NCT05137041

A phase IIIB randomized, open label, two arms and parallel group clinical trial to assess the efficacy and safety of FIRTECH (Infrared Therapy Patch), for treating patients suffering from mild to moderate acute low back pain

Study Name: IRPATCH

Version 4 / 22 July 2022

Regulatory Sponsor:	**SAR&D Sanofi-Aventis Recherche & Développement** 1 Avenue Pierre Brossolette 91380 Chilly-Mazarin France
Study Product:	FIRTECH Infrared Therapy Patch
Protocol Identifiers:	Study Number: LPS16453 WHO Universal Trial Number: U1111-1255-4648

Statement of Compliance

This document is a protocol for a human research study. This study will be conducted according to US and International standards of Good Clinical Practice, applicable government regulations and Institutional research policies and procedures.

All individuals responsible for the design and conduct of this study have completed Human Subjects Protection Training and are qualified to be conducting this research prior to the enrollment of any subjects.

As Principal Investigator, I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol. Modifications to the study are acceptable only with an approved protocol amendment. I agree to obtain approval from the IRB and/or regulatory bodies of competent jurisdiction, for the protocol and informed consent before initiating the study, to obtain consent from subjects prior to their enrollment in the study, to collect and record data as required by this protocol and case report forms, to prepare adverse event and study reports as required by this protocol and to maintain study documentation for the period of time required.

_____ _____

[Print Name/Title of Principal Investigator] Date

As a Sub-Investigator, I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol. Modifications to the study are acceptable only with an approved protocol amendment. I agree to obtain approval from the IRB and/or regulatory bodies of competent jurisdiction, for the protocol and informed consent before initiating the study, to obtain consent from subjects prior to their enrollment in the study, to collect and record data as required by this protocol and case report forms, to prepare adverse event and study reports as required by this protocol and to maintain study documentation for the period of time required.

_____ _____

[Print Name/Title of Sub- Investigator] Date
[Print Location if multi-site protocol]

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[Print Name/Title of Sub- Investigator] Date
[Print Location if multi-site protocol]

Version History

Version #	Approval Date	Significant Changes from Previous Version
Version 1	24 September 2020	Original Protocol Version
Version 2	12 April 2021	Amendment 1: • to reflect recent optimized shape of the patch to improve hold • to consider COVID pandemic context • to address German Ethics Committee requests
Version 3	29 March 2022	Amendment 2: Admin change on Protocol Synopsis to Study centers
Version 4	22 Jul 2022	Amendment 3: Revision of Inclusion and exclusion criteria

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Study Synopsis

Title	A phase IIIB randomized, open label, two arms and parallel group clinical trial to assess the efficacy and safety of FIRTECH (Infrared Therapy Patch), for treating patients suffering from mild to moderate acute low back pain.
Short Title	Efficacy and Safety of FIRTECH in Patients with Mild to Moderate Acute Low Back Pain
Protocol Numbers	LPS16453
Study Sponsor	SAR&D Sanofi-Aventis Recherche & Développement
Principal Investigator	TBD
Study Design	This is an open label, randomized, patch arm vs. and no-patch control arm, clinical trial.
Study Duration	12 months
Study Center(s)	Approximately 10 centers in Germany and Italy
Objectives	**Primary:** To assess the efficacy of the ITP FIRTECH for treating subjects suffering from mild to moderate acute low back pain **Secondary:** • To assess the efficacy of ITP FIRTECH on the subject disability. • To assess the efficacy of ITP FIRTECH on the degree of subject mobility. • To assess the safety of ITP FIRTECH
Number of Subjects	200 enrolled subjects: 180 evaluable subjects (90 in each arm).
Main Inclusion / Exclusion Criteria	**Inclusion:** 1. Male or female subjects who are ≥18 years and < 65 years. 2. Subjects suffering from mild to moderate acute low back pain. • Low back pain (lumbar back pain) is defined as pain in the back from the level of the lowest rib down to the gluteal fold. • Acute episode is defined as acute pain with less than 1 month duration. • With intensity ≤ 6 on 0-10 Numerical Rating Scale (NRS) **Exclusion:** 1. Subjects suffering from any neurological pathology which could be responsible for the pain. 2. Subjects suffering from leg pain irradiation. 3. Subjects suffering from chronic lumbar pain of any etiology. 4. Subjects with chronic arthrosis and neurological symptoms 5. Subjects experiencing recent significant trauma (i.e., injury related to a fall from a height or motor vehicle crash, or from a minor fall or heavy lifting in a subject with osteoporosis or possible osteoporosis), 6. Subjects with major or progressive motor or sensory deficit, new-onset bowel or bladder incontinence or urinary retention, loss of anal sphincter tone, saddle anesthesia, history of cancer metastatic to bone, and suspected spinal infection. 7. Subjects clinically diagnosed with anxiety and/or depression 8. Subjects using any medication for their pain within the last 48 hours within enrollment into the study 9. Subjects taking any systemic medication for their pain within the last 24 hours (48 hours for diclofenac or corticosteroids).

	10. Subjects currently using recreational or illicit drugs or with a recent history of drug or alcohol abuse or dependence. 11. Subjects with any other medical condition that would interfere with efficacy and safety assessments based on investigator's judgment. 12. Subjects having received non pharmaceutical LBP treatment (physiotherapy, heat treatment or massage) within 12 hours prior enrollment 13. Subjects having received spinal injection back pain treatment within 6 months prior enrollment 14. Subjects having received surgery due to back pain or rehabilitation due to back pain in the last 12 months 15. Subjects with a known sensitivity to paracetamol 16. Known cutaneous hypersensitivity to plaster 17. Subjects participating in another clinical study within the past 30 days 18. Subjects who are pregnant or breastfeeding. Contraception is mandatory 19. Subjects having damaged, non-intact, or scarred skin in or near the point of patch application. 20 Subjects having a known skin sensitivity. 21. Subjects having impaired blood circulation.
Study Device	FIRTECH Infrared Therapy Patch
Duration of Device Exposure	5 days
Reference Therapy	None
Endpoints	**Primary:** A Numerical Rating Scale (NRS) responder at Day 5 at the on-site evaluation (defined as ≥ 30% decrease from baseline of the instantaneous pain and no rescue medication). **Secondary:** • Normalized Sum of Pain Intensity Difference (PID, which equals the NRS change from baseline) over 5 days ($SPID_{0-5}$). • Roland-Morris Disability Questionnaire (RMDQ) score improvement (%) from baseline to Day 5. • Mobility evaluation: change from baseline to Day 5 • Time to reach acceptable pain **Other secondary endpoints** • Time to reach no pain (NRS = 0) • Time course of PID over time from baseline to Day 5 on-site evaluation • Time course of Pain relief over time from baseline to Day 5 on-site evaluation • Normalized Sum of Pain relief over 5 days (TOTPAR0- 5) • Safety. **Exploratory endpoints** • Frequency of use of rescue medication • Description of "worst pain" evaluation • Description of "least pain" evaluation • Description of "average pain" evaluation
Statistical Methods	For efficacy evaluations, Fisher's exact tests will be performed to compare proportions (like proportion of responders for the primary endpoint) questionnaires and time-course data will be summarized by visit, time-to-event

	data will be displayed and analyzed using the Kaplan–Meier method and tested using the log rank test. Efficacy data will be summarized and analyzed under the Intent-to-Treat paradigm. Safety, tolerability and compliance will be summarized under the "As Treated" paradigm: frequencies and proportions will be summarized as per actual arm (patch/no patch)

Abbreviations

AE	Adverse Event
CRF	Case Report Form
DSE	Device Specific Event
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LBP	Low Back Pain
NRS	Numerical Rating Scale
PHI	Protected Health Information
PID	Pain Intensity Difference
RMDQ	Roland-Morris Disability Questionnaire
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TEAE	Treatment Emergent Adverse Event
TOTPAR	Normalized Sum of Pain relief over 5 days
UADE	Unanticipated Adverse Device Effect
VRS	Verbal Rating Scale

1 Study Contact Information

1.1 Sponsor Contact Information

SAR&D Sanofi-Aventis Recherche & Développement
1 Avenue Pierre Brossolette
91380 Chilly-Mazarin
France

1.2 Principal Investigator Contact Information

TBD
[Investigator Address]
[Investigator Office Phone]
[Investigator Mobile Phone]
[Investigator E-mail]

1.3 Sub-Investigators Contact Information

TBD
[Investigator Address]
[Investigator Office Phone]
[Investigator Mobile Phone]
[Investigator E-mail]

1.4 Key Study Personnel

1.4.1 Clinical Study Monitor

ICON Clinical Research

1.4.2 Medical Monitor

Sanofi- Aventis Recherche & Développement

1.4.3 Statistician

ICON Clinical Research

2 Introduction / Background and Rationale

Low back pain (lumbar back pain) is defined as pain in the back from the level of the lowest rib down to the gluteal fold. An acute pain episode is defined, as acute pain with less than 1 month duration, however, there is non consistency across international guidelines to define acute versus chronic pain [1].

Back pain affects between 60% and 80% of all people at some time in their life. Fifteen to forty-five percent of adults suffer LBP, and 1/20 (5%) people present to a healthcare professional with a new episode. Low back pain is most common between the ages of 35 to 55 years. About 30% of European workers reported that their work caused LBP. Prevalence varies across countries, ranging from 13% to 44%. In 50% to 80% of people with acute LBP, symptoms recur within 1 year, indicating a high recurrence rate. Thirty-three percent of people still endure moderate-intensity pain and 15% experience severe pain 1 year after the initial episode. Fifty percent of episodes nearly completely resolve within two weeks, and 80% by six weeks[2].

Patients with peripheral pain may achieve pain relief with currently recommended first-line oral treatments, which are also associated with systemic adverse events. Topical treatments are currently considered second-line options, but their safety profiles are better than oral treatments.

Infrared Therapy Patches (ITP) are Class I Medical Devices and can relieve painful symptoms without the use of drugs. The effects duration varies according to each person's state of health.

The objective of the LPS16453 study is to determine the efficacy and safety of the ITP FIRTECH compared with no-patch control arm for treating acute mild to moderate low back pain.

The study is designed as open label with a no-patch control arm. The following items had been taken into account in this decision:

- It is necessary to provide controlled data in support of the therapeutic effect. These types of body pain are self-limiting and many patients will improve even without any treatment. Just observing treated patients and recording their improvement (post- versus pre-treatment) will not allow description of the level of effect coming from the patch.
- There is no real sham (placebo). The double blind approach is impossible to reach. In fact, the active compound is part of the tissue structure:
    - The purpose of the clinical study is to prove the efficacy of re- emitted IR energy for pain relief. This is not specifically limited to the IR re-emitted from particles such as titanium dioxide. Other components of the patch such as the fabrics also re-emit IR.
    - The efficacy of the patch maybe therefore not only be associated with the used ceramic particles, but with the entire patch respectively re-emitting IR.
    - In theory, the placebo of the IR emitting patch should be designed as a non-emitting patch (i.e., all materials of construction have zero emissivity). All materials emit and re-emit IR (to various degrees). Therefore, a completely non-emitting placebo device cannot be produced/manufactured.
    - The similar tissue has effect of reflection of the emitted infrared radiation; this patch would not be a placebo in the true sense of the definition.

- All study participants have access to rescue medication. Treatment is available and even a delay in the treatment will not automatically result in a worsening of the medical condition.

The study will be performed according to all local regulations.

3 Device Description

The device consists of a patch [redacted] applied to the skin surface. The FIRTECH patch consists of two layers, a TNT (Polypropylene) support coated with an adhesive containing Titanium Dioxide, printed in the upper part. It contains a film of transparent polyethylene terephthalate (PET) that serves as a protective support for the adhesive layer. This protective film is pre-cut to facilitate easier application of the patch to the skin. Titanium dioxide belongs to the category of molecule with a high emittance, the intrinsic ability to "receive" and "re-emit" specific wavelengths. Specifically, the emittance of titanium dioxide is located in a range of infrared (IR) frequencies that notoriously have an interesting therapeutic aspect.

[redacted] the composition listed in *Table 1.*

Table 1. FIRTECH Infrared Therapy Patch Composition

Support	Non woven fabric – white (Polypropylene) [CAS #9003-07-0]
Adhesive	Polyacrylate [CAS #25133-97-5]
Protective support	Polyethylene terephthalate [CAS #25038-59-9]
Chemical element	Titanium Dioxide [CAS #13463-67-7] and Synthetic wax (poly(alpha-olefins, alkenes, C>10 alpha-, polymerised))

The medical device under review contains no analgesics, no tissues or blood products or cells, or their derivatives, of human or animal origin. [redacted]

All investigational devices will have the following label statement: **CAUTION – For Investigational Use Only**.

4 Device Accountability

4.1 Device Receipt

Devices will be shipped directly to the investigator from the Sponsor. Upon receipt by the Investigator, devices will be inventoried and stored as per Section 4.2 below. For inventory purposes, each device will be assigned an inventory number which will be recorded on an inventory log.

4.2 Device Storage

Devices will be stored in a restricted access location with access by the Investigator or designee only. Devices will be stored under ambient conditions. There are no special handling requirements for this device.

4.3 Device Dispensing

Devices will be dispensed by the Investigator, or designee, as needed for each Subject. For device accountability, device inventory numbers will be recorded on the Subject's case report form, and the Subject's ID number will be recorded on the inventory log. The inventory log will be reconciled with Subject records during the monitoring visits and this reconciliation will be noted on the device inventory form, and signed and dated by the study team designee.

4.4 Device Disposition

At the end of the study period, the Subject will return to the investigational site to have the patch removed. If the patch is removed or if it peels off prior to its scheduled removal, Subjects are instructed to apply a new patch at home. All the used and unused patches have to be returned to the investigational site at Visit 2

4.5 Return or Destruction of Unused Devices

Returned and/or unused devices are to be destroyed or returned to the Sponsor at the Sponsor's discretion. All devices must be accounted for in the inventory log. If devices are to be returned to the Sponsor, the Sponsor will provide shipping instructions at that time.

5 Study Objectives

5.1 Primary Objective

The Primary objective of the study is to assess the efficacy of the ITP FIRTECH for treating subjects suffering from mild to moderate acute low back pain.

5.2 Secondary Objectives

The Secondary objectives of this study are listed below:

- To assess the efficacy of ITP FIRTECH on the subject disability.
- To assess the efficacy of ITP FIRTECH on the degree of subject mobility.
- To assess the safety of ITP FIRTECH

5.3 Exploratory Objectives

Exploratory objectives for this study include:

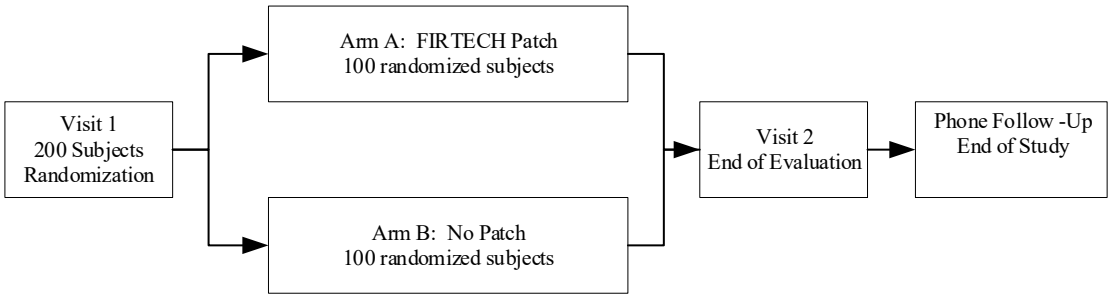
- To assess the frequency and use of rescue medication
- To assess the subject evaluations of least, average , and worst pain

6 Study Design

6.1 Overview of Study Design

This is an, open label, randomized, proof-of-concept clinical trial; comparing the ITP FIRTECH with a no-patch control arm. The study will be performed in Medical Centers and an online e-diary will be used.

A total of 2 site visits and 1 phone contact are planned during a maximum of 6 days of study duration, as shown in *Figure 2*.



Day 1	Day 1 to Day 5	Day 5	Day 6
At Study Center: *Subject enrollment *e-diary activation *Baseline assessments *Randomization *Patch application for Arm A	**At Home** *Diary completion	**At Study Center** *On-site assessments *Patch removal	End of Study Discharge

Figure 2. Study Schema

6.2 Anticipated Duration of the Clinical Investigation

The estimated study duration from first enrollment to last Subject visit is approximately 2 months. This study duration will require approximately 5 subjects to be enrolled per week at each site.

6.3 Evaluation Criteria / Efficacy and Safety

6.3.1 Primary Efficacy Clinical Endpoint

A Numerical Rating Scale[3] (NRS) responder at Day 5 at the on-site evaluation (defined as ≥ 30% decrease from baseline of the instantaneous pain[4] and no rescue medication)

6.3.2 Secondary Efficacy Clinical Endpoint(s)

Key secondary endpoints

- Normalized Sum of Pain Intensity Difference (PID, which equals the instantaneous NRS change from baseline) over 5 days ($SPID_{0-5}$). The Sum of Pain Intensity Difference (SPID) is to be calculated by multiplying the PID score at each post dose time point by the duration (in hours) since the preceding time point. The Normalized Sum of Pain Intensity Difference ($SPID_{0-5}$) is to be calculated as the $SPID_{0-5}$ divided by the total duration time..

$$Normalized\ SPID_{0-5} = \frac{\sum_{i=1}^{9}(T_i - T_{i-1}) * PID_i}{T_9 - T_0},$$

where $T_0 = 0$, T_i – actual time and PID_i – Pain Intensity Difference score at time T_i. Pain Intensity Difference, in turn, is defined as $PID_i = PI_i - PI_0$ where PI_0 - Pain Intensity at time T_0.

- Roland-Morris Disability Questionnaire[5] (RMDQ) score improvement (%) from baseline to Day 5. Details of the scoring of the Roland-Morris Disability Questionnaire are provided in Section 17.1.
- Mobility evaluation[6,7]: change from baseline to Day 5. The mobility evaluations (Schober's Test or Fingertip to Floor Test) are described in Section 17.2.
- Time to reach acceptable pain. Time from randomization to the first report of acceptable pain; if that event never occurs, the tine will be censored at the final visit.

Other secondary endpoints

- Time to reach no pain (NRS = 0). Time from randomization to the first report of NRS=0; if that event never occurs, the tine will be censored at the final visit.
- Time course of PID (see above) over time from baseline to Day 5 on-site evaluation
- Time course of Pain relief over time from baseline to Day 5 (VRS)
- Normalized Sum of Pain relief over 5 days ($TOTPAR_{0-5}$). Total pain relief (TOTPAR) is calculated by multiplying the pain relief score at each post-dose time point by the duration (in hours) since the preceding time point. The Normalized Sum of Pain Relief ($TOTPAR_{0-5}$) is to be calculated as the Total Pain Relief divided by the total duration time.

$$Normalized\ TOTPAR_{0-5} = \frac{\sum_{i=1}^{9}(T_i - T_{i-1}) * PAR_i}{T_9 - T_0},$$

where $T_0 = 0$, T_i – actual time and PAR_i – Pain Relief score at time T_i.

6.3.3 Exploratory Endpoints

- Frequency of use of rescue medication
- Description of "worst pain" evaluation
- Description of "least pain" evaluation
- Description of "average pain" evaluation

6.3.4 Safety Endpoints

Safety endpoints will include:

- Incidence of Adverse Events
- Incidence of Serious Adverse Events
- Incidence of Treatment Emergent Adverse Events

6.4 Study Population

Study populations are defined in Section 8.1.

6.4.1 Sample Size

The efficacy of the patch will be assessed compared with no-patch use. The primary endpoint is the occurrence of being a NRS-responder at Day 5 defined as ≥ 30% decrease from baseline of the instantaneous pain and no rescue medication. The responder proportion in the "no-patch" arm is unknown, and a variety of proportions of responders are envisaged. The targeted treatment effect size is medium (Cohen's H ranging from 0.42 to 0.45). Ninety evaluable subjects per group (180 evaluable subjects in total) are needed to reach 80% power, as shown in the following table.

Table 2. Power Calculations

N per Group	Alpha (2 sided)	Responder Rate		Cohen's H
		No Patch	Patch	
90	5%	10%	27%	0.449
90	5%	20%	39%	0.422
90	5%	30%	51%	0.432
90	5%	40%	61%	0.423
90	5%	50%	71%	0.433
90	5%	60%	80%	0.422
Powers are calculated using East 6.4				

Further assuming a dropout rate of 10%, the expected number of subjects to be randomized is a total of 200. Subjects will be randomized 1:1 to the treatment and no patch arms. The estimated number to be screened to achieve 200 randomized subjects is 260.

6.4.2 Subject Recruitment

Subjects will be recruited from the geographic areas served by the participating clinical sites. Subjects will be recruited from the individual practices of the participating clinicians.

6.4.3 Subject Screening

Subject screening will be conducted to ensure that subjects meet the study inclusion and exclusion criteria. Re-screening of subjects who have failed a previous screening will not be permitted. Documentation will be required to confirm the following:

- Subjects have not received non-pharmaceutical treatments such as physiotherapy, heat treatments or massage therapy within 12 hours prior to

enrollment.

- Subjects have not received any medications for pain within the last 24 hours (48 hours for diclofenac or corticosteroids) prior to enrollment..
- Subjects must not have received a spinal injection to treat back pain within 6 months prior to enrollment.
- Subjects must not have had surgery due to back pain or rehabilitation due to back pain within 12 months prior to enrollment.
- Female Subjects of childbearing potential are not pregnant or breastfeeding. A urine pregnancy test will be required to confirm.

6.4.4 Prior and Concomitant Therapy or Medications

6.4.4.1 Prior and Concomitant Therapies

Subjects must not have received any therapeutic patches or medications for pain within the last 24 hours (48 hours for diclofenac or corticosteroids) prior to enrollment. Subjects must not have received a spinal injection to treat back pain within 6 months prior to enrollment. Subjects must not have had surgery due to back pain or rehabilitation due to back pain within 12 months prior to enrollment. Subjects must not have received non-pharmaceutical treatments such as physiotherapy, heat treatments, massage therapy or acupuncture therapy within 12 hours prior to enrollment.

6.4.4.2 Prior and Concomitant Medications

Subjects will refrain from using analgesics and anti-inflammatory drugs except as described in Section 6.4.4.3 below during the course of their participation in this study.

6.4.4.3 Rescue Medications

During the study, subjects can be treated with up to 2 g of Paracetamol per day (rescue therapy) to be documented in the e-diary. Any other analgesics and anti-inflammatory drugs as well as any non-pharmaceutical therapy are prohibited during the study duration, if a subject needs to use one of these options, it has to be documented in the e-diary.

6.4.5 Inclusion Criteria

Subjects will be eligible to participate in the study if **all** of the following conditions exist:

1. Male or female subjects who are ≥18 years and < 65 years.
2. Subjects suffering from mild to moderate acute low back pain.

- Low back pain (lumbar back pain) is defined as pain in the back from the level of the lowest rib down to the gluteal fold.
  Acute episode is defined as acute pain with less than 1 month duration.
- With intensity ≤ 6 on 0-10 Numerical Rating Scale (NRS).

6.4.6 Exclusion Criteria

Subjects will be excluded from participation in the study if any of the following conditions exist:

1. Subjects suffering from any neurological pathology which could be responsible of the pain.
2. Subjects suffering from leg pain irradiation.
3. Subjects suffering from chronic lumbar pain of any etiology.
4. Subjects with chronic arthrosis and neurological symptoms
5. Subjects experiencing recent significant trauma (i.e., injury related to a fall from a height or motor vehicle crash, or from a minor fall or heavy lifting in a subject with osteoporosis or possible osteoporosis),
6. Subjects with major or progressive motor or sensory deficit, new-onset bowel or bladder incontinence or urinary retention, loss of anal sphincter tone, saddle anesthesia, history of cancer metastatic to bone, and suspected spinal infection.
7. Subjects clinically diagnosed with anxiety and/or depression
8. Subjects using any medication for their pain within the last 48 hours within enrollment into the study
9. Subjects taking any systemic medication for their pain within the last 24 hours (48 hours for diclofenac or corticosteroids).
10. Subjects currently using recreational or illicit drugs or with a recent history of drug or alcohol abuse or dependence.
11. Subjects with any other medical condition that would interfere with efficacy and safety assessments based on investigator's judgment.
12. Subjects having received non-pharmaceutical Lower Back Pain treatment(physiotherapy, heat treatment or massage) within 12 hours prior enrollment
13. Subjects having received spinal injection back pain treatment within 6 months prior enrollment
14. Subjects having received surgery due to back pain or rehabilitation due to back pain in the last 12 months
15. Subjects with a known sensitivity to paracetamol
16. Known cutaneous hypersensitivity to plaster
17. Subjects participating in another clinical study within the past 30 days

18. Subjects who are pregnant or breastfeeding. Contraception is mandatory
19. Subjects having damaged, non-intact, or scarred skin in or near the point of patch application.
20. Subjects having a known skin sensitivity.
21. Subjects having impaired blood circulation.

6.4.7 Exit / Discontinuation Criteria

Subjects will exit the study if any of the following conditions exist:

1. Subject voluntarily withdraws from the study.
2. Subject death.
3. Subject is non-compliant with the protocol (as defined in Section 7.9)
4. Subject's well-being, in the opinion of the Investigator, would be compromised by study continuation.
5. Subject experiences an Adverse Event leading to voluntarily withdrawal and/or requiring withdrawal as per Investigator judgement.

6.5 Premature Termination or Suspension of the Study

This study may be prematurely terminated or suspended if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and the sponsor will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant premature termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk or residual risk to participants (as described in the risk analysis performed according to ISO EN 14971).
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The Sponsor must suspend/terminate the study within 5 working days of that determination.

7 Study Procedures

7.1 Informed Consent

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable representative, and the investigator-designated research professional obtaining the consent. A blank copy of the IRB-approved form must be kept on-site and by the Investigator.

7.2 Vulnerable Populations

Recognized vulnerable populations will not be targeted for recruitment, however individual subjects within vulnerable populations may be enrolled. The Human Subject's Protections procedures employed in this protocol are sufficient to protect the rights and welfare of any subject within an eligible vulnerable population and no additional measures are necessary.

7.3 Randomization Scheme

Subjects will be randomized 1:1 to the investigational patch and no patch arms. Specific randomization procedures will be described in a separate randomization plan.

7.4 Blinding / Unblinding

This is an open label study, therefore there are no blinding / unblinding procedures.

7.5 Laboratory Testing Procedures

The only laboratory procedure utilized will be a urine pregnancy test administered to women of child-bearing potential.

7.6 Clinical Procedures

The study will be performed in Investigational Sites and an online e-diary will be used.

A total of 2 site visits and 1 phone contact are planned during a maximum of 5 days of treatment and 6 days of total study duration.

7.6.1 Day 1, Visit 1

Clinical procedures on Day 1, Visit 1 include the following:

- Verification of eligibility
- Informed Consent Signatures
- Local Physical Examination

- Collection of Vital Signs to include: Respiratory rate, Heart rate, Temperature, Blood Pressure
- Collection of Demographics to include: Age , Gender
- Collection of relevant medical history and concomitant medications
- On-line daily e-diary will be explained and activated
- Urine pregnancy testing (for women of childbearing potential only)
- Causes and/or circumstances triggering the acute back pain
- Baseline Subject symptom self-assessment
  - Pain Perception (NRS): Numerical Rating Scale[3] for pain assessments at baseline and at defined time points: 0-10 NRS; '0' representing "no pain" and '10' representing "worst pain imaginable
    - Instantaneous: pain at the moment of the evaluation
    - Average pain in the previous 12 hours.
    - Worst pain in the previous 12 hours
    - Least pain in the previous 12 hours
  - Roland-Morris Disability Questionnaire (RMDQ)[5]
- Baseline mobility assessment (physician)
- Randomization:
  - Arm A: ITP FIRTECH: Patch application according to the instruction for use in Section 17.3: The patch has to stay in position for 5 days. If the patch is taken-off or if it fell off during the study duration, the subject is invited to replace the patch at home following the instruction for use. Subject is allowed to take-off the patch at any time in case of severe skin itchiness, irritation, or skin reaction and in this case the subject has to contact the study center.
  - Arm B: no-patch: Subjects will be informed that they will not be assigned a patch in this study.
- All subjects are informed that rescue mediation (paracetamol, up to 2 g per day), while not encouraged, is allowed if necessary.
- All subjects will be informed of the prohibited medications.
- If rescue medication is taken, the exact moment(s) and the dose(s) have to be indicated in the e-diary.
- An explanation will be provided on how to use e-diary at home and providing all necessary access credentials
- All subjects will be requested to avoid bed rest and will be recommended to continue with a normal daily life activity.
- Two extra patches will be provided to the subjects.
- Instruction will be provided on how to apply a patch at home, as per protocol Section 17.3.

7.6.2 Day 1 to Day 5, At Home

The following procedures will take place while subjects are at home:

- Completion of the e-diary in the morning (e.g. 8:00 [use 24 hr time format]) (this is not applicable at Day 1)
  - Pain perception (using NRS)
    - Instantaneous: pain at the moment of the evaluation
    - Average pain in the previous 12 hours.
    - Worst pain in the previous 12 hours
    - Least pain in the previous 12 hours
  - Pain relief (Using VRS) for the question "Do you feel pain relief?" 0= 'none', 1= 'slight', 2= 'moderate', 3= 'lots', 4= 'complete'.
  - Is the Pain acceptable (binary, Yes/No)?
  - Need of rescue medication (time and dose)
- Completion of the diary in the evening (e.g. 20:00 [use 24 hr time format]) (this is not applicable at Day 5)
  - Concomitant therapies, if any
  - Daily activities to include showers, physical activities, sporting activities, etc.
  - Pain Perception (using NRS)
    - Instantaneous: pain at the moment of the evaluation
    - Average pain in the previous 12 hours.
    - Worst pain in the previous 12 hours
    - Least pain in the previous 12 hours
  - Pain relief (Using VRS)
  - Is the Pain acceptable?
  - Need of rescue medication (time and dose)
  - Adverse events
  - Need of patch removal and application of a new patch – according to instructions for use (Section 17.3) – and recording of reason.

7.6.3 Day 5, Visit 2 Patch Removal / End of Treatment

Clinical procedures on Day 5, Visit 2 (Investigational Site) include the following:

- Completion of the e-diary on site
  - Pain perception (using NRS)
    - Instantaneous: pain at the moment of the evaluation
    - Average pain in the previous 12 hours.
    - Worst pain in the previous 12 hours
    - Least pain in the previous 12 hours
  - Pain relief (Using VRS)

- Is the Pain acceptable?
- Need of rescue medication (time and dose)
- Adverse Events
- Concomitant therapies if any

- E-Diary verification
- Arm A Subjects: Patch is removed.
  - Collection of all used and unused patches.
- Arm B Subjects: subjects are informed about the end of the evaluation period
- Local physical examination, including at patch localization (only for Arm A subjects)
- Vital signs
- Roland-Morris Disability Questionnaire (RMDQ)[5]
- Mobility assessment (physician)

7.6.4 Day 6, Phone Contact: End of Study

Day 6, follow-up procedures by phone include:

Safety contact for evaluating any Adverse Events and the need or not for a safety extra visit as per Investigator judgement.

7.6.5 Unscheduled Visit

Unscheduled visits may occur for any reason if the subject or the investigator consider that it is necessary. The reason and the performed procedures will be collected in the CRF.

7.7 Follow-Up Procedures and Therapy Transitions

There are no longer-term follow-up or therapy transition procedures.

7.8 Study Timetable / Schedule of Events

Table 3. Schedule of Events

Visits	V1	At Home	V2	Phone Call	Unsch	Notes
Days	D1	D1 to D5	D5	D6		
Eligibility verification	✓					
Informed Consent	✓					
Demographics / Medical History	✓					
Physical Exam	✓		✓		✓	
Vital Signs	✓				✓	

Visits	V1	At Home	V2	Phone Call	Unsch	Notes
Days	**D1**	**D1 to D5**	**D5**	**D6**		
Urine Pregnancy Test	✓					For women of child-bearing potential only
E-diary Activation	✓					
Randomization	✓					
E-diary Completion	✓	✓*	✓**			*2 times per day at the same times **On-site evaluations
Pain perception	✓	✓	✓			
Pain-relief evaluation		✓	✓			
Pain acceptable perception		✓	✓			
Rescue Medication Needed		✓	✓			
Roland-Morris Disability Questionnaire	✓		✓			
Mobility assessment	✓		✓			Schober's Test or Fingertip-to-floor test
Adverse Event assessment	✓	✓	✓	✓	✓	
Patch application / removal	✓		✓		✓	Patch(es) has(have) to be used for 5 days. • If the patch is taken-off for a safety reason, the subject has to contact the study center. • If the patch falls off, the subject has to replace it as soon as possible The subject will complete the diary card, informing about the patch replacement, the reason of change, and the time spent with no patch.
Concomitant therapies	✓	✓	✓	✓	✓	
e-diary review			✓		✓	

7.9 Study Protocol Compliance / Treatment Adherence

Subject compliance to the protocol will be defined as

- Subjects comply with study visit schedule
- Subjects complete the e-diary as instructed

Subjects will be considered compliant if they complete at least 80% of the required e-diary entries, and attend all scheduled visits. Non-complaint subjects will not be replaced. Compliance to the e-diaries does not impact the primary endpoint, as that is determined as a change from baseline.

7.10 Deviations from the Clinical Protocol

When a deviation from the protocol is identified for an individual subject, the investigator must document the deviation on a Protocol Deviation Form and contact the sponsor (or its acting representative). A description of the deviation from the protocol and justification must be recorded on the Protocol Deviation Form.

7.11 Subject Withdrawal

7.11.1 Subject Withdrawal

Subjects who withdraw (or are withdrawn) will not be replaced. Subjects may be withdrawn from the study for any of the reasons described in Section 6.4.7. Upon withdrawal, subjects will, if possible, be assessed by the Day 5 procedures for study exit. Termination of the study treatment does not affect subject safety, therefore no termination specific procedures are required. Termination of study treatment does not require any specific therapy or treatment transitions.

7.11.2 Data Collection and Follow-Up for Withdrawn Subjects

Subjects who withdraw or are withdrawn from the study will not be replaced. Data collected prior to the withdrawal will be maintained and included in the data analysis.

7.12 Subject Compensation

Subject compensation for study participation will be detailed in the Informed Consent.

8 Data Collection and Analysis

A separate Statistical Analysis Plan (SAP) will be prepared for this study which will contain a detailed description of the statistical analysis. The SAP will be approved by the sponsor and the SAP sign-off will take place before the database lock. The sections below provide an overview and summary of the analyses to be detailed in the Statistical Analysis Plan.

8.1 Subject Descriptions

The Clinical Study Report will provide data listings at a per subject level. Demographics and baseline characteristics data will be summarized and reported using descriptive statistics (means, standard deviations, and ranges for quantitative variables and frequencies and percentages for qualitative variables) for each patch group for all subjects. Prior and concomitant therapies and medications will be included in the subject data listings, and will be summarized as per randomized assignment.

Protocol deviations will be listed by subject and summarized for each patch group by deviation type. Protocol deviations will also be reviewed for trends. Endpoint data will be summarized and analyzed as described below (Section 8.3).

8.2 Subject Population(s) for Analysis

The subject populations for analysis include the following:

- The Intent-To-Treat (ITT): any subject randomized into the study, regardless of compliance with study procedures.
- Evaluable for Efficacy: any subject randomized into the study that had the NRS evaluation done at baseline and day 5.
- Safety: any subject randomized into the study and, if randomized to the "patch" arm, had the device installed.

8.3 Statistical Methods

Descriptive analyses will include summary statistics (using n, mean, standard deviation, inter quartile range, median, minimum, and maximum) for quantitative variables or number and percentage of subjects in each category for qualitative data. When requested, all statistical tests will be conducted at 2-sided using 5% alpha level. Besides, multiplicity for secondary parameters will be considered in the SAP.

8.3.1 Efficacy Analyses

8.3.1.1 Primary Analysis

Descriptive analysis will be conducted for the instantaneous pain on NRS (A Numerical Rating Scale[3]). The summary statistics will be presented for observed values at Day 5 and change from baseline to Day 5 for each group (patch, no-patch).

The rate of NRS-responders at Day 5 where NRS-response is defined as ≥ 30% decrease from baseline of the instantaneous pain and no rescue medication will be presented descriptively for each group (patch, no-patch), along with an associated 95% confidence interval.

The hypothesis that there is no difference in the rate of responders will be tested between the group with patch and no-patch group at Day 5 using Fisher's exact test and presented with its associated p-value.

8.3.1.2 Secondary Analyses

Under the secondary analyses (key and other), descriptive and inferential analysis, where applicable, will be conducted for the following:

- Normalized Sum of Pain Intensity Difference ($SPID_{0-5}$): the descriptive and inferential analyses will be conducted for Day 5.
- Roland-Morris Disability Questionnaire[5] (RMDQ) score: descriptive analysis will be conducted for the observed values at baseline and Day 5, as well as for change (improvement (%)) from baseline to Day 5. Inferential analysis will be conducted for change (improvement (%)) from baseline to Day 5.
- Mobility evaluation[6,7]: descriptive analysis will be conducted for the observed values at baseline and Day 5, as well as for change from baseline to Day 5. Inferential analysis will be conducted for change from baseline to Day 5.
- Time to reach acceptable pain and time to reach no pain: descriptive and inferential analysis will be conducted based on the data obtained in between baseline and final visit assessments.
- Normalized Sum of Pain relief ($TOTPAR_{0-5}$): the descriptive and inferential analyses will be conducted for Day 5.
- Time course of PID and time course of Pain relief (VRS): descriptive analysis will be conducted for the observed values from baseline to Day 5.
- Frequency of Adverse Events: descriptive analysis will be conducted based on the data obtained in between baseline and final visit.

The inferential analysis for the Normalized Sum of Pain Intensity Difference ($SPID_{0-5}$), Roland-Morris Disability Questionnaire[5] (RMDQ) score, Mobility evaluation[6,7] , Normalized Sum of Pain relief ($TOTPAR_{0-5}$), will be based on the analysis of covariance (ANCOVA) model with the group (patch, no-patch) as fixed effect and baseline pain intensity as a continuous covariate. The Least-Square Means, Standard Errors and 95% Confidence Intervals for each group (patch, no-patch) will be estimated and provided, along with the Least-Square Means, Standard Errors and 95% Confidence Intervals for the difference between group with patch and no-patch group. Additional effects will be added to the model in case of need.

The inferential analysis of time-to-event endpoints (time to reach acceptable pain, time to reach no pain) will include summary, display, and analysis using Kaplan-Meier estimation method. The comparison of survival distributions between the group with patch and no-patch group will be done by the Log-Rank test. During the analysis, if the event if interest never occurs, the time will be censored at the final visit.

These analyses will be based on the ITT population, using the ITT paradigm (i.e. as randomized).

8.3.1.3 Exploratory Analyses

The exploratory analyses will consist from:

- Assessing the frequency of use of Rescue Medication: descriptive analysis will be conducted for the observed values at baseline, baseline to Day 5 period and Day 5 assessments (through eDiary entries).
- Descriptions of "worst pain", "least pain" and "average pain": descriptive analysis will be conducted for the observed values at baseline, baseline to Day 5 period and Day 5 assessments, as well as for change from baseline to Day 5.

Inferential analysis for description of "worst", "least" and "average" pain will be conducted similar to secondary endpoints analysis for change from baseline at Day 5 using analysis of covariance (ANCOVA) model.

8.3.1.4 Compliance Analysis

8.3.1.4.1 eDiary Compliance (%)

Compliance will be measured based on the completion of e-Diaries. Subject will be considered as compliant if at least 80% of e-Diaries are completed, otherwise, if less than 80% of e-Diaries are completed, subject will be considered as non-compliant.

Descriptive statistics (e.g. mean, median, etc.) will be provided for the compliance (%), as well as summarized in categories: "<80%", "80% - 100%" using frequency tables. The number and percentage of compliant and non-compliant subjects will be presented as well, using the ITT paradigm (i.e. as randomized) and safety populations.

8.3.1.4.2 Patch use Compliance (Days)

Patch Use Compliance will be measured based on the number of days subject wears a patch. Subject will be considered as compliant if a patch is worn at

least for 4 days. Otherwise, if less subject wears a patch for less than 4 days, subject will be considered as non-compliant.

Descriptive analysis will be conducted for Patch Use Compliance (Days), as well as Patch Use Compliance (Days) will be summarized in categories: "1 day", "2 days", "3 days", "4 days", "5 days" and ">5 days" using frequency tables. The number and percentage of compliant and non-compliant subjects will be presented as well, using the ITT paradigm (i.e. as randomized).

8.3.1.5 Adjustments for Multiple Testing

Adjustment for multiple testing will be done as follows:

- The multiplicity of key secondary endpoints will be handled using a False Discovery Rate (FDR) approach. Nominal p-values will also be displayed.
- For the other secondary endpoints and the exploratory endpoints, p-values will be provided for descriptive purpose only.
- The number of adverse events defined as other secondary endpoint will be analyzed only with descriptive statistics (no p-value will be provided).

8.3.2 Safety Analyses

8.3.2.1 Adverse Events

Adverse events are defined as listed in Section 9.1. Adverse event reporting for the purposes of regulatory compliance is described in Section 9.4.

The Adverse Events will be summarized by frequencies and percentages of subjects with at least one AE and presented in the Clinical Study Report using the Safety population and the "as treated" paradigm (i.e. according to if they actually had a patch installed, or not).

8.3.2.2 Other Safety Analyses

Safety assessments (Vital Signs, Physical Examination, etc.), concomitant medications and procedures, will be reported using descriptive statistics, if applicable, and frequencies and percentages. The safety summaries will be based on the Safety population and under the "as treated" paradigm (i.e. according to if they actually had a patch installed, or not).

9 Safety and Adverse Events

9.1 Definitions

Standard definitions for utilization in medical device trials are provided below.

Adverse Event (AE)

Adverse Event shall mean any untoward medical occurrence in a patient who takes or uses a product, and which does not necessarily have a causal relationship with that product. An Adverse Event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease, temporally associated with the use of such a product, whether or not considered related to that product.

Serious Adverse Event (SAE)

Serious Adverse Event is any untoward occurrence occurring in a clinical trial or a performance evaluation subject to authorization which has led, could have led or could lead, directly or indirectly, to the death of a subject, a user or another person or to a serious deterioration in their state of health, without regard to whether the event was caused by the medical device.

Important medical events are events that may not be immediately life-threatening, but are clearly of major clinical significance and may be SAEs. They may jeopardize the subject, and may require intervention to prevent one or the other serious outcomes noted above.

Incident

Incident means any malfunction, failure, change in the characteristics or performance or improper labelling or instructions for use of a medical device which has led, could have led or could lead directly or indirectly to death or to a serious deterioration in the state of health of a patient, user or other person; a malfunction shall also be deemed to be a defect in usability which causes misuse.

Treatment Emergent Adverse Event (TEAE)

A treatment emergent adverse event is an event that emerges during treatment (as defined in Section 7.6), having been absent pretreatment, or worsens relative to the pretreatment state.

Hospitalization

Hospitalization shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the

preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Adverse Event Relationships to the Study Device

The relationships between adverse events and the study device will be characterized by the definitions below.

- *Unrelated:* This category applies to those adverse events which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.)
- *Possibly Related:* This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the study device administration appears unlikely but cannot be ruled out with certainty. An adverse experience may be considered possibly related if or when (at least two of the following):
  - It follows a reasonable temporal sequence from administration of the study device.
  - It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
  - It follows a known pattern of response to the study device.
- *Probably Related:* This category applies to those adverse events which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study device. An adverse experience may be considered probably related if or when (at least three of the following):
  - It follows a reasonable temporal sequence from administration of the study device.
  - It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject.
  - It disappears or decreases on cessation or reduction in device exposure. There are important exceptions when an adverse event does not disappear upon discontinuation of the device, yet device-relatedness clearly exists.
  - It follows a known pattern of response to the study device.

- *Definitely Related:* An adverse event may be considered definitely related if or when
  - The event is a known effect of the device, or procedure
  - The event follows an obvious sequence of time, from the device's implantation or activation, or procedure, for which the event is directly attributed to the administration, implantation, activation, or procedure.
  - The event ceases with discontinuation of the device, or procedure (and reoccurs on restarting).

Device Malfunction/Failure – Device Specific Events

A device specific event (DSE) is any malfunction of the device, related or not to the device, resulting or not in the subjects undergoing undesirable or harmful experience, that occurs in relation with the conduct of the study.

Device malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Refer to trouble shooting guide (to be provided by Sponsor) to identify device malfunction/failure and for subsequent steps.

Device malfunction may or may not result in the subject experiencing a harmful effect.

All AEs/SAEs associated with a device failure are by definition device related.

9.2 Safety Monitoring Plan

Procedures for ensuring subject safety are addressed throughout this protocol, and a separate Data Safety Monitoring Plan will not be required. Any incidental findings associated with clinical procedures will be provided to the subject with a recommendation for follow-up with their primary physician. The site Principal Investigator, or designee, will serve as the Emergency Medical Safety Contact for subject enrolled at that site.

9.2.1 Anticipated Risks / Risk Mitigation

The anticipated risks associated with this clinical protocol include minor skin hypersensitivity reactions such as skin irritation due to the patch adhesive. This risk is considered minor and will be assessed at patch removal and/or if the patch is removed prior to study completion. Risk is mitigated by patch removal as soon as such reactions are detected.

9.2.2 Medical Monitoring for Participant Safety

The Principal Investigator will oversee the safety of the study, including careful assessment and appropriate reporting of adverse events as outlined in Section 9.4. Medical monitoring will include a regular assessment of the number and type of serious adverse events. The Medical Monitor will be appointed by the Sponsor or the Sponsor's CRO designee.

9.3 Anticipated Adverse Events

No Serious Adverse Events are anticipated for this trial. Anticipated adverse events include minor skin irritation at the site of patch application as described above. The frequency of occurrence of skin irritation is unknown.

9.4 Adverse Event Reporting

All Adverse Events occurring during the study period must be recorded and reported to the Sponsor within 24 hours. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that study treatment or participation is not the cause.

The Investigator will promptly review documented adverse effects and abnormal test findings to determine:

1) if the abnormal test finding should be classified as an adverse effect;
2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or, if applicable, other study treatment or diagnostic product(s); and
3) if the adverse effect meets the criteria for a serious adverse effect.

If the Investigator's final determination of causality is "unknown and of questionable relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s)", the adverse effect will be classified as *associated with the use of the investigational device or study treatment or diagnostic drug product(s)* for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the investigational device or, if applicable, other study treatment or diagnostic product(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

9.4.1 Adverse Events

All observed or volunteered adverse effects and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s) will be recorded in the subjects' case histories. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit:

1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a serious adverse effect) and;

2) an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at an acceptable level.

Adverse Events that do not qualify as Serious Adverse Events, or as Unanticipated Adverse Device Effects will be reported to the Sponsor at designate interval determined by the Sponsor.

Adverse Events that do not qualify as Serious Adverse Events, or as Unanticipated Adverse Device Effects will be reported the IRB with the continuing review progress report.

9.4.2 Serious Adverse Events

Investigators must report serious adverse events to the Study Sponsor within 24 hours of learning of the event. A serious adverse event form must be completed by the Investigator and faxed to the Study Sponsor or designee within 24 hours. Study Sponsor contact information for Serious Adverse Event Notification:

ICON Clinical Research
888-723-9952 (Telephone)

At the time of the initial report, the following information should be provided:

- Study Identifier
- Study Center
- Subject Number
- Event Description
- Date of Onset
- Whether study treatment was discontinued
- Reason the event is classified as serious
- Investigator assessment of association between event and study device
- Current Status

Serious Adverse Events that are at least possibly related must be reported to the IRB/EC within 10 working days.

9.4.3 Unanticipated Adverse Device Effects (UADE)

Investigators are required to submit a report of a UADE to the Sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the event.

Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to all reviewing IRB/ECs, and participating Investigators within 10 working days after the Sponsor first receives notice of the effect.

If the Adverse Event is Serious, Unanticipated, Device Related, and determined by the Sponsor to present an unreasonable risk to subjects, the Sponsor must terminate the study within 5 working days of that determination.

10 Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the General Data Protection Requirements (GDPR). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Source Documents

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the *Source Data* recorded on the *Source Documents*.

10.3 Case Report Forms and e-diaries

The study case report form (CRF) and the e-diary are the primary data collection instruments for the study. All data requested on the CRF must be recorded. All missing data must be explained.

A Case Report Form will be completed for each subject enrolled into the clinical study. The investigator-sponsor will review, approve and sign/date each completed CRF; the investigator's signature serving as attestation of the investigator's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic. The electronic system used for data recording will provide for electronic signatures and audit traceability.

E-diaries for subject self-reported data will be maintained independent of the CRFs. E-diary information will be captured in a separate database and will be reviewed for completeness.

10.4 Clinical Reports

The clinical study reports that will be developed for this study include the Final Clinical Study Report to be submitted to governing IRB/ECs. The Sponsor will be responsible for the preparation of the final Clinical Study Report. The final Clinical Study Report will be prepared within 90 days of trial completion.

10.5 Records Retention

The investigator will retain the specified records and reports for 25 years after the completion of the study. Investigators will notify the Sponsor at least 30 days prior to any scheduled destruction of records.

11 Study Monitoring, Auditing, and Inspecting

This study will be monitored according to Good Clinical Practice guidelines. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

11.1 Study Monitoring Plan

ICON will conduct monitoring visits at study initiation, study completion, and during the study as required. During these visits the monitor/s will review all aspects of the study to ensure that the CIP and applicable regulatory requirements and ISO14155:2011 standard are adhered to. Monitoring activities will include checking CRFs and verifying data

against source documentation, reviewing ICFs, checking the Device Accountability Log, and ensuring that the Site Study File is up to date and contains all the required documentation. ICON CRAs will be contacting sites regularly to ensure continuous oversight of study process and follow-up on action items. Independent monitoring of the clinical study for clinical protocol compliance will be conducted periodically by qualified staff. In consideration of COVID-19 pandemic issues, where possible/feasible remote source data verification, remote monitoring and remote investigational site closure visits may be employed.

11.2 Auditing and Inspection

The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and institutional compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable institutional compliance and quality assurance offices.

12 Protocol Amendments After Study Initiation

Should changes in the study plan or protocol become necessary in the course of the clinical trial, those specific changes will be discussed and agreed upon by the Sponsor, its acting representative if appropriate, Investigator, and appropriate IRB/EC approval obtained before the changes are implemented. All changes must be documented as protocol amendments.

13 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice, applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board/Ethics Committee (IRB/EC), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB/EC concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the Sponsor before commencement of this study.

14 Study Finances

14.1 Funding Source

This study is funded by Sanofi Aventis Groupe.

14.2 Conflicts of Interest

Conflicts of interest or perceived conflicts of interest will be addressed in accordance with the policies of the participating institutions.

15 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

16 References

1. Guideline on the clinical development of medicinal products intended for the treatment of pain European Medicines Agency, 2016; EMA/CHMP/970057/2011
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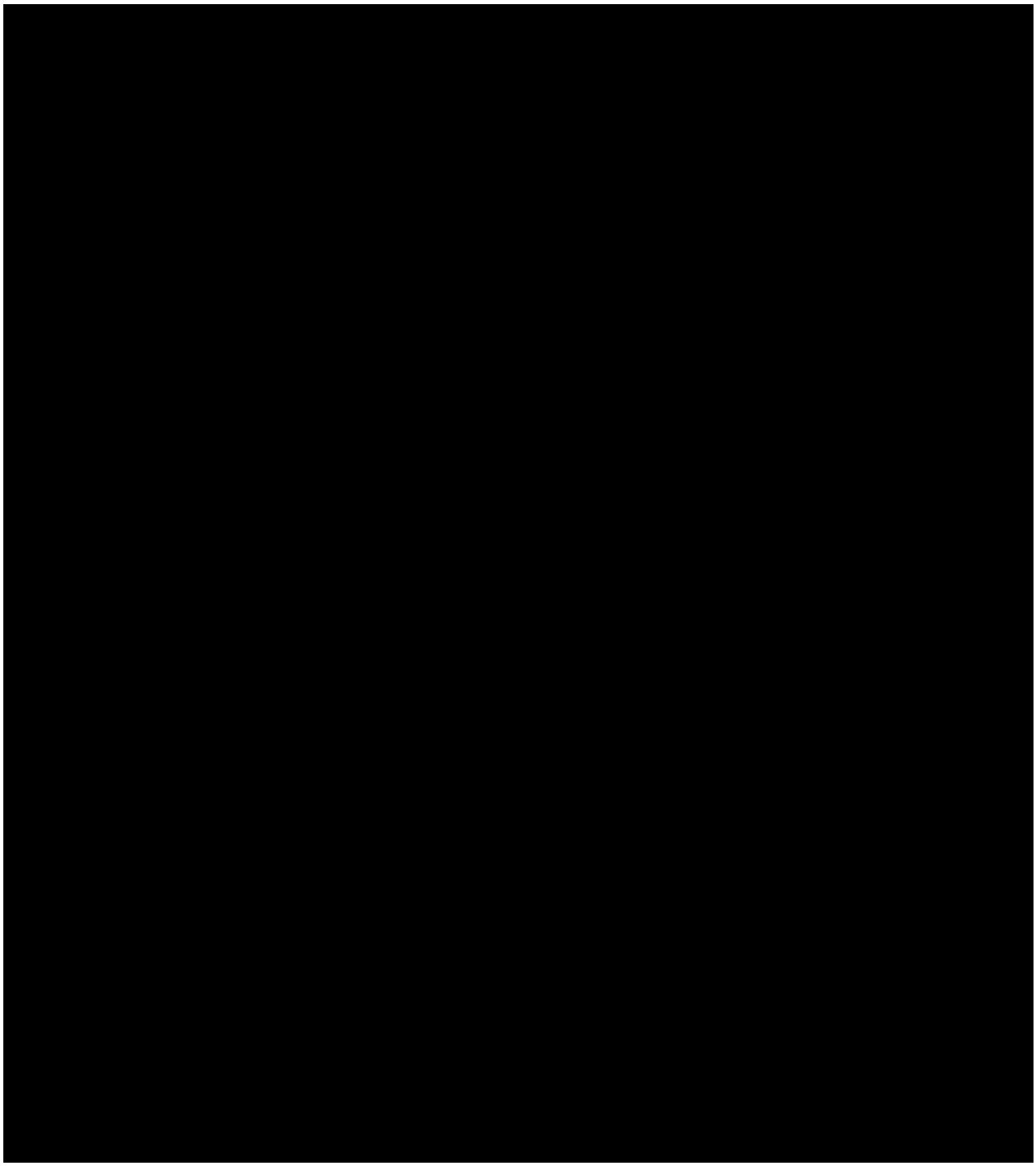
4. Dworkin RH, Turk DC, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain 2009; 146:238-244.
5. The Roland-Morris Disability Questionnaire and the Oswestry Disability Questionnaire. Spine 2000; 25: 3115-3124.
6. Schober P (1937). "Lendenwirbelsäule und Kreuzschmerzen". *Much Med Wochenschr*. **84**: 336–339.
7. Perret C, Poiraudeau S, Fermanian J, Colau MM, Benhamou MA, Revel M. Validity, reliability, and responsiveness of the fingertip-to-floor test. Archives of Physical Medicine and Rehabilitation 2001;82(11):1566-70.

17 Appendices and Attachments

17.1 Roland-Morris Low Back Pain and Disability Questionnaire

The Roland-Morris Disability Questionnaire (RMDQ) is a self-administered disability measure in which greater levels of disability are reflected by higher numbers on a 24-point scale. The RMDQ has been shown to yield reliable measurements, which are valid for inferring the level of disability, and to be sensitive to change over time for groups of subjects with low back pain.

Scoring instructions



Interpretation of scores

Roland and Morris did not provide descriptions of the varying degrees of disability (e.g. 40%-60% is severe disability). Clinical improvement over time can be graded based on the analysis of serial questionnaire scores. If, for example, at the beginning of treatment, a subject's score was 12 and, at the conclusion of treatment, their score was 2 (10 points of improvement), we would calculate an 83% (10/12 x 100) improvement.

17.2 Mobility Test

Mobility will be tested by Schober's Test or Fingertip-To-Floor Test. The choice of the test used for the mobility assessment will be done depending on the feasibility study.

SCHOBER'S TEST

Procedure

- Subject is standing, examiner marks the L5 spinous process by drawing a horizontal line across the subject's back.
- A second line is marked 10 cm above the first line.
- Subject is then instructed to flex forward as if attempting to touch his/her toes, examiner re-measures distance between two lines with subject fully flexed.

FINGERTIP-TO-FLOOR TEST [Perret 2001]

The procedure for Fingertip-to-floor (FTF) test follow the recommendation of the American Psychological Association: the subject stood erect on a platform 20-cm high with shoes removed and feet together. He/she was asked to bend forward as far as possible, while maintaining the knees, arms, and fingers fully extended. The vertical distance between the tip of the middle finger and the platform is measured with a supple tape measure and is expressed in centimeters. The vertical distance between the platform and tip of the middle finger is positive when the subject did not reach the platform and negative when he could go further.

17.3 Instructions for Patch Use

BEFORE APPLYING THE PATCH

- The patch should be applied to undamaged, clean, dry, non-oily skin.
- Too greasy or creamy skin or too much body hair can impair the adhesion of the patch. Appropriate preparation of the skin in the area of application will increase the useful life of the patch.

How to prepare the skin:

Clean the skin to remove any dirt, lotions, oils, or powders.

- Use warm water alone or with a clear soap, if possible
- Dry the skin with a clean towel or paper towel.

If you used any oily cream/ointment before (for example, a moisturizer), be sure that the skin is not oily anymore.

The area should not contain excessive hair

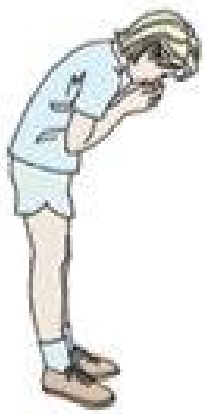
HOW TO APPLY THE PATCH

Closely follow the application instructions

Ask someone to help you apply the patch correctly, if needed

<u>STEP 1. What to take care for:</u>

- Slightly bend over to stretch the lower back skin. This increases the adherence of the patch.



STEP 2.

- Precisely locate zone for patch application as indicated on the picture: place the patch in the lower back region.

STEP 3. The application of the patch. Ask someone to help on this step

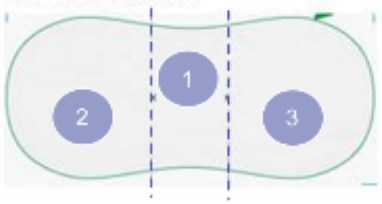
Open the package carefully and take out the patch

- Remove the **central part (1)** of the transparent protective film and place the patch in the center of the defined pain area. Press the patch firmly into place. Be careful not to touch the adhesive surface of the patch.
- Remove the **second part (2)** of the transparent protective film, stretch this side of the patch a little and immediately place it on the skin and press it firmly.

- Now remove the **last part (3)** of the transparent protective film, stretch this side of the plaster a little and immediately place it on the skin and press it firmly.

Press the patch for 30 seconds to make sure it's firmly attached to your skin: using the palm of your hand, press down firmly on the whole patch, use your fingers to press along the edges.

The patch should be smooth, with no bumps, folds or air bubbles. If the patch is not stuck well, **do not re-stick it** – use another patch instead.



AFTER APPLYING THE PATCH
Keep the patch on your skin and continue your life normally.

Patch doesn't produce any warming or cooling effect – it is non-noticeable while wearing.

Please note that even if edges start to peel off, you can still keep the patch on the skin for up to 5 days

In case the first patch falls off, apply the second patch to the same area, closely following the instructions again.

Recommendations:

- The patch is water-resistant, which means that it remains active even when it is wet. You can shower with it. After you shower, gently pat the patch dry with a towel without rubbing.
- Avoid very hot water, sauna, steam bath, bathing or swimming, as this can cause the patch to peel off.
- Avoid to wear tight clothes that can increase the risk of the patch peeling off.
- Avoid to apply any oily substance on the patch area during the time when you are wearing the patch

How to peel off the patch on Day 5:

Remove the patch by gently lifting one end and dispose as household waste. Do not reuse..

Warnings

- Store at room temperature.
- For external use only.
- Apply only to clean, dry, undamaged skin.
- Discontinue treatment in the event of evident irritation or hypersensitivity to the product.
- In case of specific blood circulation or muscular problems, seek the advice of your doctor before applying the plasters.
- Keep out of the reach of children.
- The patch should only be used by adults (> 18 years old).
- Do not use if the packaging is broken or punctured since damaged packaging could compromise efficacy and safety of the product
- Should not be used for pregnant or lactating women
- (Read the instructions for use)

[redacted]

SIGNATURE PAGE

IRPATCH Study #LPS16453; Version 4 / 22 Jul 2022