Trials

STUDY PROTOCOL

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SPIDOL study protocol for the assessment of intrathecal ziconotide antalgic efficacy for severe refractory neuropathic pain due to spinal cord lesions

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Abstract

Rationale Central neuropathic pain resulting from spinal cord injury is notoriously debilitating and difficult to treat with few currently available treatments. A novel molecule with intrathecal administration: *Ziconotide* has been approved for treatment of refractory neuropathic pain in general. It acts as a presynaptic calcium channel blocker. A pilot study has shown its potential in SCI neuropathic pain patients.

Objective The aim of this study is to determine the long-term (6 months) efficacy of chronic intrathecal ziconotide for the treatment of neuropathic SCI pain.

Study design Multicenter, Randomized, Comparative, Placebo controlled, Double blind clinical trial, with a crossover of random alternated periods of 6 months (placebo or ITZ) for a total of 15 months including a total of 44 patients.

Study population • Patients with SCI of various etiologies exhibiting neuropathic pain refractory to non-invasive treatments.

• > 18 years.

Intervention Intrathecal administration of ziconotide via an implanted pump.

Study outcomes *Primary study outcome*

Difference in pain intensity for all patients between effective treatment and placebo periods.

Secondary study outcomes

1. Continuous evaluation of pain intensity.
2. Percentage of patients with at least 30% of pain reduction.
3. Satisfaction level of the patient pain relief.
4. Declarations of serious adverse events.
5. Duration and intensity of spontaneous and provoked pain.
6. Quality of life.

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7. Patient global impression of change.

8. Quantification of daily dosages of analgesic drug intake.

9. Long term memory and neurocognitive effects.

10. Assessment of the patient's physical and emotional distress.

Nature and extent of the burden and risks associated with participation, benefit, and group relatedness Participation in this study is in accordance with current treatment protocols for SCI neuropathic pain in France therefore it proposes a treatment that would currently be considered regular practice even though no RCT evidence is yet available. The study gives patients the advantage of directly testing versus placebo a treatment that otherwise entails significant constraints.

A Data Safety Monitoring board (DSMB) will be created for continuous safety analysis. Furthermore, patients will be followed in specialized pain centers offering the possibility of continuing their treatment after the study period.

Introduction and rationale

Spinal cord injury is a major public health issue due to the long-term incapacitating sequalae patients suffer. While occurring through many mechanisms SCI may lead to severe loss of function—requiring intense lifetime patient care. In addition, SCI may also damage the sensory system leading to hypoesthesia and subsequently also, to severe, debilitating pain directly related to the SCI.

Pain in relation with spinal cord injury (SCI)

Definition and classification

A form of pain of particular interest in SCI is neuropathic pain caused by a lesion or a disease of the somatosensory nervous system [1]. This is now recognized as a common form of chronic pain [2, 3]. SCI often results from trauma but also has numerous nontraumatic forms [4] all potentially leading to chronic neuropathic pain in addition to or independent from base deficits. Chronic neuropathic pain in SCI patients is notoriously severe and difficult to treat [5].

Pain in relation with SCI has been classified in the « International Spinal Cord Injury Pain (ISCIP) Classification» [6]. This classification includes 2 main types of neuropathic pain in relation with SCI:

- *At-level SCI pain* is neuropathic pain perceived in a segmental pattern anywhere within the dermatome of the neurological level of injury and/or within the three dermatomes below this level. This includes pain due to syringomyelia, if at the level. Neuropathic pain associated with cauda equina damage is radicular in nature, and therefore defined as at-level SCI (neuropathic) pain, regardless of distribution.
- *Below-level SCI pain* refers to neuropathic pain that is perceived more than three dermatomes below the dermatome of the neurological level of injury. Below-level SCI pain can occur in patients with complete or incomplete injuries.

Pathophysiology of pain in relation with SCI

Despite advances in basic science and clinical investigations, the pathophysiological mechanisms of pain following spinal cord injury remain incompletely known [7].

Recent clinical and neurophysiological studies suggest that the various pain types arise through distinct pathophysiological mechanisms. *Ongoing burning pain* primarily reflects spontaneous hyperactivity in nociceptive-fiber pathways, originating from "irritable" nociceptors, regenerating nerve sprouts or denervated central neurons. *Paroxysmal sensations* can be caused by several mechanisms; for example, electric shock-like sensations probably arise from high-frequency bursts generated in spinal dorsal horn neurons. Most human and animal findings suggest that *brush-evoked allodynia* originates from Aβ fibers projecting onto previously sensitized nociceptive neurons in the dorsal horn, with additional contributions from plastic changes in the brainstem and thalamus [8].

The final mechanism underlying pain is the result of deafferentation that leads to the permanent neurochemical changes at each level of the central nervous system: in the dorsal horn neurons, brainstem nuclei, in the thalamic nuclei and possibly at the cortical level, thus producing spontaneous discharges of central nociceptive neurons resulting in chronic pain [9, 10].

Repeated and exaggerated discharges of spinal nociceptive neurons via the mechanisms described above gives rise to phenomenon termed long-term potentiation (LTP), defined as an increase in synaptic efficacy resulting in facilitation of chemical transmission lasting for hours in vitro and that can persist for periods or months or years in vivo [11].

This central sensitization could be reduced by blocking neuronal excitatory membrane channels, such calcium

channels the activation of which is necessary for synaptic release. Ziconotide is a sea snail toxin which if infused in the subarachnoid space can specifically block CaV 2.2 channels—thus being a selective inhibitor for transmission in the nociceptive system both at the spinal and cerebral levels.

Prognosis of pain in relation with SCI

Reports show that two-thirds of SCI patients report chronic pain (pain lasting over several years), with one-third experiencing severe pain [2, 3, 12]. Central neuropathic pain is estimated to occur in up to 40% of these patients [3] and is underestimated in relation with age [13]. Estimates of the overall prevalence of pain after SCI range from 25 to 96%, with severe pain from 30 to 51% [14]. Pain is therefore a common and disabling symptom in patients with SCI. It can significantly impact functional capacity, independence, psychological well-being, work capacity, and quality of life [15]. Its impact on the ability to function is estimated in similar terms with the impact of ability to walk, loss of sexual function, and decreased ability to control bowel or bladder function [16]. It is reported in general to worsen over time and to be resistant to therapy making it a real clinical challenge.

Current reference treatments

Neuropathic pain in patients suffering from SCI is commonly treated with the tricyclic antidepressants and anticonvulsants [3]. Nevertheless, these are less effective than for other types of neuropathic pain [17]. A number of other drugs and techniques have been used with varying degrees of success, like local anesthetics, clonidine, morphine, and ketamine [5], all limited by significant side effects. Opioids in particular have not demonstrated good long-term efficacy in CNP while displacing significant hyperalgesia associated with their chronic use.

Surgical techniques such as neuromodulation and lesioning techniques have been tried with inconstant results. Spinal cord stimulation seems to be highly dependent on the integrity of the dorsal columns and is effective only in cases of incomplete lesions [18]. DREZ lesioning may be a useful technique when the main component of the pain is at-level but does not seem to be beneficial for below-level pain [19].

Intrathecal morphine has shown similarly disappointing results as the oral and i.v. routes [20, 21].

Since 2004 and 2005, the FDA and EMA respectively have approved the use of the non-opioid agent ziconotide for intrathecal treatment, including in cases of neuropathic pain, making it therefore a potential candidate for the treatment of pain related to spinal cord injury [22].

Experimental treatment: ziconotide

Description

Ziconotide is a specific blocker for calcium channels type 2.2 [23] which mostly found in the pre-synaptic axonal terminations of first-order nociceptive neurons. It is a toxin, of a sea snail—conus magus—discovered in 1982 [24] specifically binding to calcium channels type 2.2 and reducing trans-synaptic transmission without necessarily blocking it [25].

Ziconotide is a peptide with 25 amino acids usable exclusively via intrathecal administration. The volume of distribution is equal to that of CSF volume given its high hydro-solubility with uniform concentrations through the CSF. Thereafter, it will penetrate into the nervous tissue over a depth of several millimeters with a clear gradient.

Its receptors Ca-2.2v are widely distributed throughout the CNS in the dorsal horn but also in the brain: thalamus, hippocampus, and somatosensory areas.

At the level of the dorsal horn, Ca-2.2v are present in high density, situated superficially in Rexed layers I-V and therefore accessible to intrathecal infusion of ziconotide. Ziconotide selectively binds to Ca-2.2v in a concentration and density-dependent fashion [26] leading to a higher reduction of calcium influx in regions exposed to higher concentrations of ziconotide and/or with higher density of receptors. Decreasing transmission at the level of the dorsal horn, ziconotide inhibits nociceptive signals in the spinothalamic pathway.

Calcium channels type 2.2 are also present in other brain regions such as the thalamus, hippocampus, and primary and secondary sensory cortices. Their presence in hippocampus and cerebral cortex may explain the development of some neurological side effects such as memory disturbances, paresthesias, and or visual disturbances.

Clinical effects of ziconotide are thought to result mainly through the blocking of the spinothalamic pathway at the level of the synapse situated in the dorsal horn. This has been demonstrated in a rat mammalian pain model where it produces a potent antinociceptive effects [27]. After intrathecal infusion, ziconotide displays linear kinetics consistent with the hydrophilic property of this molecule that is cleared rapidly in the CSF [26].

Due to exclusive intrathecal use, ziconotide can be chronically infused via an implanted system with a catheter connected to a subcutaneous pump requiring an implantation (minor) surgery. In France, a prior test period is mandatory to check the efficacy of the therapy and the absence of side effects.

The first clinical trials of ITZ used relatively high doses [28, 29] of up to 96 µg per day after fast titration protocols (increment of 2.5 µg/day). This led to the development of

frequent side effects. Current clinical practice and recommendations for the use of ITZ limit the daily dosage to 20 µg per day with a titration not surpassing 0.5–1 µg/day. This significantly limits side effects with less than 10% of patients halting the treatment at doses considered efficacious.

Clinical studies

Three randomized controlled studies used ITZ, for various indications as cancer pain or neuropathic pain [28–30]. Pooled together these studies included 366 patients. Patients were randomized to receive 5 or 6 days of intrathecal ziconotide or placebo. The main evaluation criterion was the intensity of pain measured on a VAS scale. Studies demonstrated a significant decrease of 50 and 30%, respectively, in VAS score between pre-inclusion and maximum dose. Around 88% of patients reported side effects as described above.

A randomized controlled study with longer follow-up has been performed over a 3-week period [28]. This used lower doses (up to 20 µg/day) and slower titration (1 µg/day). The final average dose was 7.5 µg/day. Two hundred twenty patients, 75% suffering from neuropathic pain, were randomized. Average VAS was 80.7/100 at inclusion. This decreased by 7.2 in the placebo group and 14.7 in the ziconotide group. This VAS difference, although considered minimal, was statistically significant.

A pilot open-label study using intrathecal ziconotide has been performed in France including patients with pain related to spinal cord lesions. The cohort of patients was followed by the Pain Clinic of the Neurological and Neurosurgical Hospital in Lyon (CETD de l'Hôpital "Pierre Wertheimer» Hospices Civils de Lyon [31]. This study constitutes the basis for the current protocol and sample size calculations.

Twenty patients were recruited suffering from chronic and refractory pain related to SCI. At inclusion, patients were examined to determine the neurological level of injury, the neuropathic nature of the pain, its features (continuous and/or paroxystic) and territory of distribution distinguishing between at-level pain and below-level pain as defined by the international SCI pain classification [6].

Patients were tested pre-implantation and were considered responders if a reduction of VAS greater than or equal to 40% or if they declared a degree of satisfaction of more or equal to 40%. Responders were implanted with a continuous infusion pump if no SAEs were declared. After permanent pump implantation, patients were followed on average for 3.59 years (± 1.94).

Out of the twenty patients tested, 14 patients finally responded (70%), only eleven patients (55%) were implanted due to SAE in 3 other responder patients.

In responder patients at baseline VAS was 7.91/10 and 4.31/10 at last follow-up, i.e., 45% decrease ($p=0.02$ Wilcoxon rank-sum). At 1 month follow-up, mean VAS had decreased by 3.4 points (54.8%, $p=0.001$ Wilcoxon rank-sum).

Over the follow-up period, the dose of ziconotide increased. At 1 month after implantation, average dose was 2.85 µg/day whereas 5.44 µg/day at the last follow-up. Complications in this study occurred in three patients which were not implanted in spite of a positive test: CPK increase (two cases), urinary retention (one case).

In summary, Brinzeu et al. showed a potential interest of long-term use of ITZ in SCI neuropathic pain in a pilot study of 20 patients.

Current regulatory status of the experimental treatment

Ziconotide has been accepted for intrathecal human use by the Food and Drug Administration since 28/12/2004 and has received European-wide market authorization from the European Medicines Agency since the 21/02/2005 (EMEA/H/C/000551). Azur Pharma commercializes ziconotide as Prialt® (commercial name) since 2010 worldwide with the exception of Europe. For the European market, Prialt® is marketed by Eisai Ltd United Kingdom. The Haute Autorite de Sante (HAS) Transparency committee published a report on Prialt® (Ziconotide – N02BG08) on the 14th of May 2008 detailing its use in France.

Ziconotide is authorized for the treatment of all chronic pain patients in whom the pain is severe enough to require intrathecal analgesia. Prialt ® has market approval (autorisation de mise sur le marché) in France since 21/02/2005.

The pump used in this protocol for chronic IT infusion is a model from Medtronic company (USA): Synchromed II (ref 8637), which is an implanted pump with a variable programmable flow rate capable of delivering an accurate infusion volume. The associated catheter is a specific device from Medtronic Company (USA) (ref 8731SC and 8709SC). The CE labeling has been obtained on 30 August 2002, as Class IIa notification by TÜV (0123) in Germany. On 27 May 2008, a report by the HAS (Commission d'évaluation des produits et prestations) has described the conditions of use for pain treatment: IT administration of antalgic drugs: morphine and ziconotide, for treatment of severe chronic pain refractory to opioids and non-opioids treatments by systemic route.

The therapy concerned by this protocol, ITZ by implanted programmable pump for refractory pain, is currently reimbursed by the national social assurance. This treatment is currently in use in several French pain centers.

Study justification

As described, painful patients with SCI are notoriously difficult to treat [20]. Pharmacologic therapies, specifically targeted on central neuropathic pain, are mostly ineffective. Additionally, non-pharmacological therapies are rarely efficient for SCI pain, as recently reviewed as well as IT morphine [20, 21].

ITZ is approved for use in France since 21/02/2005 for chronic paint treatment.

Previous studies with ITZ have focused on a general population of chronic pain patients including neuropathic, cancer, and non-cancer pain like in AIDS patients. Randomized controlled studies in specific populations such as SCI neuropathic pain patients are lacking.

Previously, we have performed a pilot study, including a cohort of patients with pain related to SCI, in which ITZ demonstrated 75% of responder rate (VAS decrease of 40%) and 55% of these patients benefit from long-term ITZ. However, this was an uncontrolled open-label cohort study.

Several side effects of ITZ have been reported, most of them neuro-psychological in relation with memory and cognition and related to fast increases of the IT dose. Slow increases of ITZ dose is proposed in this protocol to avoid such neurological side-effects, SPIDOL will also assess the safety of long-term ITZ therapy.

Ziconotide is one of the most expensive invasive pharmacological treatments currently available for refractory neuropathic pain making long-term efficacy and medico-economic data of great value. So, data on long-term efficacy/side effects, whether positive or not, could be of great value from a point of view.

Analysis of the differential responses induced by ITZ on separate pain features may give insights both into the mechanisms of action of ziconotide and even on the processes generating the pain. Such symptom-related assessment should also contribute to the selection of patient candidates for ITZ treatment. This approach is in line with emerging mechanism-based approach to neuropathic pain that might aid in tailoring the therapy and could be useful for drug development [8].

This study will be the first RCT focused on treating a specific well-defined population of SCI pain with ITZ and a long-term FU. The pilot study previously performed in this targeted population is supporting this hypothesis.

Objectives

Primary objective

The main objective is to assess the analgesic effect of chronic intrathecal ziconotide (ITZ) infusion via an implanted pump, compared to placebo, for spinal refractory neuropathic pain after 6 months of treatment.

Secondary objectives

Evaluation between the 2 groups of treatment:

1. Long term analgesic effect of ITZ
2. Analgesic effect of at least 30%
3. Patient satisfaction in terms of pain relief with the treatment at, V7 and V14 compared to V0.
4. Serious adverse events
5. Analgesic effect on different pain features (spontaneous–provoked, continuous–paroxysmal)
6. Modification of health-related quality of life induced by treatment
7. Patient global impression of change at V1, V7, and V14.
8. Modification of oral analgesic drug intake
9. Long-term memory and neurocognitive effects induced by ITZ
10. Impact of pain on the physical and emotional aspects of the patient

Endpoints

Primary endpoint

The primary endpoint is the comparison, for each patient, of the mean pain intensity between two conditions: under ITZ and IT placebo, after 6 months of treatment, using a numeric rating scale (NRS of 11 points)(32) within the last 2 weeks before the end of treatment.

Secondary endpoints

Secondary endpoints are the comparison between the 2 arms of:

1. Continuous evaluation of pain intensity by numeric rating scale
2. Percentage of patients with at least 30% of pain reduction base on numeric scale within the last 2 weeks before the end of treatment.
3. Satisfaction level of the patient pain relief using a numeric scale at V7 and V14 compared to V0.
4. Declaration of serious adverse event (psychiatric disorders, suicidal risk, infection, urinary retention, CPK elevation > 5 ULN, device related, hallucinations…) throughout the study (from signature of consent and at each month during the pump refill visit at the hospital).

    - Psychiatric disorders and suicidal risk will be measured using the Mini International Neuropsychiatric Interview questionnaire [33] (MINI) at V0-V7-V14. The MINI questionnaire is a structured diagnostic interview, which lasts for 15 min. It allows

identifying the main psychiatric disorders from DSM-IV axe1 (American Psychiatric Association). It can be used by clinicians (psychiatrist and psychologist) after a short period of training.
- Suicidal risk will be assessed using the CSSRS [34] (Colombian suicide Severity Rating Scale) in between the V0-V7-V14 visits.

5. Duration (average time per day) and intensity (numeric rating scale) of spontaneous–provoked pain, continuous–paroxysmal pain at V0, V7, and V14.
6. Quality of life will be assessed using the SF12 questionnaire [35] at V0, V7, V14
7. Patient global impression of change using a numeric scale at V1, V7, and V14.
8. Quantification of daily dosages of analgesic drug intake with differentiation of class of analgesics at V0, V7, and V14
9. Long-term memory and neurocognitive effects induced by ITZ will be assessed at V0, V7, and V14 using:
   - McNair scale to test the impact on memory [36]
   - HADS scale to assess depression and anxiety [37]. The HADS scale is an auto questionnaire of 14 items, divided in 2 subscales of 7 items (anxiety and depression).
   - BRIEF-A questionnaire to assess behavioral manifestations of executive functions. The BRIEF-A is an ecological test to assess executive functions among adults from 18 to 93 [38].
10. Pain catastrophizing scale (PCS) score to assess the patient's physical and emotional distress associated with their pain condition measure at V0, V7, and V14 [39].

Study design

This study is a multicenter, randomized, comparative, placebo-controlled, double-blind clinical trial, with a crossover of random alternated periods of 6 months (placebo or ITZ) for a total of 15 months.

Each patient will receive alternatively treatment or placebo, for 6 months. The treatment for each period will be randomly assigned. A washout period of 1 month will be applied between the two periods of infusion.

This cross-over scheme can be applied to the studied situation because of the absence of significant expected persistent effect of the treatment after a period of washout (the half-life of ITZ is 60 days at 37 °C, the medical state of the patient will not evolve during the study, the judgment criteria can be measured several times during the study (numeric scale of pain), and the attrition risk between 2 periods is very low because of the reduce number of centers able to provide these specific medical care.

The study protocol is built according to SPIRIT reporting guidelines and practices [40].

At the end of the study, if ITZ efficacy is demonstrated, patients from both groups will be proposed to continue the ziconotide treatment as part of their standard treatment—which is currently reimbursed by the French National Health Insurance (Assurance Maladie).

Study population

Inclusion criteria

- Patients > 18 year old
- Patients with stabilized SCI
- Patients with refractory neuropathic pain with DN4 score > 4 at selection and failure at least of 2 classes of antineuropathic pain drugs alone or in association and failure of local therapeutics
- Pain > 5/10 on numeric scale
- Patients with a positive trial test to ziconotide either by lumbar puncture or by continuous infusion above the lesion level via an implanted catheter
- Evaluation performed both by a multidisciplinary team in a pain center and a rehabilitation center
- Signed informed consent
- Patients benefiting from a social insurance system or a similar system

Non-inclusion criteria

- Life expectancy < 5 years
- Suffering from other neuropathic pain or chronic pain due to cancer
- Being treated with spinal cord stimulation, nerve stimulation, intrathecal analgesic delivery system with analgesic drug (except Baclofen) until the last 6 months

  Implant ITZ surgery contraindication:
  - MRI contrindication (pacemaker, claustrophobia…)
  - Anesthesia contraindication
  - Coagulation disorder not treated at the time of the study (TCA>1.3 OR INR>1.4)
  - Immunosuppression
  - Current infection or infection not treated at the beginning of the treatment (CRP>12 mg/L)

- Critical respiratory and/or heart illness
- Meningitis, ventriculitis, cutaneous infection, bacteremia, septicemia
- The ITZ pump cannot be implanted at 2.5 cm or less of the skin surface
- Insufficient build to support pump and treatment (patient under 30 kg)
- Spine deformation leading to surgical difficulties to implant the ITZ pump

- Unable to operate the ITZ equipment or comply with study requirements
- Suspicion of psychotropic substance abuse and/or alcohol abuse
- Current or planned pregnancy for women of childbearing age
- Women of childbearing age without effective contraception (oral contraception or intrauterine device or contraceptive implant)
- Patient with uncontrolled neurological urinary tract disorders or non-neurological urinary tract disorders (e.g., prostatism)
- Patient under or planning to go under electromagnetic transcranial stimulation or planning to
- Patient unable to understand the purpose of the trial or refusing to follow treatment and post-treatment instructions
- Patient with history of psychiatric disorder or hallucination
- Participation to another trial that would interfere with this trial
- Patient under legal protection

Exclusion criteria

Patients with psychiatric disorder validated by the Mini score (Mini International Neuropsychiatric Interview) will be excluded from the study (excluding criteria for tobacco, dysthymia, recreational or therapeutic cannabis consumption, gambling, and video games addiction).

Source of recruitment and feasibility

A total of 8 French centers have confirmed their participation.

Each center involved in the "SPIDOL" study has been selected to have a multidisciplinary team associating neurosurgeons, algologists, and MPR physicians with experience in management of SCI patients and chronic neuropathic pain. Moreover, the use of ITZ therapy, as routine pain therapy, is mandatory in each center.

Table 1 gives a list of centers with relative allocation of recruitment.

Sample size calculation

With a cross-over experimental design, each subject is considered as its own control. The statistical test to be considered is a paired *T*-test. This test is used to verify the null hypotheses that the average of intra-individual difference of response between placebo and active treatment is null.

Based on the results of the pilot study [31], the mean delta reduction of pain with ITZ is 3 on numeric scale with intra patient standard deviation of 2.5. Considering that the minimal clinical pertinent reduction of pain should be 2 and that ITZ is compared to placebo, we should expect the difference between the 2 groups to be a minimum of

Table 1 Participating centers and main investigators

Centres investigateurs	Adresses centres investigateurs	Noms investigateurs principaux	Expected inclusions
Hôpital Pierre Wertheimer, HCL, Lyon	Hospices Civils de Lyon Groupement Hospitalier Est Hôpital Pierre Wertheimer 59, Boulevard Pinel 69394 LYON	Pr Mertens Patrick Dr Brinzeu Andrei	10
Hôpital Foch, Suresnes	Hôpital Foch 40 rue Worth 92151 Suresnes	Dr Jarraya Bechir	6
CHU Nantes	CHU Nantes—Hotel dieu 1, place Alexis Ricordeau 44000 Nantes	Pr Buffenoir-Billet Kévin	5
CHU Angers	CHU Angers 4, rue Larrey 49933 Angers cedex 9	Pr Menei Philippe	5
Hôpitaux Civils, Colmar	Hôpitaux Civils de Colmar 39 Avenue de la Liberté 68024 Colmar Cedex	Dr Voirin Jimmy	4
Hôpital Timone,AP-HM, Marseille	AP-HM Hôpital La Timone 278 Rue Saint-Pierre 13005 Marseille	Pr Regis Jean-Marie Dr Anne Balossier	5
Hôpital Pasteur, CHU Nice	CHU Nice Hôpital Pasteur 30 Voie Romaine CS 51069 06001 Nice Cedex 1	Dr Fontaine Denys	5
Hôpital St Joseph, Marseille	Hôpital St Joseph 26 boulevard de Louvain 13008 Marseille	Dr Barat Jean-Luc	4

2 on numeric scale. According to Machin et al. [5], with alpha = 5% and power $(1-\beta)=90\%$, a total of 34 patients are needed. These are to be recruited over 2 years, corresponding to 1.42 per month for all the centers.

To anticipate potential exit of patients from the protocol during the study, we plan to include 10 more patients, so a total of 44 patients, corresponding to 1.83 patients per month.

Methods

Trial design

See section Study Design.

A description of the study flow is given in Fig. 1 whereas the study calendar can be found in Table 2.

The total duration of the study is 45 months between the inclusion of the first patient and the end of follow-up of the last patient. This time includes the following:

- Preparation of the study including ethics, regulatory, and legal consideration as well as opening of the 8 centers: 6 months
- The recruitment of patients: 24 months (after ethics, regulatory, and legal authorizations)
- One month between oral consent + psychological test and the beginning of the treatment
- The 12 months of treatment with ziconotide or placebo + 1 month of wash-out

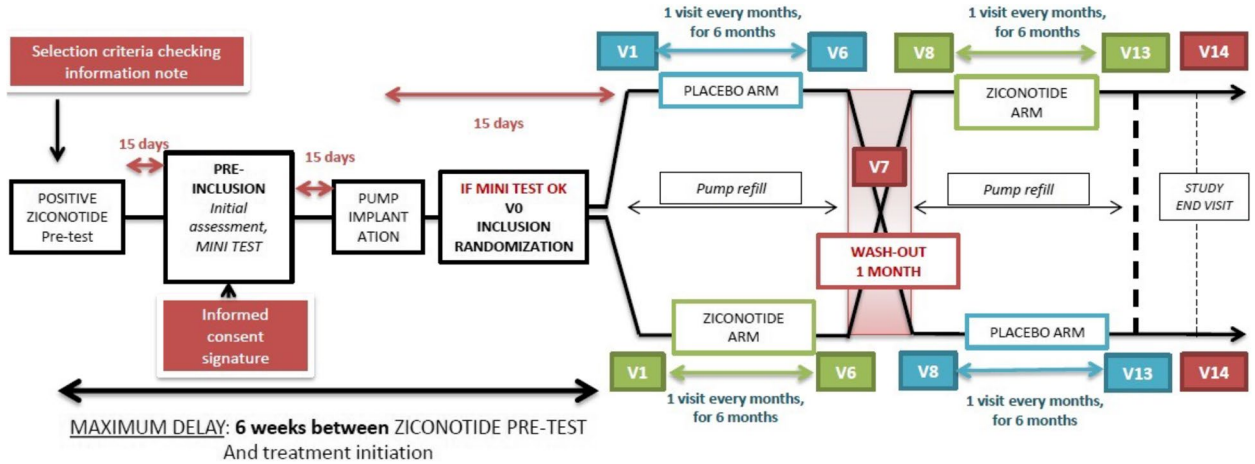

Fig. 1 Study flow

Table 2 Study timeline. V0 to V14 represent the succesive patient visits for the purposes of this study. V0 is the inclusion visit (see heading « Visit Schedule»), V1–V6 represent the first phase; V7 is the evaluation after the first phase and cross-over, V8–V13 are the second phase visits and finally V14 is the final visit

Study duration	Screening	Pre-inclusion	Inclusion V0	Treatment (each month + / − 1 week)			V14 EOS
				V1-V2-V3-V4-V5-V6	V7 (cross over)	V8-V9-V10-V11-V12-V13	
Inclusion / non-inclusion criteria	✓						
Informed consent if positive test		✓					
Randomization			✓				
Pump implantation		✓					
Clinical data			✓	✓	✓	✓	✓
VAS Pain*			✓	✓	✓	✓	✓
MINI		✓			✓		✓
SF12			✓		✓		✓
McNair, HADS, BRIEF-A, PCS questionnaire			✓		✓		✓
CSSRS questionnaire				✓		✓	
Treatment compliance/ medical events	✓			✓		✓	✓
Adverse events		✓	✓	✓	✓	✓	✓

- The end of the study is the date of the last follow-up visit of the last person participating to the study, or when the last patient's last visit window is closed, whichever is the earliest.

Setting

The recruitment, treatment, and follow-up of patients will be carried out by investigators in the neurosurgical, or the algologist or the physical medicine and rehabilitation units participating to the study.

Visit schedule

Intrathecal pain therapy is routine treatment for patients with severe refractory pain and according to HAS recommendations ITZ may be proposed to patients with refractory neuropathic pain after a test period. Patients meeting eligibility criteria (candidates having tested positive to ITZ) will be proposed to enter this study by the participant pain clinics. The inclusion visit (V0) is therefore scheduled after the implantation of the IT pump. This is followed by visits 1–6 for the first phase of treatment with its initiation at V1 according to randomization and subsequent adjustments made at each FU visit from V2 to V6. At V7, the first phase of treatment ends with a detailed evaluation and the cycle is taken up again after crossover (V8 to V13). V14 is the final study visit. Routinely patients with SCI pain are tested for the efficacy of ITZ and the test phase is not the object of this study. However, some recommendations and suggestions are made:

- Testing phase

Patients will be tested according to the test protocol. First, an evaluation of cerebrospinal fluid (CSF) circulation will be conducted with MRI. If a block or a suspicion of block in the CFS circulation is identified, patients will be tested with a continuous infusion test. The other patients will first be tested with an LP test. Patients considered responders will be the target population of this study.

A proposed protocol used during the pilot study is as follows:

LP test

Three LPs are performed with a 72-h interval between. Boluses of ziconotide are administered with progressively increasing dosages. Doses are respectively 0.5, 1.0, and 1.5 µg diluted in 2 mL of saline. Patients are monitored for vital, neurological signs just before LP and every hour for the first 24 h after LP and then every 4 h for the subsequent 24 h. Biological values including creatin phosphokinase and creatinine are measured 24 h after the first LP and at the end of LP test period. The ward nurse assessed thereafter VAS and adverse effects (AEs – 6.1.3) during each visit (just before the LP and 1, 4, 8, 12, 24, and 48 h after the LP). After 24 h, patients are asked to grade their degree of pain reduction from 0 to 100% and their degree of satisfaction with the therapy.

Patients are considered responders if a reduction of VAS greater than or equal to 40% or if they declared a degree of satisfaction of more or equal to 40%. Responders to the LP test are implanted with a continuous infusion pump. Patients having severe adverse effects (AEs) during the test period are not implanted with a permanent pump as well as patients not desiring the therapy.

Continuous infusion test

An intrathecal catheter is connected to a subcutaneous small reservoir (see below for technique). An external pump (Cane Crono 5 Infusion Pump, Applied Medical Technology, and Italy) is connected to the subcutaneous site via a HUBER needle. Then a continuous infusion is performed at dosage from 2 to 10 µg maximum per day with an increment of 1 µg every 3 days. Pain is evaluated every 4 h for the VAS and every day for the degree of satisfaction. As for LP test patients are considered responders if a reduction of VAS greater than or equal to 40% or if they declared a degree of satisfaction of more or equal to 40%.

Some patients might already be implanted with a Syncromed II pump with Baclofen treatment. These patients will be proposed to participate to the study and go through the testing phase using the pump (continuous infusion test).

Finally, according to local practices, the neurosurgeon can decide to implant directly the Syncromed II pump for the pre-test phase (according to the procedure below). This allows a more accurate infusion dose, in case of failure to reduce of VAS greater than or equal to 40% or if they declared a degree of satisfaction of more or equal to 40%, the pump can be used for Baclofen treatment and in case of success, the pump is already implanted for the study. This procedure is not study related but is becoming a standard of care in several centers, starting with Lyon.

- Pump implantation:

Pump implantation technique is at the choice of the neurosurgeon and respect the current practice. Detailed recommendations for the implant technique are found in the supplementary material.

For patients receiving IT analgesics, a pump with 40-mL reservoir is preferable. But under special

conditions, a smaller 20-mL pump may be acceptable. If a smaller pump is used, the steering committee should be advised to adapt the treatment protocol.

Details pertaining to the pump implantation are as follows.

Before intrathecal infusion testing, the subarachnoid space may be checked for absence of CSF blockage by T2 MRI sequences of the entire spinal or by myelography. For these patients, the intrathecal catheter should be implanted above the lesioned level. In all other patients, the catheter may be implanted in the lumbar region with the tip facing the conus medularis whatever the lesional level.

The pump must be placed at the right depth. If the skin coating is not thick enough, the pump implantation must be under fascia.

Lumbar catheters are generally implanted using a percutaneous technique with a TUOHY needle. The position of the tip was verified by intraoperative radiology. In case of blockage, supralesional catheter is placed surgically trough an interlaminar approach. A midline incision of the dura is performed and the catheter was passed in cranial direction with the tip placed two or three vertebral levels above the lesioned level. A circular suture is made to fix the catheter to the dura and ensure watertight closure. An injection site is placed subcutaneously in the abdominal region (usually on the left flank) and connected to the catheter after checking the CSF flow.

Permanent, subcutaneous continuous infusion pumps are implanted in cases were LP tests or continuous infusion tests are positive. A Syncromed II pump by Medtronic Inc., WI, USA, is to be implanted. Both the 20-mL (ref 8637) and the 40-mL (ref 8637) pumps may be used according to the dosage used during testing and patient morphology (see above).

The study population is the population of patients having tested positive to an LP test or a continuous infusion test. Patients that are non-responders are not to be implanted according to HAS recommendations and are not to be included in SPIDOL study. They are readdressed to their respective pain centers for alternative pain therapies.

- Subject screening

Patients selected for the study will meet the neurosurgeon to propose the intrathecal treatment and inclusion in the study. Non-inclusion in the study does not preclude ITZ. He explains its purpose, both strategies studied, the randomization process, the objectives, the risks and benefits, and the follow-up visits following treatment strategy. He gives them a written information letter containing all these elements and a participation consent form. After a time of reflexion of 15 days corresponding to the wash-out phase of the pre-test needed before the psychological test, the patient will be pre-included in the study if he agrees to consent (written informed consent).

Pre-inclusion visit

For patients corresponding to the inclusion criteria and having given written informed consent, exclusion criteria will be tested with the Mini International Neuropsychiatric Interview questionnaire (MINI) to evaluate main psychiatric disorders. Tobacco consumption, dysthymia, recreational or therapeutic cannabis consumption, video games or gambling are not included in the MINI evaluation or as criteria of exclusion as these addictions will not interact with the PRIALT® prescription. However, the neuropsychologist in charge of the patient evaluation can decide, on any of these criteria, to exclude the patient if an addiction or a behavior that can interact with the PRIALT® prescription is identified.

- Inclusion visit (V0)

The inclusion visit will be performed for patients without any psychiatric disorders tested by MINI. At this visit a first full assessment will be performed:

  - Exact localization of the spinal cord injury
  - Full neurologic workup
  - Sensory deficit chart
  - Pain distribution chart
  - Overall pain at the moment of assessment (VAS), pain estimation over the past week (VAS – Baseline) using an electronic pain diary
  - Pain description in the following terms: at level/below level pain, continuous/paroxystic pain with quantification of each (VAS)
  - Quantification of daily dosages of analgesic drug intake with differentiation of class of analgesics
  - Quality of life scale (SF12)
  - Mc Nair scale for memory complains
  - HADS scale for depression and anxiety
  - BRIEF-A questionnaire for impact on behavioral manifestations of executive functions
  - PCS to assess the patient's physical and emotional distress associated with their pain condition

All this information will be re-evaluated at the end of each study phase (V7 and V14) and at the wash-out phase.

- Randomization procedure

After giving his consent passing through the MINI test, the inclusion visit, and the pump implantation, randomization is performed. Randomization will be centralized and balanced between each participating center.

The group assignment of an included patient will be based on the chronological order of entry into the study according to a predetermined randomization list. The randomization list will be only detained by the biostatistics unit, the local pharmacy, and the CAP.

The randomization procedure will be carried out by the investigator using a secure and dedicated web server. The coordination center of the study will be alerted by email of the patient inclusion and of the following information: the patient initials, his date of birth (month and year), and the inclusion date.

A number is allocated to the patient, corresponding to a couple of prescription (placebo and ITZ) in a specific order. This prescription is sent to the hospital pharmacy of each center which will then deliver the anonymized treatment.

- Treatment

1) Experimental treatment: Ziconotide

Ziconotide is currently available with a concentration of 100 µg/mL. Marketed vials have volume of 1 or 5 mL solution for infusion. If dilution is required, ziconotide must be diluted aseptically with preservative-free sodium chloride 9 mg/ml (0.9%) solution.

The experimental treatment in SPIDOL consists of ziconotide solution that will be prepared by each local pharmacy team, in 5- or 10-mL vials with constant concentration of 10 µg/mL. So, the daily dosage will be set only by control of the injected volume. This strategy using a solution with constant concentration facilitates the blinding of the solution injected. Moreover, the 10 µg/mL dosage allows to optimize the consumption of the solution. Pumps will be refilled every 30 days. Initial dosage will be established by the treating team according to the response to the ziconotide pre-test. An increase in dose may be performed at any of the refill visits. Interim visit between refill visits for only dose adjustment is allowed once only to avoid too fast increase of daily dosage. The magnitude of increase is the decision of the treating physician (as long as it remains with the recommended limits by the HAS) but most likely augmentations will be at maximum 1 µg per month and maximum achieved doses allowed in SPIDOL study is 20 µg/day.

To use a minimum amount of drug, pumps will be filled according to the volume injected per thirty-day period with 10, 20, 30, or 40 mL of product. In this way, the maximum possible dose is 13.3 µg per day. In order not to cap the maximum dose, patients requiring higher doses should be seen more frequently than 1 month. Refill volumes should be as follows:

For dosages above 13.3 µg per day, the steering committee should be consulted.

2) Placebo:

The placebo treatment consists in standard saline solution (preservative-free sodium chloride 9 mg/ml (0.9%) solution) which will be presented exactly in vials as presented for the treatment (volume, color, shape, and size of the vial). Treating physicians will not be aware of the actual contents of the pump and will increase the volume of injected placebo as a treatment solution (as ziconotide 10 µg/mL).

- Cross-over administration treatment

1) First phase (6 months) (V1 to V6)

Two weeks after pump implantation the treatment is started at a dose determined during the test. Initial dose of around 3 µg per day is advisable. It is advisable to start the infusion with a short hospital stay. This can be also performed through several visits during the first week of treatment. Further increases in dose should be performed either at pump refill visits or at interim instance between refills. The duration of the first phase is 6 months of treatment.

Patients having been tested through continuous testing and responding to doses higher than 3 µg per day, should be initiated at the efficient dose determined by the test. Sufficient hospital length of stay or outpatient clinic visits should be provided to initiate safely such a dose. Same speed of increase of the dose as during the test phase should be used but the recommendation is to use a step of 0.5 µg per day after an initial start at 3 µg per day until the efficient test phase dose is reached.

Each month after the initiation of the first phase of the treatment, a visit is organized to refill the pump with the prescription corresponding to the random first phase and a pain evaluation is performed.

At each of these monthly pump refill visits, a VAS pain evaluation is conducted, MINI are filled in by the patient and AE are collected.

At the end of the last dose of treatment of the first phase the pain level is evaluated using a numeric scale

and all the other assessments are performed by blinded physicians.

Initial dosage increases and visits for refill and follow-up are in concordance with usual scheduled visits for patients receiving intrathecal ziconotide or other pain IT treatment as routine treatment.

Schedule for initial doses and follow-up visits during treatment phase:

- Treatment initiation:
  - 2 weeks after the pump implantation
  - Initial injected volume of 0.3 mL per day (equivalent to 3 µg per day if active treatment)
- Titration to calculated dose during the test phase:
  - Short hospital stay preferable
  - Incremental increase to the desired dose (i.e., effective test dose) by 0.5 µg per day
  - For doses above 1 mL per day steering committee should be consulted
  - Dose titration will be halted at the effective dose determined during the test period (regardless of result—since some patients receive placebo)
  - After the end of dose titration, the pump may require a refill to ensure sufficient drug for the duration up to the next refill visit—this is allowed at each visit
- Refill visits each month after the initiation of the treatment. The choice of reducing the refill interval to 1 month is to avoid any product decay in the interim period and is formal, 6 refill visits must be scheduled at 1-month intervals after the initiation period of each phase.
  - Each day the patient assesses his/her mean pain on an electronic dairy
  - At each refill visit, patients will be tested by the blinded physician for pain scores, screened for adverse effects.
  - Pump refills are performed in the same fashion as refills for other patients requiring IT treatment as per center habits.
  - The refill agent will be prepared in pharmacy at the previsioned volume for that instance with allowance for dosage increase at that visit or at a potential interim visit.
- An interim visit to adjust dosage on patient demand may be scheduled between the visits. A single visit is allowed—since side effects are in relation with the speed at which the dose is increased. The amount of increase is left to the choice of the treating physician as long as it does not surpass the HAS recommendations. The advised dose increase is 0.5 µg per day in the case of active treatment.
- The last refill visit is the end of study phase visit. At this visit, the pumps will be filled with serum saline for the wash-out period and all primary and secondary outcome tests will be performed.

2) Wash-out period (V7)

A wash-out period of 1 month is organized to rule out the potential carry over effect; during this period, the pump is filled with preservative-free sodium chloride 9 mg/ml (0.9%) solution (allowing flushing the dead space of the catheter). All primary and secondary outcome measures and tests will be performed at the end of the wash-out period before the initiation of the second phase of treatment.

3) Second phase (6 months) (V8 to V13)

The second phase also last for 6 months. The second intrathecal infusion is initiated with refill of the pump with the random second preparation (placebo or ITZ) on the exact same protocol in terms of refill visit and questionnaires as the first phase but with the other product compared to the first phase. An initiation period of the second phase will be purported just as for the first phase with exactly the same schedule for visits. The last pump refill visit will occasion the end of study visit at which point all outcome measures will be again performed (Table 3).

All the assessments are performed by blinded physicians; in fact, all physicians are blinded to the presence or not of active treatment. Unblinding occurs after the completion of the end of study visit initiating the post follow-up treatment.

4) Telemedicine

During both phase of treatment each patient will be asked, on a daily basis, to evaluate his pain using a VAS

Table 3 Pump refill volumes

Desired dose per day	Programmed volume per day	Refill volume per 30 days
3 µg	0.3 mL	10 mL (= 100 µg ziconotide)
3.3–6.6 µg	0.33–0.66 mL	20 mL (= 200 µg ziconotide)
6.7–10 µg	0.67–1 mL	30 mL (= 300 µg ziconotide)
10–13.3 µg	1–1.33 mL	40 mL (= 400 µg ziconotide)

scale. This data will be collected directly on the eCRF thanks to a patient-specific access with a username and password. In order to respect the confidentiality (MR001 CNIL), the access code will be transferred by the data manager of the study to the patient via his physician or Clinical Research Associate. The Clinsight software will be used for this study.

This will allow the pain evaluation to be as accurate as possible and this will participate to reduce the attrition risk of the study.

All along the study, the patient will be able to take all available analgesic treatments except interventional therapies (infiltrations, botulinum toxin, Cutenza, neurostimulation in all its forms).

- Last visit (V14) and follow-up post treatment:

During the last visit, the patient will be informed in which period he was under active treatment and may choose whether to continue/reinitiate active treatment with ziconotide. The patient will take the appropriate decision after discussion and agreement with his physician. Those deciding to continue to receive the drug will be followed as similar patients receiving IT treatment (for ziconotide once a month refill visits) but outside the study frame. The optimal ziconotide dose observed during the study will be proposed for further use. This will be considered the minimal dose at which the patient had the greatest decrease in pain score without severe adverse effects or intolerable side effects (as defined by the patient). Patients not choosing active treatment will be readdressed to the pain center for testing of other treatment strategy.

Blinding methods and unblinding procedure

Blinding procedure will be systematic thanks to the indistinguishable nature of the active product and placebo and their packaging. It will be organized by each local pharmacy of the participating centers.

Only the statistician in charge of the production of the randomization list, the Centre Anti-Poison of Lyon, and the authorized pharmaceutical team responsible for packaging, labeling, and distribution of TU to the sites will have access to a decoded list.

Unblinding procedure will be possible 24 h/24 h, 7/7 days, simply by phone call to the Centre Anti Poison de Lyon (CAP—04 72 11 69 11). The CAP physician will be able to proceed to the unblinding if required upon request of investigator. Unblinding will be reserved for clinical conditions where study treatment knowledge is likely to influence the management of the adverse event.

A participation card will be provided to subjects enrolled in the study, including the telephone number of the CAP, as well as the information necessary for the unblinding request.

Study calendar

See Table 2 for the study calendar.

Temporary or permanent termination

- Of study participation

Any termination of study participation such as ceasing to follow-up for the study or early withdrawal should be clearly documented in the eCRF. The termination of normal follow-up in the clinical study is when the patient completes the visits after the second phase of treatment. The participation of a patient will be permanently stopped and the patient will be considered prematurely withdrawn from the study in the following cases:

  - Withdrawal of consent at any time during the study, without any explanation and without penalty or prejudice to the patient's healthcare, as required by Authority Regulation.
  - Presence of an exclusion criterion (prior to randomization);
  - Violation of a protocol, defined as any event violating the patient's right, safety or well-being, or affecting the integrity of the research (including the non-compliance with eligibility criteria);
  - Upon decision of the investigator, in case the patient is lost to follow-up despite several attempts to contact him. The death record of the patient will be searched.
  - In the investigator's opinion, if further participation in the study would be detrimental to the subject's well-being.
  - CPK increased > 5 ULN, or associated with clinical signs of myopathy or rhabdomyolysis
  - Infection of pump site or scar
  - Pump malfunction

In case of withdrawal of consent, no additional data will be included in the study database. Data already included will be kept and used for data analysis. If the patient decides not to withdraw his consent, data from his normal follow-up will be collected in the database.

These subjects will not be replaced, as study dropouts have been included in the calculation of the sample size.

- Of the study

The research can be temporarily or permanently stopped for the following reasons:

  - Upon decision of the coordinating investigator, the sponsor or the competent authority;
  - In case of the knowledge of data jeopardizing the achievement of the study due to the patient safety;
  - In case of publication of new scientific data questioning the research;
  - In case of serious adverse events which DSMB recommends the termination of the research, as it considered it (a) serious and unexpected, (b) involving the safety of the patients, and (c) suspected to be related to the research.
  - On request of Health authorities

Premature discontinuation of study treatment is not considered as a study drop-out. In accordance with the principle of intention to treat, all randomized subjects who received a treatment unit will be considered in their allocated treatment group in the analysis.

Identification of the data to be collected directly into the case report form

The documentation of the inclusion and non-inclusion criteria will be made directly by the examiner using a specific form to be considered as a source document. For each patient, this form will be filed in the CRF binder.

Unblinding procedure

In case of serious adverse events (SAE), unblinding procedure will be organized by the pharmacovigilance service. If the distribution of SAE is unbalanced, the DSMB will be alerted and will then determine the relationship between the type of treatment (ziconotide or placebo) and the occurrence of the event.

Unblinding procedure required by the physicians will be restricted to the patient management modifications.

Whatever the causal relation selected, the patient, regardless of the randomization group, will not be excluded from the study and will be followed up according to the protocol. This deviation from the protocol will be collected and documented.

Experimental treatment given to study participants

Experimental group

The medical treatment concerned by this research project is the ziconotide PRIALT®.

Control group

The control group will be a placebo (preservative-free sodium chloride 9 mg/ml (0.9%) solution) with the exact same form, size, and taste as the experimental treatment.

Other treatment used for research purposes

No other treatment is used for the purposes of the study (no procedure other than those used in the treatment current practice of these patients).

Permitted and prohibited treatments

Prohibited treatment during the study will be instrumentation not specified in the experimental/control group and clonidine, bupivacaine, and propofol. As propofol is a frequently used anesthetic, its prohibition will be indicated in the information notice. The anesthetist should then use another anesthetic.

Considering the contraindications to the use of ziconotide PRIALT®, women of childbearing age should have effective contraception (oral contraception or intrauterine device or contraceptive implant). Contraception should be maintained throughout study participation.

Statistical analysis

Descriptive analysis

A descriptive analysis will be performed on all recorded quantitative (average, median, max min, quartile) and qualitative (frequency and percentage) parameters with their associated confidence level.

The hypothesis of normality of distribution for the quantitative variables will be verified graphically with a histogram and statistically with the Kolmogorov–Smirnov test. Log transformation or outliers' exclusion might be used if necessary.

The intention to treat population (including subject randomized according to randomized treatment assignment, regardless of noncompliance, protocol deviations, withdrawal, and anything that happens after randomization) and the per protocol population (patients completing the study protocol without any major protocol violations) will be described in detail.

Treatment of missing, unused, or invalid data

All data regarding the primary endpoint will be used for statistical analysis. The missing or invalid data regarding the other endpoints will be reviewed by the principal investigator and the person in charge of the data analysis. They will decide if the data can be taken into account in the analysis or not. Multiple random imputations might be used to replace or complete missing data.

Protocol deviation

A description of protocol deviation (lost to follow-up, non-compliance with trial drug, problem with the pump…) which could interfere with the interpretation of the results, and be considered as potential bias will be realized. The reasons for protocol deviation will be analyzed.

Intermediate analysis

No intermediate analysis will be performed upon the primary endpoint so as to keep sufficient statistical power.

Carry over effect evaluation

In order to check the assumption of a negligible carryover effect, a pre-test will be conducted according to Wellec et al. (2012). In case the carry over effect exist between the first and second phase, then the analysis will be restricted to the first phase of the study and conducted as if the study was 2 parallel groups.

Main criteria analysis

The main analysis will concern the intra-individual comparison of the average pain measured under placebo and under ziconotide using a numeric scale.

First, after confirmation for a negligible carry over effect a paired *T*-test or a Wilcoxon signed rank test, according to the normality of the distribution, will be conducted to compare the intra patient treatment effect between the 2 sequence of treatment allocation.

Second, being repeated measures (daily basis pain evaluation with VAS), the treatment effect on pain will be estimated by a mixed-effect linear model (Proc Mixed, SAS) to account for the repeated measurement that yield period, sequence, and carryover effect. It will also allow us to model the various sources of intra patient and inter patient variability. A first step will be to evaluate the last 2 weeks of treatment: indeed, there is a long period of dose adaptation and stabilization. Secondly, an evaluation on the whole treatment period will be conducted.

Secondary criteria analyses

The following secondary analysis will be conducted:

- Proportion will be compared in between the 2 groups using a chi-square test or a Fisher exact test if the conditions of application of chi-square test are not met.
- On the exact same process as describe above for the primary endpoint, repeated quantitative variables such as SF12, McNair, PCS, HADS, BRIEF-A, satisfaction, duration, and intensity of provoked pain, continuous – paroxysmal pain will be compared between treatments using mixed-effect linear model [35, 37–39].

Modification of statistical plan

The information presented above constitutes the basis for the statistical analysis plan for this study. This plan may be revised over the duration of the study in order to accommodate any amendments to the clinical trial protocol or adapt to any unforeseen difficulties in carrying out the study, which could impact the planned analysis.

The plan will be edited before the review of the data if needed; any revisions will be made before the database freezing. The analyses provided may be completed during this review. Thereafter, any changes to the analysis plan will result in a new version, including justification for the changes. All will be archived in the study file. The final statistical analysis plan will be made available on request from the study organizers and as supplementary material for the final publication if not published as a standalone text prior to this.

Statistical software

The SAS Institute Inc. software version 9.4 will be used to perform all analyses according to the programs and the applicable procedures within the clinical research unit.

The statistical tests are bilateral, and the level of significance was set to 5% ($p < 0.05$).

Statistical analysis unit

Data management and statistical analysis will be conducted by the Unité de recherche et d'épidémiologie Clinique du pôle de santé publique des Hospices Civils de Lyon.

Data quality insurance

Source document requirements

According to the guidelines for Good Clinical Practices, the study monitor has to check the case report form entries against the source documents. The Informed Consent Form will include a statement by which the patients allow the sponsor's duly authorized personnel (trial monitoring team) to have direct access to original medical records which supports data on the electronic Case Report Form (e.g., patient's medical file, appointment books, original laboratory records). These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information (according to confidentiality rules).

Case report form

The case report form will only include the data necessary for an analysis for a scientific publication. Other patient data necessary for their follow-up outside of this study will be collated in their medical file.

A specific online module of the electronic CRF available on a smartphone is proposed to the patients so that they can provide daily information about their pain at home.

Electronic CRF

All information required by the protocol will be recorded in the case report form using the electronic CRF Clinsight from ENNOV Clinical (Paris, France ennov.com). Data must be collected as it is obtained and explicitly recorded in these case report forms. All missing data must be encoded. This electronic case report form will be put in place in each center through an internet portal for recording the data. A help document for using this tool will be provided to the investigators.

The completion of the case report form by the investigator through the internet allows the study coordination center to rapidly see the data at a distance. The investigator is responsible for the accuracy, quality, and pertinence of all the data entered. Furthermore, during entry, these data are immediately verified thanks to coherence checks. As such, the investigator must validate any value changes in the CRF. These changes are part of an audit trail. A reason may be optionally integrated as a comment. A print-out will be requested at the end of the study, authenticated (dated and signed) by the investigator. A copy of the authenticated document destined for the sponsor must be archived by the investigator.

Data management

The Department of Clinical research and epidemiology will be responsible for data processing in accordance with their data management procedures. Data will be entered electronically via a web browser. A data backup Twice-daily for the Ennov Clinical server, hosted at OVH, as well as a Twice-daily data backup for Hospices Civils de Lyon servers is done. On the eCRF, an audit trail records connections/disconnections (as well as connection attempts) of all users + changes to data (who, when, what, why).

The sponsor will also organize a data monitoring with the clinical research assistant who will be trained on the clinical aspects by the PI, and on the use of the electronic CRF by the data unit.

Archiving clinical trial files

The investigator shall maintain the essential clinical study documents (including source documents, clinical device accountability records, signed subject information consent forms, AE reports, and other regulatory documents) as required by the applicable regulatory requirements. The investigator should take adequate measures to prevent accidental or premature destruction of these documents. In the event of accidental destruction, the investigator must notify sponsor immediately.

The following documents will be archived under the name of the study and under the responsibility of the coordinating investigator or associated investigators in each site for 25 years.

- Signed informed consent documents for all subjects.
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communication between the investigator and CPP;
- Composition of the CPP or other applicable statement.
- Record of all communications between the investigator and the sponsor
- List of sub-investigators and other appropriately qualified persons to whom the Principal Investigator has delegated significant trial-related duties, together with their roles in the study and their signatures.
- Copies of CRFs pages and of documentation of corrections for all subjects.
- Device-accountability records.
- All other source documents (i.e., subject records, hospital records, laboratory records);
- All other documents as listed in Section 8 of the consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial). Essential clinical study documents shall be retained for at least 15 years following the date of the end of the study.

These documents shall be retained for a longer period, however, if required by additional applicable regulatory requirements or by an agreement with the sponsor. The investigator must, therefore, obtain approval in writing from the sponsor prior to the destruction of any records.

The investigator shall notify the sponsor to any change in the location or status of any essential, clinical-study documents. The sponsor shall be responsible for informing the investigator when these documents no longer need to be retained.

The sponsor is also responsible for organizing the storage of the statistical analyses and the final study report for the required duration of archiving.

No moving or destruction can be carried out without the agreement of the sponsor. At the end of the 25 years, the sponsor will be consulted for the destruction. All data, documents, and reports may be the subject of an audit or inspection.

Safety assessment

Definitions

Definitions of adverse events are in concordance with French law: according to article R1123-46 of French Public Health Code.

Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient or subject which does not necessarily have a causal relationship with the investigational medicinal product.

Adverse reaction

An adverse reaction is any noxious and untoward medical occurrence with a reasonable causality with the investigational medicinal product at any dose.

Unexpected adverse reaction

Adverse reaction which nature, severity, frequency, or evolution is not consistent with the safety reference information mentioned in the Summary of Product Characteristics or in the investigator's brochure when the product is not authorized.

Serious Adverse Events (SAE)

A serious adverse event (SAE) means any untoward medical event that:

- Results in death; or
- Is life-threatening for any person who participates in the clinical trial; or
- Requires in patient hospitalization or prolongation of existing hospitalization; or
- Results in persistent or significant disability / incapacity; or
- Results in a congenital anomaly / birth defect; or,
- Is an important medical event that does not meet the criteria listed above:
- An event that may be considered as "potentially serious," including certain biological abnormalities
- A medically relevant event according to the investigator's judgment
- An event requiring medical intervention to prevent the evolution towards one of the aforementioned condition

For instance, these events could be intensive treatment in hospital emergency rooms or at the patient's home for allergic bronchospasm, convulsive seizure, or coagulation disorders.

The term "life-threatening" is reserved for an immediate threat to life, at the time of the adverse event, regardless of the consequences of any corrective or palliative therapy.

Certain circumstances requiring hospitalization do not fall under the criterion of severity: "hospitalization / prolongation of hospitalization."

Refer to paragraph 6.2.3 for serious adverse events that do not require prompt notification to the sponsor.

New issue

Any new data that may lead to a reassessment of the benefits and risks of the research or of the product being researched, to changes in the use of this product, to the conduct of research, or to documents relating to the research, or to suspend or interrupt or modify the protocol of research or similar research.

Responsibilities of the investigator

Procedures for detection and reporting of the adverse events

Adverse events must be investigated, reported and recorded, treated, and evaluated from the first visit (inclusion V0) until the end of study and their resolution.

All adverse events must be recorded in the Adverse Event Reporting Forms of the Case Report Form (CRF). Each observed adverse event will be recorded individually. The intensity of the event will be graded according to the following classification:

- Mild (grade 1): No disruption of normal daily activity
- Moderate (grade 2): Discomfort sufficient to reduce or affect normal daily activity
- Severe (grade 3): Incapacity and inability to work or perform normal daily activity
- Life-threatening (grade 4)
- Death (grade 5)

All adverse events should be graded

All adverse events of severe intensity, life-threatening grade, and death (grade 3 or above) shall be considered as SERIOUS and must be notified to the sponsor without delay unless they are described in paragraph 6.2.3 as not to be notified without delay to the sponsor.

Grades 1 and 2 of the following adverse events from CTCAE classification will not be recorded neither in the "Adverse event" section of the CRF, neither in SAE form for this study:

a) Cephalgia
b) Diarrhea
c) Constipation
d) Dizziness
e) Visual disorder
f) Confusion, disorientation
g) Hallucinations
h) Language difficulty
i) Memory disorder
j) Walking ability disorder
k) Mood disorders
l) Drowsiness, asthenia
m) Urinary retention
n) CPK increased
o) Deficiency of the pump and catheter
p) Psychiatric disorders
q) Admission for social or administrative reasons;
r) Hospitalization scheduled in the protocol;
s) Transition to a day hospital scheduled for the follow-up of the studied condition or for an intercurrent disease already known at inclusion;

Under dose and overdose, any grade will be recorded in the "Adverse event" section of the CRF. If associated with serious adverse event (grade ≥ 3 CTCAE), a SAE form should be sent to the sponsor.

AE of grade ≥ 3will be recorded in the adverse event section of the CRF and in SAE form for this study.

Serious adverse event reporting

The investigator evaluates each adverse event in terms of severity.

The investigator shall notify to the sponsor all serious adverse events and serious incidents occurring during the trial, without delay and no later than 24 h from the day on which the investigator becomes aware of it, with the exception of those identified in the protocol as not requiring notification without delay.

This initial notification shall be the subject of a written report and shall be followed by one or more additional detailed written report(s) within the 8 days following the first notification.

The investigator faxes at + 33 (0)4 72 11 51 90 a SAE form dated and signed, with at least these 4 points which are mandatory to submit the SAE:

- An investigator
- A subject
- An experimental product (if applicable)
- An adverse event

The investigator must document the event as well as possible (by means of copies of laboratory results or reports of examinations or hospitalizations, including relevant negative results, ensuring documents are anonymized and entering the patient's number and code), medical diagnosis and establish a causal relationship between the serious adverse event and the drug(s).

The patient who has experienced a SAE must be followed until complete resolution, stabilization at an acceptable threshold according to the investigator or recovery to the previous state, even if the patient has been withdrawn from the trial. The investigator has to inform the sponsor by fax on + 33 (0)4 72 11 51 90 using the form (check the box: follow-up).

Serious adverse events that do not require prompt notification to the sponsor.

- Evolution of the disease studied without aggravation since the inclusion of the patient
- Hospitalization for medical or surgical treatment scheduled before the research;
- Admission to emergencies lasting less than 24 h (not related to the treatment)

Adverse events are to be collected in the case report form (CRF).

Adverse events with specific interest

Some events require special monitoring and will be notified as a SAE (upon request of the sponsor, a Data Safety Monitoring Board (DSMB), a pharmaceutical company or competent authorities):

- Catheter dysfunction (5%/year), pump dysfunction (< 1/1000) with lack of therapy effect
- Neuropsychiatric disorders in particular any suicide attempts, suicide ideation
- Any fall with fracture or trauma
- Traffic accident due to drowsiness
- CPK increased > 5 ULN, or associated with clinical signs of myopathy or rhabdomyolysis

In utero exposition

If a woman becomes pregnant during the research or if her partner is involved in the research, pregnancy must be reported to the sponsor. The participation in this study of woman having begun a pregnancy during the study will be interrupted. Prior to IT testing of ziconotide, a pregnancy test will be performed in active women of childbearing age.

The investigator informs the sponsor (by phone, fax, or email) who will send to the investigator a pregnancy form. This form must include the expected date of delivery if the pregnancy is still ongoing.

The pregnancy should be followed up by the investigator until delivery or its interruption, who also must notify the outcome to the sponsor.

If the outcome of pregnancy meets the criteria of a serious adverse event (spontaneous abortion with hospitalization, fetal death, congenital anomaly…), the investigator must follow the procedure for SAE reporting.

In case of a paternal exposition, the investigator must obtain consent form the partner to collect information concerning the pregnancy.

Causality assessment

The investigator must assess the causality of adverse events with the experimental drug(s) and with the procedures / acts added by the research. He must also assess the causality of adverse events with the other concomitant treatments taken by the patient and provide the results of this evaluation to the sponsor. The causality assessment is binary (reasonable possibility / unrelated).

Reporting time frames of SAE without delay to the sponsor by the investigator and procedures for monitoring serious adverse events.

The investigator must notify to the sponsor without delay all serious adverse events:

- From the INCLUSION OF THE PATIENT (date of signature of the 1st consent)
- Until THE END OF PARTICIPATION OF THE PATIENT
- With no time limit for serious adverse events related to the research (for instance: cancers, congenital malformations occurring in the long term after exposure to the experimental drug…).

Responsibilities of the sponsor

Declaration to the competent authorities

According to article R1123-54 of the Public Health Code, the sponsor shall report:

- To ANSM and Eudravigilance, any suspected unexpected serious adverse reaction (SUSAR) occurring in France and outside the national territory within the following time frames:
- In case of life threatening or death: without delay from the day on which the sponsor becomes aware of it, and the relevant additional information to be submitted as a follow-up report to ANSM within the 8 days following the initial report.
- For all other unexpected serious adverse reactions: no later than 15 days from the day on which the sponsor becomes aware of it, and the relevant additional information to be submitted as a follow-up report to ANSM within another 8 days following the initial report.
- to ANSM and to CPP, any new issue and, when appropriate, the measures taken without delay from the day on which the sponsor is aware of them and the relevant additional information to be submitted in the report form to ANSM within the 8 days following the initial report.

The sponsor will also prepare a Development Safety Update Report (DSUR) which will be forwarded to ANSM and CPP within the 60 days following the birth date of the study (authorization's date of ANSM).

Safety reference information for the assessment of the expectedness / unexpectedness

The expectedness or unexpectedness of a suspected serious adverse reaction is assessed from:

– Investigational Drug Reference Document n°1 (ziconotide): Summary of Product Characteristics (SmPC) of PRIALT® 25 µg/mL solution for perfusion ®
– Investigational Drug Reference Document n°2: Summary of Product Characteristics (SmPC) of NaCl 0.9% BBraun®

No addictive effects have been described with IT ziconotide in the literature.

Side effects of ziconotide described include systemic side effects (increase in serum creatine phosphokinase with potential kidney failure) but are dominated by central nervous system side effects including dizziness, nausea, confusion, nystagmus, and headache. Others may include weakness, hypertonia, ataxia, abnormal vision, anorexia, drowsiness, unsteadiness on feet, vertigo, urinary retention, pruritus, increased sweating, diarrhea, vomiting, asthenia, fever, rigors, sinusitis, muscle spasms, myalgia, insomnia, anxiety, amnesia, tremor, memory impairment, hallucinations, confusion, and induced psychiatric disorders.

Concerning the rest of the procedures performed for the patients' care (not related to the research):

– Surgery: be given before the study, before catheter and pump implantations: infection, hematoma, CSF

leakage with headache, wound healing disorders, local pains, neurological deficit, bleeding …
– Devices: catheter dysfunction (5%/year: obliteration, leakage, disconnection…), pump dysfunction (< 1/1000: battery depletion) with loss of therapy effect

Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC)

The Data Monitoring Committee (DMC) or Data Safety Monitoring Board (DSMB) is an advisory committee responsible to help the sponsor to proactively monitor and gauge patient safety and risk in the clinical trial. Therefore, the DSMB reviews the data and issues that may occur during the trial, especially the ones which are scientific, ethical and tolerance, which may change the benefit / risk ratio. Following this review, the DSMB shall provide its recommendations by writing to the sponsor. These recommendations may concern in particular the continuation, modification, or termination of the study.

The sponsor remains responsible for the decision of the measures to be implemented, based on the recommendations of the DSMB/DMC.

The modalities of organization of this DSMB/DMC are described in a charter signed by the members of the DSMB/DMC at the beginning of the research. The DSMB includes one algologist, one neurosurgeon, one physician specialized in Physical medicine and rehabilitation, one methodologist, and one biostatistician or pharmacologist. A qorum of three persons is required to organize a DSMB meeting.

The DSMB for SPIDOL is composed of:

- Dr Anthony GELIS, Physical medicine and rehabilitation, CHU Montpellier
- Dr Roland PEYRON, Algologist, CHU St Etienne
- Pr Sophie COLNAT-COULBOIS, neurosurgeon, CHU Nancy
- Pr Remy MORELLO, methodologist, CHU Caen
- Pr Jean-Louis Montastruc, pharmacologist, CHU Toulouse

Ethics, regulatory, and legal considerations

Risk/benefit ratio

The risk/benefit ratio will be described in detail in the information sheets given to the patient before inclusion.

The benefit described will be the decrease of neuropathic pain in relation with SCI. It will be precised that the total vanishing of pain, experienced by, the patient will not be a goal for this study. This information will be given to avoid any inadapted expectation of the patient. It will be described that the reduction of pain will potentially improve the daily comfort and be able to reduce oral drug consumption.

All the potential risk (described above) in relation with:

– Surgery: be given before the study, before catheter and pump implantations,
– Devices: catheter dysfunction (5%/year), pump dysfunction (< 1/1000) with loss of therapy effect
– Ziconotide: over or under dosage, nausea, neuropsychological, CPK increase, urinary retention, and the strategies to face these potential risks will be described to the patients.

For each individual who will be candidate to inclusion, in each center assessment, and discussion of the benefit/risk ratio with the patient will be performed by the multidisciplinary team including algologists, PMR physicians, and neurosurgeons. No inclusion will be performed before proof is recorded that the patient and its relatives have well understood this ratio.

Ethical conduct of the study

The sponsor and the investigator undertake to ensure that the study is conducted in conformity with:

- The protocol,
- Both the French and international good clinical practices currently in force,
- The current French and international legal and regulatory provisions.

Regulatory authority approvals/authorizations

The study protocol was submitted as per French regulation for ethics approval to the Comité de Protection des Personnes CPP (the Committee for the Protection of Persons – French Public Ethics Committee) Sud Est et outre-Mer which approved it on November 7th 2019 with the reference number 2019–038-id3583. Its agreement was transferred to the Agence Nationale de la Surete Medicamenteuse—National Agency for Drugs and Medical Device Safety who gave the final approval for the conduct of the study on May 16th 2019 (2019–001406-19).

Subject information and consent

It is the responsibility of the investigator to obtain informed consent in compliance with national requirements from each patient prior to him entering the trial or, where relevant, prior to evaluating the patient's suitability for the study.

It must be made completely and unambiguously clear to each patient that they are free to refuse to participate in the study, or that they can withdraw their consent at any time and for any reason, without incurring any penalty or withholding of treatment from the investigator.

The informed consent document used by the investigator for obtaining patient's informed consent must be reviewed and approved by the sponsor prior to Ethical Committee submission.

All this information will be presented in the information sheet and informed consent form given to the patient. The patient's free and informed written consent will be collected by the investigator or a doctor representing him before the definitive inclusion into the study. A copy of the information notice and the consent form signed by the two parties will be given to the patient; the investigator will keep the original.

Exclusion period

After inclusion, no simultaneous participation to other interventional clinical research that would interfere with the trial will be authorized during the study. At the end of the study, there will be no exclusion period.

Professional secrecy and confidentiality

The investigator is required to comply with medical confidentiality. The gathered data, including test results, will be made anonymous by any appropriate means. The sponsor and its agents are subject to the same obligations of professional secrecy like the investigators. This document and its annexes are provided to the investigators in confidence and shall be released or disclosed only to persons specifically involved in the trial with the consent or upon the request of the investigator coordinator.

A unique identification number will be assigned to each patient included in the study. The slips of the CRF will only show the patient identifier, which guarantees anonymity. Only this number will be computerized. The computer file used for the data entry and processing will be declared to the Commission Nationale Informatique et Libertés in accordance with the Act No. 2004–801 dated August 6, 2004. Computerized data entry will not be nominative. Only the investigators will know the identity of the patient in treatment.

These data are considered as indirectly nominative, the patients will be informed that a computerized data collection on their health status will be collected for the conduct of the study, in conditions that ensure confidentiality. They will also be informed of their right to access and correct the data from the investigator.

Only aggregated data where patients are not identified will be used in scientific papers (conferences, publications).

Right of access to the data and source documents

Access to the data

In conformity with the GCP:

- The sponsor is responsible for obtaining the agreement of all the parties implicated in the study in order to guarantee direct access to all the sites where the study will take place, to the source data, source documents, and reports, in the interests of quality control and audits by the sponsor;
- The investigators will provide the persons responsible for the follow-up, the quality control, or the audit of the study involving human individuals, the individual documents and data that are strictly necessary for this control, in accordance with the current legal and regulatory provisions (article L1121-3 and R.5121–13 of the public health code).

Source documents

Source documents are defined as all documents or original objects allowing the existence or accuracy of data, or a fact recorded during the clinical study, to be proven. They will be kept for 25 years by the investigator or by the hospital if it is a patient's hospital file.

The type of source document includes medical file, original copy of the biological examination results, psychological questionnaires and assessments, and imaging examination report.

The datasets analyzed during the current study and statistical code are available from the corresponding author on request after authorization by the sponsor, the legal department of the Hospices Civils de Lyon and the signature of contract between identified parts.

Data confidentiality

In accordance with provisions concerning the confidentiality of data to which persons responsible for the quality control of a study involving human individuals have access (article L.1121–3 of the public health code), and in accordance with the provisions regarding the confidentiality of information relating, in particular, to the trial, the persons who participate, and the results obtained (article R.5121–13 of the public health code), the persons having direct access to the data will take all necessary precautions to ensure the confidentiality of the information related to the trials, to the persons participating and, in particular, with regard to their identity as well as the results obtained.

These persons, such as the investigators themselves, are subject to professional confidentiality (in accordance with the conditions defined by articles 226–13 and 226–14 of the penal code).

During the research involving human individuals or at its end, the data collected on the persons participating and sent to the sponsor by the investigators (or any other specialists) will be made anonymous.

Under no circumstances should the names or the addresses of persons concerned appear.

Only the first letter of the subjects' surname and the first letter of their first name shall be recorded, accompanied by a coded number specific to the study indicating the inclusion order of the subject.

The sponsor will ensure that each person participating in the research has given their written agreement granting access to the individual data that concerns them and strictly necessary for the quality control of the study.

Any data required to support the PROTOCOL can be supplied on request after authorization by the sponsor, the legal department of the Hospices Civils de Lyon, and the signature of contract between identified parts.

Administrative procedures

Insurance

The sponsor has subscribed to an insurance policy for the entire duration of the study, covering its own civil liability as well as that of all the doctors involved in the realization of the study. It will also insure the full compensation for harmful consequences of the research for the participating persons and their beneficiaries, except with evidence, at their responsibility, that the damage is not attributable to their mistake or to that of all consultants, without the possibility of being opposed to an act by a third party or the voluntary withdrawal of the person who had initially consented to participate in the research.

The insurance contract was signed before the start of the study with the Société Hospitalière d'Assurance Mutuelle, 18 rue Edouard Rochet, 69008 Lyon, under the number 153.930.

Inspections by regulatory authorities

For the purpose of ensuring compliance with good clinical practice and regulatory agency guidelines, it may be necessary to conduct a site audit or an inspection.

By signing this protocol, the investigator agrees to allow the sponsor and its representative, and drug regulatory agencies to have direct access to his study records for review. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

These audits involve review of source documents supporting the adequacy and accuracy of data gathered in CRF, review of documentation required to be maintained, and checks on drug accountability. The sponsor will in all cases help the investigator prepare for an inspection by any regulatory authority.

Protocol amendments

No changes or amendments to this protocol may be made by the investigator or by the sponsor after the protocol has been agreed to and signed by both parties, unless such change(s) or amendment(s) have been fully discussed and agreed upon by the investigator and the sponsor.

Any change agreed upon will be recorded in writing, the written amendment will be signed by the investigator and by the sponsor and the signed amendment will be appended to this protocol.

Approval/authorization of amendments by the Ethics Committee (CPP) and National Agency for Drug and Medical Device Safety (ANSM) is required prior to their implementation, unless there are overriding safety reasons. A new consent will be collected from the people already participating in the study, if necessary.

The Scientific Steering Committee (TSSC) composed of the authors of this protocol meets once a year to discuss the general progress of the study and each time necessary to answer regulation authorities or sponsor questions or help participating centers. It will meet upon the request of the investigators, the DSMB, or the coordinating center team if necessary. The Scientific Steering Committee proposes amendments to the protocol if necessary.

The coordinating center team is composed of 3 persons: a project manager, a study coordinator, and a clinical research assistant. There are all 3 from the Public Health department of the Hospices Civils of Lyon. They are in charge of the methodological support, scientific and organizational support of the study, in collaboration with the coordinating investigator, for all participating centers and in particular for the Lyon center. They are also in charge of the link between the participating centers, the regulation authorities, and the sponsor. Finally, they follow the study inclusions and initiate the DSMB and scientific steering committee when needed.

Finally, the principal investigator of each participating center is responsible for all aspects of local organization including identifying potential recruits and taking consent. He is assisted in screening, planning study visits, and recording study data by a clinical research assistant.

Trial status

Protocol version 4 – amendment 3: July 20th, 2023.

Inclusion open since: 7/11/2020.

Inclusion period ends: June 2024.

Initially authorized for beginning of inclusion 07/11/2019.

Due to delays related to Covid beginning of inclusion was postponed to 07/11/2020.

Inclusion period will go on until June 2024.

Publication of trial results

All the data collected during this study are the property of the sponsor and may not be communicated to third parties in any event without the written agreement of the study coordinating investigator.

Any publication or communication (oral or written) will be decided by common agreement among the investigators and will comply with international recommendations: "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (http://www.cma.ca/publications/mwc/uniform.htm). The members of the steering committee will be part of the authors.

Individuals who participated in the development of the study protocol, its progress, and in the writing up of results will be the first signatories. The first author is one who take the initiative of the manuscript and who will be the main editor. All the investigators who included or monitored patients as a part of this research as well as the other collaborators involved will also be mentioned. In every publication, the Hospices Civils de Lyon will be named as sponsor and funding under the PHRC will figure explicitly.

The study was registered into a public clinical trials database (http://clinicaltrials.gov), trial number NCT03942848.

Scientific communications and reports related to this study will be carried out under the responsibility of the study's principal investigator with the agreement of the associated investigators. The co-authors of the report and the publications will be the investigators and doctors involved, in proportion to their contribution to the study, as well as the biostatistician and the associated researchers.

The publications rules will follow international recommendations [41].

Budget

The financial resources were obtained by a grant of 324,671€ (PHRC-N) from the Direction General de l'Offre de Soin from the French Ministry of Health in 2018 by award through National Competition.

It includes financial resources to cover the extra cost for this study such as:

- Pharmaceutical validation of the experimental drug and placebo, capsule processing of treatment of placebo, delivery and organization between central and local pharmacy
- Staff to organize the study (inclusion and follow-up), data collection, regulatory and ethical assessment, data management and statistical analysis, eCRF creation, and management
- Staff to conduct data monitoring, pharmacovigilance
- Insurance and management costs.

An additional 35,000€ grant was obtained from the ESTEVE company to increase the recruitment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08387-0.

Supplementary Material 1.

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The SPIDOL study group is composed of:
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Authors' contributions

AB is the chief investigator for the study protocol. He contributed significantly to: Conception and Design, Preparation of base data for sample size estimation, Statistical and Methodological Preparation, Drafting of the Manuscript, Review of the Manuscript. JB is the lead methodologist. He contributed significantly to: Conception and Design, Statistical and Methodological Preparation, Drafting of the Manuscript, Review of the Manuscript. NP is a methodologist. She contributed significantly to: Conception and Design, Drafting of the Manuscript, Review of the Manuscript. FS is a methodologist contributed significantly to: Statistical and Methodological Preparation. CG is a methodologist. She contributed significantly to: Conception and Design, Drafting of the Manuscript, Review of the Manuscript. JL is an investigator. He contributed significantly to: Conception and Design, Concept and Ethics Review (other than ERB), Statistical and Methodological Preparation, Drafting of the Manuscript, Review of the Manuscript. PM is the chief investigator for the study and the protocol coordinator. He contributed significantly to: Conception and Design, Concept and Ethics Review (other than ERB), Statistical and Methodological Preparation, Drafting of the Manuscript, Review of the Manuscript. The SPIDOL study group (i.e., MLM, BJ, PM, JV, JMR, KB, ML, DF, JLB) contributed to Concept and Ethics Review (other than ERB), Review of the Manuscript. All authors contributed to the approval of the final manuscript.

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The project is financed:
- Grant of 324,671€ (PHRC-N) from the Direction General de l'Offre de Soin from the French Ministry of Health in 2018.
- A 35,000€ grant from the ESTEVE company.

Availability of data and materials

N/A.

Declarations

Ethics approval and consent to participate

The study protocol was submitted as per French regulation for ethics approval to the Comité de Protection des Personnes CPP (the Comithee for the Protection of Persons – French Public Ethics Committee) Sud Est et outre-Mer which approved it on November 7th, 2019, with the reference number 2019-038-id3583. Its agreement was transferred to the Agence Nationale de la Surete Medicamenteuse—National Agency for Drugs and Medical Device Safety who gave the final approval for the conduct of the study on May 16th, 2019 (2019–001406-19).
Original consent in French.
The participant information materials and informed consent form are available from the corresponding author on request.

Consent for publication

Original consent in French.
The participant information materials and informed consent form are available from the corresponding author on request. This does not apply to the current manuscript—no patient data is included.

Competing interests

The authors declare that the protocol was created in the absence of any commercial or financial relationships that could be construed as potential conflict of interest.

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