Study Number: AUX-CC-902

Title of study: A multicenter observational study of the real life effectiveness and safety of Xiapex® in the treatment of Dupuytren's disease in Belgium

Principal investigator: Dr. Frederik Verstreken, Monica Hospital, Florent Pauwelslei 1, 2100 Antwerp, Belgium

Study centers: Nine clinical centers in Belgium

Publication (reference): Not published

Study period:	**Clinical phase:** IV
Study initiation date: 18 December 2013	
Study completion date: 23 July 2014	
Data lock point: 09 October 2014	

Objectives:

- To characterize the population of patients with Dupuytren's disease and treated with Xiapex® in Belgium.
- To assess the effectiveness of Xiapex® in the treatment of Dupuytren's disease.
- To assess the safety of Xiapex® in the treatment of Dupuytren's disease.

Study design:

- Non-interventional (observational), multicenter, prospective, pharmaco-epidemiological study.
- The patients were followed up as per usual clinical practice for their condition.
- The choice of medical treatment was made by the physician independently in the regular course of practice and was not influenced by the study protocol.
- The demographics, medical history related to Dupuytren's contracture, current diagnosis, symptoms and severity of the disease were collected at the baseline visit.
- The effectiveness of the treatment was assessed (Goniometry, Range of Motion) at follow-up visit(s) made in accordance with routine clinical practice.
- The safety of the treatment was assessed at all follow-up visit(s) made in accordance with routine clinical practice.
- Concomitant medications and therapies were also collected during the whole study.
- The pre-treatment and post-treatment patient global assessment using the Unité Rhumatologique des Affections de la Main (URAM) and the physician global assessment were collected at baseline and end of study visit.
- Data were recorded in an electronic case report form (eCRF).

Number of patients:

Total: 110 patients; Completed: 104 patients; Safety cohort: 108 patients; Efficacy cohort: 108 patients

Diagnosis and criteria for inclusion:

- Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) had been informed of all pertinent aspects of the study.
- Patient presenting with Dupuytren's contracture (> 20°) with palpable cord.
- Patient aged 18 years and over.

Study Number: AUX-CC-902

- Patient currently treated or going to be treated* by Xiapex®.

*The decision to prescribe Xiapex® was made by the physician independently of his/her decision to include the patient in the study.

Study drug, dose, mode of administration: Xiapex® 0.9 mg powder and solvent for solution for injection into a cord (collagenase *Clostridium histolyticum*)

Reference drug/Comparator, dose and mode of administration: Not applicable

Criteria for evaluation:

- Characterization of the population with Dupuytren's disease in Belgium and treated by Xiapex®: demographics, working status, disease duration, affected hands and joints, number of prior procedures, other syndrome, disease or predisposing conditions, current diagnosis (clinical profile and goniometry), patient's and physician's global severity assessments.
- The effectiveness of therapy was evaluated after Xiapex® treatment, at each follow-up visit and study conclusion visit, on the basis of range of motion determined by goniometry, patient's global assessment (URAM), physician's global assessment and contracture recurrence (in terms of rate and time to event).
- In the context of pharmacovigilance, adverse events (AEs) and serious adverse events (SAEs) were recorded during the whole study. They were coded using Medical Dictionary for Regulatory Activities (MedDRA; Version 17.0).

Statistical methods:

- Descriptive statistics were used to characterize all type of variables (continuous, discrete ordinal and discrete nominal).
- For continuous variables, the following parameters were calculated: number of available observations, number of missing observations, mean, standard deviation, median, minimum and maximum.
- Discrete ordinal and nominal variables were characterized by the number of available observations for each response option, number of missing observations and percentage.
- For pivotal percentages corresponding to the study endpoints (the percentage of joints achieving a degree of contracture ≤5° after the extension procedure and the percentage of joints achieving a relative contracture reduction of ≥50% after the extension procedure) exact 95% confidence intervals were also provided.
- The following exploratory inferential analyses were performed: Changes versus baseline in the effectiveness parameters using paired Student's t tests (for continuous variables) or Wilcoxon's tests (for discrete nominal or ordinal variables).

SUMMARY:

The objectives of this study were to characterize the population of patients with Dupuytren's disease and treated with Xiapex® in Belgium, and to assess the effectiveness and safety of Xiapex® in the treatment of Dupuytren's disease.

Overall, 110 patients were included in the study and 108 patients received at least one injection of Xiapex®. The number of patients completing the study was equal to 104. No study discontinuations were related to an AE or a SAE.

Patients (N=110) had a mean age ± SD of 64.4 ± 10.9 years-old (minimum – maximum = 20 – 87 years). They were 85 males (77.3%) and 25 females (22.7%). They were all Caucasians. The disease had lasted for a mean period ± SD of 8.2 ± 8.1 years. Overall, 129 hands were affected at initial diagnosis (medical

Study Number: AUX-CC-902

history of Dupuytren's disease) in the 110 patients. The majority of patients (N=64; 58.2%) had no prior treatment procedures and 26 (23.6%) patients had only one prior treatment procedure. Prior procedures consisted of fasciectomy (N=46; 54.1%), collagenase injection (N=18; 21.2%), fasciotomy (N=16; 18.8%) or dermofasciectomy (N=5; 5.9%). Seventy-four (N=74; 87.1%) prior procedures were successful and 11 (12.9%) failed.

Recurrence was observed after 48 (64.9%) of the 74 successful prior treatment procedures. Recurrence was observed after fasciectomy in 26 cases (54.2%; 4, 7 and 15 after <1 year, 1-3 years and >3 years, respectively), fasciotomy in 14 cases (29.2%; 7 after <1 year and 7 after 1-3 years), collagenase injection in 5 cases (10.4%; 3 after <1 year and 2 after 1-3 years) and dermofasciectomy in 3 cases (6.3%; 1 after <1 year, 1 after 1-3 years and 1 after >3 years). Twelve (10.9%) patients had a medical history of diabetes, 15 (13.6%) of knuckle pads, 2 (1.8%) of Peyronie's disease, 5 (4.5%) of alcoholism, 13 (11.8%) of hand trauma, 2 (1.8%) of epilepsy, 33 (30.0%) of hypercholesterolemia, 7 (6.4%) of Ledderhose's disease, 47 (42.7%) patients had a family history, 21 (19.1%) were smoking and 64 (58.2%) patients had another disease, syndrome or predisposing condition.

Overall, 116 joints were affected at baseline in the 110 patients. The majority of patients had only one (N=104; 94.5%) affected joint. Two joints were affected in 6 (5.5%) patients. Functional complaint was reported by 102 (92.7%) patients, positive table top test by 102 (92.7%) patients, appearance complaint by 24 (21.8%) patients, pain by 14 (12.7%) patients and other complaints by 2 (1.8%) patients. At the baseline visit, the majority of patients (N=82; 74.5%) considered their current contracture severe with limited functionality of the hand. It was considered moderate by 20 (18.2%) patients. The mean (± SD) baseline URAM score was 29.2 ± 10.8. In the majority of patients, at the baseline visit, the physician considered the current contracture severe with impaired functionality (N=75; 68.2%). They considered it moderate in 23 (20.9%) patients. The mean ± SD goniometry of the 116 affected joints was: Passive Extension Deficit (PED) = 53.5 ± 20.2°; Flexion = 93.4 ± 6.8° and range of motion = 39.8 ± 19.5°.

Overall, 114 injections of Xiapex® were done in the fibrous cord of 114 joints from 108 patients. Seventy-four (N=74; 64.9%) injections were done for metacarpalphalangeal (MCP) joints and 40 (35.1%) for proximal interphalangeal (PIP) joints. All joints with a fibrous cord were injected once with Xiapex®. No fibrous cord was injected twice or more. This is in agreement with the number of injections/joint (1.08) measured in a real world observational US study.[1] Overall, 102 patients had an injection in one fibrous cord and 6 patients in two fibrous cords. At follow-up visits, the mean ± SD degree of remaining contracture was 8.7 ± 13.9°, the mean absolute reduction of contracture was 45.1 ± 18.9° and the relative reduction of contracture was 86.1 ± 21.5%. The number and percentage of joints achieving a degree of contracture ≤5° after the extension procedure were equal to 72 and 64.9%, respectively. This result is in agreement with the 64% success rate measured in the study of Hurst et al.[2] The number and percentage of MCP and PIP joints achieving a degree of contracture ≤5° after the extension procedure were equal to 58 out of 73 (79.5%) and 14 out of 38 (36.8%), respectively. The number and percentage of joints achieving a relative contracture reduction of ≥50% after the extension procedure were equal to 100 and 90.1%, respectively. There was a statistically significant decrease in contracture between baseline and the follow-up visit (p<0.0001; paired Student's t test). One hundred four (104) joints (93.7%) were considered successfully treated by the investigator at the follow-up visit: 73 MCP joints (70.2%) and 31 PIP joints (29.8%). The treatment of 79 joints (71.2%) was not accompanied by a loss of working days. The number of working days lost was ≤10 for 21 joints (18.9%) and >10 days for 11 joints (9.9%). The URAM score decreased from 29.4 ± 11.0 to 12.9 ± 6.3. This

[1] Peimer CA, Skodny P, Mackowiak JI. Collagenase clostridium histolyticum for Dupuytren contracture: patterns of use and effectiveness in clinical practice. *J Hand Surg Am.* 2013;38(12):2370-2376.

[2] Hurst LC, Badalamente MA, Hentz VR, et al; CORD I Study Group. Injectable collagenase clostridium histolyticum for Dupuytren's contracture. *N Engl J Med.* 2009;361(10):968-979.

Study Number: AUX-CC-902
decrease was clinically and statistically significant (p<0.0001; paired Student's t test). A decrease of about 2.9 points on the URAM has been considered clinically relevant by Beaudreuil et al.[3] According to the physician, the level of severity decreased of at least one category for 89 joints and increased of at least one category for 1 joint. A status quo was reported for 14 joints. The decrease in the severity of contractures was statistically significant (p<0.0001; Wilcoxon's paired test). Physicians were very satisfied or quite satisfied of the treatment for 100 patients (95.3%) and were quite dissatisfied or very dissatisfied for 4 patients (3.9%). Ninety-six (96; 92.3%) out of the 104 completed patients were very satisfied or quite satisfied of their treatment and 7 (6.8%) were quite dissatisfied or very dissatisfied. This level of satisfaction corroborates the one found in the study of Witthaut et al,[4] where 92% of patients were very satisfied or quite satisfied of Xiapex® treatment. After the treatment with Xiapex®, 12 joints (10.8%) did not necessitate further actions while further cares were provided for 99 (89.2%) of joints. They consisted mainly of splinting (89.2%) or physiotherapy (0.9%). Overall, 184 AEs were reported in 84 patients (77.8%) and 175 AEs considered related to the treatment or to the procedure were reported in 82 patients (75.9%). Two AEs (1.1%) were considered severe. Concomitant medications were prescribed to treat 11 (6.0%) AEs. The most frequent AEs were local swelling (N=42; 22.8%), pain in extremity (N=19; 10.3%), ecchymosis (N=16; 8.7%), injection site haemorrhage (N=16; 8.7%), laceration (N=15; 8.2%) and injection site swelling (N=13; 7.1%). The most frequent related AEs were local swelling (N=42; 24.0%), pain in extremity (N=18; 10.3%), ecchymosis (N=16; 9.1%), injection site haemorrhage (N=16; 9.1%), laceration (N=15; 8.6%) and injection site swelling (N=13; 7.4%). The AE profile, in terms of nature, severity, frequency/rate, as well as resolution, is in agreement with the current label of Xiapex® and previous clinical trial data. No SAEs were reported in any patient.

[3] Beaudreuil J, Allard A, Zerkak D, et al; URAM Study Group. Unité Rhumatologique des Affections de la Main (URAM) scale: development and validation of a tool to assess Dupuytren's disease-specific disability. *Arthritis Care Res*. 2011;63(10):1448-1455.

[4] Witthaut J, Jones G, Skrepnik N, Kushner H, Houston A, Lindau TR. Efficacy and safety of collagenase clostridium histolyticum injection for Dupuytren contracture: short-term results from 2 open-label studies. *J Hand Surg Am.* 2013;38(1):2-11