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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Xiapex® / Collagenase *Clostridium histolyticum*

PROTOCOL NO.: B1531002

PROTOCOL TITLE: Prospective Open-Label Investigation of the Non-Surgical Treatment With Collagenase *Clostridium histolyticum* Xiapex® (X)

Study Centers: A total of 27 centers took part in the study and enrolled subjects; 2 in Denmark, 4 in France, 5 in Germany, 1 in Hungary, 3 in Italy, 5 in Spain, 3 in Sweden and 4 in the United Kingdom (UK).

Study Initiation Date and Final Completion Date: 22 December 2010 to 31 October 2012

Phase of Development: Phase 3b

Study Objectives: The objectives of this study were to evaluate the safety and efficacy of Xiapex® in subjects with Dupuytren's contracture, the recovery and associated use of health care in patients in Europe when physicians and subjects were given the opportunity to treat the affected hand (or hands) by selecting which cord and joint to treat with each injection. Specifically, this study:

- Evaluated the impact of Xiapex on the Dupuytren's contracture, the range of motion (ROM) and the subject and physician-reported treatment satisfaction and disease severity and their relationship to ROM.
- Assessed the recovery to normal activities.
- Assessed recovery time (how long overall, time to use hand, time to return to work or daily activities, amount of work or daily activity time missed or reduced, and effects on productivity and daily activities) - via a subject diary.
- Assessed the use of concomitant analgesic medications.
- Evaluated total health care resource utilization (HCRU eg, medical and allied health care visits and resources, use of splinting).
- Assessed the pattern of treatment when multiple joints and or/fingers were treated.

METHODS

Study Design: This prospective, open-label, multicenter study in subjects with Dupuytren's contracture included 2 phases. The first was an open-label treatment phase (up to 5 months

in duration) and the second was a 6-month follow-up phase. At screening, the subjects were to identify the fingers they wished to be treated and ranked these in order of preference. Before the first injection, Investigators evaluated all fingers other than the thumbs (of both hands) and also selected the first joint to be treated (they were provided with the subject's selection). The first joint to be treated was decided after a discussion between the subject and the Investigator. The reasons for the subject's and the Investigator's choices as well as deviations from the subject's pre-selected order were recorded. Prior to each new treatment cycle (Cycles 2 to 5), the Investigator selected the location of the next injection.

The study consisted of an open-label treatment phase and a follow-up phase. During the open-label treatment phase, a maximum of 5 treatment cycles of 1 injection per cycle were offered to each subject, with a maximum of 3 injections into the same cord. A treatment cycle consisted of an injection with Xiapex (0.58 mg) on injection day, a visit on Day 1 after the injection, during which a finger extension procedure was performed, and 2 visits on Days 7 and 30 after the injection. During the follow-up phase, visits took place 90 days after the last injection and 6 months after the last injection, giving a total time in the study of 11 months for a subject who elected to have 5 treatment cycles. The schedule of study procedures and evaluations is presented in Table 1.

Table 1. Schedule of Study Procedures and Evaluations

Protocol Activity	Screen Within 60[a] Days of First Injection	Injection Day[b] Before Each Injection	Injection Day After Each Injection	Day 1[c] After Injection	Day 7[c] After Injection	Day 30[c,d] After Injection	Day 90[d] After Last Treatment Cycle	Follow Up 6 Months[d] After Last Treatment Cycle
Informed consent	X							
Medical history of Dupuytren's disease	X							
General medical history and physical examination	X							
Weight and height	X							
Table Top Test	X							
Vital signs	X	X	X	X				X
ECG	X							
Safety laboratory tests[e]	X							X
Finger goniometry[f]	X	X		X	X	X	X	X
Pregnancy test[g]	X	X						X
Immunogenicity sample[h]	X							X
Inclusion/Exclusion criteria	X							
Subject ranking of finger for treatment	X							
Joint treatment selection		X						
Study drug administration		X						
Finger extension procedure				X				
Adverse events	X	X	X	X	X	X	X	X
Concomitant medications	X		X	X	X	X	X	X
Issue subject diary[i]		X						
Collect subject diary						X	X	X
Subject work and activity questionnaire[j]		X						
HCRU		X			X	X	X	X

Table 1. Schedule of Study Procedures and Evaluations

Protocol Activity	Screen Within 60[a] Days of First Injection	Injection Day[b] Before Each Injection	Injection Day After Each Injection	Day 1[c] After Injection	Day 7[c] After Injection	Day 30[c,d] After Injection	Day 90[d] After Last Treatment Cycle	Follow Up 6 Months[d] After Last Treatment Cycle
Subject global assessment of disease severity and satisfaction		X				X	X	X
Physician global assessment of disease severity and satisfaction		X				X	X	X
URAM scale[k]		X				X	X	X

ECG = Electrocardiogram; HCRU = Healthcare resource utilization; URAM = Unité Rhumatologique des Affection de la Main.

a. If a subject did not present for treatment with 60 days of screening, he/she could have been rescreened.
b. Subjects could receive up to 5 cycles of treatment with a maximum of 3 cycles to any individual cord.
c. The assessment at Day 1, Day 7 (+/- 1 day), and Day 30 after the injection was repeated for each treatment cycle.
d. Individual treatment cycles were to be no shorter than 28 days but could be up to 40 days. The window for follow-up visits was ±15 days.
e. Safety laboratory tests were performed at screening and at the end of study; they did not need to be done for every treatment cycle.
f. The angles of extension/flexion on all of the joints on both hands were measured (if applicable).
g. Pregnancy tests could also be repeated as per the request of Independent Review Board/Independent Ethics Committee or if required by local regulations.
h. Immunogenicity: antidrug antibodies (ADAs) and cross reactivity to endogenous matrix metalloproteinases (MMPs) were analyzed. Cross-reactivity analysis was added to the protocol in Amendment 1.
i. Subjects were to complete diaries on the day of the injection, then daily for 2 weeks, and then weekly to the end of the treatment cycle. After the last treatment cycle, they were to complete weekly diaries through to Day 90.
j. This particular measure was done at baseline only because it is related to Dupuytren's disease and contracture (in general). Afterwards, all work and activity reductions questions related only to treatment were asked and captured in the daily or weekly diary.
k. The URAM scale was completed only for subjects in France, the United Kingdom, Germany, Sweden, and Hungary.

Number of Subjects (Planned and Analyzed): It was planned to enroll 250 subjects. A total of 254 subjects (25 each in Denmark and Germany, 33 in France, 15 in Hungary, 29 in Italy, 49 in Spain, 32 in Sweden and 46 in the UK) were enrolled and evaluated for efficacy and safety.

Diagnosis and Main Criteria for Inclusion: Subjects who were between 18 and ≤70 years of age; had a diagnosis of Dupuytren's disease that resulted in Dupuytren's contracture of at least 20°caused by a palpable cord in at least 1 finger other than the thumb; and a positive "Table Top Test," defined as the inability to simultaneously place the affected finger(s) and palm flat against a table top.

Study Treatment: All study medications were supplied as Collagenase *Clostridium histolyticum* for injection, lyophilized powder with a sterile diluent solution. Xiapex was administered as a single injection (0.58 mg) during each treatment cycle after the pre-injection safety assessments, and the finger goniometry and joint selection evaluations had been completed. Subjects could receive up to 5 injections (1 injection per cycle) of treatment (a maximum of 3 injections in the same cord) over 5 months.

Safety, Efficacy and Other Endpoints:

Safety:

- Adverse events (AEs), vital signs, clinical laboratory parameters and anti-drug antibodies (ADAs).

Efficacy:

- Total Passive Extension Deficit (TPED: a sum of the Passive Extension Deficits [PED] in the metacarpophalangeal [MP], proximal interphalangeal [PIP], and distal interphalangeal [DIP] joints) and PED.
- Change in TPED and PED for each joint treated.
- ROM.
- Patient and physician global assessment of treatment satisfaction and disease severity.

Recovery, Hand Functionality and HCRU:

- Type and amount of concomitant pain medications.
- Total recovery time, time to use the hand, daily activities, work versus hobbies.
- Hand functionality – Unité Rhumatologique des Affections de la Main (URAM) scale was completed only for subjects in France, the UK, Germany, Sweden and Hungary.
- HCRU questionnaire.

Safety Evaluations: AEs were monitored throughout the study. Vital signs (systolic and diastolic blood pressure, respiratory rate, radial pulse, and body temperature), physical examinations (including height and weight), electrocardiograms (ECGs), and pregnancy tests were performed at specified timepoints throughout the study (Table 1). Immunogenicity to clostridial type I collagenase (AUX-I) and clostridial type II collagenase (AUX-II) and cross-reactivity of the antidrug antibodies to matrix metalloproteinases (MMPs) 1, 2, 3, 8, and 13 was assessed at screening and at the 6-month follow-up visit.

Statistical Methods: PED was measured in degrees (°) using finger goniometry and was measured for each affected MP, PIP, and DIP joint. TPED was the sum of PED in the MP, PIP, and distal interphalangeal joints within a finger. In addition, change in PED for each treated joint, change in TPED for each finger, ROM as measured by using the difference between the angle of flexion and the angle of extension of the joint, subject and physician global assessments of treatment satisfaction and disease severity, and relationship between finger ROM or TPED and subject or Investigator-reported outcomes were assessed as efficacy endpoints.

No inferential statistical analyses were carried out on any of the efficacy or safety assessments done in this study. Statistical summaries were limited to descriptive statistics for all efficacy measures and 95% confidence intervals (CIs) for the changes from baseline for selected efficacy measures. All continuous endpoints were summarized using descriptive statistics for each visit in which they were collected. Also, the changes from baseline in continuous endpoints were summarized for each postbaseline visit along with the corresponding 95% CIs. All categorical endpoints were summarized by frequency counts (ie, the number and percentage of subjects in each category) at each visit for which these data were collected.

RESULTS:

Subject Disposition and Demography: A total of 254 subjects were assigned to receive between 1 and 5 cycles of treatment with Xiapex (0.58 mg), with a maximum of 3 injections into the same cord affecting the joint. Subject disposition and data sets analyzed are presented in Table 2.

Table 2. Subject Disposition and Reasons for Discontinuation From Study: All Screened Subjects

	Number (%) of Subjects
Screened	267
Assigned to study drug[a]	254
Not treated	0
Treated	254 (100)
Treated subjects[b]	254
Completed	249 (98.0)
Discontinued study	5 (2.0)
Primary reason for discontinuation from study[c]	
Adverse event	0
Withdrawal of consent	1 (20.0)
Lost to follow up	3 (60.0)
Subject request	1 (20.0)
Investigator request	0
Other	0
Analysis sets[b]	
Safety set[d]	254 (100.0)
Full analysis set[e]	254 (100.0)

a. Percentages used the number of subjects assigned to treatment as the denominator.
b. Percentages used the number of treated subjects as the denominator.
c. Percentages used the number of subjects who discontinued from the study as the denominator.
d. The safety set included all subjects who received at least 1 dose of Xiapex.
e. The full analysis set included all subjects who received at least 1 dose of Xiapex and had at least 1 postinjection efficacy assessment.

The majority of the subjects were male (87.8%) and Caucasian (99.6%). The median age of the subjects was 62.0 years (range: 29 to 70 years).

Slightly less than half (115/254 [45.3%]) of the subjects had both hands affected with Dupuytren's disease at screening. For those subjects who had only 1 hand affected, the right hand (77/139 [30.3%] subjects) was affected by Dupuytren's disease slightly more than the left hand (62/139 [24.4%] subjects). Most subjects had between 1 and 3 fingers affected overall. Of the fingers and joints affected, the MP and PIP joints of both the little and ring fingers were the most frequently affected. All 254 (100%) subjects had a Table Top Test performed at screening. Of the 217 subjects who had the left hand tested, 161 (74.2%) had a positive Table Top Test result, and of the 222 subjects who had the right hand tested, 175 (78.8%) had a positive Table Top Test result.

All 254 (100%) subjects completed the ranking of fingers for treatment, first through fifth choice, assessment. The Investigator selected the fingers and joints to be treated for 251/254 (98.0%) subjects, with little finger (132 [52.6%] subjects) and ring finger (101 [40.2%] subjects) selected most frequently. The Investigator's selection of finger to be treated first matched the choice made by 246 (98.0%) subjects. The reasons for the selection where the Investigator's choice did not match the subject's choice were greater anticipated clinical response (3/5 [60.0%] subjects) and anticipated technical issue and other (both 1/5 [20.0%] subjects).

Efficacy Results:

PED: The majority of MP joints received only 1 injection. A rapid and substantial response in the reduction of the contracture (median PED) from baseline was observed on Day 1 after the first injection in MP joints that received 1 injection (80% reduction from baseline) and on Day 1 after the second injection in MP joints that received 2 injections (82.14% reduction from baseline). A further reduction in the median PED from baseline was observed by Day 7 after the first injection for MP joints that received 1 injection (100% reduction from baseline). The substantial reduction from baseline in the contracture seen at the early time points for the MP joints that received 1 or 2 injections was maintained at the follow-up visit at 6 months after the last injection. A similar response was also observed for the PIP joint, although the overall reduction in the contracture from baseline was less than that for the MP joint. PED for MP joints that received 1, 2, or 3 injections by study visit is summarized in Table 3.

Table 3 A Summary of Passive Extension Deficit for Metacarpophalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	MP Joints[a] That Received 1 Injection (N=211)		MP Joints[a] That Received 2 Injections (N=33)		MP Joints[a] That Received 3 Injections (N=9)	
Study Visit	**PED[b] (°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**
Baseline						
n	211	-	33	-	9	-
Mean (SD)	42.5 (19.09)	-	45.4 (18.23)	-	52.8 (23.06)	-
Median	40.0	-	40.0	-	50.0	-
IQR	30.0 - 60.0	-	30.0 - 60.0	-	40.0 - 60.0	-
Min, max	0, 90	-	10, 80	-	20, 90	-
Change from baseline to Day 1 after first injection[c]						
n	207	205	33	33	9	9
Mean (SD)	-28.2 (21.63)	-64.05 (50.894)	-15.6 (16.24)	-31.79 (30.374)	-22.8 (20.63)	-38.08 (28.397)
Median	-30.0	-80.00	-15.0	-35.71	-25.0	-29.41
IQR	-42.0 - -10.0	-100.00 - -45.45	-25.0 - 0.0	-50.00 - 0.00	-35.0 - -5.0	-66.67 - -25.00
Min, max	-90, 25	-100.0, 250.0	-50, 10	-83.3, 33.3	-60, 0	-70.0, 0.0
95% CI[d]	-31.2, -25.2	-	-21.4, -9.9	-	-38.6, -6.9	-
Change from baseline to Day 7 after first injection[c]						
n	209	207	32	32	9	9
Mean (SD)	-32.9 (18.38)	-79.05 (28.703)	-14.4 (17.02)	-31.42 (35.897)	-22.2 (16.60)	-41.84 (23.892)
Median	-30.0	-100.00	-15.0	-33.33	-20.0	-50.00
IQR	-45.0 - -20.0	-100.00 - -63.64	-21.0 - -2.5	-50.00 - -8.33	-30.0 - -10.0	-60.00 - -17.65
Min, max	-80, 12	-100.0, 33.3	-60, 18	-100.0, 50.0	-50, 0	-66.7, 0.0
95% CI[d]	-35.4, -30.4	-	-20.6, -8.3	-	-35.0, -9.5	-
Change from baseline to Day 30 after first injection[c]						
n	209	207	33	33	9	9
Mean (SD)	-35.7 (18.37)	-85.21 (25.332)	-14.7 (17.30)	-30.73 (33.580)	-18.1 (17.95)	-31.22 (28.906)
Median	-35.0	-100.00	-10.0	-33.33	-20.0	-33.33
IQR	-50.0 - -21.0	-100.00 - -77.78	-20.0 - -6.0	-50.00 - -16.67	-30.0 - -10.0	-50.00 - -20.00
Min, max	-80, 10	-100.0, 16.7	-60, 24	-100.0, 66.7	-50, 10	-75.0, 20.0
95% CI[d]	-38.2, -33.2	-	-20.8, -8.6	-	-31.9, -4.3	-
Baseline before second injection						
n	-	-	33	-	9	-
Mean (SD)	-	-	30.4 (18.60)	-	35.8 (16.29)	-
Median	-	-	25.0	-	30.0	-
IQR	-	-	20.0 - 40.0	-	20.0 - 40.0	-
Min, max	-	-	0, 74	-	20, 62	-
Change from baseline to Day 1 after second injection[c]						

Table 3 A Summary of Passive Extension Deficit for Metacarpophalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	MP Joints[a] That Received 1 Injection (N=211)		MP Joints[a] That Received 2 Injections (N=33)		MP Joints[a] That Received 3 Injections (N=9)	
Study Visit	**PED[b] (°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**
n	-	-	33	31	9	9
Mean (SD)	-	-	-19.7 (17.12)	-65.13 (42.144)	-21.9 (6.29)	-69.65 (29.247)
Median	-	-	-20.0	-82.14	-20.0	-50.00
IQR	-	-	-26.0 - -5.0	-100.00 - -50.00	-27.0 - -20.0	-100.00 - -50.00
Min, max	-	-	-60, 10	-100.0, 50.0	-30, -10	-100.0, -33.3
95% CI[d]	-	-	(-25.8, -13.7)	-	(-26.7, -17.1)	-
Change from baseline to Day 7 after second injection[c]						
n	-	-	33	31	9	9
Mean (SD)	-	-	-19.3 (16.69)	-63.93 (41.775)	-19.9 (9.62)	-61.71 (31.742)
Median	-	-	-20.0	-75.00	-20.0	-50.00
IQR	-	-	-26.0 - -10.0	-100.00 - -50.00	-20.0 - -20.0	-100.00 - -38.71
Min, max	-	-	-58, 20	-100.0, 66.7	-40, -5	-100.0, -16.7
95% CI[d]	-	-	-25.2, -13.4	-	-27.3, -12.5	-
Change from baseline to Day 30 after second injection[c]						
n	-	-	32	30	9	9
Mean (SD)	-	-	-19.9 (17.33)	-64.57 (39.062)	-11.9 (9.06)	-37.25 (31.253)
Median	-	-	-20.0	-70.71	-10.0	-43.55
IQR	-	-	-30.0 - -7.5	-100.00 - -50.00	-20.0 - -10.0	-50.00 - -16.67
Min, max	-	-	-68, 10	-100.0, 50.0	-27, 0	-100.0, 0.0
95% CI[d]	-	-	(-26.1, -13.6)	-	(-18.9, -4.9)	-
Baseline before third injection						
n	-	-	-	-	9	-
Mean (SD)	-	-	-	-	22.8 (15.23)	-
Median	-	-	-	-	20.0	-
IQR	-	-	-	-	10.0 - 30.0	-
Min, max	-	-	-	-	0, 50	-
Change from baseline to Day 1 after third injection[c]						
n	-	-	-	-	9	8
Mean (SD)	-	-	-	-	-13.0 (10.17)	-73.33 (41.096)
Median	-	-	-	-	-10.0	-100.00
IQR	-	-	-	-	-20.0 - -7.0	-100.00 - -43.33
Min, max	-	-	-	-	-30, 0	-100.0, 0.0

Table 3 A Summary of Passive Extension Deficit for Metacarpophalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	MP Joints[a] That Received 1 Injection (N=211)		MP Joints[a] That Received 2 Injections (N=33)		MP Joints[a] That Received 3 Injections (N=9)	
Study Visit	**PED[b] (°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**
95% CI[d]	-	-	-	-	(-20.8, -5.2)	-
Change from baseline to Day 7 after third injection[c]						
n	-	-	-	-	9	8
Mean (SD)	-	-	-	-	-7.3 (11.36)	-44.17 (54.649)
Median	-	-	-	-	-10.0	-41.67
IQR	-	-	-	-	-10.0 - 0.0	-100.00 - -10.00
Min, max	-	-	-	-	-30, 10	-100.0, 50.0
95% CI[d]	-	-	-	-	(-16.1, 1.4)	-
Change from baseline to Day 30 after third injection[c]						
n	-	-	-	-	9	8
Mean (SD)	-	-	-	-	-5.6 (6.82)	-35.54 (49.122)
Median	-	-	-	-	-10.0	-26.67
IQR	-	-	-	-	-10.0 - -5.0	-75.00 - -15.48
Min, max	-	-	-	-	-10, 10	-100.0, 50.0
95% CI[d]	-	-	-	-	(-10.8, -0.3)	-
Baseline before first injection						
n	201	-	33	-	9	-
Mean (SD)	42.6 (18.86)	-	45.4 (18.23)	-	52.8 (23.06)	-
Median	40.0	-	40.0	-	50.0	-
IQR	30.0 - 58.0	-	30.0 - 60.0	-	40.0 - 60.0	-
Min, max	0, 90	-	10, 80	-	20, 90	-
Change from baseline to 6 months after last injection[c]						
n	207	205	32	32	9	9
Mean (SD)	-36.8 (20.17)	-86.41 (31.567)	-33.4 (18.26)	-72.58 (34.429)	-36.4 (16.36)	-73.79 (24.858)
Median	-35.0	-100.00	-34.0	-84.52	-35.0	-74.12
IQR	-50.0 - -22.0	-100.00 - -84.31	-40.0 - -25.0	-100.00 - -56.92	-40.0 - -20.0	-100.00 - -66.67
Min, max	-82, 20	-100.0, 200.0	-70, 14	-100.0, 38.9	-63, -20	-100.0, -33.3
95% CI[d]	(-39.6, -34.1)	-	(-40.0, -26.8)	-	(-49.0, -23.9)	-

Table 3 A Summary of Passive Extension Deficit for Metacarpophalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	MP Joints[a] That Received 1 Injection (N=211)		MP Joints[a] That Received 2 Injections (N=33)		MP Joints[a] That Received 3 Injections (N=9)	
Study Visit	**PED[b] (°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**

CI = confidence interval; IQR = interquartile range; max = maximum; min = minimum;
MP = metacarpophalangeal; N = number of joints that received the specified number of injections;
n = number of joints that received the specified number of injections and had goniometric data available at that visit; PED = passive extension deficit; SD = standard deviation.

a. The joint could be the metacarpophalangeal joint in any finger of either hand.
b. PED was the passive extension deficit provided for the joint treated for that injection.
c. For 6 months after the last injection, the baseline PED value was the PED value taken closest to and before the administration of the first injection.
d. 95% confidence interval for the change in PED from baseline.

PED for PIP joints that received 1, 2, or 3 injections by study visit is summarized in Table 4.

Table 4. A Summary of Passive Extension Deficit for Proximal Interphalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	PIP Joints[a] That Received 1 Injection (N=98)		PIP Joints[a] That Received 2 Injections (N=18)		PIP Joints[a] That Received 3 Injections (N=6)	
Study Visit	**PED[b](°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**
Baseline						
n	98	-	18	-	6	-
Mean (SD)	49.8 (20.84)	-	60.8 (23.67)	-	65.8 (21.08)	-
Median	45.0	-	65.0	-	60.0	-
IQR	35.0 - 60.0	-	50.0 - 78.0	-	55.0 - 80.0	-
Min, max	15, 94	-	10, 95	-	40, 100	-
Change from baseline to Day 1 after first injection[c]						
n	98	98	17	17	6	6
Mean (SD)	-26.1 (21.69)	-51.70 (47.660)	-23.9 (18.75)	-48.70 (37.235)	-18.3 (19.41)	-25.97 (26.721)
Median	-25.0	-58.57	-20.0	-45.65	-15.0	-21.67
IQR	-40.0 - -10.0	-100.00 - -12.50	-40.0 - -10.0	-75.00 - -21.43	-30.0 - 0.0	-50.00 - 0.00
Min, max	-90, 33	-100.0, 220.0	-60, 0	-100.0, 0.0	-50, 0	-62.5, 0.0
95% CI[d]	-30.4, -21.7	-	-33.6, -14.3	-	-38.7, 2.0	-
Change from baseline to Day 7 after first injection[c]						
n	97	97	18	18	6	6
Mean (SD)	-32.0 (19.50)	-65.67 (39.899)	-26.6 (18.12)	-49.96 (31.158)	-18.3 (22.06)	-24.03 (34.077)
Median	-30.0	-75.00	-24.0	-57.74	-17.5	-24.17
IQR	-40.0 - -20.0	-100.00 - -53.85	-38.0 - -15.0	-66.67 - -21.43	-35.0 - 0.0	-58.33 - 0.00
Min, max	-90, 31	-100.0, 206.7	-68, 0	-100.0, 0.0	-50, 10	-62.5, 25.0
95% CI[d]	-35.9, -28.0	-	-35.6, -17.6	-	-41.5, 4.8	-
Change from baseline to Day 30 after first injection[c]						
n	98	98	18	18	6	6
Mean (SD)	-29.0 (19.19)	-57.82 (41.115)	-19.4 (16.88)	-34.14 (24.402)	-19.2 (24.58)	-25.86 (33.999)
Median	-30.0	-64.72	-12.5	-30.48	-17.5	-24.17
IQR	-40.0 - -16.0	-86.67 - -35.71	-30.0 - -10.0	-50.00 - -16.67	-30.0 - 0.0	-50.00 - 0.00
Min, max	-94, 31	-100.0, 206.7	-58, 0	-74.4, 0.0	-60, 10	-75.0, 18.2
95% CI[d]	-32.8, -25.1	-	-27.8, -11.1	-	-45.0, 6.6	-

Table 4. A Summary of Passive Extension Deficit for Proximal Interphalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	PIP Joints[a] That Received 1 Injection (N=98)		PIP Joints[a] That Received 2 Injections (N=18)		PIP Joints[a] That Received 3 Injections (N=6)	
Study Visit	**PED[b](°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**
Baseline before second injection						
n	-	-	18	-	6	-
Mean (SD)	-	-	44.4 (21.54)	-	46.7 (24.01)	-
Median	-	-	40.0	-	40.0	-
IQR	-	-	34.0 - 60.0	-	30.0 - 65.0	-
Min, max	-	-	5, 90	-	20, 85	-
Change from baseline to Day 1 after second injection[c]						
n	-	-	15	15	6	6
Mean (SD)	-	-	-15.7 (17.60)	-45.64 (47.066)	-14.2 (13.93)	-42.54 (45.030)
Median	-	-	-10.0	-57.14	-7.5	-20.83
IQR	-	-	-40.0 - 0.0	-100.00 - 0.00	-20.0 - -5.0	-100.00 - -7.69
6Min, max	-	-	-42, 6	-100.0, 17.6	-40, -5	-100.0, -5.9
95% CI[d]	-	-	-25.5, -6.0	-	-28.8, 0.5	-
Change from baseline to Day 7 after second injection[c]						
n	-	-	18	18	6	6
Mean (SD)	-	-	-16.3 (15.25)	-39.32 (37.268)	-13.7 (13.66)	-34.51 (35.485)
Median	-	-	-12.5	-29.17	-10.0	-26.02
IQR	-	-	-30.0 - -5.0	-64.29 - -14.29	-30.0 - -2.0	-75.00 - -5.00
Min, max	-	-	-45, 6	-100.0, 17.6	-30, 0	-75.0, 0.0
95% CI[d]	-	-	-23.9, -8.7	-	-28.0, 0.7	-
Change from baseline to Day 30 after second injection[c]						
n	-	-	18	18	6	6
Mean (SD)	-	-	-13.6 (14.44)	-41.49 (39.506)	-8.8 (8.61)	-22.05 (25.799)
Median	-	-	-14.5	-39.01	-9.0	-21.54
IQR	-	-	-20.0 - 0.0	-75.00 - 0.00	-15.0 - -5.0	-50.00 - -5.88
Min, max	-	-	-40, 10	-100.0, 16.7	-20, 5	-50.0, 16.7
95% CI[d]	-	-	-20.8, -6.4	-	-17.9, 0.2	-
Baseline before third injection						
n	-	-	-	-	6	-
Mean (SD)	-	-	-	-	40.8 (22.45)	-
Median	-	-	-	-	37.5	-
IQR	-	-	-	-	20.0 - 50.0	-
Min, max	-	-	-	-	20, 80	-

Table 4. A Summary of Passive Extension Deficit for Proximal Interphalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	PIP Joints[a] That Received 1 Injection (N=98)		PIP Joints[a] That Received 2 Injections (N=18)		PIP Joints[a] That Received 3 Injections (N=6)	
Study Visit	**PED[b](°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**
Change from baseline to Day 1 after third injection[c]						
n	-	-	-	-	6	6
Mean (SD)	-	-	-	-	-16.7 (10.33)	-58.04 (44.259)
Median	-	-	-	-	-20.0	-67.86
IQR	-	-	-	-	-20.0 - -10.0	-100.00 - -12.50
Min, max	-	-	-	-	-30, 0	-100.0, 0.0
95% CI[d]	-	-	-	-	-27.5, -5.8	-
Change from baseline to Day 7 after third injection[c]						
n	-	-	-	-	**6**	6
Mean (SD)	-	-	-	-	-16.3 (11.60)	-51.31 (33.063)
Median	-	-	-	-	-16.5	-47.50
IQR	-	-	-	-	-20.0 - -10.0	-70.00 - -42.86
Min, max	-	-	-	-	-35, 0	-100.0, 0.0
95% CI[d]	-	-	-	-	-28.5, -4.2	-
Change from baseline to Day 30 after third injection[c]						
n	-	-	-	-	6	6
Mean (SD)	-	-	-	-	-12.5 (6.89)	-41.31 (24.991)
Median	-	-	-	-	-15.0	-46.43
IQR	-	-	-	-	-15.0 - -10.0	-50.00 - -30.00
Min, max	-	-	-	-	-20, 0	-75.0, 0.0
95% CI[d]	-	-	-	-	-19.7, -5.3	-
Baseline before first injection						
n	93	-	17	-	6	-
Mean (SD)	48.6 (20.40)	-	59.6 (23.89)	-	65.8 (21.08)	-
Median	45.0	-	60.0	-	60.0	-
IQR	35.0 - 60.0	-	50.0 - 70.0	-	55.0 - 80.0	-
Min, max	15, 94	-	10, 95	-	40, 100	-
Change from baseline to 6 months after last injection[c]						
n	93	93	18	18	6	6
Mean (SD)	-21.3 (23.61)	-41.11 (41.901)	-22.0 (24.37)	-29.14 (34.745)	-21.7 (21.60)	-33.02 (26.815)
Median	-20.0	-42.11	-22.5	-28.80	-17.5	-30.30
IQR	-30.0 - -5.0	-75.00 - -12.50	-45.0 - 0.0	-61.54 - 0.00	-30.0 - -5.0	-50.00 - -12.50
Min, max	-94, 25	-100.0, 100.0	-65, 10	-81.3, 33.3	-60, 0	-75.0, 0.0

Table 4. A Summary of Passive Extension Deficit for Proximal Interphalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	PIP Joints[a] That Received 1 Injection (N=98)		PIP Joints[a] That Received 2 Injections (N=18)		PIP Joints[a] That Received 3 Injections (N=6)	
Study Visit	**PED[b](°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**	**PED[b] (°)**	**% Change in PED**
95% CI[d]	-26.2, -16.4	-	-34.1, -9.9	-	-44.3, 1.0	-

CI = confidence interval; IQR = interquartile range; max = maximum; min = minimum; N = number of joints that received the specified number of injections; n = number of joints that received the specified number of injections and had goniometric data available at that visit; PED = passive extension deficit; PIP = proximal interphalangeal; SD = standard deviation.

a. The joint could be the proximal interphalangeal joint in any finger of either hand.
b. PED was the passive extension deficit provided for the joint treated for that injection.
c. For 6 months after the last injection, the baseline PED value was the PED value taken closest to and before the administration of the first injection.
d. 95% confidence interval for the change in PED from baseline.

TPED: The majority of fingers (259/346) received only 1 injection. Median TPED at baseline before the first injection was lower for those fingers that only received a total of 1 injection (55.0°) than it was for those fingers that received a total of 2 (85.0°) or 3 (80.0°) injections. Overall, the median TPED at 6 months after the last injection was reduced further in fingers that received only 1 injection than in those that received 2 or 3 injections; however, the change from baseline in median TPED for fingers that received 2 injections (-50.0) was greater than fingers that received 1 or 3 injections, for which the median TPED was similar (change from baseline in median TPED for both was -35.0).

ROM: Notable increases from baseline were observed in ROM of the MP joints, although the response was not as rapid as that seen for PED. Median ROM was 45.0° and 50.0° at baseline before the first injection for MP joints that received 1 or 2 injections, respectively. Median ROM increased from baseline to Day 30 by 33.5° after the first injection for MP joints that received 1 injection. Similarly, median ROM increased from baseline to Day 30 by 15.0° after each of the first and second injections for MP joints that received 2 injections.

The increase from baseline (ie, before the first injection) in median ROM was maintained at 6 months after the last injection for MP joints that received 1 or 2 injections and was similar between those MP joints that received 1 or 2 injections (35.5°, 95% CI [34.6, 40.2] for MP joints that received 1 injection and 30.0°, 95% CI [22.7, 38.6] for MP joints that received 2 injections). Increases from baseline were observed in ROM of the PIP joints that received 1 or 2 injections at 6 months after the last injection: 16.0°, 95% CI (15.0, 24.7) for PIP joints that received 1 injection and 12.5°, 95% CI (6.7, 29.3) for PIP joints that received 2 injections; however, the increases were less than those observed for the MP joints and more variation was seen. ROM for MP joints that received 1, 2, or 3 injections by study visit is summarized in Table 5, and ROM for PIP joints that received 1, 2, or 3 injections by study visit is summarized in Table 6.

Table 5. A Summary of Range of Motion for Metacarpophalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	MP Joints[a] That Received 1 Injection (N=211)		MP Joints[a] That Received 2 Injections (N=33)		MP Joints[a] That Received 3 Injections (N=9)	
Study Visit	**ROM[b] (°)**	**% Change in ROM**	**ROM[b] (°)**	**% Change in ROM**	**ROM[b] (°)**	**% Change in ROM**
Baseline						
n	208	-	30	-	9	-
Mean (SD)	46.1 (19.62)	-	44.5 (16.38)	-	37.8 (23.20)	-
Median	45.0	-	50.0	-	40.0	-
IQR	30.0 - 60.0	-	30.0 - 55.0	-	30.0 - 50.0	-
Min, max	0, 90	-	10, 80	-	0, 70	-
Change from baseline to Day 1 after first injection[c]						
n	204	201	30	30	9	8
Mean (SD)	17.2 (24.20)	71.98 (191.405)	12.0 (20.31)	53.51 (107.278)	14.4 (22.28)	68.32 (142.244)
Median	18.0	28.57	12.5	30.30	5.0	9.13
IQR	0.0 - 30.0	0.00 - 85.71	0.0 - 25.0	0.00 - 66.67	0.0 - 20.0	0.00 - 76.67
Min, max	-55, 90	-71.4, 2300.0	-30, 50	-60.0, 500.0	-10, 60	-25.0, 400.0
95% CI[d]	13.8, 20.5	-	4.4, 19.6	-	-2.7, 31.6	-
Change from baseline to Day 7 after first injection[c]						
n	206	203	29	29	9	8
Mean (SD)	27.6 (20.16)	116.36 (369.424)	16.5 (17.49)	62.28 (117.207)	21.7 (16.39)	78.31 (99.498)
Median	25.5	50.00	15.0	28.57	20.0	47.78
IQR	16.0 - 40.0	28.57 - 115.00	5.0 - 26.0	9.09 - 66.67	10.0 - 30.0	11.31 - 104.17
Min, max	-86, 74	-220.0, 4700.0	-14, 60	-30.4, 600.0	0, 50	0.0, 300.0
95% CI[d]	24.9, 30.4	-	9.8, 23.1	-	9.1, 34.3	-
Change from baseline to Day 30 after first injection[c]						
n	206	203	30	30	9	8
Mean (SD)	34.6 (18.70)	149.61 (488.816)	15.7 (18.61)	61.26 (119.250)	17.6 (17.96)	83.75 (156.628)
Median	33.5	68.75	15.0	29.29	15.0	29.17
IQR	20.0 - 49.0	32.35 - 138.10	10.0 - 21.0	14.29 - 66.67	10.0 - 30.0	8.33 - 80.00
Min, max	-11, 90	-16.9, 5900.0	-34, 60	-73.9, 600.0	-10, 50	-25.0, 460.0
95% CI[d]	32.1, 37.2	-	8.8, 22.6	-	3.8, 31.4	-

Table 5. A Summary of Range of Motion for Metacarpophalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	MP Joints[a] That Received 1 Injection (N=211)		MP Joints[a] That Received 2 Injections (N=33)		MP Joints[a] That Received 3 Injections (N=9)	
Study Visit	**ROM[b] (°)**	**% Change in ROM**	**ROM[b] (°)**	**% Change in ROM**	**ROM[b] (°)**	**% Change in ROM**
Baseline before second injection						
n	-	-	33	-	9	-
Mean (SD)	-	-	58.0 (20.09)	-	54.2 (16.29)	-
Median	-	-	60.0	-	60.0	-
IQR	-	-	46.0 - 70.0	-	50.0 - 70.0	-
Min, max	-	-	10, 90	-	28, 70	-
Change from baseline to Day 1 after second injection[c]						
n	-	-	33	33	9	9
Mean (SD)	-	-	11.1 (22.15)	40.20 (90.947)	21.9 (6.29)	47.65 (30.196)
Median	-	-	12.0	17.14	20.0	40.00
IQR	-	-	0.0 - 20.0	0.00 - 45.45	20.0 - 27.0	28.57 - 50.00
Min, max	-	-	-50, 60	-71.4, 440.0	10, 30	16.7, 100.0
95% CI[d]	-	-	3.3, 19.0	-	17.1, 26.7	-
Change from baseline to Day 7 after second injection[c]						
n	-	-	32	32	9	9
Mean (SD)	-	-	15.8 (14.96)	38.85 (55.661)	19.3 (10.68)	44.60 (40.538)
Median	-	-	15.0	26.67	20.0	28.57
IQR	-	-	10.0 - 24.5	13.39 - 44.95	20.0 - 20.0	28.57 - 40.00
Min, max	-	-	-20, 52	-40.0, 216.7	0, 40	0.0, 133.3
95% CI[d]	-	-	10.5, 21.2	-	11.1, 27.5	-
Change from baseline to Day 30 after second injection[c]						
n	-	-	32	32	9	9
Mean (SD)	-	-	17.5 (15.51)	49.03 (64.715)	11.9 (9.06)	27.43 (29.284)
Median	-	-	15.0	21.94	10.0	20.00
IQR	-	-	7.5 - 26.5	10.80 - 75.11	10.0 - 20.0	14.29 - 33.33
Min, max	-	-	-10, 67	-14.3, 239.3	0, 27	0.0, 96.4
95% CI[d]	-	-	11.9, 23.1	-	4.9, 18.9	-
Baseline before third injection						
n	-	-	-	-	9	-
Mean (SD)	-	-	-	-	67.2 (15.23)	-
Median	-	-	-	-	70.0	-
IQR	-	-	-	-	60.0 - 80.0	-
Min, max	-	-	-	-	40, 90	-

Table 5. A Summary of Range of Motion for Metacarpophalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	MP Joints[a] That Received 1 Injection (N=211)		MP Joints[a] That Received 2 Injections (N=33)		MP Joints[a] That Received 3 Injections (N=9)	
Study Visit	**ROM[b] (°)**	**% Change in ROM**	**ROM[b] (°)**	**% Change in ROM**	**ROM[b] (°)**	**% Change in ROM**
Change from baseline to Day 1 after third injection[c]						
n	-	-	-	-	9	9
Mean (SD)	-	-	-	-	11.0 (10.68)	16.33 (17.050)
Median	-	-	-	-	10.0	12.50
IQR	-	-	-	-	0.0 - 20.0	0.00 - 28.57
Min, max	-	-	-	-	-1, 30	-1.8, 50.0
95% CI[d]	-	-	-	-	2.8, 19.2	-
Change from baseline to Day 7 after third injection[c]						
n	-	-	-	-	9	9
Mean (SD)	-	-	-	-	5.7 (12.51)	9.52 (20.764)
Median	-	-	-	-	10.0	12.50
IQR	-	-	-	-	-4.0 - 10.0	-4.44 - 14.29
Min, max	-	-	-	-	-10, 30	-18.2, 50.0
95% CI[d]	-	-	-	-	-3.9, 15.3	-
Change from baseline to Day 30 after third injection[c]						
n	-	-	-	-	9	9
Mean (SD)	-	-	-	-	4.4 (7.68)	7.32 (12.713)
Median	-	-	-	-	10.0	12.50
IQR	-	-	-	-	0.0 - 10.0	0.00 - 14.29
Min, max	-	-	-	-	-10, 10	-14.3, 25.0
95% CI[d]	-	-	-	-	-1.5, 10.4	-
Baseline before first injection						
n	198	-	30	-	9	-
Mean (SD)	46.0 (19.47)	-	44.5 (16.38)	-	37.8 (23.20)	-
Median	45.0	-	50.0	-	40.0	-
IQR	30.0 - 60.0	-	30.0 - 55.0	-	30.0 - 50.0	-
Min, max	0, 90	-	10, 80	-	0, 70	-
Change from baseline to 6 months after last injection[c]						
n	204	201	29	29	9	8
Mean (SD)	37.4 (20.22)	170.49 (599.852)	30.7 (20.98)	103.02 (117.941)	35.9 (16.50)	212.74 (423.699)
Median	35.5	80.00	30.0	69.64	30.0	66.67
IQR	22.0 - 50.0	38.46 - 142.86	20.0 - 40.0	28.57 - 128.57	20.0 - 40.0	50.00 - 90.00
Min, max	-20, 80	-50.0, 7700.0	-24, 84	-52.2, 500.0	20, 63	28.6, 1260.0

Table 5. A Summary of Range of Motion for Metacarpophalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	MP Joints[a] That Received 1 Injection (N=211)		MP Joints[a] That Received 2 Injections (N=33)		MP Joints[a] That Received 3 Injections (N=9)	
Study Visit	**ROM[b] (°)**	**% Change in ROM**	**ROM[b] (°)**	**% Change in ROM**	**ROM[b] (°)**	**% Change in ROM**
95% CI[d]	34.6, 40.2	-	22.7, 38.6	-	23.2, 48.6	-

CI = confidence interval; IQR = interquartile range; max = maximum; min = minimum; MP = metacarpophalangeal; N = number of joints that received the specified number of injections; n = number of joints that received the specified number of injections and had goniometric data available at that visit; ROM = range of motion; SD = standard deviation.

a. The joint could be the metacarpophalangeal joint in any finger of either hand.
b. ROM was the range of motion for the joint treated at that injection.
c. For 6 months after the last injection, the baseline ROM value was the ROM value taken closest to and before the administration of the first injection.
d. 95% confidence interval for the change in ROM from baseline.

Table 6. A Summary of Range of Motion for Proximal Interphalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	PIP Joints[a] That Received 1 Injection (N=98)		PIP Joints[a] That Received 2 Injections (N=18)		PIP Joints[a] That Received 3 Injections (N=6)	
Study Visit	**ROM[b] (°)**	**% Change in ROM**	**ROM[b] (°)**	**% Change in ROM**	**ROM[b] (°)**	**% Change in ROM**
Baseline						
n	98	-	18	-	6	-
Mean (SD)	45.3 (21.61)	-	34.4 (20.59)	-	30.8 (29.05)	-
Median	50.0	-	27.5	-	30.0	-
IQR	30.0 - 60.0	-	20.0 - 44.0	-	10.0 - 55.0	-
Min, max	0, 85	-	10, 80	-	-10, 70	-
Change from baseline to Day 1 after first injection[c]						
n	98	92	17	17	6	6
Mean (SD)	17.3 (25.43)	68.09 (146.584)	12.9 (20.37)	58.29 (111.818)	19.2 (20.10)	76.26 (232.220)
Median	15.0	31.88	15.0	47.06	20.0	33.33
IQR	0.0 - 35.0	0.00 - 80.00	5.0 - 20.0	8.33 - 66.67	0.0 - 30.0	-9.09 - 100.00
Min, max	-49, 90	-57.6, 900.0	-44, 50	-100.0, 450.0	-5, 50	-200.0, 500.0
95% CI[d]	(12.2, 22.4)	-	(2.4, 23.4)	-	(-1.9, 40.3)	-
Change from baseline to Day 7 after first injection[c]						
n	97	91	18	18	6	6
Mean (SD)	27.3 (20.68)	93.79 (168.356)	22.3 (14.76)	94.41 (117.033)	16.7 (24.01)	83.48 (223.284)
Median	26.0	50.00	20.0	58.33	17.5	26.19
IQR	11.0 - 40.0	20.00 - 88.89	10.0 - 35.0	28.57 - 116.67	-10.0 - 35.0	-18.18 - 116.67
Min, max	-47, 90	-55.3, 1150.0	0, 52	0.0, 500.0	-10, 50	-150.0, 500.0
95% CI[d]	(23.2, 31.5)	-	(14.9, 29.6)	-	(-8.5, 41.9)	-
Change from baseline to Day 30 after first injection[c]						
n	98	92	18	18	6	6
Mean (SD)	26.9 (20.24)	101.87 (225.526)	17.3 (17.32)	80.67 (122.967)	19.2 (24.58)	99.75 (259.838)
Median	26.0	50.38	10.0	33.33	17.5	33.33
IQR	15.0 - 40.0	24.72 - 80.00	4.0 - 30.0	6.25 - 133.33	0.0 - 30.0	-18.18 - 100.00
Min, max	-35, 88	-41.2, 1750.0	0, 52	0.0, 500.0	-10, 60	-150.0, 600.0
95% CI[d]	(22.8, 31.0)	-	(8.7, 25.9)	-	(-6.6, 45.0)	-
Baseline before second injection						
n	-	-	18	-	6	-
Mean (SD)	-	-	49.4 (20.54)	-	50.0 (24.29)	-
Median	-	-	50.0	-	55.0	-
IQR	-	-	30.0 - 70.0	-	45.0 - 70.0	-
Min, max	-	-	10, 85	-	5, 70	-
Change from baseline to Day 1 after second injection[c]						
n	-	-	15	15	6	6
Mean (SD)	-	-	10.8 (20.14)	32.41 (58.091)	8.3 (19.41)	29.40 (51.498)

Table 6. A Summary of Range of Motion for Proximal Interphalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	PIP Joints[a] That Received 1 Injection (N=98)		PIP Joints[a] That Received 2 Injections (N=18)		PIP Joints[a] That Received 3 Injections (N=6)	
Study Visit	**ROM[b] (°)**	**% Change in ROM**	**ROM[b] (°)**	**% Change in ROM**	**ROM[b] (°)**	**% Change in ROM**
Median	-	-	10.0	28.57	5.0	18.45
IQR	-	-	0.0 - 20.0	0.00 - 63.64	-5.0 - 20.0	-7.14 - 80.00
Min, max	-	-	-25, 40	-35.7, 200.0	-15, 40	-33.3, 100.0
95% CI[d]	-	-	(-0.4, 22.0)	-	(-12.0, 28.7)	-
Change from baseline to Day 7 after second injection[c]						
n	-	-	18	18	6	6
Mean (SD)	-	-	15.4 (17.92)	50.24 (69.550)	9.5 (13.40)	33.89 (41.013)
Median	-	-	12.5	25.00	10.0	27.38
IQR	-	-	0.0 - 30.0	0.00 - 75.00	0.0 - 15.0	0.00 - 60.00
Min, max	-	-	-20, 46	-28.6, 225.0	-8, 30	-11.4, 100.0
95% CI[d]	-	-	(6.5, 24.4)	-	(-4.6, 23.6)	-
Change from baseline to Day 30 after second injection[c]						
n	-	-	18	18	6	6
Mean (SD)	-	-	13.6 (14.97)	33.98 (47.317)	8.8 (8.61)	31.79 (37.559)
Median	-	-	15.0	21.43	9.0	23.81
IQR	-	-	0.0 - 28.0	0.00 - 50.00	5.0 - 15.0	11.43 - 40.00
Min, max	-	-	-10, 40	-33.3, 150.0	-5, 20	-8.3, 100.0
95% CI[d]	-	-	(6.2, 21.1)	-	(-0.2, 17.9)	-
Baseline before third injection						
n	-	-	-	-	6	
Mean (SD)	-	-	-	-	53.3 (22.29)	
Median	-	-	-	-	57.5	
IQR	-	-	-	-	55.0 - 70.0	
Min, max	-	-	-	-	10, 70	
Change from baseline to Day 1 after third injection[c]						
n	-	-	-	-	6	6
Mean (SD)	-	-	-	-	11.7 (21.37)	33.01 (48.770)
Median	-	-	-	-	20.0	32.47
IQR	-	-	-	-	10.0 - 20.0	28.57 - 54.55
Min, max	-	-	-	-	-30, 30	-50.0, 100.0
95% CI[d]	-	-	-	-	-10.8, 34.1	
Change from baseline to Day 7 after third injection[c]						
n	-	-	-	-	6	6
Mean (SD)	-	-	-	-	15.8 (9.70)	26.21 (17.001)
Median	-	-	-	-	17.5	27.92
IQR	-	-	-	-	10.0 - 25.0	14.29 - 41.67
Min, max	-	-	-	-	0, 25	0.0, 45.5
95% CI[d]	-	-	-	-	5.6, 26.0	

Table 6. A Summary of Range of Motion for Proximal Interphalangeal Joints That Received 1, 2, or 3 Injections by Study Visit (Full Analysis Set)

	PIP Joints[a] That Received 1 Injection (N=98)		PIP Joints[a] That Received 2 Injections (N=18)		PIP Joints[a] That Received 3 Injections (N=6)	
Study Visit	**ROM[b] (°)**	**% Change in ROM**	**ROM[b] (°)**	**% Change in ROM**	**ROM[b] (°)**	**% Change in ROM**
Change from baseline to Day 30 after third injection[c]						
n	-	-	-	-	6	6
Mean (SD)	-	-	-	-	10.8 (5.85)	17.69 (9.839)
Median	-	-	-	-	12.5	19.81
IQR	-	-	-	-	10.0 - 15.0	14.29 - 25.00
Min, max	-	-	-	-	0, 15	0.0, 27.3
95% CI[d]	-	-	-	-	4.7, 17.0	
Baseline before first injection						
n	93	-	17	-	6	-
Mean (SD)	46.8 (20.87)	-	35.8 (20.27)	-	30.8 (29.05)	-
Median	50.0	-	30.0	-	30.0	-
IQR	35.0 - 60.0	-	20.0 - 44.0	-	10.0 - 55.0	-
Min, max	0, 85	-	10, 80	-	-10, 70	-
Change from baseline to 6 months after last injection[c]						
n	93	89	18	18	6	6
Mean (SD)	19.9 (23.60)	86.33 (234.675)	18.0 (22.78)	91.43 (162.608)	16.7 (26.39)	125.72 (236.707)
Median	16.0	31.58	12.5	54.55	12.5	37.88
IQR	4.0 - 30.0	5.45 - 75.00	0.0 - 35.0	0.00 - 111.76	0.0 - 30.0	0.00 - 100.00
Min, max	-27, 80	-50.0, 1900.0	-10, 65	-100.0, 650.0	-15, 60	-21.4, 600.0
95% CI[d]	(15.0, 24.7)	-	(6.7, 29.3)	-	(-11.0, 44.4)	-

CI = confidence interval; IQR = interquartile range; max = maximum; min = minimum; N = number of joints that received the specified number of injections; n = number of joints that received the specified number of injections and had goniometric data available at that visit; PIP = proximal interphalangeal; ROM = range of motion; SD = standard deviation.

a. The joint could be the proximal interphalangeal joint in any finger of either hand.
b. ROM was the range of motion for the joint treated at that injection.
c. For Days 1 through 30, the baseline values were those ROM values taken closest to and before the administration of that particular injection. For 6 months after the last injection, the baseline ROM value was the ROM value taken closest to and before the administration of the first injection.
d. 95% confidence interval for the change in ROM from baseline.

Patient and physician global assessment of treatment satisfaction and disease severity:
According to the patient global assessment, subjects considered their Dupuytren's contracture to have reduced in severity from baseline to Day 30 after the first injection, with a concurrent median percentage improvement of 80% (range: 0 to 100). A similar reduction in severity and median percentage improvement (≥70%) in the subject's Dupuytren's contracture was observed for Cycles 2 to 5. Most subjects were either satisfied or very satisfied with their treatment at Day 30 after each injection. The reduction in severity and

percentage improvement in the subject's Dupuytren's contracture and the satisfaction with treatment observed during the treatment cycles were maintained at Day 90 and at 6 months after the last injection. The patient global assessment of disease severity and treatment satisfaction is summarized in Table 7 for Cycle 1.

Table 7. Patient Global Assessment of Disease Severity and Satisfaction With Treatment (Full Analysis Set): Cycle 1

Visit	Question and Response	Total (N=254) n (%)
Before first injection	Severity of Dupuytren's contracture[a]	
	Number of subjects assessed	254
	Normal (no contracture)	2 (0.8)
	Mild	40 (15.7)
	Moderate	128 (50.4)
	Severe	84 (33.1)
Day 30 after first injection	Severity of Dupuytren's contracture[a]	
	Number of subjects assessed	253
	Normal (no contracture)	63 (24.9)
	Mild	114 (45.1)
	Moderate	55 (21.7)
	Severe	21 (8.3)
	Overall satisfaction with treatment[a]	
	Number of subjects assessed	253
	Very satisfied	153 (60.5)
	Satisfied	73 (28.9)
	Neither satisfied nor dissatisfied	16 (6.3)
	Dissatisfied	6 (2.4)
	Very dissatisfied	5 (2.0)
	Percentage improvement Dupuytren's contracture[a]	
	Number of subjects assessed	252
	Mean (SD)	71.5 (28.33)
	Median	80.0
	IQR	60.0 - 90.0
	Min, max	0, 100

IQR = inter-quartile range; max = maximum; min = minimum; N = number of subjects in the dataset; n = number of subjects with indicated observation; SD = standard deviation.

a. Percentages were calculated using the number of subjects who responded to the question at that visit.

Most subjects (>70%) considered their Dupuytren's contracture to have reduced by 1 or more degrees of severity from baseline to 6 months after their last injection. The change in the subject's self-reported disease severity from baseline to 6 months after the last injection is summarized in Table 8.

Table 8. Change in Subject's Self-Rating of Disease Severity From Baseline to 6 Months After the Last Injection (Full Analysis Set)

	Subject's Self-Rating of Disease Severity at 6 Months After Last Injection			
Subject's Self-Rating of Disease Severity at Baseline	**Normal (No Contracture) n (%)[a]**	**Mild n (%)[a]**	**Moderate n (%)[a]**	**Severe n (%)[a]**
Normal (no contracture)	2 (0.8)	0	0	0
Mild	16 (6.5)	15 (6.0)	6 (2.4)	2 (0.8)
Moderate	45 (18.1)	52 (21.0)	20 (8.1)	7 (2.8)
Severe	15 (6.0)	29 (11.7)	28 (11.3)	11 (4.4)

n = number of subjects with indicated observation.

a. Percentages were calculated using the number of subjects who provided self-ratings of disease severity at baseline at Cycle 1 and at 6 months after the last injection as their denominator.

The Investigator's also considered the severity of the subject's Dupuytren's contracture to have been reduced, and most Investigators assessed the change in the severity of the subject's Dupuytren's contracture to have very much improved or much improved during the treatment period. The Investigators were also either very satisfied or satisfied with the treatment of most of the subjects. The Investigator's responses during the treatment cycles were maintained during the follow-up period, although the Investigators were more conservative with their responses at the visit 6 months after the last injection. The physician global assessment of disease severity and satisfaction with treatment is summarized in Table 9 for Cycle 1.

Table 9. Physician Global Assessment of Disease Severity and Satisfaction With Treatment (Full Analysis Set): Cycle 1

Visit	Question and Response	Total (N=254) n (%)
Before first injection	Physician's rating of the severity of subject's Dupuytren's contracture[a]	
	Number of subjects assessed	254
	Normal (no contracture)	0
	Mild	51 (20.1)
	Moderate	138 (54.3)
	Severe	65 (25.6)
Day 30 after first injection	Physician's rating of the severity of subject's Dupuytren's contracture[a]	
	Number of subjects assessed	250
	Normal (no contracture)	60 (24.0)
	Mild	106 (42.4)
	Moderate	62 (24.8)
	Severe	22 (8.8)
	Physician's assessment of change in Dupuytren's contracture severity compared to study entry[a]	
	Number of subjects assessed	250
	Very much improved	121 (48.4)
	Much improved	88 (35.2)
	Minimally improved	26 (10.4)
	No change	14 (5.6)
	Minimally worse	1 (0.4)
	Much worse	0
	Very much worse	0
	Physician's overall satisfaction with treatment[a]	
	Number of subjects assessed	250
	Very satisfied	134 (53.6)
	Satisfied	90 (36.0)
	Neither satisfied nor dissatisfied	14 (5.6)
	Dissatisfied	7 (2.8)
	Very dissatisfied	5 (2.0)

N = number of subjects in the dataset; n = number of subjects with indicated observation.

a. Percentages were calculated using the number of subjects for whom the Investigators responded to the question at that visit.

For the majority of subjects, the Investigator rated the subject's disease severity as less severe at 6 months after the last injection than at baseline. The change in the Investigator's rating of the subject's disease severity from baseline to 6 months after the last injection is summarized in Table 10.

Table 10. Change in Investigator's Rating of Subject's Disease Severity From Baseline to 6 Months After the Last Injection (Full Analysis Set)

	Investigator's Rating of Disease Severity at 6 Months After Last Injection			
Investigator's Rating of Disease Severity at Baseline	**Normal (No Contracture) n (%)[a]**	**Mild n (%)[a]**	**Moderate n (%)[a]**	**Severe n (%)[a]**
Normal (no contracture)	0	0	0	0
Mild	18 (7.3)	27 (10.9)	4 (1.6)	1 (0.4)
Moderate	41 (16.5)	60 (24.2)	25 (10.1)	9 (3.6)
Severe	8 (3.2)	26 (10.5)	18 (7.3)	11 (4.4)

n = number of subjects with indicated observation.

a. All percentages were calculated using the number of subjects for whom the Investigators provided ratings of the subject's disease severity both at baseline and at 6 months after the last injection as their denominator.

Correlations between the subject- and Investigator-reported outcomes and the mean change from baseline in the subject's ROM or TPED at 6 months after the last injection are summarized in Table 11.

Table 11. Correlations Between Subject- or Investigator-Reported Outcomes and Change From Baseline in Range of Motion or Total Passive Extension Deficit at 6 Months After the Last Injection (Full Analysis Set)

Correlation[a]	At 6 Months After the Last Injection		
	Subject's Mean Change From Baseline in ROM (°) per Treated Joint[b] N=243 r (95% CI)	Subject's Total Change From Baseline in ROM (°) for All Treated Joints[c] N=243 r (95% CI)	Subject's Total Change From Baseline in TPED (°) for All Treated Fingers[d] N=249 r (95% CI)
Subject's overall satisfaction with treatment[e]	0.335 (0.218, 0.442)	0.257 (0.135, 0.371)	-0.184 (-0.302, -0.061)
Investigator's overall satisfaction with subject's treatment[e]	0.371 (0.257, 0.474)	0.244 (0.121, 0.358)	-0.206 (-0.322, -0.083)
Investigator's assessment of change in the severity of the subject's treated contractures[f]	0.280 (0.159, 0.392)	0.197 (0.073, 0.315)	-0.170 (-0.288, -0.047)

CI = confidence interval; DIP = distal interphalangeal; MP = metacarpophalangeal; N = number of subjects analyzed; PED = passive extension deficit; PIP = proximal interphalangeal; r = correlation value; ROM = range of motion; TPED = total passive extension deficit.

a. Spearman's correlation.
b. The difference in ROM from baseline to 6 months after the last injection was determined for each treated joint. These differences were then averaged to determine the mean change in ROM per joint for each subject.
c. ROM values for all treated joints were summed both at baseline and at 6 months after the last injection. The total change in ROM for each subject was calculated as the difference between these 2 values.
d. TPED values for all treated fingers was calculated by summing the values of the PED for the MP, PIP, and DIP joints for each finger that received treatment. The subject's change from baseline in TPED was calculated as the difference between TPED for all treated fingers at 6 months after the last injection minus the TPED for those same fingers at baseline.
e. The overall satisfaction ratings were assigned the following values in this analysis: very dissatisfied = 1; dissatisfied = 2; neither satisfied nor dissatisfied = 3; satisfied = 4; and very satisfied = 5.
f. The Investigator's assessments of the change in severity of the subject's treated Dupuytren's contractures were assigned the following values in this analysis: very much worse = 1; much worse = 2; minimally worse = 3; no change = 4; minimally improved = 5; much improved = 6; and very much improved = 7.

Type and amount of concomitant pain medications: A total of 44.5% subjects received 1 or more pain medications during the study. Concomitant pain medication was taken for a median of 2.0 days. The majority of subjects (96.9%) received local anesthetic for the extension procedure.

Total recovery time, time to use hand, daily activities, work versus hobbies: Subjects rapidly returned to their normal activities after each injection. The median time to recovery to normal activities was ≤4.0 days after each of the first, second, and third injections, with a low

percentage of subjects (5.88% to 13.91%) having not recovered 15 days after each injection. During the first 2 weeks after each injection in Cycles 1 to 3, less than half (between 30.1% and 43.9%) of subjects were absent from work, had to reduce their work hours, or had to modify their usual job duties due to the Dupuytren's contracture treatment. The median number of days that subjects were absent from work, had to reduce their work hours, or had to modify their usual job duties was ≤3 days (range: 2.0 to 3.0 days) during Cycles 1 to 3, which corroborated the observed time to recovery to normal activities.

More than half (51.0% to 72.6%) of subjects were unable to participate in their usual hobbies for a median of ≤5 days (range: 3.0 to 5.0 days) during the first 2 weeks after each injection in Cycles 1 to 3, although the percentage of subjects affected reduced with increasing treatment cycles. Most subjects (approximately 93%) were fitted for a night splint and wore the splint for a median of between 10 and 12 nights during Cycles 1 to 3. Overall, a low number of subjects were treated in Cycles 4 and 5, so a low number of subjects responded to the questionnaire in Cycle 4 (n=15 or 19) and Cycle 5 (n=5 or 6).

Hand functionality: The median total URAM scale score decreased (indicating an improvement) from baseline to Day 30 after the injection for each treatment cycle, with the exception of Cycle 4, and also decreased from baseline to each of the follow-up visits. The URAM scale total score is summarized by study visit in Table 12.

Table 12. URAM Scale Total Score by Study Visit (Full Analysis Set)

Cycle	Study Visit	n	URAM Total Score[a] Mean (SD)	Median	IQR	Min, Max
1	Baseline[b]	85	15.2 (8.24)	13.0	10.0 – 22.0	0, 32
	Day 30	89	5.5 (6.61)	3.0	0.0 – 8.0	0, 29
	Change from baseline to Day 30	85	-9.5 (7.01)	-9.0	-14.0 – -5.0	-25, 5
2	Baseline[b]	47	9.3 (7.32)	7.0	4.0 – 13.5	0, 36
	Day 30	51	5.5 (7.02)	4.0	0.0 – 8.0	0, 36
	Change from baseline to Day 30	47	-3.8 (6.34)	-3.4	-8.0 – 0.0	-23, 13
3	Baseline[b]	31	9.4 (8.39)	8.0	3.0 – 13.0	0, 36
	Day 30	31	5.6 (7.18)	3.0	0.0 – 9.0	0 - 32
	Change from baseline to Day 30	31	-3.8 (5.24)	-4.0	-7.0 – 0.0	-15, 7
4	Baseline[b]	15	8.3 (8.97)	6.0	1.1 – 13.5	0, 32
	Day 30	15	8.1 (9.56)	5.6	1.0 – 13.0	0, 32
	Change from baseline to Day 30	15	-0.2 (6.14)	0.0	-3.0 – 2.0	-11, 16
5	Baseline[b]	9	11.0 (11.03)	9.0	2.0 – 16.0	0, 32
	Day 30	9	6.3 (9.32)	2.3	0.0 – 6.0	0, 28
	Change from baseline to Day 30	9	-4.7 (5.16)	-3.4	-4.0 – -2.0	-16, 0
Follow-up	Baseline[b]	82	15.4 (8.24)	13.0	10.0 – 23.0	0, 32
	Day 90 after the last injection	108	3.6 (6.51)	1.0	0.0 – 4.0	0, 29
	Change from baseline to Day 90 after the last injection	82	-11.2 (8.86)	-11.0	-18.0 – -5.0	-27, 12
Follow-up	Baseline[b]	83	15.3 (8.21)	13.0	10.0 – 23.0	0, 32
	6 months after the last injection	126	3.3 (6.36)	0.5	0.0 – 4.0	0, 38
	Change from baseline to 6 months after the last injection	83	-11.0 (8.83)	-10.0	-18.0 – -5.0	-31, 9

IQR = interquartile range; Max = maximum; Min = minimum; n = number of subjects with indicated observation; SD = standard deviation; URAM = Unité Rhumatologique des Affection de la Main.

a. The URAM total score was defined as the sum of all 9 URAM scale questions (0 – 45), each of which was scored on a 0 to 5 scale as follows: 0 = without difficulty; 1 = with very little difficulty; 2 = with some difficulty; 3 = with much difficulty; 4 = almost impossible; 5 = impossible. If responses were provided to ≤4 questions, the URAM total scale score was considered missing. If responses to ≥5 questions were provided, then the URAM total scale score was computed using the average score of the answered questions as the imputed response to the missing questions.

b. Baseline for Cycles 1 through 5 were the values reported before the injection at that cycle. Baseline values for the follow-up visits were the values reported before the injection in Cycle 1.

HCRU: A very small percentage (ranging from 0% to 8.3%) of subjects at any time point during Cycle 1 attended any of the following additional health care visits or used other services because of their Dupuytren's disease: physician visits, other than protocol visits; physical, hand, or occupational therapy or had home health care visits; had any outpatient or day case surgeries; or had diagnostic/therapeutic procedures, with the highest percentage (8.3%) attending physician visits other than protocol visits on Day 7 after the injection. Of note, a low percentage (≤4.8%) of subjects had physical, hand, or occupational therapy or home health care visits for their Dupuytren's disease at any time point during Cycle 1 (for those subjects who had therapy or home health care visits, the median number of visits made was 1.0 to 2.0).

A lower percentage of subjects (ranging from 0% to 4.5%) attended additional health care visits or used other services because of their Dupuytren's disease at any time point during

Cycles 2 and 3, and during the follow-up phase compared with Cycle 1. Low numbers of subjects were treated in Cycles 4 and 5.

Safety Results: There were no deaths or discontinuations due to AEs during the study. The treatment-emergent AEs (TEAEs) that occurred during this study are summarized in Table 13.

Table 13. Summary of Treatment-Emergent Adverse Events (Safety Set)

	All Treated Subjects (N=254) n (%)
Total number of treatment-emergent adverse events[a]	1167
Subjects with:	
Adverse events	223 (87.8)
Serious adverse events	10 (3.9)
Life-threatening serious adverse events	1 (0.4)
Severe adverse events	16 (6.3)
Treatment-related adverse events	208 (81.9)
Subjects who withdrew from study due to an adverse event	0

N = number of subjects in the data set; n = number of subjects with indicated observation.

a. An adverse event was considered to be treatment emergent if the event started on or after the date of the first Xiapex injection and on or before the date of the last follow-up visit.

TEAEs were reported for 223 (87.8%) subjects and treatment-related TEAEs were reported for 208 (81.9%) subjects. The most frequently reported all-causality and treatment-related TEAEs (reported for ≥2% subjects) are summarized in Table 14 and Table 15, respectively.

Table 14. All Causality Treatment-Emergent Non Serious Adverse Events for Events Having a Frequency ≥2% (Safety Set)

MedDRA System Organ Class Preferred Term	Total (N=254) n (%)
Any adverse event	212 (83.5)
Blood and lymphatic systems disorders	21 (8.3)
Lymphadenopathy	17 (6.7)
Lymph node pain	6 (2.4)
General disorder and administration site condition	153 (60.2)
Oedema peripheral	111 (43.7)
Injection site pain	53 (20.9)
Pain in extremity	65 (25.6)
Injection site haematoma	39 (15.4)
Haematoma	49 (19.3)
Injection site swelling	23 (9.1)
Injection site oedema	20 (7.9)
Tenderness	15 (5.9)
Axillary pain	10 (3.9)
Injection site vesicles	10 (3.9)
Injection site haemorrhage	9 (3.5)
Injection site erythema	8 (3.1)
Malaise	6 (2.4)
Infections and Infestations	7 (2.8)
Nasopharyngitis	7 (2.8)
Injury poisoning and procedural complications	100 (39.4)
Skin laceration	37 (14.6)
Contusion	34 (13.4)
Procedural pain	31 (12.2)
Surgical skin tear	18 (7.1)
Post procedural swelling	9 (3.5)
Post procedural complication	8 (3.1)
Investigations	6 (2.4)
Blood glucose increased	6 (2.4)
Musculoskeletal and connective tissue disorder	82 (32.3)
Pain in extremity	65 (25.6)
Arthralgia	16 (6.3)
Joint swelling	11 (4.3)
Musculoskeletal pain	6 (2.4)
Nervous system disorders	15 (5.9)
Paresthesia	8 (3.1)
Headache	7 (2.8)
Skin and subcutaneous tissue disorders	15 (5.9)
Ecchymosis	17 (6.7)
Pruritus	13 (5.1)
Blood blister	12 (4.7)
Vascular disorders	49 (19.3)
Haematoma	49 (19.3)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the data set; n = number of subjects with indicated observation.

Table 15. Treatment-Related, Treatment-Emergent Adverse Events Reported for ≥2% Subjects by MedDRA Preferred Term (Safety Set)

MedDRA Preferred Term	Total (N=254) n (%)
Number of subjects with any related, treatment-emergent adverse events	208
Oedema peripheral	108 (42.5)
Pain in extremity	61 (24.0)
Injection site pain	53 (20.9)
Haematoma	47 (18.5)
Injection site haematoma	39 (15.4)
Contusion	33 (13.0)
Skin laceration	33 (13.0)
Procedural pain	29 (11.4)
Injection site swelling	23 (9.1)
Injection site oedema	20 (7.9)
Surgical skin tear	16 (6.3)
Ecchymosis	15 (5.9)
Lymphadenopathy	15 (5.9)
Tenderness	15 (5.9)
Pruritus	13 (5.1)
Arthralgia	12 (4.7)
Blood blister	12 (4.7)
Joint swelling	11 (4.3)
Axillary pain	10 (3.9)
Injection site vesicles	10 (3.9)
Injection site haemorrhage	9 (3.5)
Injection site erythema	8 (3.1)
Post procedural swelling	8 (3.1)
Paraesthesia	7 (2.8)
Post procedural complication	7 (2.8)
Lymph node pain	6 (2.4)
Post procedural haematoma	5 (2.0)

AE and SAEs are not separated out.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the data set; n = number of subjects with indicated observation; SAE = serious adverse event.

A life-threatening treatment-emergent serious AE (SAE; colon cancer), which was considered not to be related to study drug, was reported for 1 (0.4%) subject.

Treatment-emergent SAEs were reported for 10 (3.9%) subjects. SAEs that were considered to be related to study drug were reported for 2 subjects: transaminases increased and pain in extremity. No other significant AEs were reported. Treatment-emergent SAEs are listed in Table 16.

Table 16. Treatment-Emergent Serious Adverse Events by Subject

Serial Number	MedDRA Preferred Term	Start Day	Stop Day	Causality	Outcome/Severity
1	Aortic valve disease mixed	190	616	Not related	Resolved/moderate
	Dyspnoea	190	616	Not related	Resolved/moderate
	Postoperative wound infection	284	293	Not related	Resolved/moderate
2	Ileus paralytic	291	297	Not related	Resolved/severe
	Intestinal haemorrhage	291	297	Not related	Resolved/severe
	Road traffic accident	291	291	Not related	Resolved/severe
3	Epistaxis	140	145	Not related	Resolved/severe
4	Transaminases increased	299	-	Possibly	Ongoing/severe
5	Groin infection	27	45	Not related	Resolved/mild
	Groin abscess	79	84	Not related	Resolved/mild
	Colon cancer	95	-	Not related	Ongoing/life-threatening
	Groin abscess	140	-	Not related	Ongoing/mild
6	Back pain	120	205	Not related	Resolved/mild
7	Dupuytren's contracture operation	112	114	Not related	Resolved/moderate
8	Pneumothorax	9	19	Not related	Resolved/severe
9	Femoral neck fracture	166	227	Not related	Resolved/severe
10	Pain in extremity	2	3	Definitely	Resolved/severe

MedDRA = Medical Dictionary for Regulatory Activities.

There were no temporary or permanent discontinuations due to AEs. No subjects died during the study.

Very few laboratory abnormalities were reported. For the shift from baseline to 6 months after last injection, no Common Terminology Criteria for Adverse Events (CTCAE) grade 3 to 5 abnormalities were reported for any hematology parameter, and no grade 4 or 5 laboratory abnormalities were reported for any clinical chemistry parameter. An SAE of transaminases increased was reported for 1 subject, which was considered to be related to study drug. Other AEs of laboratory abnormalities were reported, but these were not considered to be related to study drug. No other clinically significant laboratory abnormalities were reported.

No clinically significant change from baseline was observed for any vital signs parameter. A physical examination and an electrocardiogram were done only at screening. No abnormality was considered by the Investigators to be a contraindication for enrolling a subject in the study. A total of 2.4% (6/248) subjects at screening and 92.1% (220/239) subjects at 6 months after the last injection were positive for anti-AUX-I antibodies with median antibody titers of 1.323 (0.00 to 4.65) $\log_{10}$ and 2.6221 (0.08 to 6.08) $\log_{10}$, respectively. A total of 1.2% (3/248) subjects at screening and 90.0% (215/239) subjects at 6 months after the last injection were positive for anti-AUX-II antibodies with median antibody titers of 4.140 (1.26 to 4.15) $\log_{10}$ and 2.124 (0.29 to 5.56) $\log_{10}$, respectively.

Subjects who were positive for anti-AUX-I or anti-AUX-II antibodies at screening and 6 months after the last injection did not test positive for cross-reactivity to endogenous MMP-1, -2, -3, -8, or -13. These results included 9 samples for the anti-AUX-I antibody cross-reactivity to MMPs and 23 samples for the anti-AUX-II antibody cross-reactivity to

MMPs that were analyzed but exceeded the validated freeze-thaw stabilities. The affected results were not validated.

As no sample was positive for the cross-reactivity to any one of the specified MMPs, analysis to determine the level of inhibition in MMP enzyme activity assays was not carried out.

There is no evident correspondence between the neutralizing antibody data and the overall study data.

CONCLUSIONS:

- A rapid and substantial decrease in median PED from baseline was observed after the first injection into the cord of MP joints that received only 1 injection (80%, 100%, and 100% reduction from baseline on Days 1, 7, and 30, respectively) and, although less so, into the cord of PIP joints that received only 1 injection (58.57%, 75.0%, and 64.72% reduction from baseline on Days 1, 7, and 30, respectively). The reduction for the MP joint was maintained at 6 months after the last injection.

- An increase in median ROM from baseline, which reflected the reduction in PED, was observed after the injection. On Day 30 after the first injection, median ROM had increased from baseline by 33.5^{o} for MP joints and by 26.0^{o} for PIP joints that each received only 1 injection. The increase for the MP joint was maintained at 6 months after the last injection.

- Correlations of 0.197 to 0.371 were observed between the subject- and Investigator-reported outcomes and the mean change from baseline in the subject's ROM or total change from baseline in the subject's ROM at 6 months after the last injection. Correlations of -0.206 to -0.170 were observed between the subject- and Investigator-reported outcomes and the total change from baseline in the subject's TPED at 6 months after the last injection.

- Most subjects and Investigators considered the Dupuytren's contracture to have reduced in severity and had a high level of treatment satisfaction.

- The median time to recovery to normal activities was ≤4.0 days after each of the first, second, and third injections, with a low proportion of subjects (5.88% to 13.91%) having not recovered 15 days after each injection.

- The most frequently taken concomitant analgesic medication was paracetamol, which was taken by 96/254 subjects. Concomitant pain medication was taken for a median of 2.0 days.

- A very small percentage (range: 0% to 8.3%) of subjects during any 1 treatment cycle or during the follow-up phase attended additional health care visits or used other services.

- The little and ring fingers, and the MP joint were most frequently treated first. Most subjects received 1 or 2 injections. Most subjects were administered the first injection into the cord of their most severely affected joint and finger. For subjects who received multiple treatments, most had either 1 or 2 joints treated. For the subjects who received multiple treatments, no distinct pattern of treatment (ie, joint, finger, hand) was observed.

- Xiapex was considered to be well tolerated and the overall safety profile observed in this study was consistent with previous clinical studies and with the summary of product characteristics.