# 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:<br>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<br>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