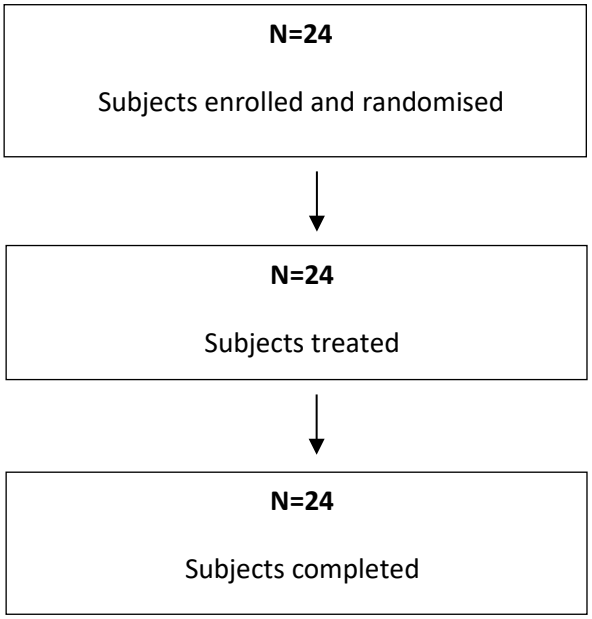
**Participant flow**



## Baseline characteristics

| Demographic data | Enrolled set N=24 |
|---|---|
| **Sex** | |
| Female – n (%) | 13 (54.2 %) |
| Male – n (%) | 11 (45.8 %) |
| **Age (years)** | |
| Mean ± SD | 40.1±9.9 |
| Median (range) | 42.0 (21 – 55) |
| **Body weight (kg)** | |
| Mean ± SD | 66.55±12.78 |
| Median (range) | 63.75 (45.1 – 96.9) |
| **Height (cm)** | |
| Mean ± SD | 169.8±9.2 |
| Median (range) | 170.0 (155 – 187) |
| **Body Mass Index (kg/m$^2$)** | |
| Mean ± SD | 22.95±3.09 |
| Median (range) | 22.10 (18.5 – 29.6) |
| **Race** | |
| White – n (%) | 23 (95.8 %) |
| Asian – n (%) | 1 (4.2 %) |

## Outcome measures

### Analysis of plasma diclofenac after single application

Main diclofenac plasma PK parameters after single application of DHEP 2.6% (T) and DHEP 1.3% (R). N=24.

| **Diclofenac PK parameters** | **DHEP 2.6% (T) N=24** | **DHEP 1.3% (R) N=24** |
|---|---|---|
| **$C_{max0\text{-}24h(SD)}$ (ng/mL)** | 5.72±3.88 | 3.97±2.68 |
| **$C_{24h(SD)}$ (ng/mL)** | 5.53±3.73 | 3.80±2.68 |
| **$t_{max0\text{-}24h(SD)}$ (h)** | 24.00 (12.50 – 24.00) | 22.50 (15.00 – 24.00) |
| **$C_{max0\text{-}12h(SD)}$ (ng/mL)** | -- | 2.65±1.66 |
| **$C_{12h(SD)}$ (ng/mL)** | 3.98±3.13 | 2.64±1.65 |
| **$t_{max0\text{-}12h\ (SD)}$ (h)** | -- | 12.00 (9.00 – 12.00) |
| **$AUC_{0\text{-}24h}$ (ng/mL×h)** | 79.55±59.51 | 54.05±35.25 |
| **$AUC_{0\text{-}12h\ (SD)}$ (ng/mL×h)** | -- | 16.23±11.68 |

*Values are arithmetic means ± SD, except for $t_{max}$: median (min-max)*

Outcome of the statistical test of diclofenac plasma PK parameters after single application of DHEP 2.6% (T) and DHEP 1.3% (R). N = 24.

| **Treatment comparison** | **Parameter** | **PE%** | **90% CI** |
|---|---|---|---|
| T *vs.* R | **$C_{max0\text{-}24h(SD)}$** | 135.16% | 117.80 – 155.07 |
| | **$AUC_{0\text{-}24h}$** | 129.25% | 112.79 – 148.10 |
| | | **Wilcoxon signed rank test p-value** | |
| | **$t_{max0\text{-}24h(SD)}$** | 0.1240 | |

*PE: Point estimate, calculated as ratio of geometric means; CI: confidence interval*

**Analysis of plasma diclofenac after multiple applications**

Main diclofenac plasma PK parameters after multiple applications of DHEP 2.6% once a day (T) and DHEP 1.3% twice a day (R). N=24.

| **Diclofenac PK parameters** | **DHEP 2.6% o.d. (T) N=24** | **DHEP 1.3% b.i.d. (R) N=24** |
|---|---|---|
| **$C_{max0\text{-}24h(RD)}$ (ng/mL)** | 5.63±2.72 | 4.34±2.11 |
| **$C_{24h(RD)}$ (ng/mL)** | 4.50±2.28 | -- |
| **$t_{max0\text{-}24h(RD)}$ (h)** | 4.00 (0.00 – 24.00) | 4.00 (4.00 – 24.00) |
| **$C_{max0\text{-}12h(RD)}$ (ng/mL)** | -- | 4.10±1.95 |
| **$C_{12h(RD)}$ (ng/mL)** | -- | 3.01±1.45 |
| **$t_{max0\text{-}12h\ (RD)}$ (h)** | -- | 4.00 (0.00 – 12.00) |
| **$C_{min0\text{-}24h}$ (ng/mL)** | 3.26±1.62 | 2.37±1.26 |
| **$C_{min0\text{-}12h}$ (ng/mL)** | -- | 2.62±1.34 |
| **$C_{ave0\text{-}24h}$ (ng/mL)** | 4.27±1.98 | 3.30±1.60 |
| **$C_{ave0\text{-}12h}$ (ng/mL)** | -- | 3.27±1.59 |
| **$Flu_{(0\text{-}24h)}$ (%)** | 55.61±10.82 | 60.75±18.43 |
| **$AUC_{0\text{-}24h(RD)}$ (ng/mL×h)** | 102.39±47.60 | 79.24±38.37 |
| **$AUC_{0\text{-}12h\ (RD)}$ (ng/mL×h)** | -- | 39.19±19.03 |

*Values are arithmetic means ± SD, except for $t_{max}$: median (min-max)*

Outcome of the statistical test of diclofenac plasma PK parameters after multiple applications of DHEP 2.6% once a day (T) and DHEP 1.3% twice a day (R). N=24.

| **Treatment comparison** | **Parameter** | **PE%** | **90% CI** |
|---|---|---|---|
| T *vs.* R | **$C_{max0\text{-}24h(SD)}$** | 127.13% | 114.36 – 141.33 |
| | **$AUC_{0\text{-}24h}$** | 127.24% | 116.37 – 139.14 |
| | | **Wilcoxon signed rank test p-value** | |
| | **$t_{max0\text{-}24h(SD)}$** | 0.3252 | |

*PE: Point estimate, calculated as ratio of geometric means; CI: confidence interval*

## Adverse events

Overview of TEAEs: number of TEAEs and number of subjects with TEAEs. Safety set

| Category | DHEP 2.6% o.d. (T) N=24 | | DHEP 1.3% b.i.d. (R) N=24 | | Overall N=24 | |
|---|---|---|---|---|---|---|
| | N AEs | n (%) subjects | N AEs | n (%) subjects | N AEs | n (%) subjects |
| All TEAEs | 4 | 4 (16.7) | 1 | 1 (4.2) | 5 | 5 (20.8) |
| Related | 3 | 3 (12.5) | 0 | 0 (0.0) | 3 | 3 (12.5) |
| Not related | 1 | 1 (4.2) | 1 | 1 (4.2) | 2 | 2 (8.3) |
| Leading to discontinuation | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) |
| SAEs | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) |

Number of subjects reporting and number of reported TEAEs by treatment, system organ class (SOC) and preferred term (PT). Safety set

| MedDRA description SOC and PT term | DHEP 2.6% o.d. (T) N=24 | | DHEP 1.3% b.i.d. (R) N=24 | |
|---|---|---|---|---|
| | AEs n | Subjects n (%) | AEs n | Subjects n (%) |
| **Total number of AEs and of subjects with at least one AE** | **4** | **4 (16.7)** | **1** | **1 (4.2)** |
| **General disorders and administration site conditions** | **2** | **2 (8.3)** | **1** | **1 (4.2)** |
| Application site erythema | 2 | 2 (8.3) | 0 | 0 |
| Influenza like illness | 0 | 0 | 1 | 1 (4.2) |
| **Nervous system disorders** | **1** | **1 (4.2)** | **0** | **0** |
| Headache | 1 | 1 (4.2) | 0 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | **1** | **1 (4.2)** | **0** | **0** |
| Oropharyngeal pain | 1 | 1 (4.2) | 0 | 0 |