NCT05137041

STATISTICAL ANALYSIS PLAN

TITLE PAGE

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

Version 4.0: DEC 12, 2022

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DECLARATION

I, the undersigned, declare that I have prepared the statistical analysis plan along with TLF mockups and that to the best of my knowledge this document is internally consistent with protocol and scientifically rational.

Prepared by:

Signature:

Title: Senior Biostatistician

Organization: Veranex

I, the undersigned declare that I have reviewed the statistical analysis plan along with TLF mockups and that to the best of my knowledge the document is internally consistent with protocol and scientifically rational.

Reviewed by:

Signature:

Title: Project Manager

Organization: ICON plc

AUTHORIZATION: I, the undersigned, declare that I have reviewed the statistical analysis plan along with TLF mock-ups and that to the best of my knowledge the document accurately reflects the protocol objectives.

Authorized by:

Signature:

Title: Global Medical Statistician

Organization: Sanofi

REVISION HISTORY

Version	Date	Author	Reasons
1.0	**DEC 08, 2021**	[redacted]	**Initial Version.**
2.0	**SEP 12, 2022**	[redacted]	**Modification of the NRS response definition in the "Section 5.1.7.1 Primary analysis".** **Modification of the "Section 5.1.7.4.2 Use of rescue medication" to detail its definition and new protocol version with revised enrolment criteria.**
3.0	**DEC 01, 2022**	[redacted]	**Analysis Timepoints update according to the Memo to File (NTF 019 dated 22NOV2022).** **Addition of sensitivity analysis and corresponding Sensitivity Analysis Population.** **Addition of Full Analysis Set.** **Addition of MedDRA and WHO drug dictionary versions.**
4.0	**DEC 12, 2022**	[redacted]	**Modification of mITT, FAS, and Sensitivity Analysis Populations.** **Modification of the Time to Reach Acceptable Pain definition.** **Modification of Time-to-event endpoints analysis.** **Implementation of the analysis by actual treatment group for the Safety Population.**

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ANCOVA	Analysis of Covariance
CI	Confidence Intervals
CRF	Case Report Form
CTMS	Clinical Trials Management System
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
FAS	Full Analysis Set
IA	Interim Analysis
ICF	Informed Consent Form
IQR	Inter Quartile Range
ITP	Infrared Therapy Patches
ITT	Intent-to-Treat
LS Means	Least-Square Means
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NRS	Numerical Rating Scale
NTF	Note to File
PAR	Pain Relief Score
PD	Protocol Deviation
PID	Pain Intensity Difference
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RMDQ	Roland-Morris Disability Questionnaire
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model

Abbreviation or special term	Explanation
SDTMIG	Study Data Tabulation Model Implementation Guide
SE	Standard Error
SI	International System
SOC	System Organ Class
SPID	Sum of Pain Intensity Difference
TEAE	Treatment-Emergent Adverse Event
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Listings, and Figures
TOTPAR	Total Pain Relief
TTAP	Time to Reach Acceptable Pain
TTNP	Time to Reach No Pain
UADE	Unanticipated Adverse Device Effect
WHODRUG	World Health Organization Drug Dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods and data handling methods to be followed during the final reporting and analyses of data collected for the study Protocol LPS16453.

This SAP should be read in conjunction with the study protocol, case report form (CRF), e-diary Data Export Specification and corresponding Mapping Specification. This version of the plan has been developed using protocol version 4 dated 22JUL2022, CRF version 4.0 dated 30AUG2022and e-diary Data Export Specification – Lunexis Engage version 2.0 dated 26JUL2021 along with associated Mapping Specification version 2.0 dated 26JUL2021.

2 STUDY DETAILS

2.1 Study Objectives

2.1.1 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.

2.1.2 Secondary Objectives

The Secondary objectives of this study are listed below:

1. to assess the efficacy of ITP FIRTECH on the subject disability;
2. to assess the efficacy of ITP FIRTECH on the degree of subject mobility;
3. to assess the safety of ITP FIRTECH.

2.1.3 Exploratory Objectives

Exploratory objectives for this study include:

1. to assess the frequency and use of rescue medication;
2. to assess the subject evaluations of least, average, and worst pain.

2.2 Study Endpoints

2.2.1 Primary Endpoint

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).

2.2.2 Secondary Endpoints

The Secondary endpoints of this study are listed below:

1. normalized Sum of Pain Intensity Difference (PID, which equals the instantaneous NRS change from baseline) over 5 days ($SPID_{0-5}$);
2. Roland-Morris Disability Questionnaire (RMDQ) score improvement (%) from baseline to Day 5;
3. mobility evaluation: change from baseline to Day 5;
4. time to reach acceptable pain;
5. time to reach no pain (NRS = 0);
6. time course of PID over time from baseline to Day 5 on-site evaluation;
7. time course of Pain relief over time from baseline to Day 5 (VRS);
8. normalized Sum of Pain relief over 5 days ($TOTPAR_{0-5}$).

2.2.3 Exploratory Endpoints

Exploratory objectives for this study include:

1. frequency of use of rescue medication;
2. description of “worst pain” evaluation;
3. description of “least pain” evaluation;

4. description of "average pain" evaluation.

2.2.4 Safety Endpoints

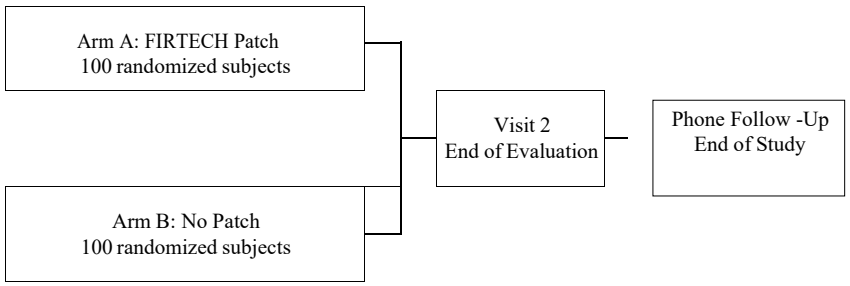
Safety endpoints will include:

1. incidence of Adverse Events;
2. incidence of Serious Adverse Events;
3. incidence of Treatment Emergent Adverse Events.

2.3 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 Centres 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 1. Details on the schedule of events are provided in Table 1.

Figure 1. Study Schema



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

Table 1. 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	✓				✓	
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			✓		✓	

2.4 Determination of 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

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.

2.5 Randomization

Subjects will be randomized 1:1 to the investigational patch and no patch arms.

2.6 Blinding

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

3 DATA ANALYSIS CONSIDERATION

3.1 General Considerations

The statistical analyses will be performed using SAS Version 9.4 (or higher). All tables, figures and listings will be produced in landscape format.

Data will be presented at each scheduled timepoint (nominal time), where applicable.

Unless otherwise specified, the baseline will be defined as the last non-missing assessment prior to patch application (FIRTECH Patch) or randomization (No Patch) at Day 1 Visit 1.

The change from baseline will be calculated as the following:

$$Change\ from\ Baseline\ =\ (Observed\ Value)\ -\ (Baseline\ Value).$$

The percent change from baseline will be calculated as the following:

$$Percent\ Change\ from\ Baseline\ (\%) = \frac{(Observed\ Value)\ -\ (Baseline\ Value)}{(Baseline\ Value)} * 100\ \%.$$

The total number of subjects in the study group (N) under the stated set of subjects will be displayed in the header of summary tables.

All study data will be included in the study data listings. Listings will be displayed by subject in chronological order, if not stated otherwise.

For tabulated summaries, only the scheduled visits will be included in the summary tables. Unscheduled assessments will be listed.

Medications will be coded with the WHO drug dictionary (WHO Drug global B3 September 2021). Medical History, Adverse Events, and Non-drug therapies will be coded using Medical Dictionary for Regulatory Activities (MedDRA, version 24.1). The dictionary versions will remain the same throughout the course of the study.

3.2 General guideline for descriptive summaries

For continuous variables, n mean, median, standard deviation, first quartile (Q1), third quartile (Q3), inter quartile range (IQR), minimum and maximum will be presented for each treatment group and category.

For categorical variables, count and % of subjects/counts in each treatment group and/or category will be presented. Percentages will be based on the number of subjects with non-missing values, if not specified otherwise.

3.3 General guideline for inferential analysis

All statistical tests will be conducted at 2-sided using 5% alpha level.

The inferential analysis of quantitative variables based on analysis of covariance (ANCOVA) model with the treatment group as fixed effect and baseline instantaneous pain NRS as a continuous covariate will be conducted with estimating and providing the Least-Square Means (LS Means), Standard Errors (SE) and 95% Confidence Intervals (CI) for each treatment group along with the LS Means, SE and 95% CI for the difference between treatment groups. Additional effects will be added to the model in case of need and described in CSR.

The inferential analysis of time-to-event endpoints will include summary, survival curves, and analysis using Kaplan-Meier estimation method. The comparison of survival distributions between treatment groups will be done by the Log-Rank test.

The inferential analysis of key secondary endpoints will be adjusted for multiplicity using a False Discovery Rate approach (Benjamini-Hochberg) within a separate analysis table that will consist nominal and adjusted p-values. Tables with original inferential key secondary analyses will be presented with the nominal p-values.

3.4 Analysis Timepoints for e-diary Questionaries

The analysis timepoints will be derived for questionaries collected via e-diary (for an extract based on Data Export Specification 2.0) as defined in Table 3.

The study day will be calculated as the following:

$$Study\ Day\ =\ (Completed\ Date) - (Randomization\ Date)\ + 1.$$

Adverse events, medication usage and patch application data collected via e-diary will not be used for analysis. Those are being transcribed by the site from the diary into the CRF database that will be used for analysis.

In consistency with Section 3.1, assessments collected at Day 1 Visit 1 will be considered as the baseline (if for FIRTECH Patch arm the assessment was done before the Patch application). Analysis timepoints “Baseline” and “Day 5 Visit 2” are derived only for on-site evaluations.

Table 3: Analysis Timepoints for eDiary

Study Day	Questionnaire Name	Analysis Timepoints
Day 1[a]	Daily Diary (Visit 1 Day 1) or Evening Daily Diary when Protocol Deviation (PD) comment completed as mentioned in the NTF number: 019, dated 22 Nov 2022 and when the associated PD occurrence date is equal to the CRF Visit 1 date.	Baseline
Day 1	Roland-Morris Disability Questionnaire	Baseline
Day 1	Evening Daily Diary	Day 1 Evening
Day 2	Morning Daily Diary	Day 2 Morning
Day 2	Evening Daily Diary	Day 2 Evening
Day 3	Morning Daily Diary	Day 3 Morning
Day 3	Evening Daily Diary	Day 3 Evening
Day 4	Morning Daily Diary	Day 4 Morning
Day 4	Evening Daily Diary	Day 4 Evening
Day 5	Morning Daily Diary	Day 5 Morning
Day 5[a]	Daily Diary (Visit 2 Day 5) or Morning Daily Diary when PD comment completed as mentioned in the NTF number: 019, dated 22 Nov 2022 and when the associated PD occurrence date is equal to the CRF Visit 2 date.	Day 5 Visit 2
Day 5	Roland-Morris Disability Questionnaire	Day 5 Visit 2

[a] According to the Memo to file "CRF Documentation of on-site Day 1 Visit 1 and Day 5 Visit 2 assessments done in the evening and in the morning respectively" (NTF number: 019, dated 22 Nov 2022) there are instances of subjects having their on-site eDiary evaluations ("Daily Diary (Visit 1 Day 1)" and/or "Daily Diary (Visit 2 Day 5)") incorrectly recorded as at-home evaluations ("Evening Daily Diary" and/or "Morning Daily Diary" respectively). Per this memo, this data issue cannot be updated at the data level. In addition to that, there were entered special documented PDs that can be considered as confirmation from the site that corresponding measurements were indeed collected on-site during the corresponding Visit 1/ Visit 2. Therefore, subjects with these specific PDs will be analyzed as one having their on-site evaluations collected with their specified eDiary records ("Evening Daily Diary" and/or "Morning Daily Diary" respectively) considered as corresponding on-site evaluations ("Daily Diary (Visit 1 Day 1)" and/or "Daily Diary (Visit 2 Day 5)"), including the derivation of baseline, populations, and Analysis Timepoints.

4 ANALYSIS POPULATION AND TREATMENT GROUPS

4.1 Analysis Populations

The following populations will be considered for the study:

4.1.1 Intent-to-Treat (ITT) Population

The ITT population will be defined as all subjects randomized. This population will be used for demographic analysis.

4.1.2 Modified Intent-to-Treat (mITT) Population

The mITT population will be defined as all subjects randomized that had the NRS evaluation done at baseline and Day 5 Visit 2 with the exclusion of subjects without any pain at baseline (i.e. baseline instantaneous pain NRS score equal to "0"). This population will be used for the primary endpoint analysis.

4.1.3 Full Analysis Set (FAS)

The FAS population will be defined as all subjects randomized that had the NRS evaluation done at baseline and that were not using any rescue medication (as defined in Section 5.1.7.4.2) starting from randomization to Day 5 Visit 2 or starting before the study and still ongoing at randomization with the exclusion of subjects without any pain at baseline (i.e. baseline instantaneous pain NRS score equal to "0"). This population will be used for key secondary, other secondary and exploratory analyses.

4.1.4 Sensitivity Analysis Population

The Sensitivity Analysis population will be defined as all subjects from the mITT population with the exclusion of subjects with protocol deviations described in the Memo to file "CRF Documentation of on-site Day 1 Visit 1 and Day 5 Visit 2 assessments done in the evening and in the morning respectively" (NTF number: 019, dated 22 Nov 2022). The algorithm for excluding subjects from this population may be expanded based on a review of analysis results and such extensions will be documented separately.

This population will be used for the sensitivity analysis of primary endpoint.

4.1.5 Safety Population

The Safety population will be defined as all subjects randomized into the study and, if randomized to the "patch" arm, had the device installed. This population will be used for partial demographic analysis and all safety analyses. Subjects will be analyzed according to the treatment actually received (i.e. as-treated).

4.2 Treatment Groups

For summary statistics, subjects will be presented by the following treatment groups:

- FIRTECH Patch – all subjects randomized to Arm A: FIRTECH Infrared Therapy Patch;
- No Patch – all subjects randomized to Arm B: No Patch.

For all analyses based on the Safety population, subjects will be presented by the specified treatment groups according to following:

- FIRTECH Patch – all subjects received the Arm A: FIRTECH Infrared Therapy Patch;
- No Patch – all randomized subjects that have not received the Arm A: FIRTECH Infrared Therapy Patch (i.e., Arm B: No Patch.).

5 ANALYSIS METHODS

5.1.1 Disposition

Disposition will be summarized descriptively using counts and percentages for All Subjects by treatment group and overall. The number and percentage of subjects screened, screen failures, randomized and completed the study will be presented, together with number and percentage of subjects who prematurely discontinued from the study along with reasons for study discontinuation will be summarized.

A listing of subject's disposition status will be provided. The number of subjects in each analysis population will be summarized descriptively with counts and percentages separately. A listing of subject's inclusion to analysis sets will be provided. A subject's eligibility with inclusion/exclusion criteria completions or violations will be listed.

5.1.2 Demography and Baseline Characteristics

Demographic data and baseline characteristics will include:

- Sex;
- Childbearing Potential;
- Age (years).

Demographics and baseline characteristics will be summarized descriptively by treatment group and overall and by protocol version (< 4.0 /4.0) and overall. Summary statistics (e.g., number of subjects, mean and standard deviation, Q1, Q3, median, IQR, minimum and maximum) will be generated for all continuous variables (i.e., age) and the number and percentage of subject within each category will be presented for all categorical variables (i.e., sex and childbearing potential). The summary results will be based on the ITT population.

5.1.3 Medical History

Medical history will be coded using MedDRA (version 24.1), listed, and summarized with descriptive statistics by System Organ Class (SOC) and Preferred Term (PT) for ITT population by treatment group and overall.

5.1.4 Pregnancy and Childbearing Potential

For female subjects, pregnancy test and/or childbearing potential will be listed for ITT population.

5.1.5 Prior and Concomitant Medications

Medications will be coded with the WHO drug dictionary (WHO Drug global B3 September 2021), listed and presented by ATC Class 2 and Preferred Term (PT) for Safety population by treatment group and overall.

If a medication cannot be found in WHO dictionary, it will be coded as "WHO Code Not Defined".

Each medication will be classified as prior, concomitant or both.

Any medication taken within 4 weeks (28 days) before the first patch application (for the FIRTECH Patch treatment group) or randomization (for the No Patch treatment group) will be considered as prior.

Any medication taken on or after the first patch application (for the FIRTECH Patch treatment group) or randomization (for the No Patch treatment group) or with a start date prior to and ongoing at the time of the first patch application (for the FIRTECH Patch treatment group) or randomization (for the No Patch treatment group) will be considered as concomitant.

In case when start/stop date is incomplete, or medication is ongoing, the following assumption will be made for Prior/Concomitant classification:

- If there is reasonable possibility that medication was taken within 4 weeks (28 days) before the first patch application (for the FIRTECH Patch treatment group) or randomization (for the No Patch treatment group), the medication will be considered as prior;
- If there is no evidence that medication was taken before the first patch application (for the FIRTECH Patch treatment group) or randomization (for the No Patch treatment group), medication will not be classified as prior;
- If there is a reasonable possibility that medication was taken on or after the first patch application (for the FIRTECH Patch treatment group) or randomization (for the No Patch treatment group) and there is no evidence that medication intake was stopped prior to, then medication will be classified as concomitant.

Prior medications will be summarized and listed with ATC Class 2 and PT for Safety population by treatment group and overall.

Concomitant medications will be summarized and listed with ATC Class 2 and PT for Safety population by treatment group and overall.

5.1.6 Protocol Deviations

Protocol deviations will be listed and summarized with descriptive statistics by Deviation Type and Deviation Sub-Type for ITT population by treatment group and overall.

5.1.7 Efficacy Analysis

5.1.7.1 Primary Analysis

Instantaneous pain on NRS will be summarized for actual values and change from baseline with descriptive statistics for the ITT and FAS populations by treatment group and by analysis timepoint (from Baseline to Day 5 Visit 2).

NRS-response will be defined as ≥30% decrease from the baseline of the instantaneous pain and no rescue medication (Section 5.1.7.4.2).

The number and percentage of NRS-responders at Day 5 Visit 2 will be presented descriptively by treatment groups, along with associated 95% confidence intervals.

The difference in the rate of responders at Day 5 Visit 2 will be tested between treatment groups using two-sided Fisher's exact test at the 5% error level (alpha = 0.05) and presented with its associated p-value. The null hypothesis H_0 that there is no difference in the rate of responders will be tested against the alternative hypothesis H_A that there is a difference in the rate of responders:

$$H_0: p_T - p_C = 0$$

$$H_A: p_T - p_C \neq 0$$

Where p_T denote the rate of responders at Day 5 Visit 2 in the FIRTECH Patch treatment group (treatment, T) and p_C denote the rate of responders at Day 5 Visit 2 in the No Patch treatment group (control, C). This analysis will be based on the mITT population.

A sensitivity analysis will be conducted by executing the primary endpoint analysis for subjects from the Sensitivity Analysis population. A list of subjects excluded from the Sensitivity Analysis population will be provided along with the reason for their exclusion.

5.1.7.2 Key Secondary Analyses

Key Secondary analyses will be based on the FAS population.

5.1.7.2.1 Normalized Sum of Pain Intensity Difference

Pain Intensity Difference (PID) will be defined as instantaneous NRS change from baseline. The Sum of Pain Intensity Difference (SPID) will be calculated by multiplying the PID score at each post-baseline analysis timepoint by the duration (in hours) since the preceding timepoint. The Normalized $SPID_{0\text{-}5}$ will be calculated as the SPID over 5 days 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 $T_0 = 0$ (baseline), T_i – actual time (hours) from T_0 and PID_i – Pain Intensity Difference score at time Ti. Pain Intensity Difference, in turn, will be calculated as: $PID_i = PI_i - PI_0$, where PI_0 - Pain Intensity at time T_0.

Normalized $SPID_{0\text{-}5}$ will be summarized with descriptive statistics for treatment groups and analyzed by ANCOVA model with the treatment group as fixed effect and baseline instantaneous pain NRS as a continuous covariate.

5.1.7.2.2 Mobility Evaluation

Mobility evaluation (Schober's Test score and Fingertip to Floor Test score) will be summarized for actual values and change from baseline with descriptive statistics by treatment group and by visit (Baseline Visit 1, Day 5 Visit 2). Change from baseline for mobility evaluation scores will be analyzed by ANCOVA model with the treatment group as fixed effect and baseline instantaneous pain NRS as a continuous covariate.

5.1.7.2.3 Roland-Morris Disability Questionnaire

Subject's Roland-Morris Disability Questionnaire (RMDQ) score will be defined as the total number of out of 24 statements from RMDQ questionary that subject marked as appropriate (result "Yes" in e-diary).

RMDQ score will be summarized for actual values and percent change from baseline with descriptive statistics by treatment group and by analysis timepoint (Baseline Visit 1, Day 5 Visit 2). Percent change from baseline for RMDQ score will be analyzed by ANCOVA model with the treatment group as fixed effect and baseline instantaneous pain NRS as a continuous covariate.

5.1.7.2.4 Time to Reach Acceptable Pain

Time to reach acceptable pain (TTAP) will be defined as the time (hours) from baseline subject symptom self-assessment date and time (Day 1 Visit 1, Pain Perception) to the first report of post-baseline acceptable pain. If that event never occurs, the time will be censored with the last response. If there are no post-baseline assessments collected, then the time will be censored with baseline subject symptom self-assessment.

TTAP will be listed and analyzed with cumulative distributions ($F(t)$) and the corresponding summaries using cumulative incidence estimates ($\widehat{F}(t) = 1 - \widehat{S}(t)$) based on the Kaplan-Meier survival estimates ($\widehat{S}(t)$). The 95% confidence limits ($\hat{F}_L(t), \hat{F}_U(t)$) for point estimates will be evaluated using 95% confidence limits for survival estimates ($\hat{S}_L(t), \hat{S}_U(t)$) as follows:

$$\hat{F}_L(t) = 1 - \hat{S}_U(t);\ \hat{F}_U(t) = 1 - \hat{S}_L(t).$$

The comparison between treatment groups will be done by the Log-Rank test.

5.1.7.2.5 Adjustments for Multiple Testing

The multiplicity of key secondary endpoints will be handled using a False Discovery Rate approach (Benjamini-Hochberg) within a separate analysis table that will consist nominal and adjusted p-values. Tables with original inferential key secondary analyses will be presented with the nominal p-values.

p-values from key secondary endpoints analyses will be interpreted in a confirmatory way only in case the primary endpoint was statistically significant. Otherwise, they will be interpreted as exploratory.

The final approach will be specified in the footnote of the table with multiplicity adjustment depending on the results of primary endpoint analysis.

5.1.7.3 Other Secondary Analyses

Other Secondary Analyses will be based on the FAS population.

5.1.7.3.1 Time to Reach No Pain

Time to reach no pain (TTNP) will be defined as the time (hours) from baseline subject symptom self-assessment date and time (Day 1 Visit 1, Pain Perception) to the first report of instantaneous pain NRS=0. If that event never occurs, the time will be censored with the last evaluation of pain perception. If there are no post-baseline assessments collected, then the time will be censored with baseline subject symptom self-assessment.

TTNP will be listed and analyzed with cumulative distributions ($F(t)$) and the corresponding summaries using cumulative incidence estimates ($\widehat{F}(t) = 1 - \widehat{S}(t)$) based on the Kaplan-Meier survival estimates ($\widehat{S}(t)$). The 95% confidence limits ($\hat{F}_L(t), \hat{F}_U(t)$) for point estimates will be evaluated using 95% confidence limits for survival estimates ($\hat{S}_L(t), \hat{S}_U(t)$) as follows:

$$\hat{F}_L(t) = 1 - \hat{S}_U(t);\ \hat{F}_U(t) = 1 - \hat{S}_L(t).$$

The comparison between treatment groups will be done by the Log-Rank test.

5.1.7.3.2 Time Course of Pain Intensity Difference

PID score will be summarized with descriptive statistics by treatment group and by analysis timepoint. Additionally, box plots of mean PID scores will be presented graphically by treatment group and by analysis timepoint. The specified figure will be supported by a corresponding summary table.

5.1.7.3.3 Time Course of Pain Relief

Pain Relief score will be summarized with descriptive statistics by treatment group and by analysis timepoint. Additionally, box plots of mean pain relief scores will be presented graphically by treatment group and by analysis timepoint. The specified figure will be supported by a corresponding summary table.

5.1.7.3.4 Normalized Sum of Pain Relief

Total pain relief (TOTPAR) will be calculated by multiplying the pain relief score (0='none', 1='slight', 2='moderate', 3='lots', 4='complete') at each post-baseline analysis timepoint by the duration (in hours) since the preceding timepoint. The Normalized Sum of Pain Relief over 5 days ($TOTPAR_{0\text{-}5}$) will be calculated as the TOTPAR 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 .

Normalized $TOTPAR_{0\text{-}5}$ will be summarized with descriptive statistics for treatment groups and analyzed by ANCOVA model with the treatment group as fixed effect and baseline instantaneous pain NRS as a continuous covariate.

5.1.7.4 Exploratory Analyses

5.1.7.4.1 Pain Perception – Average Pain, Worst Pain and Least Pain

Pain Perception, including NRS of Average Pain, Worst Pain and Least Pain, will be summarized for actual values and change from baseline with descriptive statistics for FAS population by treatment group and by analysis timepoint (from Baseline to Day 5 Visit 2).

Change from baseline for NRS of Average Pain, Worst Pain and Least Pain at Day 5 Visit 2 will be analyzed by ANCOVA model with the treatment group as fixed effect and baseline instantaneous pain NRS as a continuous covariate.

5.1.7.4.2 Use of Rescue Medication

Rescue medication will be defined as receiving paracetamol (authorized), any other analgesics and anti-inflammatory drugs as well as any non-pharmaceutical therapy (prohibited) for treating pain starting from randomization to DAY 5 Visit 2 or starting before the study and still ongoing at randomization. Each use of rescue medication will be classified according to Study Day ([Start date] – [Randomization date] + 1).

The number and percentage of subjects using rescue medication will be presented for treatment groups by Study Day (Starting from Randomization to Day 5 Visit 2, Starting before the Study and still ongoing at Randomization, Day 1, Day 2, Day 3, Day 4, Day 5) and overall.

Summary of Use of Rescue Medication will be based on the Safety population.

Additionally, all medications and non-drug treatments/procedures received on Day 6 will be listed and summarized for the Safety population.

5.1.7.5 Compliance Analysis

5.1.7.5.1 eDiary Compliance (%)

eDiary Compliance will be measured based on the number of completed e-Diaries out of 12 (10 for pain perception and 2 for RMDQ). A subject will be considered as compliant if at least 80% of eDiaries are completed, otherwise, if less than 80% of eDiaries are completed, a subject will be considered as non-compliant.

The number and percentage of compliant and non-compliant subjects will be presented along with the descriptive summary of eDiary Compliance (%) for treatment groups.

Summary of eDiary Compliance will be based on the Safety population.

5.1.7.5.2 Patch Use Compliance

Patch use compliance will be measured based on the number of days the subject wears a FIRTECH patch without reapplication (duration of wearing the patch after the first application till the first removal). Subject will be considered as patch use compliant if the first patch is worn at least for 4 days. Otherwise, subject will be considered as non-compliant.

The number and percentage of compliant and non-compliant subjects will be presented along with descriptive summary of Patch Use Compliance (Days) and number and percentage of subjects from following Patch Use Compliance categories:

- 1 day;
- 2 days;
- 3 days;
- 4 days;
- 5 days;
- > 5 days.

Summary of patch use compliance will be based on the Safety population.

5.1.8 Safety Analysis

The following variables will be evaluated to assess the safety:

- Adverse Events
- Vital Sign.
- Physical Examination

5.1.8.1 Adverse Events (AE)

All verbatim AE terms will be coded using the MedDRA (version 24.1), listed and summarized by SOC and PT for Safety Population by treatment group and overall.

Treatment-Emergent Adverse Events (TEAEs) will be defined as AEs not present prior to the first patch application (FIRTECH Patch) or randomization (No Patch), or AEs present before that worsened after the first patch application (FIRTECH Patch) or randomization (No Patch). If a partially missing date of onset allows the possibility that an AE may be a TEAE it will be presumed to be a TEAE. Unanticipated Adverse Device Effect (UADE) will be defined as any serious TEAE related to the study device.

TEAEs will be analysed by treatment group and overall. UAED will be analysed only for FIRTECH Patch treatment group.

AEs will be summarized by treatment group and overall by the number and percentage of subjects who experienced at least one AE of any of the following types: any AE, any TEAE, any device-related

TEAE, any serious TEAEs, any UADE, any SAE leading to death, any TEAE leading to study discontinuation, any serious TEAEs leading to study discontinuation.

TEAEs will be summarized by the highest relationship to study device (Related or Not Related) and maximum severity (Mild, Moderate, Severe). If the relationship of AE or TEAE to the study device is unknown, then the event will be classified as Related.

5.1.8.2 Vital Signs

Vital signs, including measurements of respiratory rate (breathes per minute), heart rate (beats per minute), temperature (Celsius), systolic and diastolic blood pressure (mmHg), will be listed and summarized for actual values and change from baseline with descriptive statistics for Safety population by treatment group and by visit (Baseline Visit 1 and Day 5 Visit 2).

5.1.8.3 Physical Examination

The physical examination will be listed and summarized for the Safety population by treatment group and overall by the number and percentage of subjects with abnormalities of the spine (lumbar lordosis, scoliosis, kyphosis, other), asymmetry and integumentary findings on the lower back (mole, scar, birth mark, discolouration, other) by visit (Baseline Visit 1 and Day 5 Visit 2).

5.1.9 Subgroup Analyses

No Subgroup analyses will be conducted in this trial.

5.1.10 Interim Analysis

No Interim analyses will be conducted in this trial.

5.1.11 Changes to Analyses Specified in Protocol

The following changes have been made to analyses specified in the protocol:

- It was specified by the protocol to use the randomization time as the starting point for time-to-event endpoints. But exact time (hours) of randomization is not collected in corresponding CRF form. Considering that, the time of the baseline subject symptom self-assessment during Day 1 (Visit 1) is used instead.
- It was specified by the protocol to compare the use of rescue medication with baseline. But according to the definition (see Section 5.1.7.4.2), there could not be a baseline rescue medication. Considering that, there is no comparison with baseline.
- It was specified by the protocol to conduct the eDiary Compliance summary in categories "<80%", "80%-100%" using frequency tables. But those are equal to the number of non-compliant (<80%) and compliant (80%-100%) subjects. Considering that, it was specified to present only the number of compliant and non-compliant subjects.

- It was specified by the protocol to use Intent-to-Treat population for Patch Use compliance analysis. In order to exclude non-treated subjects from analysis of treatment compliance, it is changed to Safety Population.
- It was specified by the protocol to use both Safety and Intent to Treat populations for eDiary Compliance analysis. Considering that there should be no major difference between those, it is decided to use only the Safety Population.
- It was specified by the protocol to analyze time-to-event endpoints by using Kaplan-Meier estimates for survival probabilities. Instead, those are analyzed with cumulative distributions by estimating cumulative incidence based on the Kaplan-Meier survival estimates. Log-Rank testing was kept without changes.

6 APPENDIX

Appendix 1: Tables, Figures and Listings

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Listing Number	Listing Title
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