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Post-Market Surveillance Study

SYNOCROM® *forte*
in Gonarthritis

in December 2007

Commissioned by: Croma Pharma
2100 Korneuburg, Stockerauerstrasse 181

Statistical evaluation: Dr. Robert Heinz & Partner Medical Consulting
1070 Vienna, Kaiserstraße 84/9
November 2007

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Introduction

This study was carried out in Austria, in 115 patients suffering from gonarthritis, in the period between March 2006 and August 2007.

The patients were given 3 intra-articular injections of **SYNO**CROM® ***forte*** at weekly intervals (in accordance with the Prescribing Information)

Data were recorded before each injection and at monthly intervals after the end of the therapy.

This post-marketing surveillance study looks at the data of patients whose knee joints were treated with **SYNO**CROM® ***forte***.

Statistical methods

The statistical evaluation was carried out with the REPORT/TESTIMATE program of the company idv - Datenanalyse und Versuchsplanung, Gauting/Munich. All parts of the program have been validated; the work undertaken at Heinz & Partner is carried out in accordance with the SOPs developed by IDV.

The methods used to describe data in the interim evaluation were mainly descriptive. For important quantitative variables, classical statistical parameters (mean, median, lowest value, highest value, standard deviation) were used to describe the data.

Qualitative variables, such as the assessment of the efficacy of the treatment, were analysed by calculation of frequency.

The treatment results for **SYNO**CROM® ***forte*** over time are analysed using non-parametric methods (Wilcoxon-Mann-Whitney). For all the statistical calculations, a two-tailed p value of < 0.05 is used as the significance threshold.

The table below lists the Mann-Whitney values which are used to interpret the results. The Mann-Whitney value can be between 0 and 1; a value of 0.5 indicates identity (no difference). The further away the value is from 0.5, the greater the weight attached to the difference. Thus, for example, a value of 0.64 or above indicates medium superiority and a value of 0.71 or above indicates large superiority. From a value of 0.64 (medium superiority), the difference is described as relevant superiority.

In what follows, therefore, the Mann-Whitney values will be given in addition to the p values.

Interpretation of the results	Mann-Whitney value
Large superiority	0.71
Medium superiority	0.64
Small superiority	0.56
Equality	0.50
Small inferiority	0.44
Medium inferiority	0.36
Large inferiority	0.29

Patient group

Patient data are available for a total of 115 knee joints treated with **SYNO**CROM® ***forte***. The age of the group is shown in Table 1. There is very considerable variation in the patients' ages. Both young adults of 31 years of age and elderly patients of 84 years of age were included in the post-marketing surveillance study, i.e. treated with **SYNO**CROM® ***forte***. This is a very good reflection of practice. The median age of the patients is 61 years. Their mean age is 61.6 ± 11.3 years.

Age of the patients STATISTICS

	AGE Years
Synocrom-forte	
Mean	61.6
Std Dev	11.32
Min	31.0
Lo Quar	55.0
Median	61.0
Up Quar	68.0
Max	84.0
Valid N	115

Table 1: Description of the group – Age of the patients

More women than men were included in the post-marketing surveillance study. 60% of the patients who had their knee joints treated with **SYNO**CROM® ***forte*** were women and 40% were men.

The patients' BMI (body mass index), which is calculated by dividing body weight by height (in m^2), is on average distinctly above normal. Their median BMI is approximately 27 kg/m^2. More details can be found in the following table.

BMI

STATISTICS	
	BMI
Synocrom-forte	
Mean	27.434
Std Dev	3.9260
Min	21.551
Lo Quar	24.725
Median	26.953
Up Quar	29.001
Max	40.009
Valid N	113

Table 2: Description of the group – Body Mass Index (BMI) of the patients

To provide a complete picture, the height and body weight of the patients are presented again descriptively in the following table.

Weight and height

STATISTICS		
	HEIGHT	WEIGHT
Synocrom-forte		
Mean	1.693	78.8
Std Dev	0.0876	12.25
Min	1.420	46.0
Lo Quar	1.640	69.0
Median	1.700	78.0
Up Quar	1.760	85.0
Max	1.870	115.0
Valid N	114	113

Table 3: Description of the group – Weight and height of the patients

Diagnosis

Severity of the disease

Over half (approximately 55%) of the diseased knee joints, that were treated with **SYNO**CROM® ***forte,*** are in severity category II (moderate) (Table 4). There are more patients with severe gonarthritis (28% grade III) than with mild gonarthritis (17% grade I).

Severity of the disease

```
Criterion: Grad-Gona; Group: Synoc-fort

F r e q u e n c y  C o u n t
Frequency Table                Frequency Plot
Abs. Frequency     (1 : 1.0000)
(Val=  115)  Count  Percent
GradI           20   17.39     OOOOOOOOOOOOOOOOOOO
GradII          63   54.78     OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
GradIII         32   27.83     OOOOOOOOOOOOOOOOOOOOOOOOOOOOOO
```

Table 4: Description of the group – Severity of the disease at the start of the treatment

Duration of the disease

On average, the investigated patients treated with **SYNO**CROM® ***forte*** suffered from gonarthritis for over 5 years (5.2 ± 5.7 years). As can be seen from the standard deviation, there is very considerable variation in the duration of the patients' disease, which ranges from 0.2 to 40 years (Table 5).

Duration	YEARS
Synocrom-forte	
Mean	5.22
Std Dev	5.699
Min	0.20
Lo Quar	1.50
Median	3.00
Up Quar	7.00
Max	40.00
Valid N	101

Table 5: Description of the group – Duration of the disease

Hyaluronic acid

A third (33.3%) of the knee joints treated with **SYNO**CROM® ***forte*** had previously been treated with hyaluronic acid.

The number of treatments differs. There is very considerable variation in the data. The number of previous hyaluronic acid treatments ranges from 1 to 9. The average is 3.2 ± 2.36 per patient.

	Therapy Hyaluronic Acid
Synocrom-forte	
Mean	3.2
Std Dev	2.36
Min	1.0
Lo Quar	1.0
Median	2.0
Up Quar	5.0
Max	9.0
Valid N	36

Table 6: Description of the group – Number of treatments with hyaluronic acid

Intensity of pain during / after the therapy

The intensity of the pain in the affected joints decreases during the **SYNO**CROM® ***forte*** therapy, the extent of decrease being significant (p = 0.0001) after the 2nd injection; it then remains at roughly the same level until month 11 after the end of the therapy. More details on this are provided in the following table and in Fig. 1.

Synocrom-forte	Mean	Std Dev	Min	Lo Quar	Median	Up Quar	Max	Valid N
Baseline before 1st injection	50.5	18,59	0.0	40.0	50.0	65.0	90.0	115
Before 2nd injection	45.1	20.40	0.0	30.0	48.0	55.0	100	115
Before 3rd injection	39.1	20.05	0.0	25.0	40.0	50.0	95.0	115
Pain 1 month after therapy	32.5	18.55	0.0	20.0	30.0	45.0	80.0	110
Pain 2 month after therapy	32.5	20.75	0.0	20.0	30.0	50.0	80.0	110
Pain 3 month after therapy	28.1	20.24	0.0	12.0	20.0	40.0	80.0	105
Pain 4 month after therapy	29.5	19.84	0.0	20.0	23.01	40.0	80.0	102
Pain 5 month after therapy	28.9	19.72	0.0	15.0	25.0	40.0	80.0	102
Pain 6 month after therapy	29.1	20.50	0.0	15.0	25.0	40.0	90.0	100
Pain 7 month after therapy	27.9	19.69	0.0	10.0	28.0	40.0	80.0	97
Pain 8 month after therapy	26.7	19.67	0.0	10.0	20.0	40.0	80.0	94
Pain 9 month after therapy	27.1	20.38	0.0	10.0	30.0	40.0	75.0	93
Pain 10 month after therapy	28.1	21.05	0.0	10.0	30.0	42.0	82.0	89
Pain 11 month after therapy	28.9	22.40	0.0	10.0	20.0	45.0	80.0	79

Table 7: Pain intensity (VAS scale) after the therapy; 1st injection to month 11

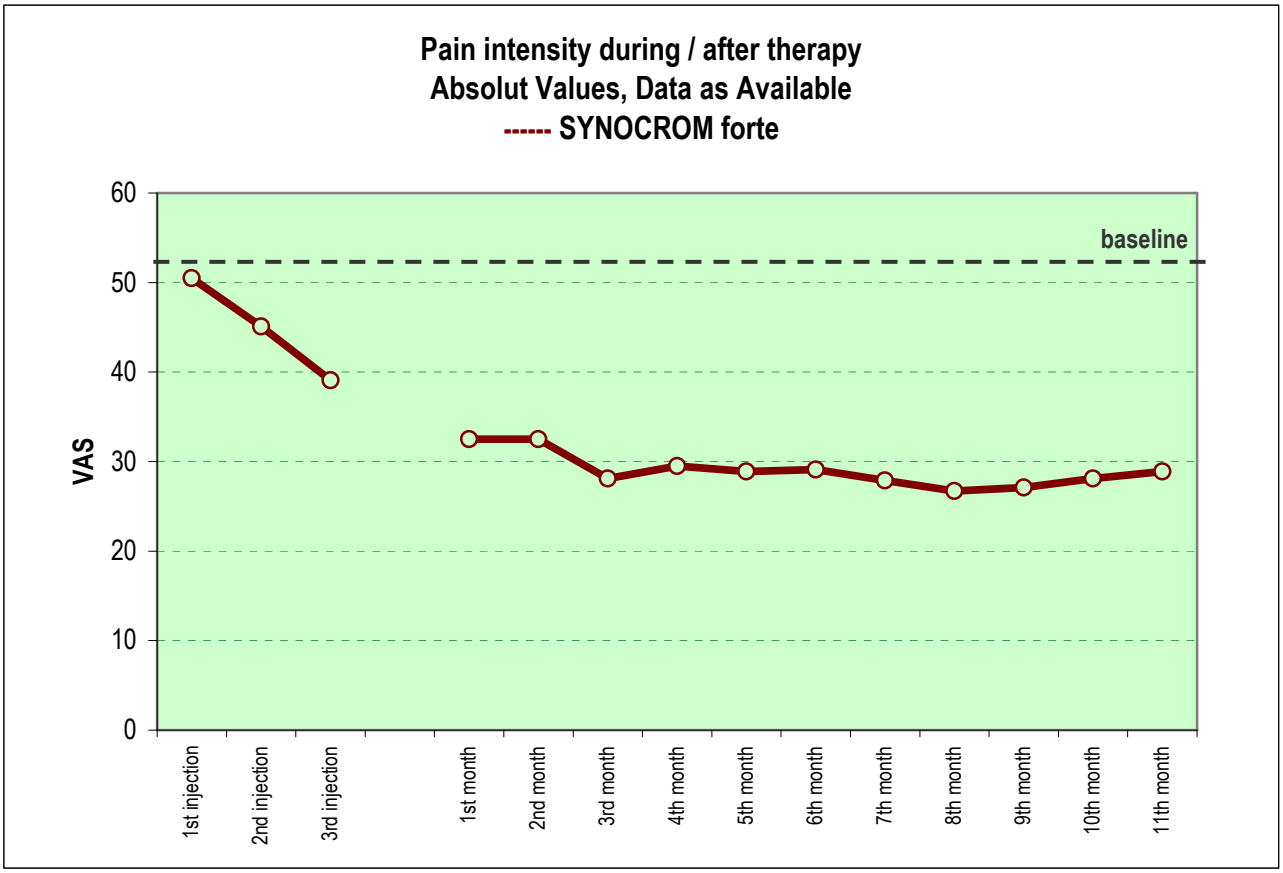

Fig. 1: Pain intensity (VAS scale) during / after the end of the therapy

Pain intensity, according to disease severity

At the start of the therapy (before and after the first injection) there are significant and clinically relevant differences in the intensity of the patients' pain, depending on the severity of the disease. Patients with grade I gonarthritis have a significantly lower VAS score ($p = 0.0016$) than patients with grade II gonarthritis or grade III gonarthritis ($p = 0.0010$). These differences persist up to the 2nd injection ($p = 0.049$ and $p = 0.0188$). At the 3rd injection there are no longer any significant differences in pain intensity.

More details can be found in the following Figs.

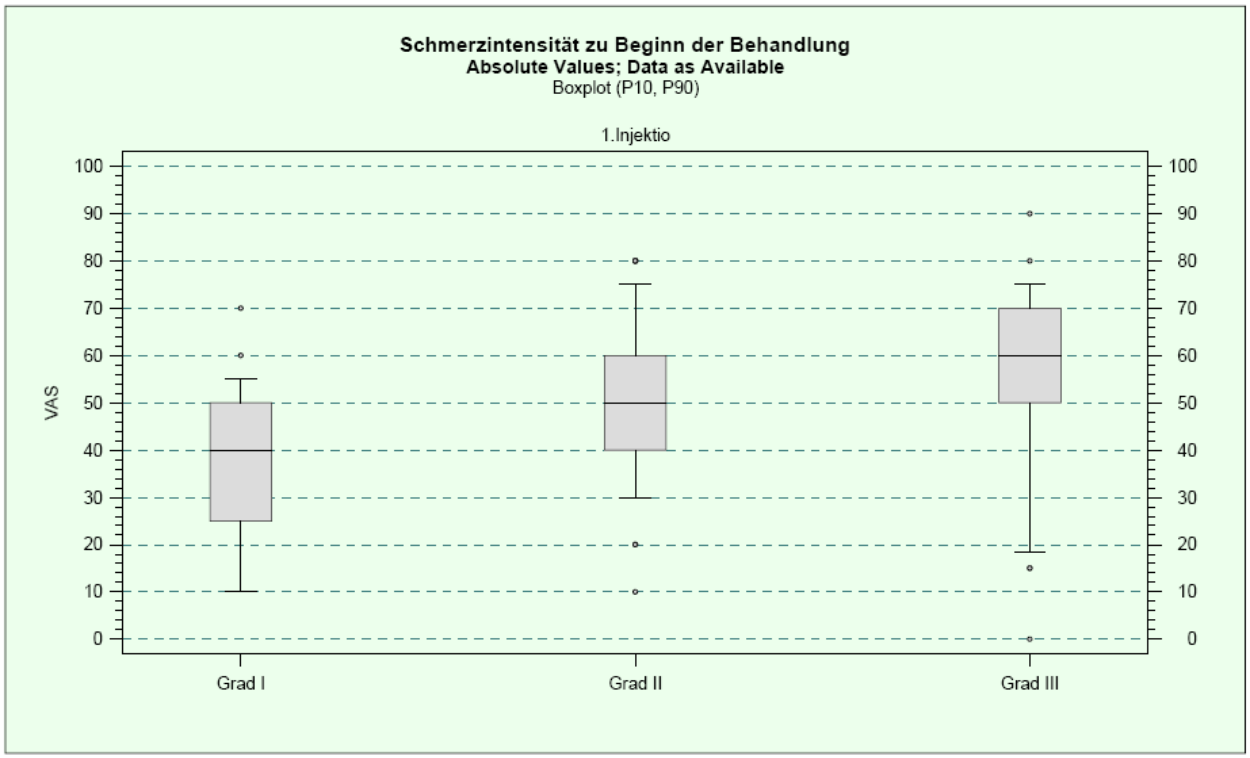

Fig. 4: Pain intensity (VAS scale) at the start of the therapy, according to disease severity (grades I-III)

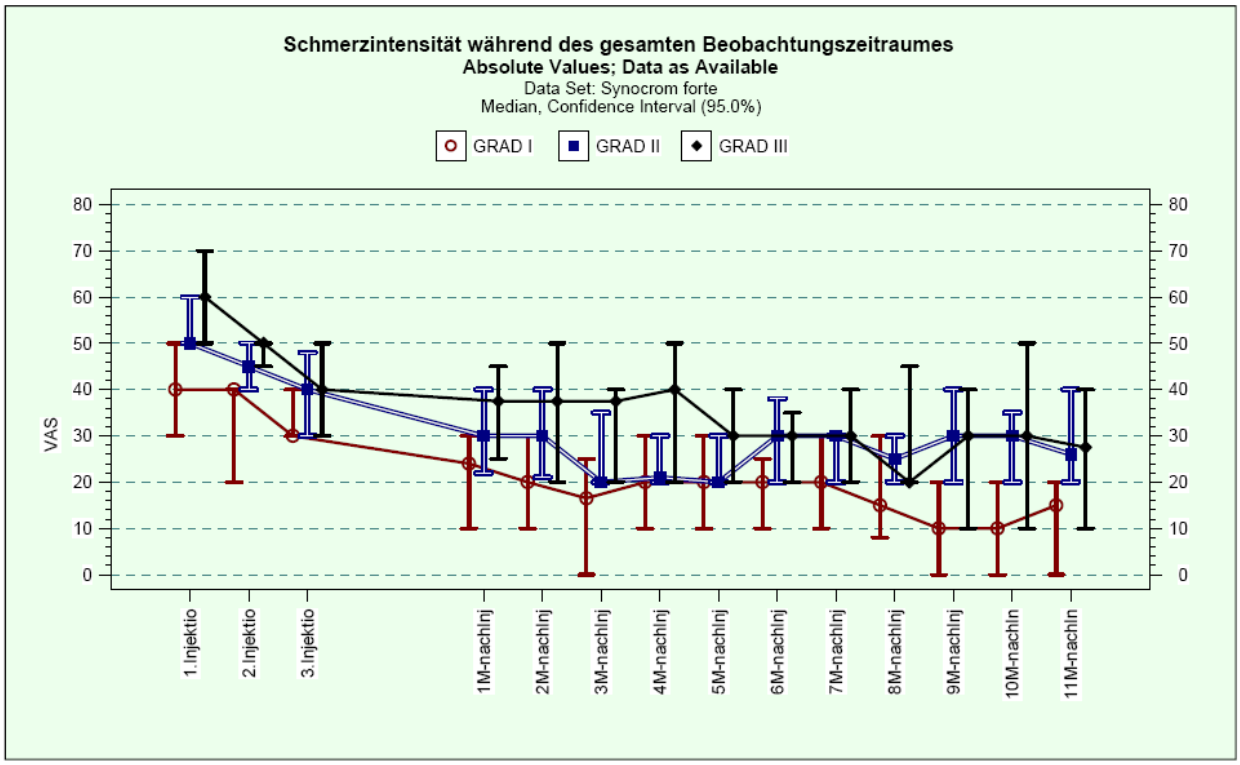

Fig. 5: Pain intensity (VAS scale), according to disease severity (grades I-III)

The following table shows the statistical parameters for pain intensity, according to disease severity, during the therapy.

SYNOCROM forte	Pain before 1st Injection	Pain before 2nd Injection	Pain before 3rd Injection
Grade 1			
Mean	37.8	36.5	32.0
Std Dev	16.90	19.34	12.92
Min	10.0	10.0	10.0
Lo Quar	25.0	20.0	25.0
Median	40.0	40.0	30.0
Up Quar	50.0	47.5	40.0
Max	70.	80.0	50.0
Valid N	20	20	20
Grade 2			
Mean	52.4	46.8	39.5
Std Dev	15.94	20.93	20.51
Min	10.0	0.0	0.0
Lo Quar	40.0	35.0	25.0
Median	50.0	45.0	40.0
Up Quar	60.0	60.0	50.0
Max	80.0	100.0	85.0
Valid N	63	63	63
Grade 3			
Mean	54.7	47.2	42.7
Std Dev	21.40	19.17	22.11
Min	0.0	0.0	0.0
Lo Quar	50.0	42.5	25.0
Median	60.0	50.0	40.0
Up Quar	70.0	52.5	60.0
Max	90.0	80.0	95.0
Valid N	32	32	32

Table 11: Pain intensity according to disease severity during the therapy

Pain intensity without outliers (P10-P90)

The following table includes only those patients treated with **SYNO**CROM® ***forte*** who had a VAS score of 20-75 at the screening examination.

	Pain before 1st Injection	Pain before 2nd Injection	Pain before 3rd Injection
Synocrom-forte			
Mean	51.4	45.6	38.8
Std Dev	14.21	17.41	18.35
Min	20.0	0.0	0.0
Lo Quar	40.0	40.0	29.0
Median	50.0	50.0	40.0
Up Quar	60.0	50.0	50.0
Max	75.0	100.0	95.0
Valid N	100	100	100

Table 12: Pain intensity (VAS scale) (without outliers at the start) during the therapy

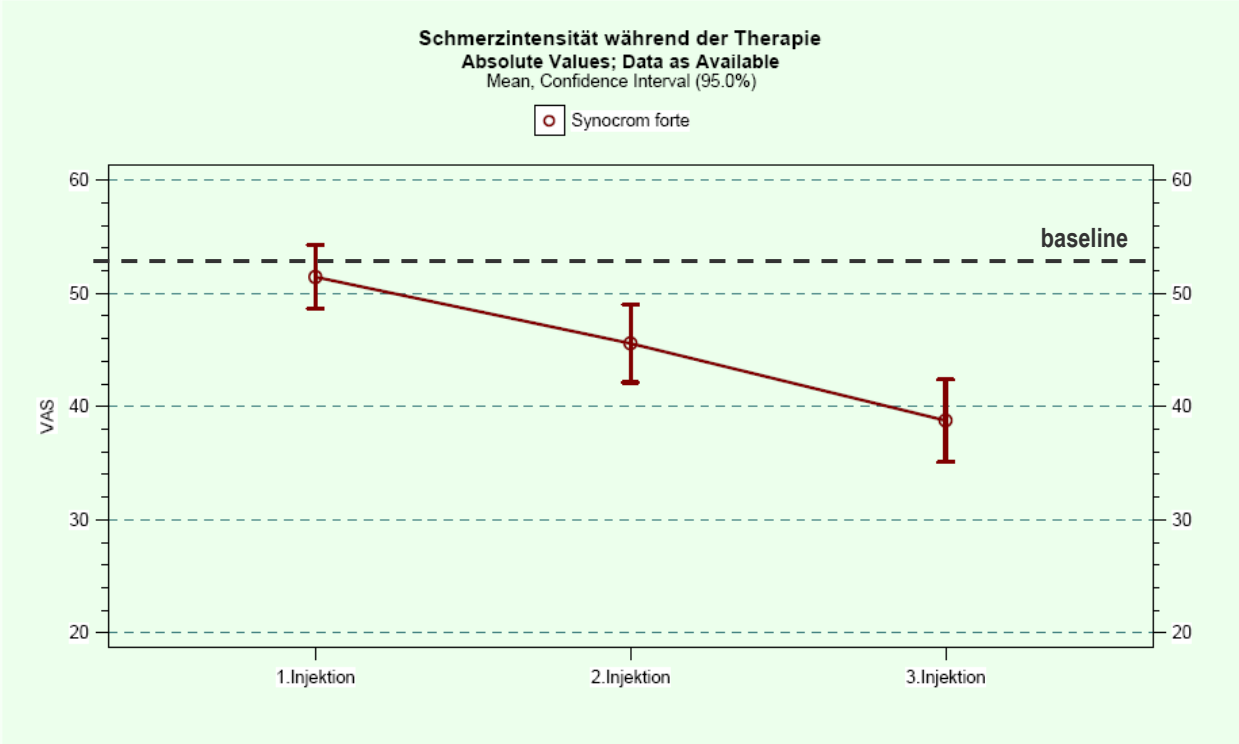

Fig. 6: Pain intensity (VAS scale) (without outliers at the start) during the therapy

Synocrom-forte	Mean	Std Dev	Min	Lo Quar	Median	Up Quar	Max	Valid N
Pain 1 month after therapy	31.8	17.75	0.0	20.0	30.0	42.5	80.0	96
Pain 2 month after therapy	32.3	20.14	0.0	20.0	30.0	50.0	80.0	96
Pain 3 month after therapy	28.0	20.05	0.0	15.0	20.0	40.0	80.0	91
Pain 4 month after therapy	29.2	19.35	0.0	20.0	23.0	40.0	80.0	90
Pain 5 month after therapy	28.9	19.14	0.0	20.0	22.5	40.0	80.0	90
Pain 6 month after therapy	29.0	20.14	0.0	15.0	25.0	40.0	90.0	87
Pain 7 month after therapy	27.0	18.44	0.0	10.0	25.0	40.0	80.0	85
Pain 8 month after therapy	26.5	19.01	0.0	10.0	20.0	40.0	80.0	83
Pain 9 month after therapy	26.8	20.32	0.0	10.0	30.0	40.0	75.0	80
Pain 10 month after therapy	27.7	20.81	0.0	10.0	30.0	42.0	82.0	78
Pain 11 month after therapy	28.2	22.02	0.0	10.0	20.0	42.5	78.0	68

Table 13: Pain intensity (VAS scale) (without outliers at the start) after the therapy; month 1 to month 11

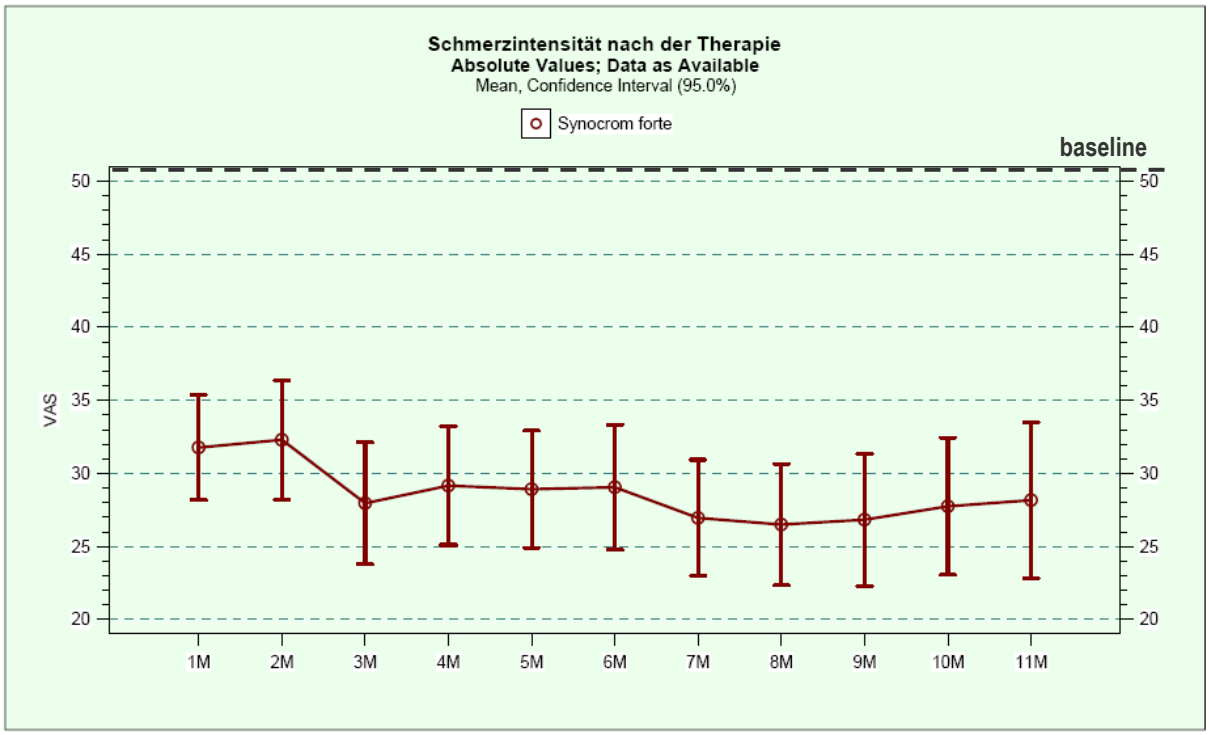

Fig. 7: Pain intensity (VAS scale) (without outliers at the start) after the therapy; month 1 to month 11

Efficacy and tolerability of the therapy

The doctors' overall assessments of the efficacy and tolerability of **SYNO**CROM® ***forte*** are summarized in the following table. Approximately 77% of the doctors rate the efficacy of the **SYNO**CROM® ***forte*** therapy as good or very good. Approximately 85% of the doctors rate the tolerability as good or very good.

Efficacy	**SYNOCROM forte N = (%)**
Very good	43 (40.95)
Good	38 (36.19)
Satisfactory	13 (12.38)
Unsatisfactory	11 (10.48)
Tolerability	
Very good	74 (69.16)
Good	16 (14.95)
Satisfactory	12 (11.21)
Unsatisfactory	5 (4.67)

Table 15: Efficacy and tolerability (assessment by doctor) after the **SYNO**CROM® ***forte*** therapy

After the first injection, over half of the patients (54%) rate the efficacy as good or very good. After the second injection, the proportion rating the efficacy as good or very good is already nearly 65%.

2nd injection/1st week	**SYNO**CROM® ***forte*** **N= (%)**
Very good	5 (4.35)
Good	57 (49.57)
Satisfactory	29 (25.22)
Unsatisfactory	24 (20.87)
3nd injection/2st week	**SYNO**CROM® ***forte*** **N= (%)**
Very good	18 (16.07)
Good	54 (48.21)
Satisfactory	30 (26.79)
Unsatisfactory	10 (8.93)

Table 16: Efficacy (assessed on the basis of the patient diary) during the therapy

Fig. 8 shows very well that, after the therapy, over 70% of the patients rate the efficacy of **SYNO**CROM® ***forte*** as good or very good. This rating is maintained until month 9 after the therapy. Only then does the proportion rating the therapy as good or very good drop a little below 70%.

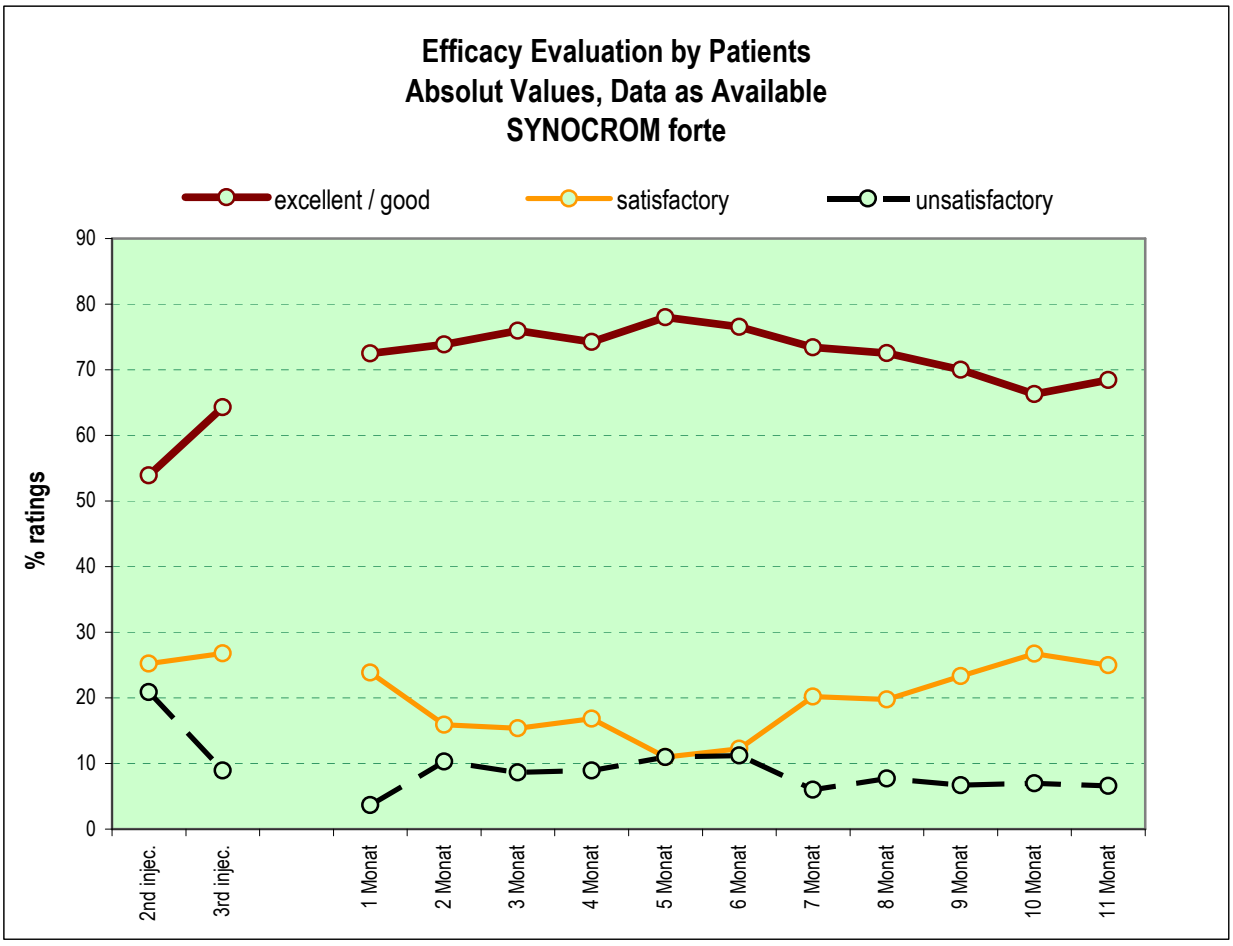

Fig 8: "Very good" and "good" efficacy ratings (%) after the injection therapy

2nd injection/1st week	**SYNO**CROM® ***forte*** **N= (%)**
Very good	5 (4.35)
Good	57 (49.57)
Satisfactory	29 (25.22)
Unsatisfactory	24 (20.87)
3nd injection/2st week	**SYNO**CROM® ***forte*** **N= (%)**
Very good	18 (16.07)
Good	54 (48.21)
Satisfactory	30 (26.79)
Unsatisfactory	10 (8.93)
1st month after the therapy	**SYNO**CROM® ***forte*** **N= (%)**
Very good	21 (19.27)
Good	58 (53.21)
Satisfactory	26 (23.85)
Unsatisfactory	4 (3.67)
N=	109
2nd month after the therapy	
Very good	24 (22.43)
Good	55 (51.4)
Satisfactory	17 (15.89)
Unsatisfactory	11 (10.28)
N=	107
3rd month after the therapy	
Very good	26 (25)
Good	53 (50.96)
Satisfactory	16 (15.38)
Unsatisfactory	9 (8.65)
N=	104
4th month after the therapy	
Very good	30 (29.70)
Good	45 (44.55)
Satisfactory	17 (16.83)
Unsatisfactory	9 (8.91)
N=	101
5th month after the therapy	
Very good	31 (31.0)
Good	47 (47)
Satisfactory	11 (11)
Unsatisfactory	11 (11)
N=	100

6th month after the therapy	**SYNO**CROM® ***forte*** **N= (%)**
Very good	28 (28.57)
Good	47 (47.96)
Satisfactory	12 (12.24)
Unsatisfactory	11 (11.22)
N=	98

7th month after the therapy	
Very good	28 (29.79)
Good	41 (43.62)
Satisfactory	19 (20.21)
Unsatisfactory	6 (6.38)
N=	94
8th month after the therapy	
Very good	25 (27.47)
Good	41 (45.05)
Satisfactory	18 (19.78)
Unsatisfactory	7 (7.69)
N=	91
9th month after the therapy	
Very good	27 (30)
Good	36 (40)
Satisfactory	21 (23.33)
Unsatisfactory	6 (6.67)
N=	90
10th month after the therapy	
Very good	27 (31.4)
Good	30 (34.88)
Satisfactory	23 (26.74)
Unsatisfactory	6 (6.98)
N=	86
11th month after the therapy	
Very good	26 (34.21)
Good	26 (34.21)
Satisfactory	19 (25.0)
Unsatisfactory	5 (6.58)
N=	76

Table 17: Efficacy (assessed on the basis of the patient diary) after the therapy

Side effects – swelling

There are no reports of any side effects, either active-substance-related events or non-active-substance-related events

Swelling occurred in only rare cases during the treatment. 8 cases of swelling were reported (7.7%) in all; none of them were rated as severe.

In all, only 4 cases of swelling (3.8%), rated as "moderate", were treated by the doctor.

Data are available on the intensity of the swelling in 7 cases and on the associated measures in 6.

In 2 cases of swelling in knees treated with **SYNO**CROM® ***forte***, the intensity was "mild", and in 5 cases it was "moderate".

Swelling **SYNO**CROM® ***forte***

Score	Intensity of swelling
Mild Moderate Severe	2 5 --
Valid No.	7

Total N=115

Score	Intensity of swelling
Mild Moderate Severe	28.57% 71.43% --

Table 18: Severity of the swelling that occurred during the therapy

The following table shows the patients with swelling, the intensity of the swelling, and the measures taken.

Swelling **SYNO**CROM® ***forte***

Intensity: 1 = mild, 2 = moderate, 3 = severe		
Swelling case 1	Intensity	Measure
1	1	None
1	1	Monitoring only
1	2	Voltaren rapid
1	--	--
1	2	--
1	2	Drainage of 26 ml on 10.08
1	2	Cryotherapy
1	2	Cryotherapy

Table 19: Intensity of swelling, and measures taken, in each patient during treatment with **SYNO**CROM® ***forte***

To sum up, an overview of the swelling that occurred:

Swelling **SYNO**CROM® ***forte***

Score	Swelling
Yes	8
No	96
Valid No.	104

Total N=115

Score	Swelling
Yes	7.69%
No	92.31%

Table 20: Number of swelling cases that occurred during the therapy

Additional medication for the treatment of gonarthritis

A little over a third of the patients (35.2%) whose joints were treated with **SYNO**CROM®***forte*** used additional medication to treat their gonarthritis.

Therapy in addition to **SYNO**CROM® ***forte***

Score	Additional therapy Additional the.
Yes No	37 68
Missing Valid No.	10 105

Total N=115

Score	Additional therapy Additional the.
Yes No	35.24% 64.76%

Table 21: Number of patients using additional therapy

The additional medication is principally pain therapy, such as Seractil, Voltaren, or suchlike. More details can be found in the following overview table. The information shown about additional therapy is as reported by the investigating physicians.

Additional medication **SYNO**CROM® ***forte***

Additional therapy 1=Yes	
1	NSAID (Xefo 8 mg or Parkemed 500 mg
1	Condrusulf
1	Parkemed 500 mg 1x1
1	Voltaren 50
1	Voltaren, Traumel
1	Voltaren
1	Condrusulf 800 mg
1	Condrusulf 800 mg tabs.
1	Condrusulf 800 mg tablets
1	Arthotec forte 1x1
1	Diclac rapid as required
1	Proxen as required
1	Voltaren rapid
1	Condrusulf
1	Deflamat 75, Deflamat 100
1	Voltaren at the start
1	Tramabene 100 mg
1	Chondroitin sulfate 800 mg 1x1/3 months
1	Chondroitin sulfate p.o.
1	Xefo 8 mg
1	Serectil 400 pain therapy
1	Diclobene
1	Xyloneural
1	Deflamat 75 mg
1	Xefo 8 mg
1	Deflamat 75 mg
1	Xefo
1	Tramal, Deflamat
1	Deflamat as required
1	1x1 Deflamat 75
1	Xefo 8 mg 2x1
1	Xefo 8 mg
1	Diclofenac
1	Seractil
1	Parkemed
1	Seractil 400 mg 3x1

Table 22: Prescribed additional therapy, per patient

Additional pain therapy

Painkillers during the therapy

The following table shows very clearly that over a third of the patients receive additional pain therapy at the start of the treatment with **SYNO**CROM® ***forte***. By the 3rd injection, the number of patients taking a product to relieve pain in the knee joint decreases.

Additional painkillers **SYNO**CROM® ***forte***

	Painkillers		
Score	1st Add.pain.th.	2nd Add.pain.th.	3rd Add.pain.th.
Yes, painkillers No	39 75	40 75	35 79
Missing Valid No.	1 114	-- 115	1 114

	Painkillers		
Score	1st Add.pain.th.	2nd Add.pain.th.	3rd Add.pain.th.
Yes, painkillers No	34.21% 65.79%	34.78% 65.22%	30.70% 69.30%

Total N=115

Table 23: Use of painkillers during the treatment with **SYNO**CROM® ***forte***

Painkillers after the therapy

There is a discernible trend towards a decrease in the number of patients taking a painkiller after the injection therapy. It still fluctuates between 25 and 30%.

Additional painkillers **SYNO**CROM® ***forte***

	Painkillers, months after the therapy				
Score	1M Add.pain.th.	2M Add.pain.th.	3M Add.pain.th.	4M Add.pain.th.	5M Add.pain.th.
Yes No	20 60	29 79	26 79	26 77	27 74
Missing Valid No.	7 108	7 108	10 105	12 103	14 101

	Painkillers, months after the therapy				
Score	1M Add.pain.th	2M Add.pain.th.	3M Add.pain.th.	4M Add.pain.th.	5M Add.pain.th.
Yes No	25.93% 74.07%	26.85% 73.15%	24.76% 75.24%	25.24% 74.76%	26.73% 73.27%

Additional painkillers **SYNO**CROM® ***forte***

	Painkillers, months after the therapy					
Score	6M Add.pain.th.	7M Add.pain.th	8M Add.pain.th	9M Add.pain.th	10M Add.pain.th	11M Add.pain.th
Yes No	27 73	26 71	20 74	22 69	26 63	20 59
Missing Valid No.	15 100	18 97	21 94	24 91	26 89	36 79

	Painkillers, months after the therapy					
Score	6M Add.pain.th	7M Add.pain.th.	8M Add.pain.th.	9M Add.pain.th.	10M Add.pain.th	11M Add.pain.th
Yes No	27.00% 73.00%	26.80% 73.20%	21.28% 78.72%	24.18% 75.82%	29.21% 70.79%	25.32% 74.68%

Table 24: Use of painkillers after the treatment with **SYNO**CROM® ***forte***