Exploratory Study Report synopsis

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A Randomised, Double-blind, Placebo-controlled Three-way Cross-over Single Center Study to Characterize the Phenotype in Patients with Morton's Neuroma and to Explore the Effect of Local Administration of Xylocaine® (lidocaine)

Study period

Date of first subject enrolled: 28 February 2011

Date of last subject completed: 15 May 2012

Sponsor's Responsible Medical Officer:

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

1. OBJECTIVES

The primary objectives of the study were:

- To characterize the baseline phenotypic Quantitative Sensory Test (QST) variables (eg, heat, cold, touch and mechanical pain perception) and pain demographics of Morton's neuroma
- To assess the effect of Xylocaine® (1 mg/mL and 10 mg/mL) compared to placebo in QST variables in the neuropathic foot

The secondary objective was:

- To evaluate safety and tolerability of Xylocaine® by assessment of AEs.

The exploratory objectives were:

- To explore the effect on pain after administration of Xylocaine® (1 mg/mL and 10 mg/mL) *vs* placebo
- To do subgroup analyses in patients displaying any hyperalgesia
- To characterize the expression of drug targets in Morton's neuroma and/or the electrophysiological properties
- To identify/explore genetic variations that may affect pharmacodynamics (PD), safety and/or tolerability related to Xylocaine® or the target. In addition, susceptibility genes and genes related to underlying disease may be explored. The blood sample for genetic research is optional.

The last exploratory objective was not carried out because no genetic analyses had been performed at the time of report writing.

2. STUDY DESIGN

2.1 Study design

This was a randomized, double-blind, placebo-controlled three-period cross-over single centre study to characterize the sensory phenotype and pain demographics, using QST and pain rating variables, of patients with Morton's neuroma and to explore the effect on these variables after local administration of a single dose (2 mL) of Xylocaine® 10 mg/mL, Xylocaine® 1 mg/mL and placebo.

2.2 TARGET SUBJECT POPULATION AND SAMPLE SIZE

To be included, patients needed to have a clinical diagnosis of Morton's neuroma with symptoms of at least 3 months duration, as well as Magnetic Resonance Imaging (MRI) assessments.

Based on the sample size calculation, the study was to include 24 valid patients (18 to 80 year old males and females). The study consisted of up to 6 Visits for each patient, an enrolment Visit (which could be performed on two different occasions) followed by three treatment Visits of approximately 2 hours each, a follow-up Visit and a final Visit including surgery of the neuroma and tissue sampling (the final Visit was originally mandatory but was later changed to optional, see Section **Error! Reference source not found.**). See **Error! Reference source not found.** for complete study flow.

3. TREATMENT, MODE OF ADMINISTRATION, DOSAGE AND DURATION OF TREATMENT

Two (2) mL of Xylocaine® 1 mg/mL, Xylocaine® 10 mg/mL or placebo was administered in a randomised order between the three treatment Visits. Injection was done from the plantar aspect of the foot, using two syringes containing 1 mL each of the study drug. One injection was made at the proximal part of the neuroma, the other at the distal part (changed from protocol text which stated that 0.5 mL was planned to be distributed at each of 4 sites around the neuroma, see Section **Error! Reference source not found.**).

4. STATISTICAL EVALUATION

Sample size was calculated taking one of the QST variables into account, HPT. The study is not dimensioned for the other variables. Neither has multiplicity been accounted for. This should be taken into account when interpreting the results.

Tests are one-sided and significance level is set at 0.05.

In order to assess the effect of Xylocaine® (1mg/mL and 10 mg/mL) in the affected foot the variables are analysed by mixed effect models with treatment, period and treatment*period interaction as fixed effects and patient as random effect. The comparison of interest is the difference between Xylocaine® 1mg/mL vs. placebo and Xylocaine® 10 mg/mL vs. placebo.

In order to characterize the baseline of this population, variables assessed predose are analysed by mixed effect models with diagnosis (affected/non-affected) foot as fixed effect and patient as random effect. The comparison of interest is the difference between affected and unaffected foot.

In general, all variables are presented using descriptive statistics and graphs as appropriate.

Continuous variables are presented with descriptive statistics (n, mean, standard deviation (SD), median, min, max). Boxplots have boxes that show 25%-, 75%- and 50%-quartiles, and have whiskers that represent the highest and lowest observation within the upper and lower fence. Upper and lower fence are defined as 1.75 times the intraquartile range (range between the 25% and 75% quartiles). Outliers are defined as observations outside the upper and lower fence and will be shown by their actual value. The mean will also be presented within the box with a symbol.

5. SUBJECT POPULATION

Totally 47 patients diagnosed with Morton's neuroma were screened for inclusion in the study and 27 fulfilled all inclusion criteria and had no exclusion criteria. One of the remaining patients performed evaluations at visit 1 but was thereafter excluded because of exclusion criteria. This patient is not included in the following analyses. Thus, 27 patients were randomized to study treatment. The main reasons for exclusion were absence of neuroma according to fMRI or the presence of two neuroma (in the affected foot), Appendix D, Table 5. There were 21 women and six men, all white. The mean age was 53 years (minimum 29, maximum 77 years). The demographics seems to correspond with the population of patients with Morton's neuroma.

Three patients discontinued before completion, two due to pregnancy (after Visit 3 and 5) and one due to own request to withdraw (after Visit 2).

The patients had on average experienced neuroma pain for 6.9 years (minimum 0.4 and maximum 26.0 years).The neuroma was located in the left foot in 11 patients (1 in web space 2 and 10 in web space 3), and in the right foot in 14 patients (six in web space two and eight in web space 3).

6. RESULTS

6.1 Morton's Neuroma Phenotype

6.1.1 Demographics, pain related

Six of the 27 patients experienced more cold sensitivity and none experienced less cold sensitivity in affected foot compared to the non affected foot. For warmth the corresponding figures were two and one patient, respectively.

6.1.2 Pain Quality Assessment Scale - PQAS

The characterization of the neuroma pain is presented below, in **Error! Reference source not found.** and **Error! Reference source not found.**, using PQAS. Ongoing pain was experienced in eight (32%) of the patients.

6.1.3 Quantitative Sensory Testing - QST

For all variables there were both hypo- and hyperphenomena in the affected foot compared to the non affected.

As in neuropathic pain conditions the results indicate absence of any specific QST change in Morton's neuroma patients.

6.1.4 Brief Pain Inventory - Short Form

Before each drug administration the pain intensity and its interference with general activity and sleep was rated using the modified BPI-SF.The mean of the average pain before the three treatments was 3.3. The corresponding mean of least pain in the last 24 hours was 0.8 and the mean of pain right now was 2.1.

The mean results were fairly similar at the three investigations before drug administration for both the BPI-SF and the QST variables. This indicates a fairly stable disease and also little or no remaining drug effect at a subsequent drug administration.

6.2 Pharmacodynamics (affected foot)

6.2.1 Injection Pain

Drug injection pain was estimated by use of question number 4 in the modified BPI-SF immediately after drug administration. The mean pain intensity was 4.1 for placebo, 2.0 for lidocaine 1mg/ml and 1.2 for lidocaine 10mg/ml. The difference between placebo and lidocaine (both 1 and 10 mg/mL) was significant ($p<0.001$)

6.2.2 QST

The results of the quantitative QST measurements in the affected foot after each treatment are summarized in the table below.

Table - QST results in affected foot (Aff) post drug administration

Variable	Exposure	Treatment	n	Mean	SD	Median	Min	Max
Median CDT (C)	Aff, post-dose	Placebo	26	18.7	3.84	18.8	15.0	26.8
		Xylocaine® 1 mg/mL	26	18.3	3.19	18.0	15.0	24.5
		Xylocaine® 10 mg/mL	26	17.1	3.44	15.0	15.0	26.0
Median HPS (mm)	Aff, post-dose	Placebo	26	6.4	13.25	0.0	0.0	48.0
		Xylocaine® 1 mg/mL	26	2.4	6.03	0.0	0.0	26.0
		Xylocaine® 10 mg/mL	26	3.0	10.83	0.0	0.0	55.0
Median HPT (C)	Aff, post-dose	Placebo	26	51.4	1.69	52.0	44.5	52.0
		Xylocaine® 1 mg/mL	26	51.7	0.68	52.0	49.3	52.0

Table - QST results in affected foot (Aff) post drug administration

Variable	Exposure	Treatment	n	Mean	SD	Median	Min	Max
		Xylocaine® 10 mg/mL	26	51.6	1.16	52.0	46.4	52.0
Median MDT (mN)	Aff, post-dose	Placebo	26	18.6	25.32	9.7	0.7	90.6
		Xylocaine® 1 mg/mL	26	25.9	32.54	11.3	1.9	90.6
		Xylocaine® 10 mg/mL	26	34.7	30.79	19.2	4.9	90.6
Median MPS (mm)	Aff, post-dose	Placebo	26	16.9	14.99	14.5	0.0	54.0
		Xylocaine® 1 mg/mL	26	16.3	16.80	11.0	0.0	56.0
		Xylocaine® 10 mg/mL	26	14.7	19.37	4.0	0.0	74.0
Median SMS (mm)	Aff, post-dose	Placebo	26	5.1	9.89	0.0	0.0	38.0
		Xylocaine® 1 mg/mL	26	6.5	15.90	1.0	0.0	79.0
		Xylocaine® 10 mg/mL	26	1.2	2.67	0.0	0.0	10.0
Sensebox Force limit	Aff, post-dose	Placebo	17	155.8	73.19	119.6	52.3	293.7
		Xylocaine® 1 mg/mL	15	168.2	95.09	151.6	44.6	331.1
		Xylocaine® 10 mg/mL	21	165.5	84.08	144.0	66.5	386.7
Sensebox VAS 0	Aff, post-dose	Placebo	12	77.9	47.82	78.7	30.3	210.3
		Xylocaine® 1 mg/mL	11	85.2	334.1	53.2	-566	864.4
		Xylocaine® 10 mg/mL	17	56.7	63.04	46.8	-98.8	202.2
Sensebox VAS 100	Aff, post-dose	Placebo	12	194.1	101.3	182.1	-31.7	363.9
		Xylocaine® 1 mg/mL	11	-171	1561	198.8	-4751	1150
		Xylocaine® 10 mg/mL	17	311.6	328.2	208.4	-436	1150
Sensebox Force	Aff, post-dose	Placebo	12	0.7	0.62	0.8	-0.8	1.6
		Xylocaine® 1 mg/mL	11	0.5	1.34	0.2	-1.5	4.0
		Xylocaine® 10 mg/mL	17	0.6	0.47	0.5	-0.2	1.7
Median WDT (C)	Aff, post-dose	Placebo	26	48.2	4.82	50.1	35.8	52.0
		Xylocaine® 1 mg/mL	26	49.3	3.40	50.6	40.8	52.0
		Xylocaine® 10 mg/mL	26	48.5	4.74	49.9	35.5	52.0
Median Windup (mm)	Aff, post-dose	Placebo	26	14.5	17.20	8.0	-2.0	71.0

Table - QST results in affected foot (Aff) post drug administration

Variable	Exposure	Treatment	n	Mean	SD	Median	Min	Max
		Xylocaine® 1 mg/mL	26	11.6	13.01	5.5	-6.0	38.0
		Xylocaine® 10 mg/mL	26	7.0	11.75	1.5	-4.0	45.0

Significant effects were seen in CDT, MDT and wind up after lidocaine 10mg/ml compared to placebo.

6.2.3 Hyperalgesia

Comparing the affected with the non-affected foot patients were considered to have hyperalgesia if ≥1.5°C lower HPT (n=3) or ≥25% higher VAS for HPS (n=3), MPS (n=11) or wind up (n =9) and an absolute difference between feet of at least 10 mm on the VAS.

There were only three patients with HPT hyperalgesia, all showing a marked effect of lidocaine 1mg/ml that contrasts the absence of a corresponding effect in healthy volunteers (**Error! Reference source not found.**). The same three patients were hyperalgesic for both HPT and HPS and also had the highest pain score for MPS. However, they rated only minimal pain after placebo and step up. Overall, all patients with hyperalgesia were similar to those without hyperalgesia regarding pain after placebo and step up, indicating that presence of hyperalgesia does not affect Morton's neuroma walking pain.

6.2.4 Pain tests

After treatment injection and QST, and before the step up test, the patient rated their pain intensity following 2 minutes of rest. The mean pain intensity was 8, 6 and 0 after placebo, lidocaine 1 mg/mL and lidocaine 10 mg/mL respectively. The difference between placebo and lidocaine10 mg/ mL is significant (p=0.006). Following 2 minutes of stepping pain intensity had increased to 16, 9 and 1 after placebo, lidocaine 1 mg/mL and lidocaine 10 mg/mL. The difference is significant between placebo and lidocaine 1mg/ml (p=0.019) and between placebo and lidocaine 10 mg/ml (p<0.001). In addition, the slope of force versus pain (Algometer VAS force) was significantly flatter (p=0.015) after lidocaine 10mg/ml compared to placebo.

7. SAFETY RESULTS

There was one AE reported in the study, Medial Epicondylitis, for patient E00001003. The AE was judged as not related to study drug. No SAEs were reported. Appendix D, Table 7.