

## **Comparative Clinical Trial**

# **Efficacy of Two Cryotherapy Devices in Common and Plantar Warts Management (STUDY No. 14E2344)**

October 2016

# Table of Contents

|                            |    |
|----------------------------|----|
| Background .....           | 3  |
| Clinical trial.....        | 3  |
| Study design .....         | 3  |
| Test devices.....          | 3  |
| Study population.....      | 3  |
| Clinical endpoints.....    | 4  |
| Safety evaluation.....     | 6  |
| Statistical analyses ..... | 6  |
| Analysis populations ..... | 6  |
| General methods.....       | 6  |
| Results .....              | 7  |
| Patient disposition .....  | 7  |
| Wart characteristics ..... | 7  |
| Safety.....                | 14 |
| Conclusion.....            | 14 |
| References.....            | 15 |

## Background

A wart is skin growth, caused by some types of the human papillomavirus (HPV). These viruses infect the top layer of skin, usually by entering the body in an area of broken skin. As a consequence, the top layer of skin starts to grow rapidly, forming a wart. Warts can grow anywhere on the body. Common warts mostly grow often on the hands, but can grow anywhere. Plantar warts grow on the soles of the feet.

Half of common warts disappear within a year and 75% within 2 years. Plantar warts also often disappear but more slowly. Treatment may be considered if a wart is painful, unsightly, exposed to trauma, or superinfected. Cryotherapy works by taking advantage of the destructive force of freezing temperatures on cells. When cell temperature sinks beyond a certain level, ice crystals begin forming inside the cells and, because of their lower density, eventually tear apart those cells. Cryotherapy inflicts irreversible damage to the cell membranes of the HPV affected cells by freezing the infected tissue.

The resulting local inflammation then leads to the development of an effective cell-mediated immune response. Cryotherapy typically uses liquids boiling at temperatures below the freezing point of water such as liquid nitrogen (-196°C), nitrous oxide (-88°C), carbon dioxide (-78°C), or mixtures of dimethyl ether and propane (DME/P) (-57°C) to generate cold by the Joule-Thomson effect.

## Clinical trial

Detailed information on this comparative study is presented in the protocol 14E2344 (23/03/2016). A summary of the set-up is described below.

### Study design

This study is an open label, evaluator blinded trial to evaluate the efficacy of Pixie<sup>®</sup> versus Wartner<sup>®</sup> for the treatment of common and plantar warts.

### Test devices

The test device, Pixie<sup>®</sup> cryogenic pen, is an innovative, safe and highly effective way to treat warts. The Pixie<sup>®</sup> pen contains liquefied nitrous oxide which upon expansion, freezes the tip of the device to -80°C (or even lower). The device is then kept in contact with the wart for the prescribed time: 15 seconds for hand warts, 40 seconds for foot warts. Pixie<sup>®</sup> can be used on adults and children to treat warts on the hands and feet, including the soles and bottom of toes. The comparator product, Wartner<sup>®</sup> cryogenic pen, uses a mixture of dimethyl ether and propane (DME/P) to freeze warts (-57°C).

### Study population

Patients enrolled in the study were subjects with common and plantar warts. Briefly, 98 subjects with warts were treated with Pixie<sup>®</sup> cryogenic pen (N=58) and comparator product Wartner<sup>®</sup> cryogenic pen (N=40). All participants received maximum three treatments. Participants were monitored for different clinical parameters after each treatment until they were cured.

## Clinical endpoints

### Primary efficacy endpoints

The primary parameter to assess clinical efficacy of Pixie® versus Wartner® was the number of treatments, needed until cured. In addition, product efficacy was evaluated by the investigator using five categories, as shown in table 1.

**TABLE 1: EVALUATION OF PRODUCT EFFICACY FOLLOWING CRYOGENIC PEN TREATMENT.**

| Score | Efficiency           |
|-------|----------------------|
| 1     | Not efficient        |
| 2     | Rather not efficient |
| 3     | Rather efficient     |
| 4     | Efficient            |
| 5     | Very efficient       |

### Secondary efficacy endpoint

The secondary parameters that were evaluated by a treatment blinded dermatologist were the diameter and roughness of the wart. Scoring is performed as shown in table 2.

**TABLE 2: EVALUATION OF WART ROUGHNESS FOLLOWING CRYOGENIC PEN TREATMENT.**

| Score | Wart roughness |
|-------|----------------|
| 0     | None           |
| 1     | Light          |
| 2     | Moderate       |
| 3     | Severe         |
| 4     | Very severe    |

In addition, the thickness of the wart was recorded for common warts and the presence of a small dark spot for plantar warts. For both assessments, the following classification scheme was used, as indicated in table 3.

**TABLE 3: EVALUATION OF WART THICKNESS (COMMON WARTS) AND PRESENCE OF SMALL DARK SPOT (PLANTAR WARTS), FOLLOWING CRYOGENIC PEN TREATMENT.**

| Score | Wart thickness (common warts) / Presence small dark spots (plantar warts) |
|-------|---|
| 0     | Absence   |
| 1     | Light   |
| 2     | Moderate  |
| 3     | Severe  |
| 4     | Very severe   |

The healing process was assessed in terms of discontinuation of skin lines and affection of skin color. Finally, the presence or absence of a scab was evaluated.

**TABLE 4: EVALUATION OF DISCONTINUATION OF SKIN LINES AND AFFECTION OF SKIN COLOR FOLLOWING CRYOGENIC PEN TREATMENT.**

| Score | Discontinuation of skin lines / Affection skin color |
|-------|--|
| 0     | None   |
| 1     | Light  |
| 2     | Moderate   |
| 3     | Severe   |
| 4     | Very severe  |

## Safety evaluation

Safety assessment consisted of evaluation of the skin condition by an investigator, at the end of the study. Based on the observed local signs, the product received a score of 0 to 3, as indicated in table 5.

**TABLE 5: EVALUATION OF TOLERANCE (SAFETY) FOLLOWING CRYOGENIC PEN TREATMENT.**

| Score | Tolerance |
|-------|-----------|
| 0     | Low       |
| 1     | Moderate  |
| 2     | Good      |
| 3     | Very good |

## Statistical analyses

### Analysis populations

**Per Protocol:** subjects that were cured after a maximum of three treatments, omitting subjects that were not cured after less than three treatments.

**Safety:** subjects who received at least one treatment and that have a final assessment for tolerance.

Efficacy endpoints will be analysed for the per protocol analysis population, safety endpoints for the safety population.

### General methods

Continuous data will be summarized by their mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized by frequencies and percentages.

Chi-square test for independence was used to compare the cured versus not cured number of subjects, after a maximum of three treatments, between the Pixie® and Wartner® treated subjects.

All descriptive and statistical analyses were performed in R version 3.3.0. (R development core team, 2016) by an independent statistician. A  $p$ -value  $< 0.05$  was considered as statistical significant. No imputation of missing data is performed. The amount of missing data is presented in the tables wherever appropriate.

## Results

### Patient disposition

In total, data on 88 subjects were included in this analyses, one subject (No. 209) from the Wartner® group was lost to follow-up after the baseline visit. Another subject (No. 207) from the Wartner® group did receive only two treatments and was not cured after the second treatment.

Two subjects from the Pixie® group were lost to follow-up and one subject was withdrawn of consent after the first treatment. Another four subjects from the Pixie® group received only two treatments and were not cured after two treatments. One subject from the Pixie® group was excluded by the validation committee.

For the per protocol analyses (efficacy endpoints), the Pixie® group contained 50 subjects and the Wartner® group contained 38 subjects. For the safety analyses, the Pixie® group contained 55 subjects and the Wartner® group contained 39 subjects.

### Wart characteristics

In the Pixie® group, 50% (29/58) of the subjects were treated for a plantar wart, whereas 48.7% (19/39) In the Wartner® group.

### Primary efficacy endpoint

The efficacy of treatment with Pixie® versus comparator Wartner® was compared in terms of the number of treatments needed to be cured. Table 6 summarizes the number of subjects who were cured or not cured after a maximum of three treatments.

**TABLE 6: NUMBER OF TREATMENTS NEEDED TO BE CURED.**

| Treatment | Cured after X treatment(s) |               |               | Not cured after 3 treatments |
|-----------|----------------------------|---------------|---------------|------------------------------|
|           | X=1                        | X=2           | X=3           |                              |
| Pixie®    | 34.0% (17/50)              | 28.0% (14/50) | 20.0% (10/50) | 18.0% (9/50)                 |
| Wartner®  | 10.5% (4/38)               | 18.4% (7/38)  | 18.4% (7/38)  | 52.6% (20/38)                |

Overall, significant ( $\chi^2 = 11.7$ ,  $p < 0.001$ ) more subjects from the Pixie® group (82.0%, 41/50) were cured after a maximum of three treatments in comparison with the Wartner® group (47.4%, 18/38). Of note, significant ( $\chi^2 = 6.5$ ;  $p = 0.01$ ) of the subjects from the Pixie® group were cured after one treatment, this was only 10.5% in the Wartner® group.

Efficacy of the treatment was scored, from not efficient to very efficient, by an investigator after each visit. The distribution over the different categories by treatment is shown in Table 7.

**TABLE 7: EFFICACY OF TREATMENT WITH PIXIE® VERSUS WARTNER®.**

| Treatment | Statistic                 | Category             | Total number of treatments |                 |                 | Last visit    |
|-----------|---------------------------|----------------------|----------------------------|-----------------|-----------------|---------------|
|           |                           |                      | 1                          | 2               | 3               |               |
| Pixie®    | Efficacy, % (n/N)         | Not efficient        | 0% (0/50)                  | 0% (0/33)       | 0% (0/19)       | 0% (0/50)     |
|           |                           | Rather not efficient | 6% (3/50)                  | 9.1% (3/33)     | 5.3% (1/19)     | 2% (1/50)     |
|           |                           | Rather efficient     | 22% (11/50)                | 30.3% (10/33)   | 31.6% (6/19)    | 12% (6/50)    |
|           |                           | Efficient            | 36% (18/50)                | 24.2% (8/33)    | 10.5% (2/19)    | 10% (5/50)    |
|           |                           | Very efficient       | 36% (18/50)                | 36.4% (12/33)   | 52.6% (10/19)   | 76% (38/50)   |
|           | <b>Total evaluable, N</b> |                      | 50                         | 33 <sup>A</sup> | 19 <sup>A</sup> | 50            |
| Wartner®  | Efficacy, % (n/N)         | Not efficient        | 2.6% (1/38)                | 0% (0/34)       | 0% (0/27)       | 0% (0/38)     |
|           |                           | Rather not efficient | 13.2% (5/38)               | 23.5% (8/34)    | 11.1% (3/27)    | 7.9% (3/38)   |
|           |                           | Rather efficient     | 47.4% (18/38)              | 23.5% (8/34)    | 40.7% (11/27)   | 31.6% (12/38) |
|           |                           | Efficient            | 26.3% (10/38)              | 35.3% (12/34)   | 25.9% (7/27)    | 21.1% (8/38)  |
|           |                           | Very efficient       | 10.5% (4/38)               | 17.6% (6/34)    | 22.2% (6/27)    | 39.5% (15/38) |
|           | <b>Total evaluable, N</b> |                      | 38                         | 34 <sup>A</sup> | 27 <sup>A</sup> | 38            |

<sup>A</sup> Total evaluable number of subjects decreases with treatment, cured subjects receive a maximum score of 5 (very efficient) during their last evaluation e.g. a subject that is cured after one treatment is not evaluated after a second treatment

The better cure rate that was observed for the Pixie® group was also reflected in the investigator opinion on product efficacy. During the last visit, Pixie® was found to be very efficient for 76% (38/50) of the subjects, whereas very efficient was observed for 39.5% (15/38) of the subjects in the Wartner® group. This difference in efficacy was significant ( $\chi^2 = 12.0, p < 0.001$ ). One subject (No. 146) from the Pixie® group who was not cured, received a score of 5 (very efficient) after the 3rd treatment, the diameter of the wart was indeed very small (0.09 cm), indicating that the wart was almost disappeared.

#### Secondary efficacy endpoints

Summary statistics on the roughness of the wart, the thickness (common warts) and presence of a small dark spot (plantar warts) are presented in table 8, table 9, and table 10, respectively.



**TABLE 8: SUMMARY STATISTICS OF THE ROUGHNESS OF THE WART AT BASELINE AND IN FUNCTION OF NUMBER OF TREATMENTS (TRT's).**

| Treatment       | Statistic                     | Roughness     |               |               |                  |
|-----------------|-------------------------------|---------------|---------------|---------------|------------------|
|                 |                               | Baseline      | After 1 TRT   | After 2 TRT's | After 3 TRT's    |
| Pixie®          | Median                        | 1             | 1             | 1             | 0.5              |
|                 | Min                           | 1             | 0             | 0             | 0                |
|                 | Max                           | 3             | 2             | 2             | 2                |
|                 | N                             | 50            | 50            | 33            | 20               |
|                 | Category, % (n/N)<br>none (0) | 0% (0/50)     | 32% (16/50)   | 39.4% (13/33) | 50% (10/20)      |
|                 | light (1)                     | 62% (31/50)   | 62% (31/50)   | 51.5% (17/33) | 40% (8/20)       |
|                 | moderate (2)                  | 34% (17/50)   | 6% (3/50)     | 9.1% (3/33)   | 10% (2/20)       |
|                 | severe (3)                    | 4% (2/50)     | 0% (0/50)     | 0% (0/33)     | 0% (0/20)        |
|                 | very severe (4)               | 0% (0/50)     | 0% (0/50)     | 0% (0/33)     | 0% (0/20)        |
|                 | Statistic                     |               |               |               |                  |
| Wartner®        | Median                        | 1             | 1             | 1             | 1                |
|                 | Min                           | 0             | 0             | 0             | 0                |
|                 | Max                           | 2             | 4             | 2             | 3                |
|                 | N                             | 37            | 38            | 34            | 27               |
|                 | Category, % (n/N)<br>none (0) | 2.7% (1/37)   | 10.5% (4/38)  | 20.6% (7/34)  | 25.9% (7/27)     |
|                 | light (1)                     | 64.9% (24/37) | 81.6% (31/38) | 76.5% (26/34) | 70.4%<br>(19/27) |
|                 | moderate (2)                  | 32.4% (12/37) | 5.3% (2/38)   | 2.9% (1/34)   | 0% (0/27)        |
|                 | severe (3)                    | 0% (0/37)     | 0% (0/38)     | 0% (0/34)     | 3.7% (1/27)      |
| very severe (4) | 0% (0/37)                     | 2.6% (1/38)   | 0% (0/34)     | 0% (0/27)     |                  |

**TABLE 9: SUMMARY STATISTICS OF THE THICKNESS OF COMMON WARTS AT BASELINE AND IN FUNCTION OF NUMBER OF TREATMENTS (TRT'S).**

| Treatment | Statistic                     | Thickness     |               |               |               |
|-----------|-------------------------------|---------------|---------------|---------------|---------------|
|           |                               | Baseline      | After 1 TRT   | After 2 TRT's | After 3 TRT's |
| Pixie®    | Median                        | 2             | 1             | 0             | 0             |
|           | Min                           | 1             | 0             | 0             | 0             |
|           | Max                           | 3             | 2             | 2             | 1             |
|           | N                             | 27            | 27            | 17            | 6             |
|           | Category, % (n/N)<br>none (0) | 0% (0/27)     | 37% (10/27)   | 64.7% (11/17) | 83.3% (5/6)   |
|           | light (1)                     | 44.4% (12/27) | 48.1% (13/27) | 29.4% (5/17)  | 16.7% (1/6)   |
|           | moderate (2)                  | 40.7% (11/27) | 14.8% (4/27)  | 5.9% (1/17)   | 0% (0/6)      |
|           | severe (3)                    | 14.8% (4/27)  | 0% (0/27)     | 0% (0/17)     | 0% (0/6)      |
|           | very severe (4)               | 0% (0/27)     | 0% (0/27)     | 0% (0/17)     | 0% (0/6)      |
|           | Statistic                     |               |               |               |               |
| Wartner®  | Median                        | 2             | 1             | 1             | 1             |
|           | Min                           | 1             | 0             | 0             | 0             |
|           | Max                           | 2             | 2             | 2             | 2             |
|           | N                             | 20            | 20            | 18            | 13            |
|           | Category, % (n/N)<br>none (0) | 0% (0/20)     | 10% (2/20)    | 27.8% (5/18)  | 15.4% (2/13)  |
|           | light (1)                     | 45% (9/20)    | 60% (12/20)   | 50% (9/18)    | 69.2% (9/13)  |
|           | moderate (2)                  | 55% (11/20)   | 30% (6/20)    | 22.2% (4/18)  | 15.4% (2/13)  |
|           | severe (3)                    | 0% (0/20)     | 0% (0/20)     | 0% (0/18)     | 0% (0/13)     |
|           | very severe (4)               | 0% (0/20)     | 0% (0/20)     | 0% (0/18)     | 0% (0/13)     |

**TABLE 10: SUMMARY STATISTICS ON PRESENCE OF SMALL DARK SPOT FOR PLANTAR WARTS AT BASELINE AND IN FUNCTION OF NUMBER OF TREATMENTS (TRT's).**

| Treatment | Statistic                     | Presence of small dark spot |               |               |               |
|-----------|-------------------------------|-----------------------------|---------------|---------------|---------------|
|           |                               | Baseline                    | After 1 TRT   | After 2 TRT's | After 3 TRT's |
| Pixie®    | Median                        | 0                           | 0             | 0.5           | 1             |
|           | Min                           | 0                           | 0             | 0             | 0             |
|           | Max                           | 4                           | 3             | 2             | 3             |
|           | N                             | 23                          | 23            | 16            | 13            |
|           | Category, % (n/N)<br>none (0) | 60.9% (14/23)               | 69.6% (16/23) | 50% (8/16)    | 38.5% (5/13)  |
|           | light (1)                     | 26.1% (6/23)                | 8.7% (2/23)   | 37.5% (6/16)  | 15.4% (2/13)  |
|           | moderate (2)                  | 8.7% (2/23)                 | 8.7% (2/23)   | 12.5% (2/16)  | 38.5% (5/13)  |
|           | severe (3)                    | 0% (0/23)                   | 13% (3/23)    | 0% (0/16)     | 7.7% (1/13)   |
|           | very severe (4)               | 4.3% (1/23)                 | 0% (0/23)     | 0% (0/16)     | 0% (0/13)     |
|           | Statistic                     |                             |               |               |               |
| Wartner®  | Median                        | 0                           | 0             | 0             | 0             |
|           | Min                           | 0                           | 0             | 0             | 0             |
|           | Max                           | 2                           | 2             | 4             | 2             |
|           | N                             | 18                          | 18            | 16            | 14            |
|           | Category, % (n/N)<br>none (0) | 66.7% (12/18)               | 77.8% (14/18) | 68.8% (11/16) | 92.9% (13/14) |
|           | light (1)                     | 27.8% (5/18)                | 5.6% (1/18)   | 12.5% (2/16)  | 0% (0/14)     |
|           | moderate (2)                  | 5.6% (1/18)                 | 16.7% (3/18)  | 0% (0/16)     | 7.1% (1/14)   |
|           | severe (3)                    | 0% (0/18)                   | 0% (0/18)     | 12.5% (2/16)  | 0% (0/14)     |
|           | very severe (4)               | 0% (0/18)                   | 0% (0/18)     | 6.3% (1/16)   | 0% (0/14)     |

Summary statistics on the healing process are presented in table 11 to table 13.

**TABLE 11: SUMMARY STATISTICS ON THE DISCONTINUATION OF SKIN LINES AT BASELINE AND IN FUNCTION OF NUMBER OF TREATMENTS (TRT'S).**

| Treatment            | Statistic                     | Discontinuation of skin lines |               |               |               |
|----------------------|-------------------------------|-------------------------------|---------------|---------------|---------------|
|                      |                               | Baseline                      | After 1 TRT   | After 2 TRT's | After 3 TRT's |
| Pixie <sup>®</sup>   | Median                        | 2                             | 1             | 1             | 1             |
|                      | Min                           | 1                             | 0             | 0             | 0             |
|                      | Max                           | 4                             | 3             | 2             | 2             |
|                      | N                             | 50                            | 50            | 33            | 20            |
|                      | Category, % (n/N)<br>none (0) | 0% (0/50)                     | 30% (15/50)   | 39.4% (13/33) | 45% (9/20)    |
|                      | light (1)                     | 42% (21/50)                   | 44% (22/50)   | 33.3% (11/33) | 25% (5/20)    |
|                      | moderate (2)                  | 32% (16/50)                   | 22% (11/50)   | 27.3% (9/33)  | 30% (6/20)    |
|                      | severe (3)                    | 24% (12/50)                   | 4% (2/50)     | 0% (0/33)     | 0% (0/20)     |
|                      | very severe (4)               | 2% (1/50)                     | 0% (0/50)     | 0% (0/33)     | 0% (0/20)     |
|                      | Statistic                     |                               |               |               |               |
| Wartner <sup>®</sup> | Median                        | 1                             | 1             | 1             | 1             |
|                      | Min                           | 0                             | 0             | 0             | 0             |
|                      | Max                           | 3                             | 2             | 3             | 2             |
|                      | N                             | 38                            | 38            | 34            | 27            |
|                      | Category, % (n/N)<br>none (0) | 2.6% (1/38)                   | 15.8% (6/38)  | 20.6% (7/34)  | 25.9% (7/27)  |
|                      | light (1)                     | 57.9% (22/38)                 | 60.5% (23/38) | 61.8% (21/34) | 63% (17/27)   |
|                      | moderate (2)                  | 34.2% (13/38)                 | 23.7% (9/38)  | 14.7% (5/34)  | 11.1% (3/27)  |
|                      | severe (3)                    | 5.3% (2/38)                   | 0% (0/38)     | 2.9% (1/34)   | 0% (0/27)     |
|                      | very severe (4)               | 0% (0/38)                     | 0% (0/38)     | 0% (0/34)     | 0% (0/27)     |
|                      | Statistic                     |                               |               |               |               |

**TABLE 12: SUMMARY STATISTICS ON THE AFFECTION OF SKIN COLOR AT BASELINE AND IN FUNCTION OF NUMBER OF TREATMENTS (TRT's).**

| Treatment | Statistic                     | Affection on skin color |               |               |               |
|-----------|-------------------------------|-------------------------|---------------|---------------|---------------|
|           |                               | Baseline                | After 1 TRT   | After 2 TRT's | After 3 TRT's |
| Pixie®    | Median                        | 2                       | 1             | 1             | 1             |
|           | Min                           | 0                       | 0             | 0             | 0             |
|           | Max                           | 4                       | 3             | 2             | 3             |
|           | N                             | 50                      | 50            | 33            | 19            |
|           | Category, % (n/N)<br>none (0) | 2% (1/50)               | 24% (12/50)   | 39.4% (13/33) | 36.8% (7/19)  |
|           | light (1)                     | 40% (20/50)             | 50% (25/50)   | 39.4% (13/33) | 42.1% (8/19)  |
|           | moderate (2)                  | 40% (20/50)             | 22% (11/50)   | 21.2% (7/33)  | 15.8% (3/19)  |
|           | severe (3)                    | 16% (8/50)              | 4% (2/50)     | 0% (0/33)     | 5.3% (1/19)   |
|           | very severe (4)               | 2% (1/50)               | 0% (0/50)     | 0% (0/33)     | 0% (0/19)     |
|           | Statistic                     |                         |               |               |               |
| Wartner®  | Median                        | 1                       | 1             | 1             | 1             |
|           | Min                           | 0                       | 0             | 0             | 0             |
|           | Max                           | 3                       | 2             | 4             | 2             |
|           | N                             | 38                      | 38            | 34            | 27            |
|           | Category, % (n/N)<br>none (0) | 2.6% (1/38)             | 18.4% (7/38)  | 20.6% (7/34)  | 33.3% (9/27)  |
|           | light (1)                     | 60.5% (23/38)           | 57.9% (22/38) | 61.8% (21/34) | 55.6% (15/27) |
|           | moderate (2)                  | 34.2% (13/38)           | 23.7% (9/38)  | 11.8% (4/34)  | 11.1% (3/27)  |
|           | severe (3)                    | 2.6% (1/38)             | 0% (0/38)     | 2.9% (1/34)   | 0% (0/27)     |
|           | very severe (4)               | 0% (0/38)               | 0% (0/38)     | 2.9% (1/34)   | 0% (0/27)     |
|           | Statistic                     |                         |               |               |               |

**TABLE 13: SUMMARY STATISTICS ON THE PRESENCE OF A SCAB AT BASELINE AND IN FUNCTION OF NUMBER OF TREATMENTS (TRT's).**

| Treatment       | Presence of a scab |               |               |               |
|-----------------|--------------------|---------------|---------------|---------------|
|                 | Baseline           | After 1 TRT   | After 2 TRT's | After 3 TRT's |
| <b>Pixie®</b>   | 50                 | 50            | 38            | 19            |
| N               |                    |               |               |               |
| Yes, % (n/N)    | 92% (46/50)        | 74.0% (37/50) | 84.2% (32/38) | 82.4% (16/19) |
| No, % (n/N)     | 8% (4/50)          | 26.0% (13/50) | 15.8% (6/38)  | 15.8% (3/19)  |
| <b>Wartner®</b> | 38                 | 38            | 34            | 27            |
| N               |                    |               |               |               |
| Yes, % (n/N)    | 100% (38/38)       | 86.8% (33/38) | 100% (34/34)  | 88.9% (24/27) |
| No, % (n/N)     | 0% (0/38)          | 13.2% (5/38)  | 0% (0/34)     | 11.1% (3/27)  |

## Safety

Local tolerance of the treatment was assessed by the investigator at the end of the therapy. The distribution over the different categories is shown in table 14. In general, both Wartner® and Pixie® were well tolerated. In the Pixie® group, the tolerance was low or moderate for 3 and 2 subjects, respectively. However, for those subjects, a very good efficiency score was given, indicating that the wart was cured.

In the Wartner® group, very good tolerance was observed for 82.1% of the subjects, however, only 47.4% of those subjects were cured. In the Pixie® group, very good tolerance was observed in the majority (56.4%) of the subjects and for 71% of those subjects, the product was found to be very efficient. This suggests that the tolerance score measures the anticipated skin response and that this skin response in the Pixie® group is predictive of efficacious wart removal.

## Conclusion

The efficacy of Pixie® cryogenic pen versus the comparator product Wartner® cryogenic pen in subjects with common or planar warts was assessed. **After a maximum of three applications, a significantly ( $p < 0.001$ ) higher cure rate was observed for the Pixie® group (82%, 41/50) when compared to the Wartner® group was (47.4%, 18/38). Also, 3x more subjects (34%) were cured after 1 treatment with Pixie® in comparison to Wartner® (10.5%).** Both Pixie® and Wartner® are safe wart removal treatments that are well tolerated.

## References

1. BACELIERI, Rocky; JOHNSON, SANDRA MARCHESE. Cutaneous warts: an evidence-based approach to therapy. *American family physician*, 2005, 72.4: 647-652.
2. DALL'OGGIO, Federica, et al. Treatment of cutaneous warts. *American journal of clinical dermatology*, 2012, 13.2: 73-96.
3. Gibbs A, Harvey I, Sterling J, Stark R, 2002. Local treatments for cutaneous warts: systematic review. *BMJ* 325 : 1-8.
4. MICALI, Giuseppe, et al. Management of Cutaneous Warts. *American journal of clinical dermatology*, 2004, 5.5: 311-317.
5. STERLING, J. C.; HANDFIELD-JONES, S.; HUDSON, P. M. Guidelines for the management of cutaneous warts. *British Journal of Dermatology*, 2001, 144.1: 4-11.
6. ZOUBOULIS, Christos C. "Cryosurgery in dermatology." *European Journal of Dermatology* 8.7 (1998): 466-74.

**TABLE 14: LOCAL TOLERANCE OF TREATMENT WITH PIXIE® VERSUS WARTNER® OVERALL AND AS A FUNCTION OF EFFICACY.**

| Treatment | Statistic          | Category  | Overall       | Efficacy      |                      |                  |              |                |              |
|-----------|--------------------|-----------|---------------|---------------|----------------------|------------------|--------------|----------------|--------------|
|           |                    |           |               | Not efficient | Rather not efficient | Rather efficient | Efficient    | Very efficient | Missing      |
| Pixie®    | Tolerance, % (n/N) | Low       | 5.5% (3/55)   | 0% (0/3)      | 0% (0/3)             | 0% (0/3)         | 0% (0/3)     | 100% (3/3)     | 0% (0/3)     |
|           |                    | Moderate  | 3.6% (2/55)   | 0% (0/2)      | 0% (0/2)             | 0% (0/2)         | 0% (0/2)     | 100% (2/2)     | 0% (0/2)     |
|           |                    | Good      | 34.5% (19/55) | 0% (0/19)     | 5.3% (1/19)          | 21.1% (4/19)     | 5.3% (1/19)  | 57.9% (11/19)  | 10.5% (2/19) |
|           |                    | Very good | 56.4% (31/55) | 0% (0/31)     | 0% (0/31)            | 6.5% (2/31)      | 12.9% (4/31) | 71.0% (22/31)  | 9.7% (3/31)  |
|           | Missing            |           | 3             | NA            | NA                   | NA               | NA           | NA             | NA           |
| Wartner®  | Tolerance, % (n/N) | Low       | 0% (0/39)     | NA            | NA                   | NA               | NA           | NA             | NA           |
|           |                    | Moderate  | 0% (0/39)     | NA            | NA                   | NA               | NA           | NA             | NA           |
|           |                    | Good      | 17.9% (7/39)  | 0% (0/7)      | 0% (0/7)             | 42.9% (3/7)      | 28.6% (2/7)  | 28.6% (2/7)    | 0% (0/7)     |
|           |                    | Very good | 82.1% (32/39) | 0% (0/32)     | 9.7% (3/32)          | 28.1% (9/32)     | 18.8% (6/32) | 40.6% (13/32)  | 3.1% (1/32)  |
|           | Missing            |           | 1             | NA            | NA                   | NA               | NA           | NA             | NA           |