Clinical trial results:
Randomized, controlled, double-blind, multi-center trial to evaluate the efficacy and safety of an Esflurbiprofen Hydrogel Patch vs. placebo in the local symptomatic and short-term treatment of pain in acute strains, sprains or bruises of the extremities following blunt trauma, e.g. sports injuries

Summary

EudraCT number	2020-005165-14
Trial protocol	DE
Global end of trial date	09 November 2021

Results information

Result version number	v1
This version publication date	07 June 2023
First version publication date	07 June 2023

Trial information

Trial identification

Sponsor protocol code	TK-254R-0201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teikoku Seiyaku Co Ltd.
Sponsor organisation address	567 Sanbonmatsu, Higashikagawa, Kagawa, Japan, 769-2695
Public contact	Elke Klimmeck, Clinsearch GmbH, 41 417116376, e.klimmeck@clinsearch.de
Scientific contact	Elke Klimmeck, Clinsearch GmbH, 41 417116376, e.klimmeck@clinsearch.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of a Esflurbiprofen 165 mg Hydrogel Patch applied once a day compared with placebo in patients with acute blunt, soft tissue injuries of the limbs.

- The primary efficacy outcome is pain-on-movement (POM) change from baseline assessed by Visual Analogue Scale (VAS) to Visit 5 (72 hours after initiating treatment).
- Important secondary efficacy outcomes are POM on VAS at Visit 2, 3, 4, 6 and 7 (12, 24, 48, 96 and 168 hours after initiating treatment).

Protection of trial subjects:

Prior to recruitment of patients, all relevant documents of the clinical study were submitted and proved by the Independent Ethics Committees (IECs) responsible for the participating investigators. Written consent documents embodied the elements of informed consent as described in the Declaration of Helsinki, the ICH Guidelines for Good Clinical Practice (GCP) and were in accordance with all applicable laws and regulations. The informed consent form and patient information sheet described the planned and permitted uses, transfers and disclosures of the patient's personal data and personal health information for purposes of conducting the study. The informed consent form and the patient information sheet further explained the nature of the study, its objectives and potential risks and benefits as well as the date informed consent was given. Before being enrolled in the clinical trial, every patient was informed that participation in this trial was voluntary and that he/she could withdraw from the study at any time without giving a reason and without having to fear any loss in his/her medical care. The patient’s consent was obtained in writing before the start of the study. By signing the informed consent, the patient declared that he/she was participating voluntarily and intended to follow the study protocol instructions and the instructions of the investigator and to answer the questions asked during the course of the trial.

Background therapy:

Rescue medication (paracetamol, 500 mg tablets, up to 3000 mg daily) was allowed during the study, except for the 6 hours prior to V5 (72 h).

Evidence for comparator:

As comparator a placebo patch was used, that did not contain the active ingredient but was otherwise indistinguishable from the investigational drug EFHP.

Actual start date of recruitment	20 May 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 200
Worldwide total number of subjects	200
EEA total number of subjects	200

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	200
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

200 male and female adult patients were screened and randomized to the study drugs "EFHP" (n=98) and "Placebo" (n=102).

Pre-assignment

Screening details:

In total 200 patients were screened.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Eligible patients were randomized to one of two treatment arms in a ratio of 1:1.

(1) Randomization data were kept strictly confidential, accessible only to authorized persons, until the time of unblinding.
(2) The identity of the treatments was concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance and odor.

Arms

Are arms mutually exclusive?	Yes
Arm title	EFHP (Test)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Esflurbiprofen 165 mg Hydrogel Patch (EFHP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Topical use

Dosage and administration details:

All patients were treated with one patch of study drug at every visit during the first 6 visits (except for Visit 2). The first five patches were applied at the study center. The site of the first application was marked with a water-resistant pen to ensure the same application site at every treatment. Additional three patches were dispensed at Visit 6. The patients were instructed to apply one patch every day at approx. the same time. Dosing times had to be distributed as evenly as possible, preferably once every 24 hours after the last application.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo patch
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

All patients were treated with one patch of study drug at every visit during the first 6 visits (except for Visit 2). The first five patches were applied at the study center. The site of the first application was marked with a water-resistant pen to ensure the same application site at every treatment. Additional three patches were dispensed at Visit 6. The patients were instructed to apply one patch every day at approx. the same time. Dosing times had to be distributed as evenly as possible, preferably once every

24 hours after the last application.

Number of subjects in period 1	EFHP (Test)	Placebo
Started	98	102
Completed	98	102

Baseline characteristics

Reporting groups	
Reporting group title	EFHP (Test)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	EFHP (Test)	Placebo	Total
Number of subjects	98	102	200
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	98	102	200
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	33.2	34.3	
standard deviation	± 11.0	± 10.8	-
Gender categorical Units: Subjects			
Female	43	55	98
Male	55	47	102

Subject analysis sets	
Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set included all randomized patients who received at least one dose of the study drug. Safety was analyzed in this population.

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set was all randomized patients who received at least one dose of study drug. The FAS population was primary population for the analysis of efficacy. Any exclusions from the FAS population were made and documented before unblinding (e.g. never used study medication, randomized twice). Additional secondary populations might be defined before unblinding and were described in detail in the SAP. The Intention to treat (ITT) population was identical to the Full Analysis Set (FAS).

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

The Per protocol population included all patients who are randomized to the clinical trial, satisfied all of

the inclusion/exclusion criteria, received the correct IMP (as randomized), had efficacy data at the 72 hours assessment, with an adhesion score of 0, 1, 2, had taken no pain medication and had no other major protocol violations as defined during a blinded review meeting. Only the outcomes relating to the ankle POM by VAS were analyzed using this clinical trial population.

Reporting group values	SAF	FAS	PP
Number of subjects	200	200	196
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	200	200	196
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	33.7	33.7	33.9
standard deviation	± 10.9	± 10.9	± 10.9
Gender categorical Units: Subjects			
Female	98	98	97
Male	102	102	99

End points

End points reporting groups

Reporting group title	EFHP (Test)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	SAF
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety set included all randomized patients who received at least one dose of the study drug. Safety was analyzed in this population.	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set was all randomized patients who received at least one dose of study drug. The FAS population was primary population for the analysis of efficacy. Any exclusions from the FAS population were made and documented before unblinding (e.g. never used study medication, randomized twice). Additional secondary populations might be defined before unblinding and were described in detail in the SAP. The Intention to treat (ITT) population was identical to the Full Analysis Set (FAS).	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per protocol population included all patients who are randomized to the clinical trial, satisfied all of the inclusion/exclusion criteria, received the correct IMP (as randomized), had efficacy data at the 72 hours assessment, with an adhesion score of 0, 1, 2, had taken no pain medication and had no other major protocol violations as defined during a blinded review meeting. Only the outcomes relating to the ankle POM by VAS were analyzed using this clinical trial population.	

Primary: Pain-on-movement (baseline vs. V5)

End point title	Pain-on-movement (baseline vs. V5)
End point description:	
End point type	Primary
End point timeframe:	
V1 (baseline) vs. V5	

End point values	EFHP (Test)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	102		
Units: mm				
arithmetic mean (standard deviation)	-50.7 (± 11.1)	-21.6 (± 11.9)		

Statistical analyses

Statistical analysis title	Change "POM on VAS" from baseline
Comparison groups	EFHP (Test) v Placebo

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	> 0.0001
Method	ANCOVA
Parameter estimate	Treatment effect
Point estimate	-29.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.2
upper limit	-26
Variability estimate	Standard deviation

Notes:
[1] - proof-of-concept

Secondary: Pain-on-movement (baseline vs. V2)

End point title	Pain-on-movement (baseline vs. V2)

End point description:

End point type	Secondary

End point timeframe:
V1 (baseline) vs. V2

End point values	EFHP (Test)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	102		
Units: mm				
arithmetic mean (standard deviation)	-8.8 (± 7.4)	-3.6 (± 3.7)		

Statistical analyses

Statistical analysis title	Change "POM on VAS" from baseline
Comparison groups	EFHP (Test) v Placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment effect
Point estimate	-5.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	-3.7
Variability estimate	Standard deviation

Notes:
[2] - proof-of-concept

Secondary: Pain-on-movement (baseline vs. V3)

End point title	Pain-on-movement (baseline vs. V3)

End point description:

End point type	Secondary

End point timeframe:
V1 (baseline) vs. V3

End point values	EFHP (Test)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	102		
Units: mm				
arithmetic mean (standard deviation)	-21.1 (± 11.0)	-7.2 (± 6.3)		

Statistical analyses

Statistical analysis title	Change "POM on VAS" from baseline
Comparison groups	EFHP (Test) v Placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment effect
Point estimate	-13.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.3
upper limit	-11.4
Variability estimate	Standard deviation

Notes:
[3] - proof-of-concept

Secondary: Pain-on-movement (baseline vs. V4)

End point title	Pain-on-movement (baseline vs. V4)

End point description:

End point type	Secondary

End point timeframe:
V1 (baseline) vs. V4

End point values	EFHP (Test)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	102		
Units: mm				
arithmetic mean (standard deviation)	-36.6 (± 11.1)	-13.4 (± 8.3)		

Statistical analyses

Statistical analysis title	Change "POM on VAS" from baseline
Comparison groups	EFHP (Test) v Placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment effect
Point estimate	-23.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.8
upper limit	-20.5
Variability estimate	Standard deviation

Notes:
[4] - proof-of-concept

Secondary: Pain-on-movement (baseline vs. V6)

End point title	Pain-on-movement (baseline vs. V6)

End point description:

End point type	Secondary

End point timeframe:
V1 (baseline) vs. V6

End point values	EFHP (Test)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	102		
Units: mm				
arithmetic mean (standard deviation)	-60.7 (± 10.4)	-32.7 (± 14.7)		

Statistical analyses

Statistical analysis title	Change "POM on VAS" from baseline
Comparison groups	EFHP (Test) v Placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment effect
Point estimate	-28.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.5
upper limit	-24.6
Variability estimate	Standard deviation

Notes:
[5] - proof-of-concept

Secondary: Pain-on-movement (baseline vs. V7)

End point title	Pain-on-movement (baseline vs. V7)

End point description:

End point type	Secondary

End point timeframe:
V1 (baseline) vs. V7

End point values	EFHP (Test)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	102		
Units: mm				
arithmetic mean (standard deviation)	-67.9 (± 8.7)	-50.6 (± 17.9)		

Statistical analyses

Statistical analysis title	Change "POM on VAS" from baseline
Comparison groups	EFHP (Test) v Placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment effect
Point estimate	-17.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.9
upper limit	-13.9
Variability estimate	Standard deviation

Notes:

[6] - proof-of-concept

Secondary: Patch adhesion assessment (12h)

End point title	Patch adhesion assessment (12h)

End point description:

End point type	Secondary

End point timeframe:

12-h-application (Visit 2)

End point values	EFHP (Test)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	102		
Units: percent				
number (not applicable)				
Completely detached (4)	1.0	0		
≥ 0 % to < 50 % adhered (3)	0	3.9		
≥ 50 % to < 75 % adhered (2)	23.5	26.5		
≥ 75 % to < 90 % adhered (1)	46.9	50.0		
≥ 90 % adhered (0)	28.6	19.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Patch adhesion assessment (24h)

End point title	Patch adhesion assessment (24h)

End point description:

End point type	Secondary

End point timeframe:

24-h-applications (Visits 3, 4, 5, 6, 7)

End point values	EFHP (Test)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	102		
Units: percent				
number (not applicable)				
Completely detached (4)	0	0.2		
≥ 0 % to < 50 % adhered (3)	2.0	2.0		
≥ 50 % to < 75 % adhered (2)	20.6	28.4		
≥ 75 % to < 90 % adhered (1)	41.2	40.4		
≥ 90 % adhered (0)	36.1	29.0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
The observation phase for AEs began with the start of the treatment (i.e. 1st administration of IMP) and ended with the discharge of the patient from the clinical trial	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	EFHP (Test)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	EFHP (Test)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 98 (0.00%)	0 / 102 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	EFHP (Test)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 98 (1.02%)	1 / 102 (0.98%)	
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 98 (0.00%)	1 / 102 (0.98%)	
occurrences (all)	0	1	
Infections and infestations			
Oropharyngeal pain			
subjects affected / exposed	1 / 98 (1.02%)	0 / 102 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 102 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: