Clinical trial results:
A randomised, multicentre, open-label, cross-over study to investigate the efficacy and safety of Keplat® and Flector® patch in patients with pain caused by Osteoarthritis of the knee

Summary

EudraCT number	2013-000334-36
Trial protocol	HU
Global end of trial date	14 March 2014

Results information

Result version number	v1 (current)
This version publication date	19 April 2020
First version publication date	19 April 2020

Trial information

Trial identification

Sponsor protocol code	Keplat-HU01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sager Pharma Ltd.
Sponsor organisation address	Pasaréti út 122-124, Budapest, Hungary, H-1026
Public contact	Rudolf M. Tubbeh, Sager Pharma Ltd., rudy.tubbeh@sagerpharma.hu
Scientific contact	Rudolf M. Tubbeh, Sager Pharma Ltd., rudy.tubbeh@sagerpharma.hu
Sponsor organisation name	Hisamitsu UK Ltd.
Sponsor organisation address	500 Chiswick High Road, London, United Kingdom, W5RG
Public contact	Ventsislav Kelchev, Hisamitsu UK Ltd., kelchev@hisamitsu.co.uk
Scientific contact	Ventsislav Kelchev, Hisamitsu UK Ltd., kelchev@hisamitsu.co.uk

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	31 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 March 2014
Global end of trial reached?	Yes
Global end of trial date	14 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to compare effectiveness of Keplat and Flector patches in the treatment of osteoarthritis of the knee. Following evaluations are made:
- The pain VAS score of target knee
- The tenderness of the knee
- Swelling of the knee
- Amount of paracetamol tablets
- The Patient's Global assessment
- Investigator's Global Assessment

Protection of trial subjects:

The Investigator or a person designated by the Investigator did thoroughly explain the purpose and method of the study as well as any expected effects and adverse reactions to the patient before any study specific screening procedures were conducted. The patient were provided with an information sheet and given sufficient time and opportunity to enquire about the details of the trial and to decide whether or not they wished to participate in the study. The patient and the person with whom they discussed the informed consent signed and dated the consent form.
The Investigator or a person designated by the Investigator explained that the patient was completely free to refuse to enter the study or to withdraw either spoken or written from it at any time and for any reason. Similarly, the Investigator and/or Sager Pharma were free to withdraw the patient at any time for safety reasons. Any other requirements necessary for the protection of the human rights of the patient were also explained.

Background therapy:

Oral paracetamol was used as rescue medication
One tablet of Paracetamol contained 500mg acetaminophen that was manufactured according to the principles of GMP. Paracetamol was obtained from Hungarian market.

Evidence for comparator:

Flector® patch was used as a comparator.
Flector® was 10 cm x 14 cm in dimension. The dose of diclofenac epolamine was 1.30% (w/w, excluding the backing material). The sticky side of the patch was applied to a clean, dry skin at the treatment site twice a day in the morning and evening.
Flector® was manufactured according to the principles of GMP by Teikoku Seiyaku, in Kagawa, Japan.
Flector® was obtained from Hungarian market.

Actual start date of recruitment	25 June 2013
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	Hungary: 108
Worldwide total number of subjects	108
EEA total number of subjects	108

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)	88
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled between June 2013-Mar 2014, in 5 trial centers in Hungary.

Pre-assignment

Screening details:

Main inclusion criteria:
1. Male or female out-patients aged 45 years and older;
2. Unilateral or bilateral Osteoarthritis of the knee;
3. Oral NSAIDs or Paracetamol or other analgesics on a regular basis;
4. Pain intensity at least 55 mm or more on the 100mm VAS at screening
110 patients were screened, 108 treated, 103 completed the study.

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

NA

Arms

Are arms mutually exclusive?	Yes
Arm title	Keplat

Arm description:

Treated with Keplat patch for 1 week.

Arm type	Experimental
Investigational medicinal product name	Keplat
Investigational medicinal product code	M02AA10
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

20 mg milligram(s) per day, transdermal use, applied once daily.

Arm title	Flector

Arm description:

Flector®: Patch containing 1.30% (w/w, excluding the backing material) Diclofenac epolamine (14 cmx 10 cm), twice daily, considered upon the timing of bathing, showering or washing for the week. One patch was applied topically to the skin on one painful area.

Arm type	Active comparator
Investigational medicinal product name	Flector
Investigational medicinal product code	M02AA15
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Flector®: Patch containing 1.30% (w/w, excluding the backing material) Diclofenac epolamine (14 cm x 10 cm), twice daily, considered upon the timing of bathing, showering or washing for the week. One patch was applied topically to the skin on one painful area.

Number of subjects in period 1	Keplat	Flector
Started	54	54
Completed	53	53
Not completed	1	1
Adverse event, non-fatal	1	1

Period 2

Period 2 title	Washout
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:
Paracetamol treatment only

Arms

Arm title	All patients

Arm description:
Paracetamol treatment only

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	All patients
Started	106
Completed	105
Not completed	1
Adverse event, non-fatal	1

Period 3

Period 3 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:
Open-label

Arms

Are arms mutually exclusive?	Yes

Arm title	Arm 1

Arm description:

Flector

Arm type	Experimental
Investigational medicinal product name	Flector
Investigational medicinal product code	M02AA15
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Flector®: Patch containing 1.30% (w/w, excluding the backing material) Diclofenac epolamine (14 cm x 10 cm), twice daily, considered upon the timing of bathing, showering or washing for the week. One patch was applied topically to the skin on one painful area.

Arm title	Arm 2

Arm description:

Keplat

Arm type	Experimental
Investigational medicinal product name	Keplat
Investigational medicinal product code	M02AA10
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

20 mg milligram(s) per day, transdermal use, applied once daily.

Number of subjects in period 3	Arm 1	Arm 2
Started	53	52
Completed	53	52

Period 4

Period 4 title	Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

NA

Arms

Arm title	All patients
Arm description: Follow-up	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 4	All patients
Started	105
Completed	105

Baseline characteristics

Reporting groups	
Reporting group title	Period 1

Reporting group description: -

Reporting group values	Period 1	Total	
Number of subjects	108	108	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age was collected at visit 1. Descriptive statistics tables were performed.			
Units: years			
arithmetic mean	62.5		
standard deviation	± 9.2	-	
Gender categorical			
Gender (man or woman) was discrete variable. Descriptive statistics was performed.			
Units: Subjects			
Female	88	88	
Male	20	20	
Height			
Height values were collected at visit 1. Descriptive statistics tables were performed.			
Units: cm			
arithmetic mean	164.14		
standard deviation	± 8.43	-	
Weight			
Weight values were collected at visit 1. Descriptive statistics tables were performed			
Units: kg			
arithmetic mean	77.12		
standard deviation	± 12.55	-	
Pain VAS			
Pain VAS values at V1			
Units: NA			
arithmetic mean	74.9		
standard deviation	± 9.5	-	

End points

End points reporting groups

Reporting group title	Keplat
Reporting group description:	
Treated with Keplat patch for 1 week.	
Reporting group title	Flector
Reporting group description:	
Flector®: Patch containing 1.30% (w/w, excluding the backing material) Diclofenac epolamine (14 cmx 10 cm), twice daily, considered upon the timing of bathing, showering or washing for the week. One patch was applied topically to the skin on one painful area.	
Reporting group title	All patients
Reporting group description:	
Paracetamol treatment only	
Reporting group title	Arm 1
Reporting group description:	
Flector	
Reporting group title	Arm 2
Reporting group description:	
Keplat	
Reporting group title	All patients
Reporting group description:	
Follow-up	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
PP group included all randomized and completed patient without major protocol deviation (a total of 101 patients). Subgroup for “carry-over effect”: when the difference of patient VAS data between V4 and V2 exhibited more than 30mm, the patient was excluded from this population.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT group included all subjects planned to be treated (all randomized patients). Drop-out patients, patients with missing data or patient with major protocol deviation were included in the analysis (a total of 108 patients).	

Primary: Change in VAS score

End point title	Change in VAS score
End point description:	
Treatment efficacy (change in VAS between the treatments): in case of Keplat®: 24.7 mm, in case of Flector®: 23.6 mm. In total, there was 1.1 mm difference between the treatments in favour of Keplat®, but it was not significant.	
End point type	Primary
End point timeframe:	
Change V2 vs. V3 and V4 vs. V5	

End point values	Keplat	Flector		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	49		
Units: mm				
arithmetic mean (standard deviation)	-25.2 (± 24.1)	-23.2 (± 22.6)		

Statistical analyses

Statistical analysis title	Treatment efficacy comparing the treatments

Statistical analysis description:

Cross-over statistics was performed by Generalized Linear model (GLM). The sequence, patients, period and treatment effects were incorporated in the model. For residual effects, thevariables measured at start of treatments were considered as covariates. Test of Hypotheses using the Type III MS for subj(seq) as an Error Term we adapted in GLM procedure.

Comparison groups	Keplat v Flector
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	generalised Linear Model

Notes:

[1] - Statistics was performed in aspect the superiority of the Keplat® as it was described in statistical analysis plan; however in the study protocol this was not exactly defined. According study protocol 10 mm of VAS value
difference was expected between the Keplat® and Flector®.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: V1-V6	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0
Reporting groups	
Reporting group title	Safety population
Reporting group description: SF group included all subjects who apply at least 1 patch during the study (a total of 108 patients).	

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 108 (0.93%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Ileus	Additional description: Reported as severe abdominal pain in the initial report. Event occured during wash-out phase.		
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 108 (3.70%)		
Gastrointestinal disorders			
Gastroenteritis	Additional description: Mild, no relationship. Event occured during Keplat treatment.		
subjects affected / exposed	1 / 108 (0.93%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis contact	Additional description: Mild, probable relationship. Event occured during Flector treatment.		

subjects affected / exposed	1 / 108 (0.93%)		
occurrences (all)	1		
Dyshidrotic eczema	Additional description: Mild, no relationship. Event occured during wash-out period.		
subjects affected / exposed	1 / 108 (0.93%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Joint injury	Additional description: Moderate, no relationship. Event occured during wash-out period.		
subjects affected / exposed	1 / 108 (0.93%)		
occurrences (all)	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

None reported