample selections that enable logical groupings to be obtained:

- list of samples taken on the same day
- in the same study
- of the same kind
- for the same technician
- in the same freezer

Sample storage temperature is monitored by continuous recording, and the various containers are centrally alarmed. Back-up freezers are available for rapid response to any breakdown. Storage facilities are secured (electronic access code, intruder alarm, video surveillance of premises).

Today, the Biological Resource Center manages biological samples for 300 regional, national and international single- and multi-center studies. Every year, the Biological Resource Center generates between 100,000 and 120,000 biological samples for research purposes.

8.2 Biological check-up standard

The standard biological workup will be performed at each visit. 7 tubes will be taken for a total of 40 mL of whole blood at each visit, including :

- 1 x 5 mL whole blood on EDTA tube for CBC, platelets, PT, APTT, CRP, rhesus group in 2 determinations and CPK
- 1 tube of 5 mL whole blood on heparin tube for liver work-up (Transaminases (ALAT, ASAT), Gamma-GT, Total Bilirubin, Alkaline Phosphatases), kidney work-up (Creatinine, Urea), ionogram
- 1 dry tube of 5 mL whole blood for β-HCG assay (for women of childbearing age only)
- 3 x 6 mL dry tubes and 1 x 7 mL NH (sodium heparin) tube of whole blood for the determination of iron status (serum iron, ferritinemia, transferrin, total binding capacity and transferrin saturation coefficient) collected only at V0

Samples used for standard biological tests will not be kept.
If an anomaly is discovered by chance in the various biological results, the results will be communicated to the patient, who will be referred to a specialist. Unless the patient objects, his or her GP will also be informed.

8.3 Specific biological tests at V0

If the subject is a woman, an LH and FSH assay will also be performed at V0 on the 7 mL dry tube taken for the tyroid work-up, in order to estimate the need for oral contraception.
Samples used for the specific biological check-up at V0 will not be kept.
If an anomaly is discovered by chance in the various biological results, the results will be communicated to the patient, who will be referred to a specialist. Unless the patient objects, his or her GP will also be informed.

8.4 collection

These samples will be stored at the Lille University Hospital Biological Resource Center until they are exhausted. They may be reused, unless the patient objects, for pathology-related studies.
The biological collection created as part of this biomedical research will be declared to the ANSM. If the collection is kept after the end of the study, it will be declared to the competent authorities.

The sample will be taken during the V0 visit. 4 tubes will be taken for a total of 20 mL of whole blood, such as :

- 2 x 5 mL EDTA tubes are collected and centrifuged to recover plasma and buffycoat,
- 1 x 5 mL dry tube for serum bank set-up
- 1 x 5 mL citrate tube is used to obtain deplated citrated plasma.

These samples will be used for genetic analysis to explore polymorphisms in enzymatic (DaT, COMT, MAO, DDC) and non-enzymatic dopamine metabolism (ferric auto-oxidation (ceruloplasmin)).

8.5 Biological check-up exploratory

1 5 mL tube of whole blood will be collected at V0, V2 and V3 to perform the following assays:
- Markers of oxidative stress (MDA, 4-HNE, 8 oxoDG) and axonal destruction (light chain filaments)

2 5 mL whole blood in heparinized tubes will be collected at visit V0 (baseline), every week during phase 1 titration, and at visits V2 and V3 in phase 2. 24-hour urine samples will also be collected in special acid jars. These samples will be used to assay dopamine and its metabolites (HVA, 5 cysteinyl dopamine).

8.6 Total volume of blood drawn :

The total volume of blood collected during the study was approximately :
Standard bioassay: 40 mL at visit V0 and 15 mL at visits V1, V2 and V3 and at follow-up visits every 6 months after visit V3 at the end of period 2.
Specific bioassay at V0: 7 mL
Biological collection (pharmacogenetics): 20 mL at V0
Exploratory biological workup :

- Markers of oxidative stress and axonal destruction: 5 mL at V0, V2, and V3
- Dopamine and metabolite assay: 10 mL at V0, each week of phase 1 titration, then 10 mL at V2 and V3 of phase 2.

Minimum total volume: 197 mL
The volume of blood drawn may vary according to the duration of phase 1 titration.

9 EVALUATION OF SECURITY

9.1 Definitions

Adverse event: any noxious occurrence in a person undergoing research involving the human body, whether or not related to the research or the product to which the research relates.

Adverse event: any undesirable event linked to the research or the product to which the research relates.

Serious adverse event or reaction: any adverse event or reaction that :

- **leads to death,**
- **endangers the life of the person undergoing the research,**
- **requires hospitalization or prolongation of hospitalization,**
- **causes significant or lasting disability or handicap,**
- **or results in a congenital anomaly or malformation, regardless of t h e dose administered.**
- **is deemed medically serious by the investigator.**

Certain circumstances requiring hospitalization do not fall under the "hospitalization or prolongation of hospitalization" severity criterion, such as :

- **admission for social or administrative reasons**
- **protocol-defined hospitalization**
- **hospitalization for medical or surgical treatment scheduled prior to research**
- **transfer to day hospital**

Unexpected adverse event: any adverse event whose nature, severity or course is not consistent with the information on the products, procedures and methods used in the research.

New fact: any new data that may lead to a reassessment of the risk-benefit ratio of the research or of the investigational product, to changes in the use of this product, to changes in the way it is used, or to changes in the way it is used.

conduct of the research, or documents relating to the research, or to suspend or interrupt or modify the research protocol or similar research.

9.2 Expected individual and collective benefits

This therapeutic concept has previously been validated in three in vivo animal models of Parkinson's disease: the mouse intoxicated acutely and the monkey intoxicated chronically with MPTP, the rat injured unilaterally with 6 hydroxydopamine (Laloux et al., 2016; Moreau et al., in progress). After treatment with A-dopamine, motor function was restored to 100%. A powerful neuroprotective effect was even observed in the MPTP mouse model.
Two patients with advanced Parkinson's disease had already been treated with intracerebroventricular administration of dopamine without anaerobics in 1984 and 1989. Tolerance was judged to be excellent. Similarly, efficacy on motor function reached the same level as oral administration of L-dopa. However, at the time, the pathophysiology of Parkinson's disease was not as well understood as it is today. In particular, the definition of dementia and Parkinsonian psychosis was not precise, and both patients were already clearly at a stage of dementia with hallucinations which reappeared under intracerebral dopamine in the same way as with L-dopa. Similarly, the need not to maintain a constant flow rate, but to differentiate between a high dose during the day and a low dose at night, has only come to light with the more recent experience of the apomorphine and duodopa pump. The absence of tachyphylaxis is therefore expected when following the restoration of circadian rhythm.
Finally, the technological level of the pumps at the time was inferior to that of today, which may account for a more random administration, with doses less adapted to the patient's condition. Despite these major limitations, the two authors conclude that "this treatment was well tolerated for several months (notably 10 months in one patient) and seems promising if dopamine oxidation is controlled". They feared dopamine oxidation because of the tachyphylaxis observed and because preclinical publications have clearly demonstrated this (DeYebenes et al., 1987). This oxidation of dopamine has now been mastered with anaerobic dopamine. The only adverse effects reported were rhinorrhea, yawning and a very brief facial flush at the start of infusion.
The expected benefits are a major reduction in motor and non-motor complications, thanks to the concept of restoring continuous, circadian dopaminergic stimulation. Better ergonomics are also expected compared with the apomorphine pump and Duodopa®, since the pump is inside the body, as is the case for the thousands of young patients with spasticity treated with baclofen pumps or severe pain treated with morphine.
Compared with deep brain stimulation, the benefits will be the absence of worsening of axial motor skills (dysarthria and gait) and the absence of worsening of behavior (impulsivity, suicidal risk, apathy and depression), sometimes secondary to bilateral subthalamic stimulation by itself and/or to the reduction in oral dopaminergic treatment. Similarly, the operative and neurosurgical risks will be reduced compared with subthalamic stimulation, since the surgical intervention is that of a simple cerebrospinal fluid bypass, as performed in hydrocephalic newborns and demented patients with normal-pressure hydrocephalus. In contrast to deep brain implantation, DIVE requires a shallow introduction of the delivery material into the frontal cortex to reach the ventricular horn, considerably limiting the risk of deep hemorrhage.

9.3 Foreseeable individual risks linked to the protocol:

In order to limit risks, management will be multidisciplinary at the Clinical Investigation Center and the Neurology and Neurosurgery Department, which have experience of Parkinson's surgery since 1997.
Intracerebroventricular administration of treatment is not yet highly developed, but trials have already been carried out (Paul et al., 2015 with administration of PDGF-BB growth factor in Parkinson's disease; see review for neurodegenerative diseases Ruozi et al., 2012; Tovar-Y-Romo et al., 2014) and the risks are well known thanks to the data from these trials, the data from the first two patients treated with dopamine (Venna et al., 1984; Horne et al., 1989) and above all the thousands of patients treated with baclofen and morphine.

Risks associated with MRI :
For most patients, the risks or side effects associated with MRI are minimal, but it can be a source of anxiety and claustrophobia. Since an MRI scanner uses powerful magnets, there are some contraindications to the procedure (e.g. patients with permanently implanted electronic medical equipment, etc.).
In addition, the use of Gadolinium-based contrast agents in MRI may, in very rare cases, cause headaches or nausea. Only proven cases of allergy to this product and renal insufficiency constitute a contraindication to its injection. On the precautionary principle, Gadolinium cannot be injected into pregnant women.
Gadolinium injection is likely to cause pain at the needle insertion point, and there is also a small risk of ecchymosis (bruising) or local infection.

Risks associated with surgery :
- Intraoperative anesthetic risks.
- Extra-dural or sub-dural bleeding risk
- Infectious risks on equipment

Medical device risks :
- With regard to the risk of equipment malfunction, all risks have been the subject of training and the implementation of a procedure consisting in shutting down the pump, completely removing the dopamine from the pump and catheter, administering an anaerobic saline solution and resuming conventional oral treatment during the repair period.
- For safety reasons, no MRI will be performed on the pump during the 2-month study period. In the event of the need for emergency MRI for a comorbidity unrelated to the disease or treatment, a procedure for stopping and draining the pump has been planned.

Treatment-related risks :
- Adverse effects of dopamine at central level (see experimental drug file).

Risks associated with venipuncture :
- Potential side effects of blood sampling include pain at the puncture site, hematoma and a feeling of discomfort for people who are afraid of blood sampling.

9.4 Description of evaluation parameters for security

At each visit, the investigator will ask the patient whether any adverse events have occurred.

Adverse events reported spontaneously at each visit, or in response to the specific question "Have you had any unexpected events since the last visit?", or found during the patient's clinical examination, will all be recorded in the patient's observation notebook, by filling in the adverse event form, whether it's a serious or non-serious adverse event.
All serious adverse events will be notified to the promoter without delay by fax or e-mail.

The subject will benefit from full medical supervision. There will be a sufficient number of intermediate visits and the possibility of telephone contact with a medical team in the event of problems. It is recommended that the subject's referring (treating) physician be informed of his or her inclusion in the trial, if he or she agrees.

9.5 Procedures for recording and reporting undesirable events

9.5.1 Responsibilities of the investigator

9.5.1.1 Collection of undesirable events

All adverse events will be reported on the adverse event forms in the observation book. Each adverse event observed will be recorded individually. The intensity of adverse events will be determined as follows:

- mild (grade 1): no interference with the patient's daily activities ;
- moderate (grade 2): moderate interference with the patient's daily activity, but still acceptable;
- severe (grade 3): significant interference with the patient's daily activities and unacceptable ;
- life-threatening (grade 4);
- death (grade 5).

All adverse events must be graded and evaluated.

9.5.1.2 Notification of serious adverse events

The investigator must notify the sponsor of all serious adverse events occurring during the trial period, with the exception of those listed in the protocol as not requiring notification, without delay from the date of knowledge.

All serious undesirable events must be reported on a "Serious Undesirable Event" form in the observation book. This form must be sent to the promoter
(Cellule Vigilance de la Direction de la Recherche et de l'Innovation) by fax to 03 20 44 57 11 or by e-mail: vigilance.essaiscliniques@chru-lille.fr

For each undesirable event, the investigator must document the event to the best of his or her ability:

- a clear, detailed description of the event, in the form of a medical diagnosis if possible
- the severity, start and end dates of the event, and its evolution
- the causal link between this serious adverse event and :
  - procedures performed during the study
  - experimental drugs

Adverse events will be monitored by the investigator.

For each SAE, the investigator must provide the following information, anonymously and whenever possible:

- a copy of the hospitalization or extended hospitalization report
- a copy of all relevant additional test results
- any other document it deems useful and relevant

9.5.1.3 Reporting period for serious adverse events

If a research participant is involved in an SAE, it must be reported:

- from the date consent is signed,
- for the duration of the participant's follow-up in the trial (i.e. 6 weeks after the end of treatment),
- without time limit when it is likely to be due to research and experimental medicine

9.5.1.4 Report pregnancies

Pregnancy does not constitute a serious adverse event, but its occurrence during the trial must be notified without delay, on the standard pregnancy reporting form, to the sponsor, who will ensure that it runs smoothly if deemed necessary.
The investigator must follow the patient until the end of the pregnancy or its termination, and notify the sponsor of the outcome using the standard pregnancy outcome form.
If the outcome of the pregnancy falls within the definition of serious adverse events (spontaneous abortion with hospitalization, fetal death, congenital anomaly, etc.), the investigator must follow the following procedure

notification system.

9.5.2 Responsibilities of Promoter

Any event occurring during treatment will be reported. Serious adverse events, as defined by Good Clinical Practice, will be notified to the sponsor. The sponsor will inform the principal investigator and the follow-up committee. These serious adverse events will be analyzed with the advice of the principal investigator and the follow-up committee.

9.5.2.1 Serious and unexpected adverse reaction report

For each serious adverse event, the sponsor assesses the severity and causal link between the event and :

- procedures performed during the study
- the investigational drug, as

well as its unexpected nature.

The sponsor notifies the ANSM and the CPP of any suspected serious and unexpected adverse reaction:

- in the case of an unexpected serious adverse reaction resulting in death or life-threatening illness, without delay from the day on which the sponsor becomes aware of the event;
- in the case of other serious unexpected adverse reactions, no later than fifteen days after the day on which the sponsor became aware of them.

The sponsor declares, in the form of a follow-up report to the ANSM and the CPP, additional relevant information concerning :

- suspected life-threatening or fatal unexpected serious adverse reactions, within eight days of the day on which the sponsor becomes aware of them.
- other cases of suspected serious unexpected adverse reactions, within a further period of eight days from the fifteen-day period for the initial report.

9.5.2.2 Report on developments at security

In the event of a new safety event, case of abuse, misuse, pharmacodependence, accidental intoxication or misuse during this study, the sponsor will immediately send an email to the CPP and ANSM, as soon as it becomes aware of the new event and any measures taken.

9.5.2.3 annual report

Once a year for the duration of the trial, or on request, the sponsor submits a **safety report** to the ANSM and the CPP. This safety report will include an overall analysis of the safety profile of the study protocol, taking into account all relevant new safety data. Safety information will appear in the form of summary tables summarizing serious adverse events or reactions that have occurred in biomedical research.

9.6 Supervisory Board independent

In view of the study's objective, an Independent Monitoring Committee (IMC) is to be set up.
The ISC members identified for the study are responsible for protecting the safety of study participants, evaluating the safety and efficacy of all study procedures, and ensuring the smooth running and overall conduct of the study. It will be composed of two neurologists and a neurosurgeon. This committee will serve as an independent advisory group to the principal investigator and sponsor, and is required to provide recommendations on the continuation and termination of the study.
The CSI will :

- Analyze patient safety by assessing the benefit/risk balance and other factors that may influence study results;
- Take into account factors external to the study, such as scientific or therapeutic developments that may have an impact on the safety of participants or on the ethics of the study;
- Ensure the relevance of the study throughout its duration;

• Review documentation concerning serious adverse events and safety reports and make recommendations regarding the safety of study participants;
• Make recommendations on continuation, suspension, discontinuation or other modifications to the study on the basis of accumulated experience, including observed beneficial or adverse effects, to the principal investigator and study sponsor.
This committee is responsible for identifying any factors that could affect the overall conduct of the study.
The ISC will be informed immediately of any serious adverse event. All safety information will be transmitted after each patient's inclusion.
By default, the ISC will meet every six months to analyze the balance/risk. The ISC may adapt the frequency of meetings according to safety data.

Phase I in particular:
One patient will be included and followed throughout Phase I at a time.
Safety data from the first 5 patients will be analyzed before authorizing or not the continuation of inclusions.
a. In the absence of serious and unexpected adverse events after the first 5 patients (apart from the rare surgical risks of hemorrhage and infection of mild to moderate consequences, i.e. not life-threatening or functionally compromising (see section 7.1.2)), the remaining ~~15~~ patients can be included in phase 2.
b. In the event of two or more serious and unexpected adverse events, only 5 new patients may be included, on the advice of the Independent Monitoring Committee.

i. Then, in the absence of serious and unexpected adverse events, the remaining ~~10~~ patients could be included to move on to phase 2.
ii. If two further serious and unexpected adverse events occur, the Independent Monitoring Committee may decide to stop the study. This decision to stop the study if at least 4/10 patients experience serious and unexpected adverse events will serve as a clear follow-up rule for the ISC. However, this may be modulated according to the severity and diversity of the effects impacting the well-being of individuals, and whether they are totally unexpected or become predictable and manageable. (A list of expected rare adverse events has been drawn up for the surgical procedure, the dopamine and the medical device, in addition to the investigator's brochure, the investigational drug file and the medical device file. (see section 7.1.2)).

The data collected will be used to draw up and submit to ANSM a report describing all the safety and clinical data from the first 5 patients treated in phases 1 and 2.

9.7 Committee Follow-up

The Monitoring Committee is coordinated by Dr. T. OUK (Clinical Trial Vigilance, CHU de LILLE). During the study, the Monitoring Committee is informed of all adverse events (AEs). Information on AE follow-up will be sent to the committee on a regular basis. The committee will be responsible for ruling on the causality of reported AEs.

10 DATA MANAGEMENT

The individual data collected during the study will be recorded on a source document and then entered into a computer database. This data is confidential in accordance with the law of January 6, 1978.

Data will be analyzed in accordance with the reference methodology MR 001 described by the CNIL in the Unité de Méthodologie, Biostatistiques et Datamanagement headed by Pr Alain Duhamel at Lille University Hospital.

Data will be recorded in a computerized database using Ennov clinical software. This software is certified for data management in clinical trials, and follows FDA (Food and Drug Administration) recommendations. All data will be hosted on a secure server at Lille University Hospital. The software enables the development of an electronic case report and the implementation of rules for

The data is then automatically queried as it is entered. Before the database is frozen, a data manager will monitor the data using the Ennov clinical software, based on the consistency rules agreed with the project manager.

Access to data will be restricted to those directly involved in the study. Data may only be modified by an investigating physician participating in the study, or by a collaborator designated by this physician and participating in the study.

Data concerning this study will be archived for a minimum period of fifteen years from the end of the research or its early termination, without prejudice to the legislative and regulatory provisions in force.

11 ANALYSIS STATISTICS

11.1 Calculation of the number of subjects required

The primary objective of the study is to demonstrate the superiority of continuous daytime and nocturnal intracerebroventricular administration of A-dopamine using the intra-abdominal pump delivery system (DIVE device, experimental treatment) compared with standard dopaminergic treatment (optimized oral medical treatment per os) in reducing the percentage of time spent above target (percentage of time off) measured by an actimeter during the first and last weeks of each treatment period (primary endpoint). This is an initial proof-of-concept study, with the aim of demonstrating a 10% reduction in the percentage of time off with the DIVE device, considered clinically relevant (Farzanehfar et al., 2018). Considering a first-species risk of 5%, a power of 80%, and a standard deviation of the main criterion of 15% (Farzanehfar et al., 2018), it is necessary to include 37 subjects per group to highlight this difference in a parallel arm experimental design. As the experimental design is a cross-over design (the disease and the endpoint being suitable), the number of subjects to be included (N) corresponds to the number of patients per group (N1) in a parallel-arm design, taking into account the correlation between repeated measurements (periods) in the same patient (ro): N=N1(1-ro). Assuming a correlation of 0.5 between repeated measurements, 12 analyzable subjects (i.e. with data on the primary endpoint for both periods) are required. Recruitment will continue until 12 patients treated with A-dopamine are available for analysis. No interim analyses have been or will be performed. However, contrary to the anticipated capacity, the actual capacity of the central pharmacy of Lille University Hospital cannot ensure the treatment of more than 12 patients with a weekly fill. We will therefore base our analysis on the 12 patients available.

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11.2 Method and strategy analysis

Statistical analyses will be carried out using SAS software (version 9.4 or higher) at Lille University Hospital's Unité méthodologie biostatistique et datamanagement (UMBD) under the responsibility of Pr. A. Duhamel. All statistical tests will be two-sided, with a first-species risk of 5%. Quantitative variables will be described by the mean and standard deviation in the case of a Gaussian distribution, or by the median and interquartile (i.e. 25ème and 75ème percentiles) in the opposite case. The normality of distributions will be assessed graphically using histograms and the Shapiro-Wilk test. Qualitative variables will be described by the numbers and percentages of each modality. No intermediate analyses are planned. As this is a proof-of-concept study, analyses will be carried out on analyzable subjects (case-complete analyses).

11.2.1 ***Main objective:***

The cross-over design randomizes patients into 2 sequences: E-S (A-dopamine treatment in the first period followed by standard oral medical treatment in the second period) and S-E (standard oral medical treatment followed by A-dopamine treatment).
E1 denotes the value of the endpoint in the first period for the experimental treatment. S1 designates the value of the first-period judgment criterion for the standard treatment.
E2 denotes the value of the endpoint in the second period for the experimental treatment. S2 is the second-period endpoint value for the standard treatment.

To meet the main objective, the following analysis strategy will be implemented:

1) A descriptive analysis to assess the effect of the treatment (TRT) x period interaction, which represents the carry-over effect. This will be carried out by representing on the same figure E1+S2 in the "E-S" sequence group and E2+S1 in the "S-E" sequence group.
2) The effect of the TRT x period interaction will be tested using an initial linear mixed model, including treatment, period and TRT*period interaction as fixed effects, and a random patient effect to account for correlation between repeated measurements. The validity of this model will be assessed by studying the residuals. If the assumption of normality of the residuals is not accepted, the non-parametric strategy described in 3) will be adopted.
   If the TRT x period interaction term is significant, or if the descriptive analysis 1) suggests a carry-over effect, the treatment effect will be estimated on the first period data only, by comparing the endpoint between the two groups using a Student's t-test. Otherwise, the treatment effect, adjusted for the period effect, will be estimated by a second linear mixed model including only treatment and period as fixed effects.

3) If the residuals of the first linear mixed model deviate from normality, the following strategy is used.
   - The carryover effect will be tested by comparing the distribution of the sum of the judgment criterion (period 1 + period 2) according to the 2 sequence groups "E-S" and "S-E" using a Mann-Whitney U test, i.e. comparing (E1+S2) versus (E2+S1). If the carryover test is significant, or if the descriptive analysis 1) suggests a carryover effect, the treatment effect will be estimated solely on data from the first period by comparing the endpoint between the two groups E-S and S-E using a Mann-Whitney U test (i.e. E1 compared with S1).
   - If the carryover effect is non-significant, the second step consists in testing the period effect by comparing the distributions of the difference in the endpoint (period 1 - period 2) according to the 2 sequence groups "E-S" and "S-E" using a Mann-Whitney U test, i.e. (E1-S2) compared with (S1-E2). As the cross-over design takes account of the period effect, whether significant or not, the treatment effect adjusted for the period effect will be tested by comparing the distribution of (E1-S2) with that of (S1 - E2) using a Mann-Whitney U test.

11.2.2 ***Secondary objectives:***

The same analysis strategy described for the primary objective will be used to compare the following secondary endpoints:
- Other validated actimetry criteria (BKS, DKS, PTI, FDS, PTT)
- Patient diary measurements (OFF and ON times with and without dyskinesias)
- Clinical criteria (MDS UPDRS part I, II, III and IV, AIMS, DRS, CGI-patients, CGI-physician, Schwab and England scale, Epworth scale, Parkinson's Disease Sleep Scale, PDQ39)
- Cognitive measures (MOCA, NPI, PAS, LARS, ECMP)
- Qualitative psychiatric assessment
- Adverse event frequencies will be described for each treatment.

The clinical criteria, cognitive measures and qualitative assessment of the first period will be measured at V2, and those of the second period at V3.

11.2.3 ***Exploratory objectives :***

- The dose of A-dopamine obtained at the end of the titration period will be compared between the genotypes of the polymorphisms (DaT, COMT, MAO, DDC) (dominant model) by a Mann-Whitney U test.
- Blood and urine levels of dopamine and the metabolites HVA, 5-cysteinyl-dopamine and oxidative stress marker measured before DIVE treatment will be compared with levels after DIVE treatment by paired Wilcoxon tests. Pre-DIVE assays will be obtained under optimized oral treatment *prior to the start of* titration. Post-DIVE assays will be obtained at the end of the titration period.

12 QUALITY CONTROL AND ASSURANCE

The Quality Assurance approach that will be implemented means that research subjects can be cared for under the best possible conditions of safety and compliance with medical and regulatory rules.

12.1 test procedure

A set-up meeting with the principal investigator will be held before the trial begins (reminder of GCP, research organization, planned monitoring).

The investigator informs the sponsor in real time of the inclusions made.

Medical observations will be kept in the patient's file, and data relating to the study will be recorded in the observation notebooks provided for the study, in accordance with good clinical practice, covering the various stages of patient management in the protocol. Any deviation from the protocol will be reported, together with the reason for it. Data collection must be exhaustive, and will be regularly checked by a Clinical Research Assistant in accordance with protocol procedures.

12.2 Monitoring study

Monitoring of the trial will be carried out according to the monitoring plan validated before the start of the study, or on specific request by the sponsor's CRA. It will depend on the number of patients included in the study.

During on-site monitoring visits, ARCs must be able to consult :

- data collection books for included volunteers
- medical and nursing records of included patients
- investigator's binder

At a minimum, the monitoring will check the following points:

- the existence of patients, information and the presence of signed informed consents
- compliance with inclusion criteria
- primary endpoint
- monitoring and reporting of SAEs
- new facts requiring the tabling of an amendment
- pharmacy management and monitoring.
- Management and/or control of medical devices

12.3 Closing the study

At the end of the trial, closing procedures will be applied, with the filing of all documents and source data. Once the final analysis has been carried out and validated, all files and data are sealed and archived according to specific procedures in secure premises.

Data concerning this study will be archived for a minimum period of fifteen years from the end of the research or its early termination, without prejudice to the legislative and regulatory provisions in force.

13 ETHICAL CONSIDERATIONS AND

The trial will be conducted in accordance with the approved protocol, in compliance with the French Public Health Code, EU GCP and applicable regulatory requirements.
The trial will be registered on the public database ClinicalTrials.gov.

13.1 Personal Data Protection Committee and Competent Authority

Authorization from the competent authority and opinion of the CPP
The sponsor submits a request for authorization to the ANSM and obtains a favorable opinion from the CPP before starting the research, in accordance with article L1121-4 of the French Public Health Code.

Changes to the protocol
The sponsor alone is authorized to modify the protocol, in consultation with the principal investigator.

Substantial modifications are those which have a significant impact on any aspect of the research, in particular on the protection of persons, including their safety, on the conditions of validity of the research, where applicable on the quality and safety of the products tested, on the interpretation of scientific documents supporting the conduct of the research, or on the methods of conducting the research.
A request for substantial modification is sent by the sponsor either to the ANSM, or to the CPP, or to both, as appropriate, for authorization and/or opinion. On receipt of the authorization and/or favorable opinion, the amended version of the protocol is then sent to all investigators by the sponsor.

A non-substantial amendment to the protocol is a minor modification or clarification that has no impact on the conduct of the trial. These modifications will not be submitted to the competent authorities, but will be agreed between the sponsor and the investigator and clearly documented (in the study follow-up file).

13.2 Information and consent

In accordance with current regulations, trial participants will receive fair and complete information in the form of an Information Letter, specially drafted for the trial and validated by the French Comité de Protection des Personnes, which must be given to them and explained by the Investigator. In particular, the Investigator must inform the participant of the possible risks and constraints of participating in the trial.
Participants will be able to ask any questions they may have, and will be given the time they need to make an informed decision.

The trial participant must then sign the consent form with the Investigator who presented the trial, and this document must be dated the day of signing. One copy will be given to the participant, one will be kept by the Investigator, and one will be kept by the sponsor (in a sealed envelope).

The Investigator must ensure that the inclusion and exclusion criteria are met before the participant is included. No specific research procedure may be carried out before the participant has been informed and given consent to take part in the trial. Participants may withdraw their consent at any time, and all information concerning the safety of their participation must be reported to them.

13.3 CNIL

In accordance with the framework of the reference methodology (MR 001), data processing will be carried out under the conditions of confidentiality defined by the amended law of January 6, 1978 relating to information technology, files and freedoms (CNIL) as well as in compliance with the European Regulation (General Data Protection Regulation: RGPD). The data controller is the CHU de Lille, in its capacity as promoter, whose contact details are as follows: Direction de la Recherche et de l'Innovation Maison Régionale de la Recherche Clinique, Hospitalière et Universitaire 6, rue du Professeur Laguesse - CS 70 001 - 59 037 Lille Cedex. In accordance with the said RGPD, the data from this study will be processed for scientific research purposes (Article 6) as part of the performance of a public interest mission (Article 9) in which the promoter is involved. Data from this study will be stored on the CHU computer network. The data collected will be pseudo-anonymized.

Pursuant to Article L1121-1-1 of the Public Health Code and in accordance with Articles 17.3.c and 17.3.d of the RGPD, research participants have the right to request erasure and to object to the processing of their data. They will be informed that data collected prior to withdrawal of consent may not be erased and may continue to be processed under the conditions provided for by the research.
The patient has the right to obtain from the promoter (controller) the limitation of the processing under the conditions provided in Art. 18 of the RGPD. He also has the possibility of lodging a complaint with a supervisory authority (the CNIL in France). In accordance with Article 13 of the RGPD, when personal data relating to a data subject is collected from that person, the data controller shall provide him or her, at the time the data in question is obtained, with all the necessary information provided for in that article.
As part of the research, personal data will be processed to enable the results of the study to be analyzed in relation to its objective.
To this end, medical data concerning patients research participants or any other type of existing data may be transmitted to the Research Sponsor or to persons or companies acting on its behalf or conducting research projects, in France or abroad, including outside the European Union provided that the destination country is recognized by the French authorities as ensuring a sufficient and appropriate level of data protection or that appropriate safeguards to the transfer as indicated in Article 46.2 of the GDPR are in place. This data will be identified by a code number and initials. These data may also, under conditions ensuring their confidentiality, be transmitted to French and foreign health authorities.

Data concerning this study will be archived for a minimum period of thirty years from the end of the research or its early termination, without prejudice to the legislative and regulatory provisions in force.

14 FINANCING AND INSURANCE

14.1 Financing

The study budget is the responsibility of the sponsor, who must ensure that it is sufficient for the study to run smoothly.

Funding for the study will be provided by InBrain Pharma, a spin-off of the INSERM UMRS_1171 research team. Additional funding will be provided by the INSERM U1171 budget.

Pumps and anaerobic dopamine will be supplied by InBrain Pharma. PKG actimeters will be supplied free of charge by GKC (10 PKG).

14.2 Insurance

The sponsor has taken out an insurance policy covering its civil liability and that of all participants in the study, in accordance with article L1121-10 of the French Public Health Code.
The trial cannot begin without this subscription.

15 PUBLICATIONS - PROMOTION

15.1 Decision publication

In accordance with article R 5121-13 of the French Public Health Code, no written or oral comments may be made on trials without the joint agreement of the principal investigator, the scientific advisor and the sponsor by delegation.
All publications must mention the Lille University Hospital, which is the delegated promoter (Identification no. "2018_49") and InBrain Pharma, which funded the study.

The final study report will be drafted and sent to the sponsor by delegation by the principal investigator, Prof. MOREAU, and the scientific advisor, Prof. DEVOS. The promoter will then forward it to the competent authorities.

15.2 Rules for publication

The results of this study will be the subject of a scientific publication produced jointly by the investigators. It will indicate that the Lille University Hospital was the delegated promoter and that InBrain Pharma financed the study.

15.3 Valuation

These results, as well as all data relating to the research, must not be passed on to a third party under any circumstances, without prior negotiation with InBrain Pharma.

16 LIST OF APPENDICES

APPENDIX 1: BIBLIOGRAPHY

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