RESULTS REPORT

SUPLASYN vs SUPLASYN 1-SHOT

Non-Inferiority / Equivalence Analysis

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AUTHENTICATION CERTIFICATE

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1 Executive Summary

1.1 The study

This is a re-analysis of two observational and multicenter studies, namely ESSIK and ESTIK studies, performed in 8 countries between April 2014 and December 2017.

The main objective of the analysis was to compare the effectiveness of three 20mg/2ml intraarticular injections against one 60mg/6ml intraarticular injection of Hyaluronic Acid (HA) in pain reduction and functional improvement in patients with knee osteoarthritis (KOA).

Treatments' effectiveness was evaluated by means of the Oxford Knee Score (OKS), a self-administrated 12-item questionnaire, and the Visual Analog Scale (VAS) for pain, a continuous scale of pain intensity. Visits were scheduled at baseline, at 1-month and at 6-months after the HA treatments.

The total number of patients included in the study was 409. The selection was carried out using a Propensity Score Matching procedure. After this selection procedure, a sample of 252 patients was obtained (126 for each group), that was homogenous with respect to the following variables: sex, radiological grade according to Kellgren-Lawrence, previous intervention, use of painkillers, NSAIDs and SISADOA and frequency of its administration.

1.2 Main results

No differences were found between treatments groups with respect to patients' characteristics at baseline.

Both treatment groups showed significant differences in repeated measures tests performed in main outcome variables such as pain reduction and functional improvement. For each test effect sizes (Cohen's d) were calculated and values between 0.9 and 1.2 were obtained.

The analysis of non-inferiority and equivalence showed that the upper 95% Confidence Interval (CI) of each of the studied outcome variables in Suplasyn 1-shot group never fell below the non-inferiority margin and never exceeded the equivalence margin.

1.3 Conclusions

Samples were found to be homogeneous at baseline with no significant differences between groups in patients' characteristics.

Both treatment groups showed to be notably effective in pain reduction and functional improvement, with large effect sizes (Cohen's d) between 0.9 and 1.2.

When performing the analysis of non-inferiority and equivalence, we found equivalence between the two products in each variable studied, concluding that the two treatments are equivalent and not inferior to each other.

2 Patient Inclusion by Country

Table 1. List of inclusion by country

Country	Suplasyn	Suplasyn 1-shot	Total Patients included
Croatia	18	24	42
Czech Republic	9	17	26
Egypt	0	20	20
Kazakhstan	40	0	40
Malaysia	0	48	48
Portugal	0	17	17
Slovenia	13	0	13
Uzbekistan	46	0	46
Total	126	126	252

3 Methods

The statistical analysis was performed using the statistical software SPSS 22.0 for Windows. Only valid cases (n) were considered (missing values are not described).

The sample used for this analysis was obtained from two observational and multicenter studies, namely ESSIK and ESTIK studies performed in 8 countries between April 2014 and December 2017.

The total number of patients included in the study was 409. The selection was carried out using a Propensity Score Matching procedure. This procedure matches case records with similar control records contained in a single dataset. It first runs a logistic regression with the case/control group variable as the dependent variable. Then it selects a match for each case from the control group based on the propensity score from the logistic regression. The score is an estimate of the probability of membership in the case group. After this selection procedure, a sample of 252 patients was obtained (126 for each group), that was homogenous with respect to the following variables: sex, radiological grade according to Kellgren-Lawrence, previous intervention, use of painkillers, NSAIDs and SISADOA and frequency of its administration.

3.1 Outcome Measures

3.1.1 Oxford Knee Score

In this study six variations of the Oxford Knee Score were used (Harris *et al.*, 2013).

1. **Oxford Knee Score:** For each item, scores ranged from 0 (extreme difficulty) to 4 (normal function), and global score from 0 (worst score) to 48 (best score).

2. **Oxford Knee Score – Pain component** consisted of 1, 4, 5, 6, 8, 9, 10 items. This subscale was then standardized to a range from 0 (worst) to 100 (best), multiplying raw score for 3.57.

3. **Oxford Knee Score – Functional component** consisted of 2, 3, 7, 11, 12 items. This subscale was then standardized to a range from 0 (worst) to 100 (best), multiplying raw score for 5.

The last three subscales were calculated by protocol following the original Oxford Knee Score calculation. For each item, scores ranged from 1 (normal function) to 5 (extreme difficulty).

4. **Oxford Knee Score – Pain** consisted of 1, 4, 5, 8, 9 items that ranged from 5 (best) to 25 (worst).

5. **Oxford Knee Score - Range of motion** consisted of items 2, 3, 7, 12 that ranged from 4 (best) to 20 (worst).

6. **Oxford Knee Score – Walking** consisted of items 4, 6, 9, 10, 11 that ranged from 5 (best) to 25 (worst).

3.1.2 Visual Analog Scales (VAS) for Pain

VAS for pain were continuous scales of pain intensity assessing perceived pain during daily activities and at rest/night: the answers were expressed on a 100 mm line, from 0 (no pain) to 100 mm (worst pain).

3.2 Descriptive Analysis

The continuous variables were presented as central tendencies indexes (mean, median) and dispersion measures (standard deviation, minimum and maximum values), whereas categorical variables were presented as frequencies and proportions.

3.3 Group Homogeneity

Homogeneity between Suplasyn and Suplasyn 1-shot groups was further analyzed using one way analysis of variance ANOVA for numerical variables and Chi-square test for nominal variables.

3.4 Statistical Inferences

T-test and Wilcoxon test were performed in order to carry out intra-group comparisons between visits. Cohen's d effect size was calculated as a measure of improvement (effectiveness analysis). Non-parametric Friedman test were used for ordinal variables.

Comparisons between groups were performed using ANOVA tests for continuous variables and Mann-Whitney U tests for numerical variables.

3.5 Non-Inferiority– Equivalence Analysis

Non-inferiority clinical trials are being performed with an increasing frequency now-a-days. They do not simply consist of demonstrating the non-existence of significant differences, but they must demonstrate that the lower limit of the 95% confidence interval of the difference between the test and control must not exceed the limit of delta to be 95% sure that the test drug is not worse than the control by more than delta (Gupta, 2011). These margins are known as non-inferiority or equivalence margins and are established following criteria of minimum detectable differences or clinically relevant minimum differences.

Different cut-off points were determined in order to obtain the margins (Lower Bound and Upper Bound) and perform non-inferiority and equivalence analyzes.

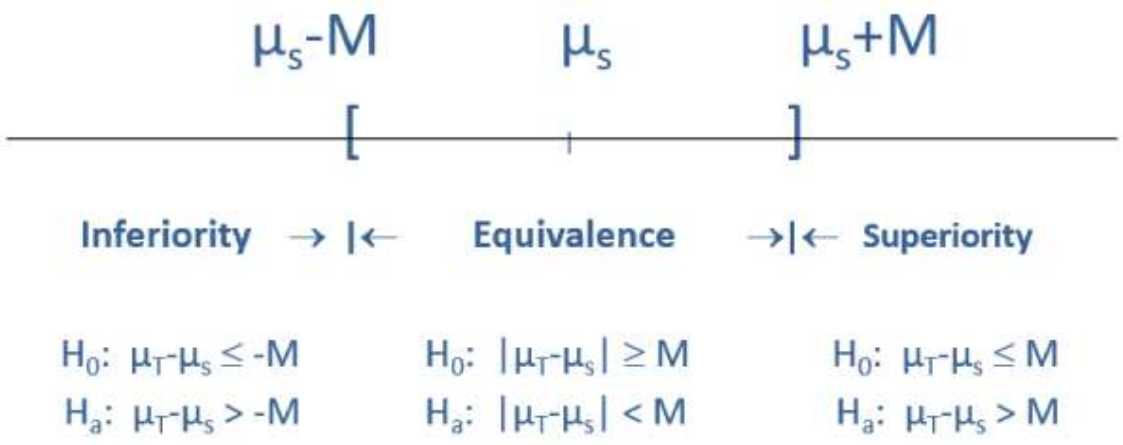
For global OKS, pain and functional OKS subscales, the half of the minimally clinically important differences (MCID) were used as cut-off point (Lee et al., 2017). The cut-off points of the other three OKS subscales (calculated by protocol) and VAS Perceived Pain variables were obtained using the proportion (6%) of the global OKS as reference, since no previous bibliographical citations of these variables were found.

3.5.1 Hypothesis testing

Considering that μT and μs are the mean responses of the Suplasyn 1-shot and Suplasyn, respectively, if μT falls within the equivalence limit of "μs− M, μs + M", one can conclude that Suplasyn 1-shot is equivalent to Suplasyn or the standard of care treatment.

Considering the left-hand side, i.e., μs < μs – M, in this case, one can conclude that Suplasyn 1-shot is inferior to Suplasyn or the standard of care treatment. Thus, μs − M ≤ μT is an indication that Suplasyn 1-shot is not inferior to the Suplasyn (Figure 1).

Figure 1. Hypothesis test



(Chow, SC. On selection of Margin in Non-Inferiority Trials (2016))

Table 2. Oxford Knee Score cut-off points for non-inferiority/ equivalence margins

Variable	Cutoff point	Proportion	Margin (M)	
			Lower Bound	Upper Bound
Oxford Knee Score	6/2= 3	6%	**Lower Bound 95CI – Cutoff point**	**Upper Bound 95CI + Cutoff point**
Oxford Knee Score: Pain component	14/2=7	7%		
Oxford Knee Score: Functional component	10/2=5	5%		
Oxford Knee Score: Pain (protocol)	1,56	6%		
Oxford Knee Score: Range of Motion (protocol)	1,25	6%		
Oxford Knee Score: Walking (protocol)	1,56	6%		
Perceived Pain	0,6	6%		

4 Descriptive Analysis

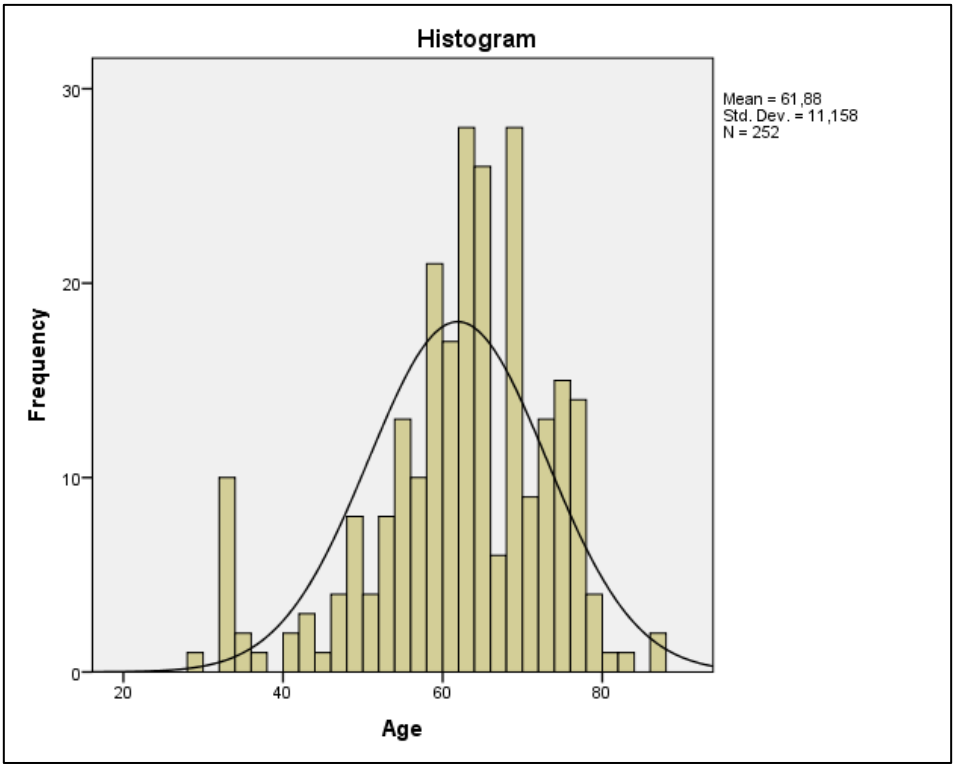
4.1 Baseline Visit (N=252)

4.1.1 Age

Table 3: Age (years)

N	252
Mean	61.88
Median	63.00
Mode	68
Std. Deviation	11.158
Minimum	29
Maximum	29

Graphic 1: Histogram: Age (years)

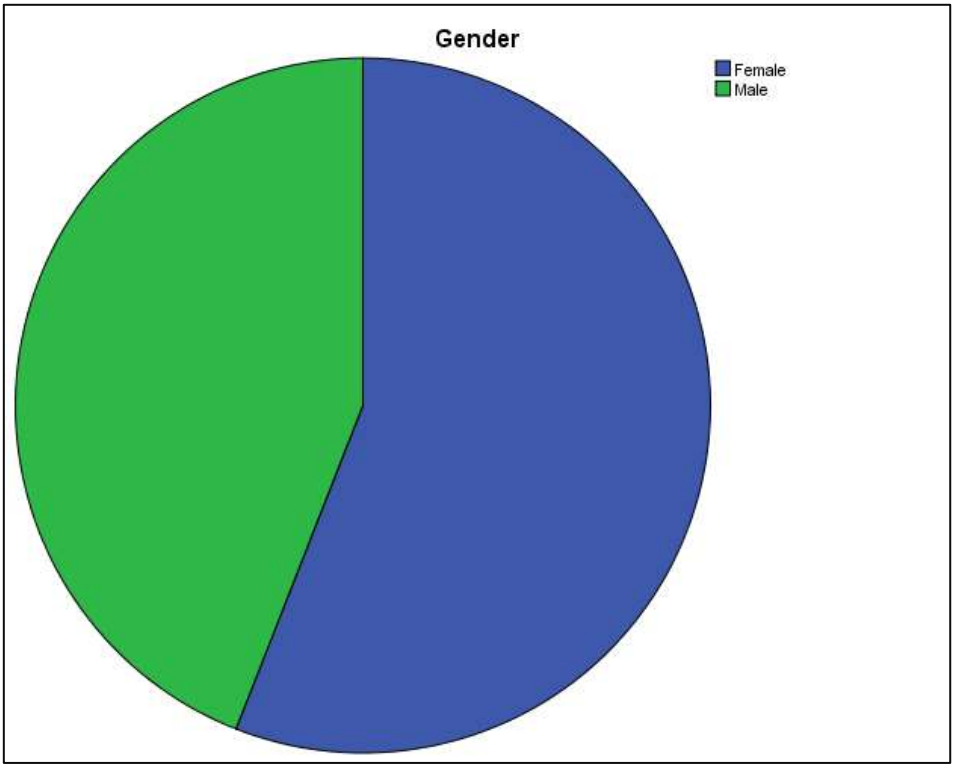


4.1.2 Gender

Table 4. Gender

	Frequency	Percent
Female	141	56.0%
Male	111	44.0%
Total	252	100.0%

Graphic 2. Gender

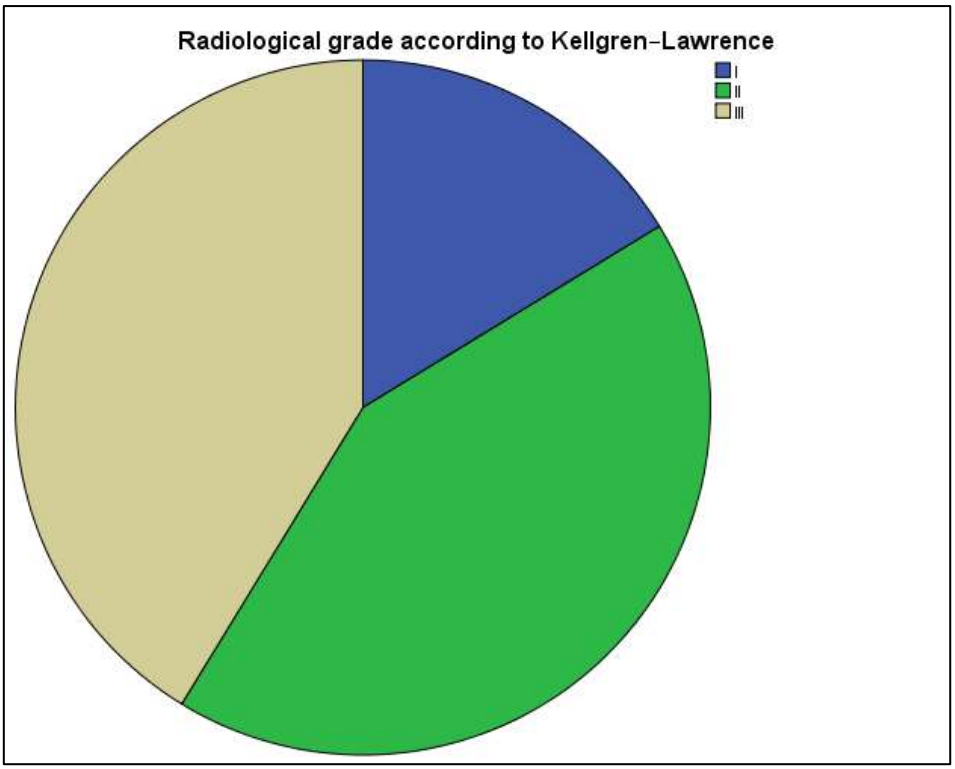


4.1.3 Radiological grade according to Kellgren–Lawrence

Table 5. Radiological grade according to Kellgren–Lawrence

	Frequency	Percent
I	41	13.3%
II	107	45.5%
III	104	45.1%
Total	252	100.0%

Graphic 3. Radiological grade according to Kellgren–Lawrence

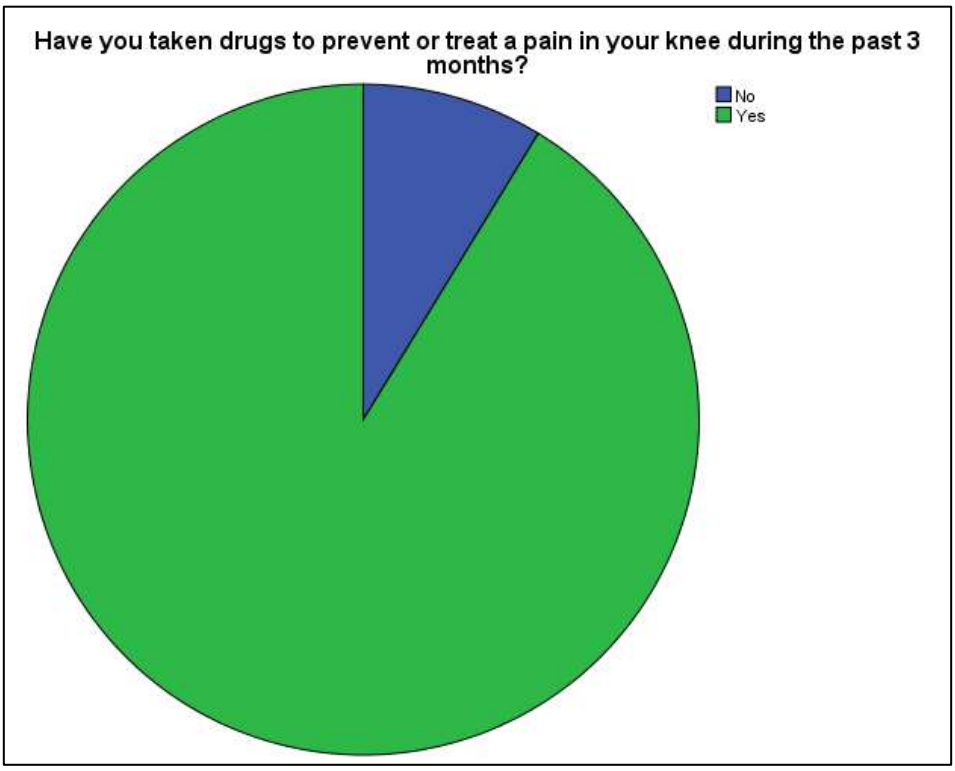


4.1.4 Have you taken drugs to prevent or treat a pain in your knee during the past 3 months?

Table 6. Have you taken drugs to prevent or treat a pain in your knee during the past 3 months?

	Frequency	Percent
No	22	8.7%
Yes	230	91.3%
Total	252	100.0%

Graphic 4. Have you taken drugs to prevent or treat a pain in your knee during the past 3 months?

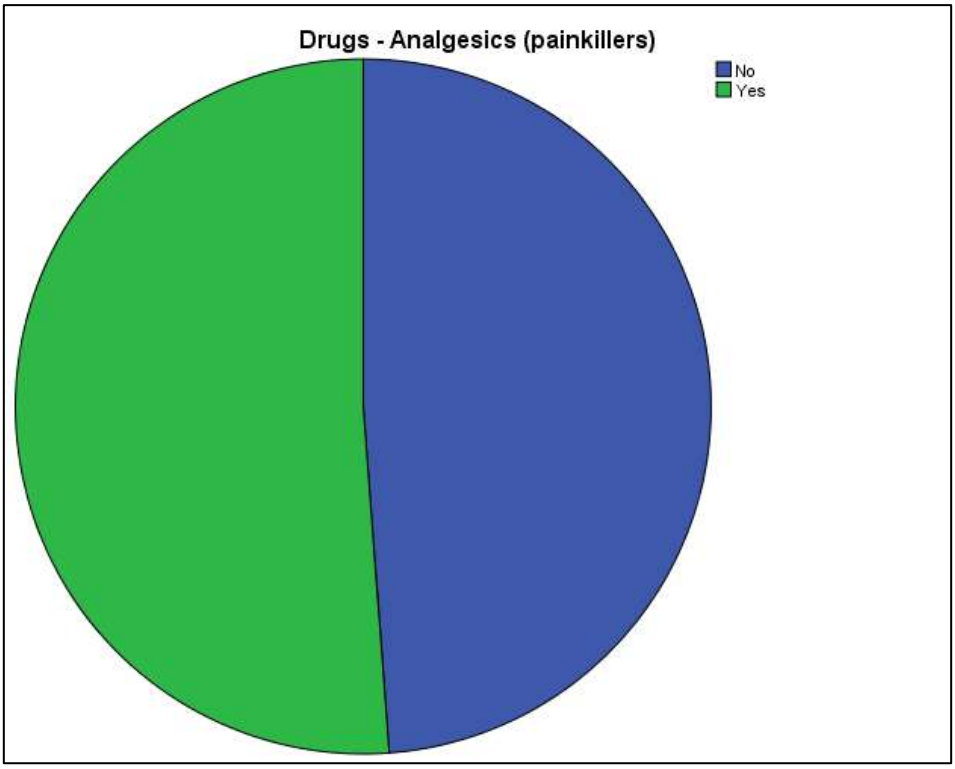


4.1.5 Analgesics (painkillers)

Table 7. Analgesics (painkillers)

	Frequency	Percent
No	123	48.8%
Yes	129	51.2%
Total	252	100.0%

Graphic 5. Analgesics (painkillers)



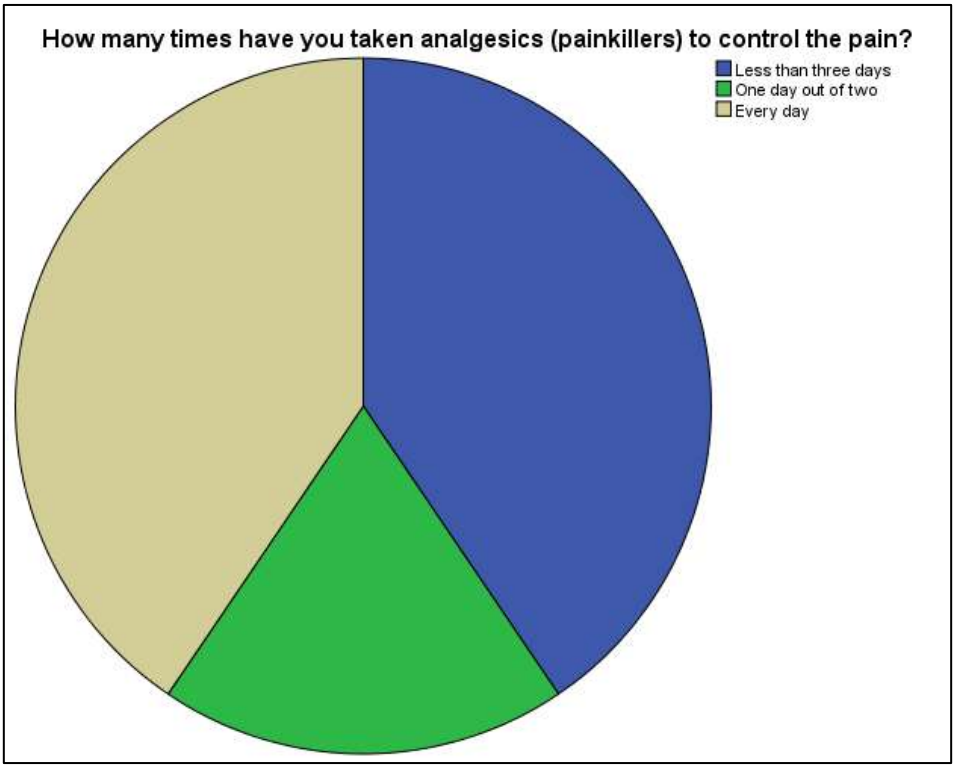
4.1.6 How many times have you taken analgesics (painkillers) to control the pain?

Table 8. How many times have you taken analgesics (painkillers) to control the pain?

	Frequency	Percent
Less than three days	47	18.7%
One day out of two	22	8.8%
Every day	47	18.7%
Total*	116	100.0%

**There are missing values on this variable (N=129)*

Graphic 6. How many times have you taken analgesics (painkillers) to control the pain?

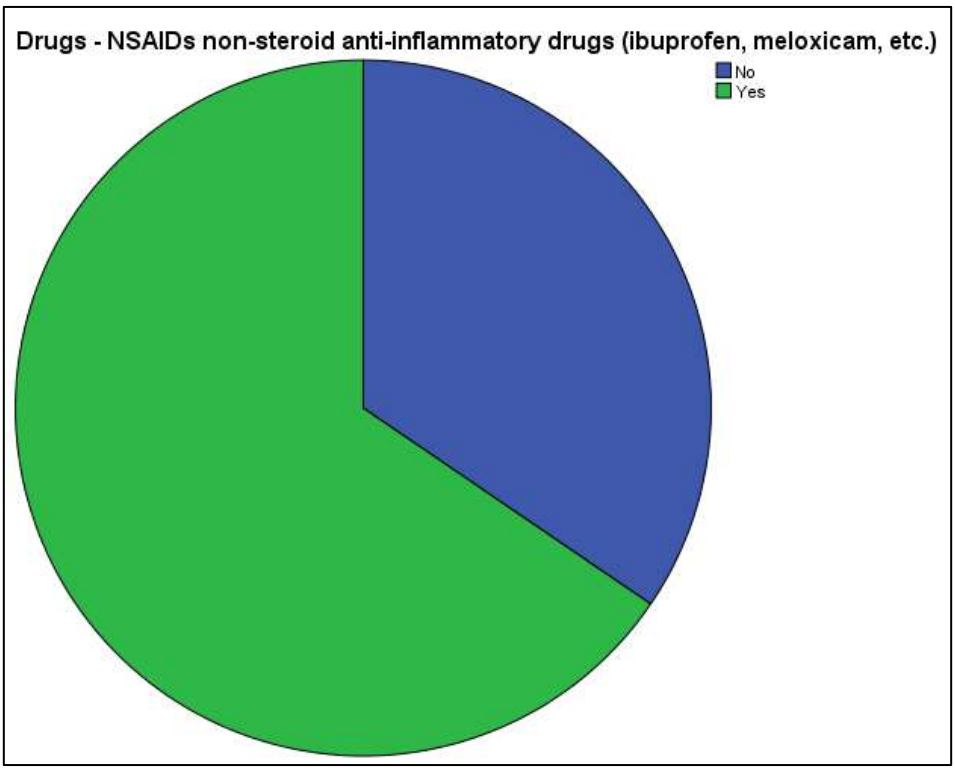


4.1.7 NSAIDs non-steroid anti-inflammatory drugs (ibuprofen, meloxicam, etc.)

Table 9. NSAIDs non-steroid anti-inflammatory drugs (ibuprofen, meloxicam, etc.)

	Frequency	Percent
No	87	34.5%
Yes	165	65.5%
Total	252	100.0%

Graphic 7. NSAIDs non-steroid anti-inflammatory drugs (ibuprofen, meloxicam, etc.)



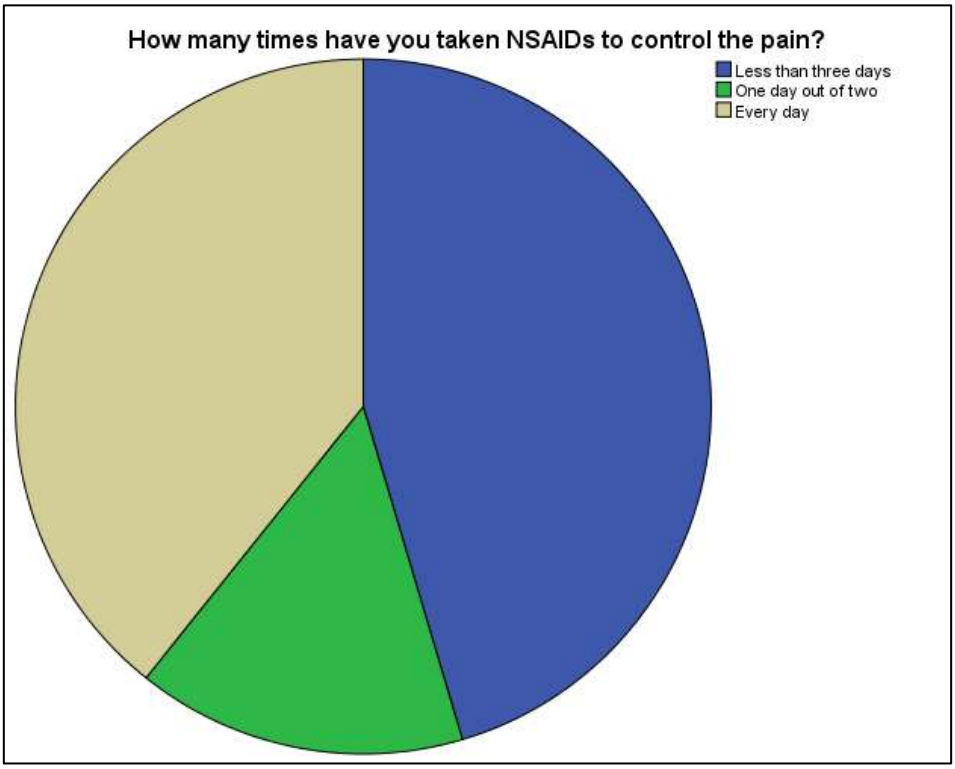
4.1.8 How many times have you taken NSAIDs to control the pain?

Table 10. How many times have you taken NSAIDs to control the pain?

	Frequency	Percent
Less than three days	74	29.4%
One day out of two	25	9.9%
Every day	64	25.4%
Total*	163	100.0%

**There are missing values on this variable (N=165)*

Graphic 8. How many times have you taken NSAIDs to control the pain?

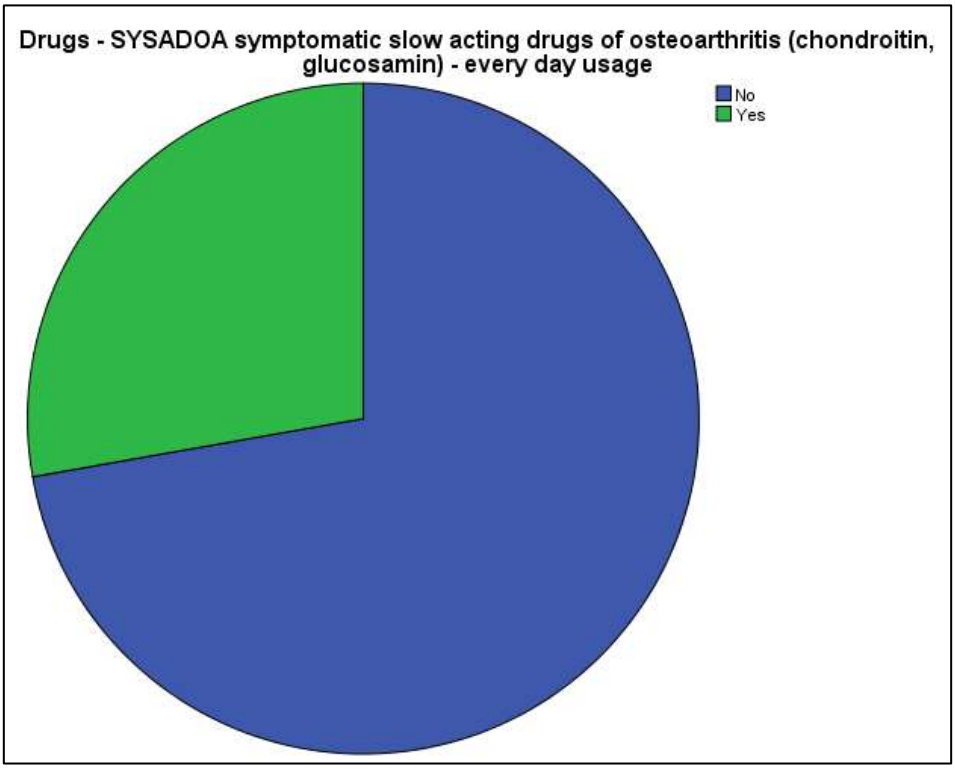


4.1.9 SYSADOA symptomatic slow acting drugs of osteoarthritis (chondroitin, glucosamine) - every day usage

Table 11. SYSADOA symptomatic slow acting drugs of osteoarthritis (chondroitin, glucosamine) - every day usage

	Frequency	Percent
No	182	72.2%
Yes	70	27.8%
Total	252	100.0%

Graphic 9. SYSADOA symptomatic slow acting drugs of osteoarthritis (chondroitin, glucosamine) - every day usage

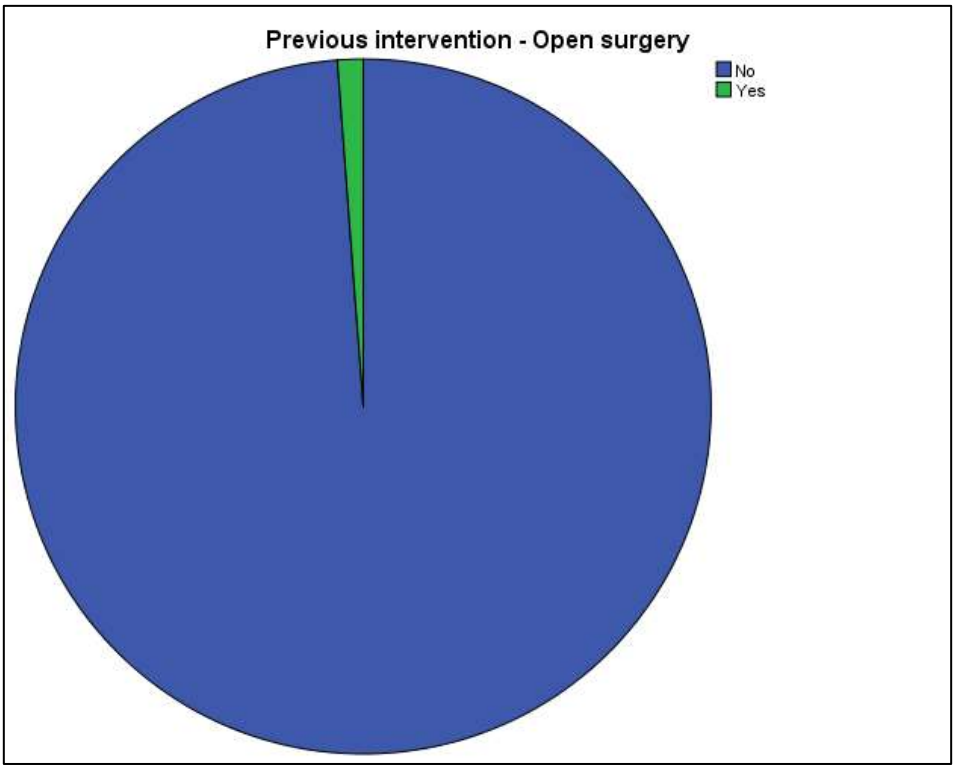


4.1.10 Previous intervention - Open surgery

Table 12. Previous intervention - Open surgery

	Frequency	Percent
No	249	98.8%
Yes	3	1.2%
Total	252	100.0%

Graphic 10. Previous intervention - Open surgery

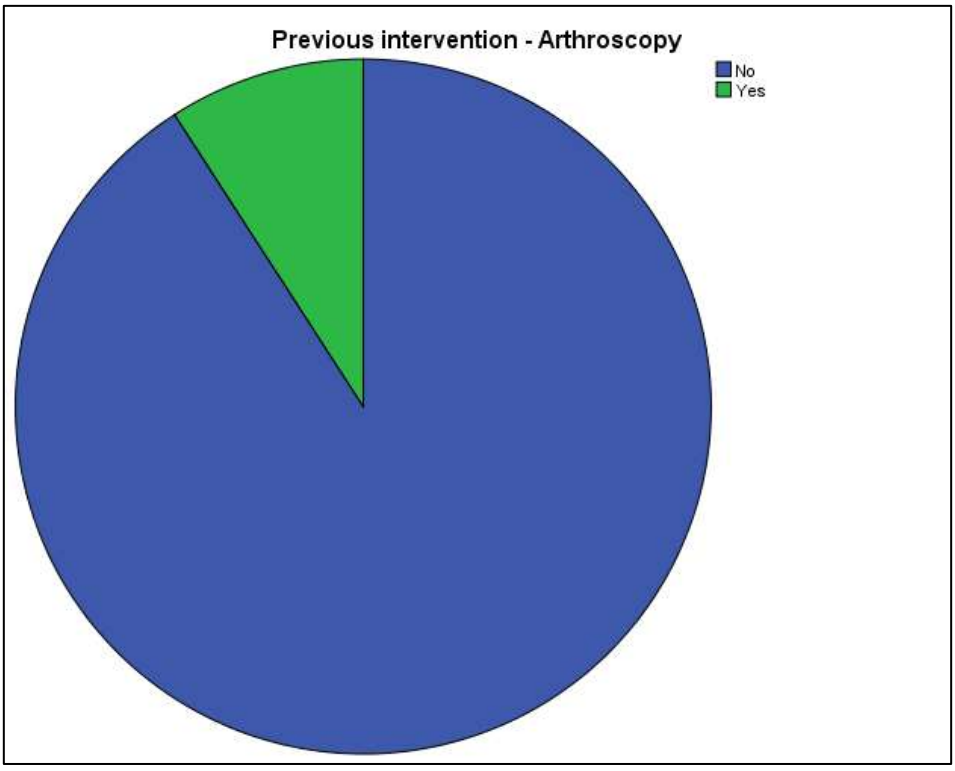


4.1.11 Previous intervention - Arthroscopy

Table 13. Previous intervention - Arthroscopy

	Frequency	Percent
No	229	90.9%
Yes	23	9.1%
Total	252	100.0%

Graphic 11. Previous intervention - Arthroscopy

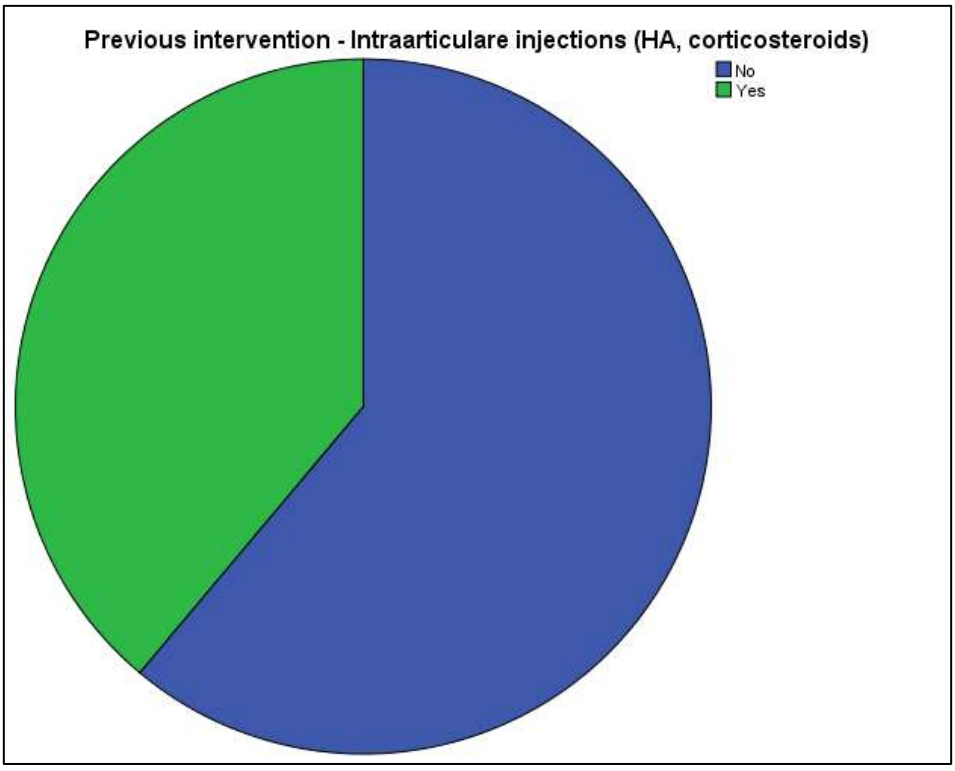


4.1.12 Previous intervention - Intraarticular injections (HA, corticosteroids)

Table 14. Previous intervention - Intraarticular injections (HA, corticosteroids)

	Frequency	Percent
No	154	61.1%
Yes	98	38.9%
Total	252	100.0%

Graphic 12. Previous intervention - Intraarticular injections (HA, corticosteroids)

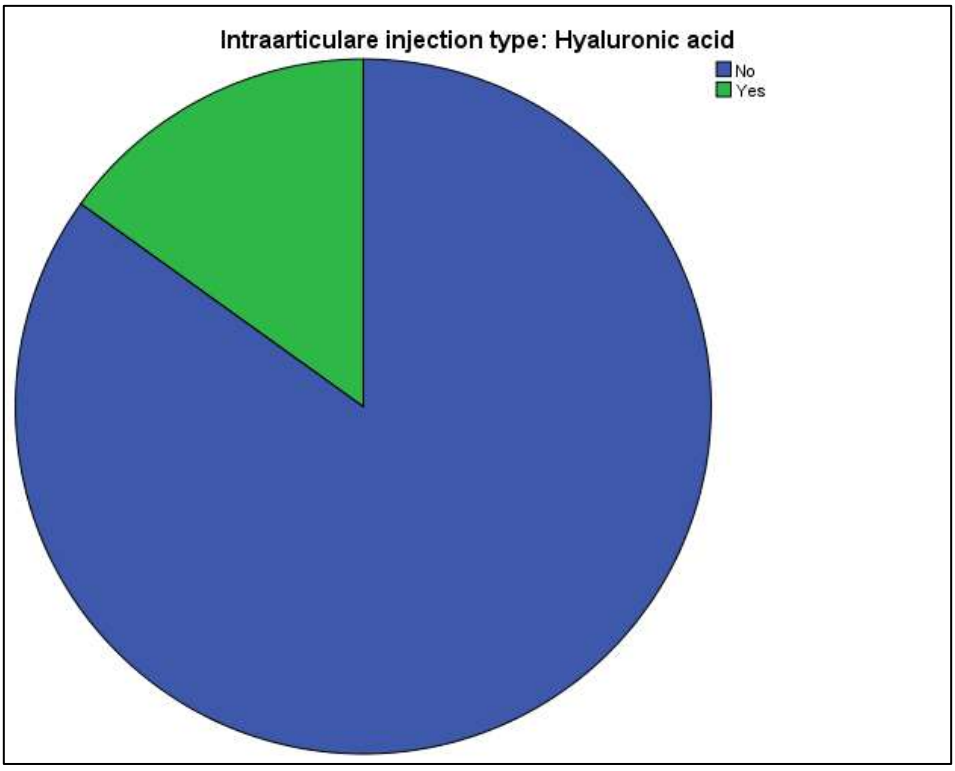


4.1.13 Intraarticular injection type: Hyaluronic acid

Table 15. Intraarticular injection type: Hyaluronic acid

	Frequency	Percent
No	214	84.9%
Yes	38	15.1%
Total	252	100.0%

Graphic 13. Intraarticular injection type: Hyaluronic acid

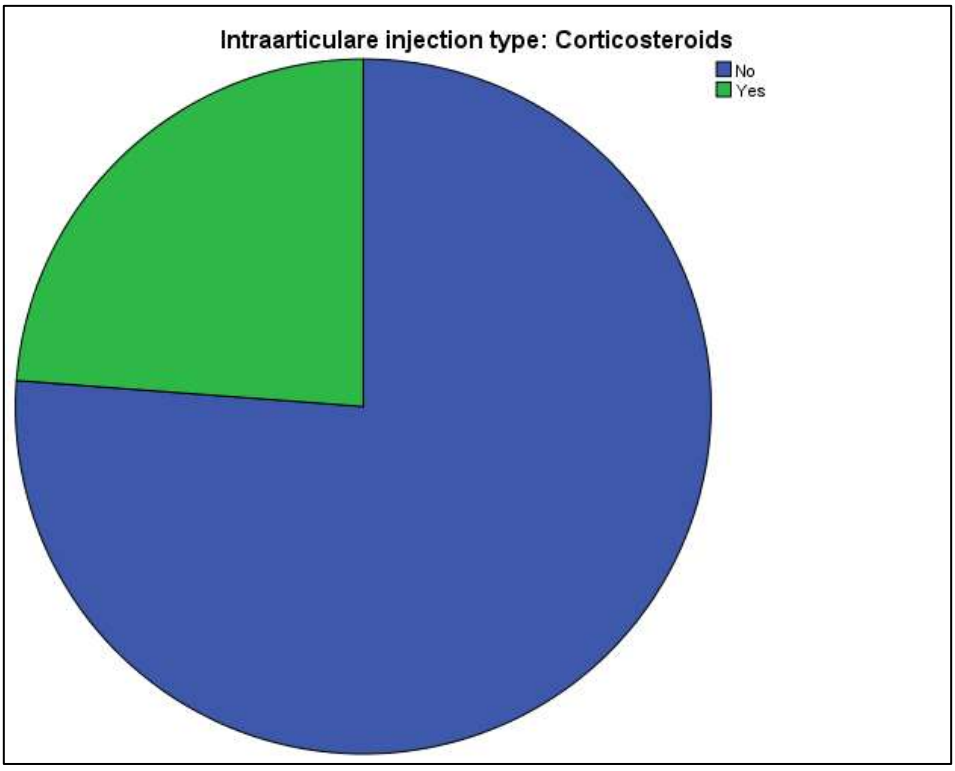


4.1.14 Intraarticular injection type: Corticosteroids

Table 16. Intraarticular injection type: Corticosteroids

	Frequency	Percent
No	192	76.2%
Yes	60	23.8%
Total	252	100.0%

Graphic 14. Intraarticular injection type: Corticosteroids

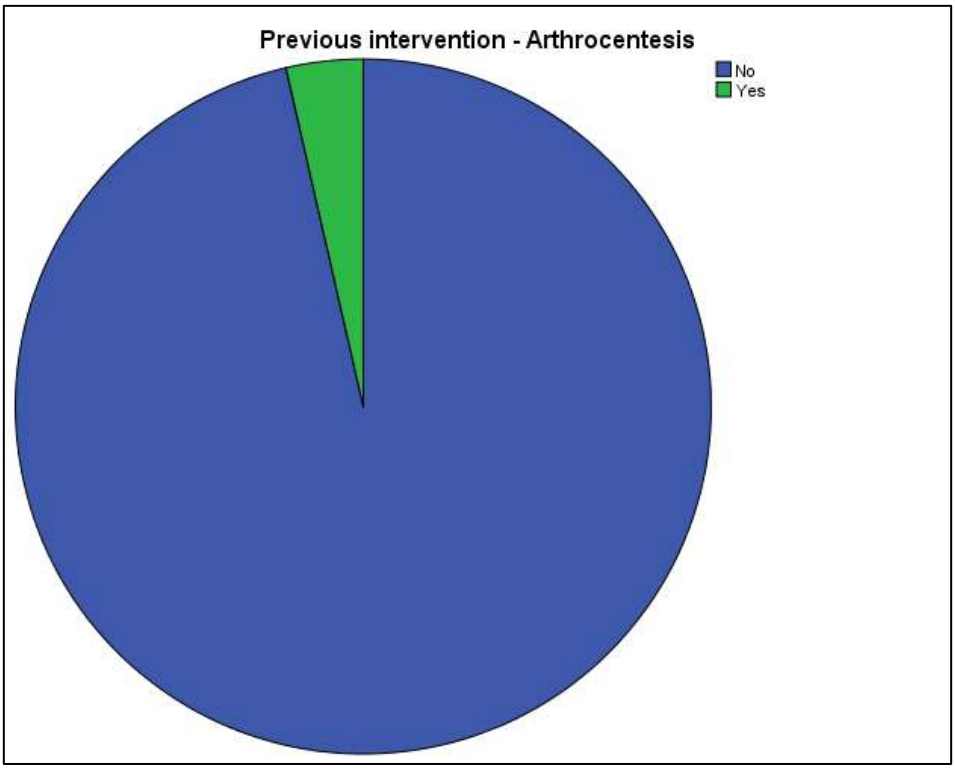


4.1.15 Previous intervention - Arthrocentesis

Table 17. Previous intervention - Arthrocentesis

	Frequency	Percent
No	243	96.4%
Yes	9	3.6%
Total	252	100.0%

Graphic 15. Previous intervention - Arthrocentesis



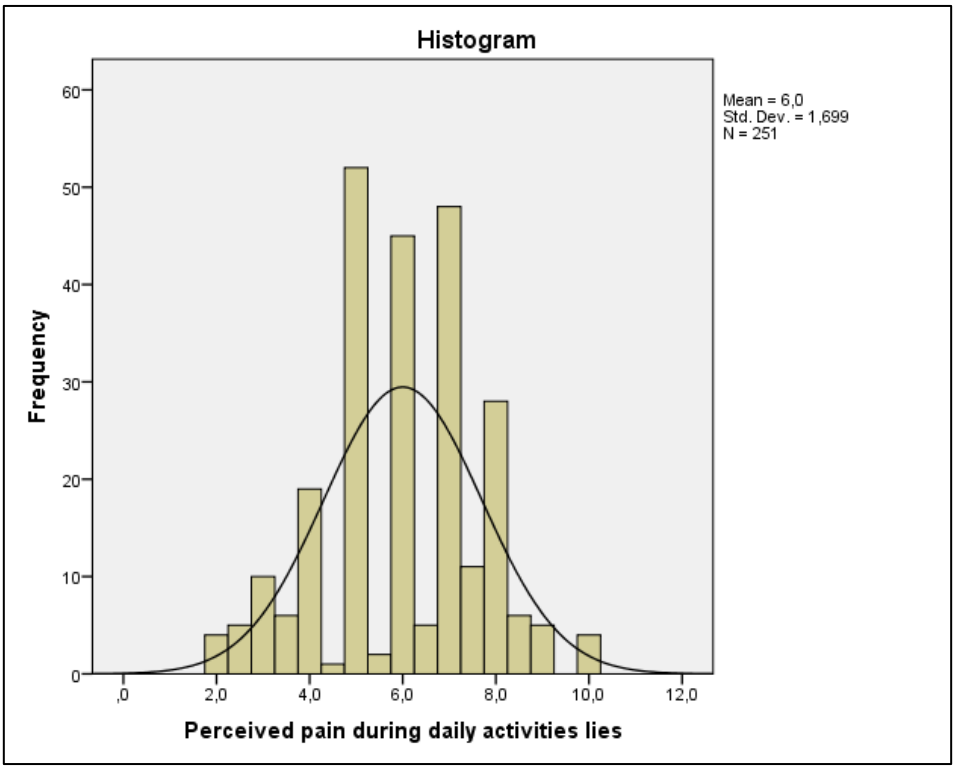
4.1.16 Perceived pain during daily activities lies

Table 18: Perceived pain during daily activities lies

N*	251
Mean	6.0
Median	6.0
Mode	5.0
Std. Deviation	1.699
Minimum	2.0
Maximum	10.0

**There are missing values on this variable (N=252)*

Graphic 16: Histogram: Perceived pain during daily activities lies



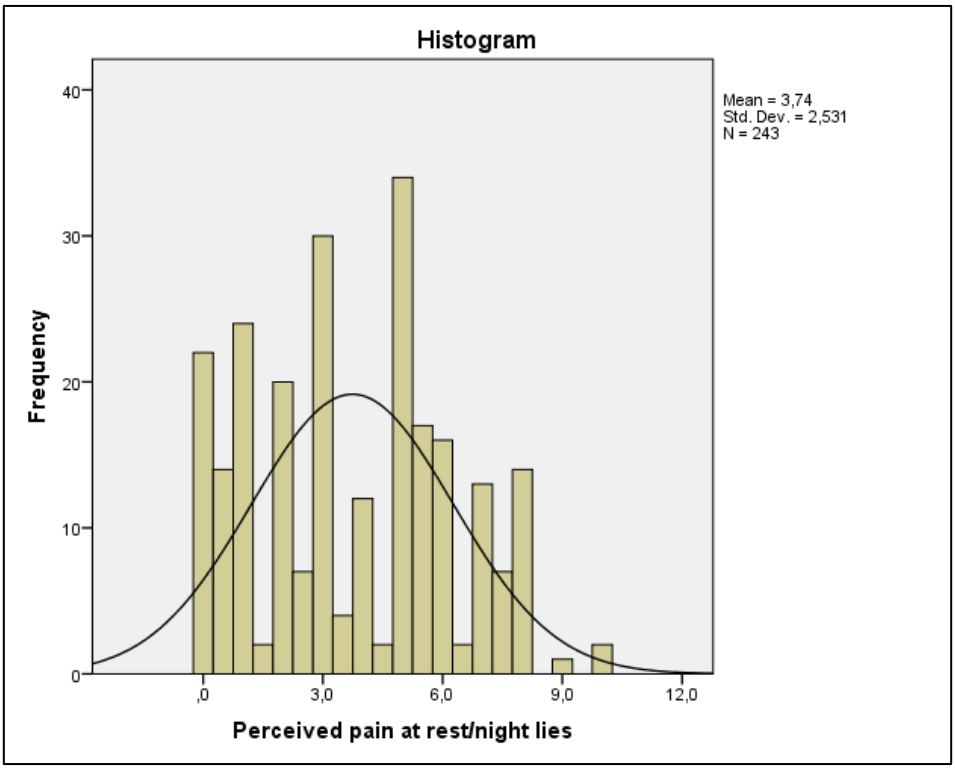
4.1.17 Perceived pain at rest/night lies

Table 19: Perceived pain at rest/night lies

N*	243
Mean	3.7
Median	3.5
Mode	5.0
Std. Deviation	2.531
Minimum	.0
Maximum	10.0

**There are missing values on this variable (N=252)*

Graphic 17: Histogram: Perceived pain at rest/night lies



4.1.18 OKSQ. During the past 4 weeks...

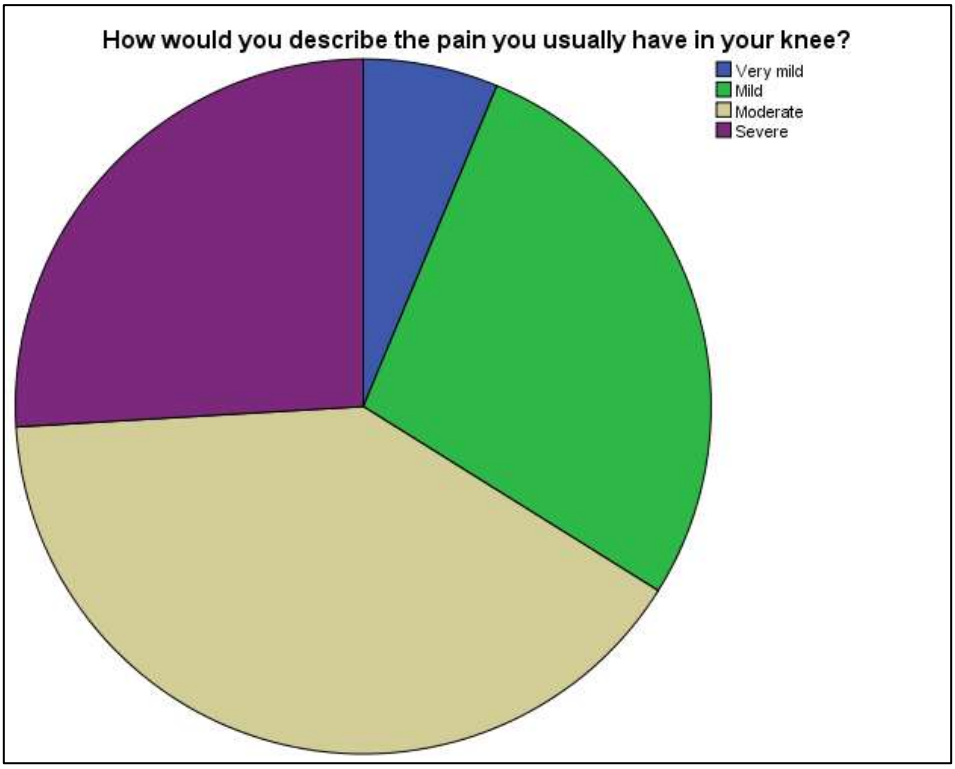
4.1.18.1 How would you describe the pain you usually have in your knee?

Table 20. How would you describe the pain you usually have in your knee?

	Frequency	Percent
Very mild	15	6.3%
Mild	66	27.6%
Moderate	96	40.2%
Severe	62	25.9%
Total*	239	100.0%

**There are missing values on this variable (N=252)*

Graphic 18. How would you describe the pain you usually have in your knee?



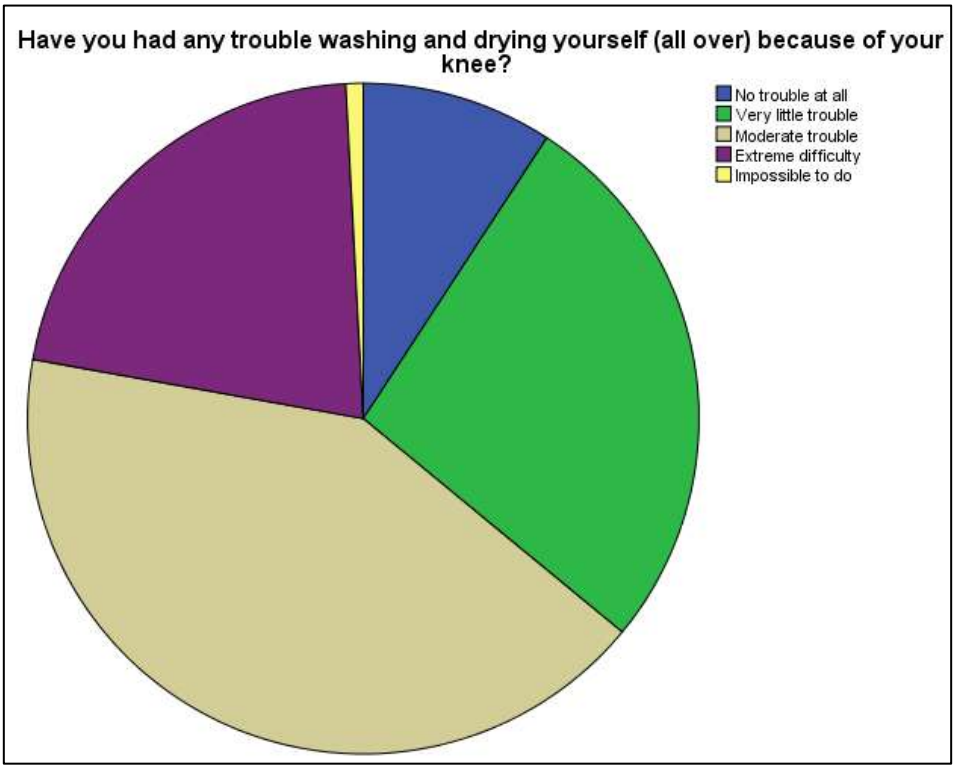
4.1.18.2 Have you had any trouble washing and drying yourself (all over) because of your knee?

Table 21. Have you had any trouble washing and drying yourself (all over) because of your knee?

	Frequency	Percent
No trouble at all	22	9.2%
Very little trouble	64	26.8%
Moderate trouble	100	41.8%
Extreme difficulty	51	21.3%
Impossible to do	2	0.9%
Total*	239	100.0%

**There are missing values on this variable (N=252)*

Graphic 19. Have you had any trouble washing and drying yourself (all over) because of your knee?



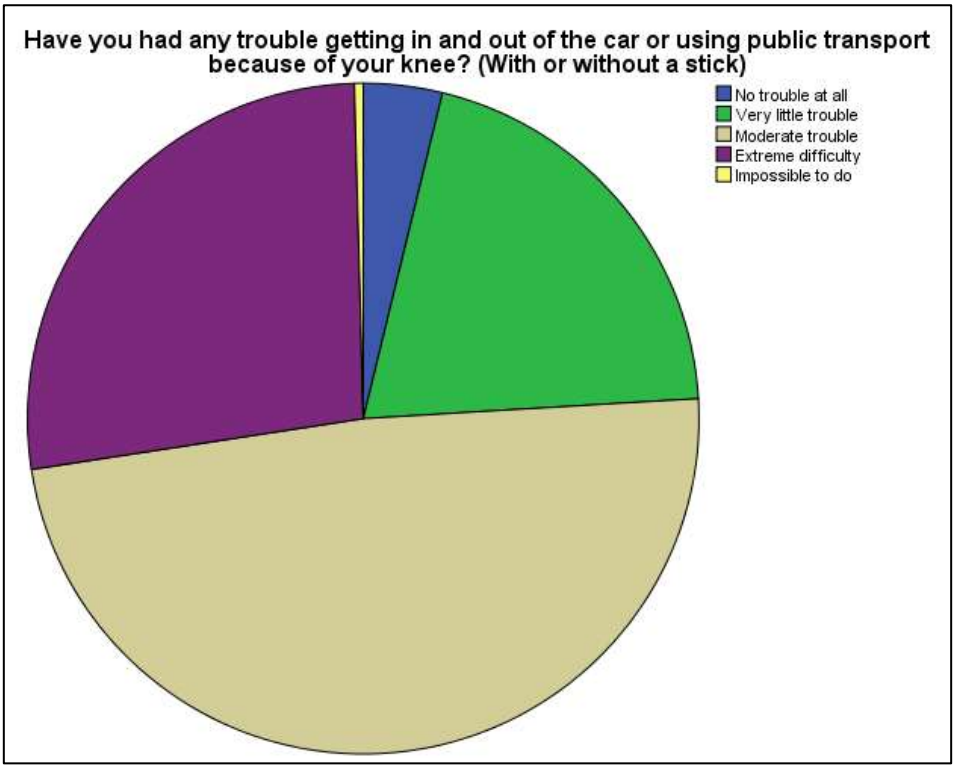
4.1.18.3 Have you had any trouble getting in and out of the car or using public transport because of your knee? (With or without a stick)

Table 22. Have you had any trouble getting in and out of the car or using public transport because of your knee? (With or without a stick)

	Frequency	Percent
No trouble at all	9	3.8%
Very little trouble	48	20.3%
Moderate trouble	115	48.5%
Extreme difficulty	64	27.0%
Impossible to do	1	0.4%
Total*	237	100.0%

**There are missing values on this variable (N=252)*

Graphic 20. Have you had any trouble getting in and out of the car or using public transport because of your knee? (With or without a stick)



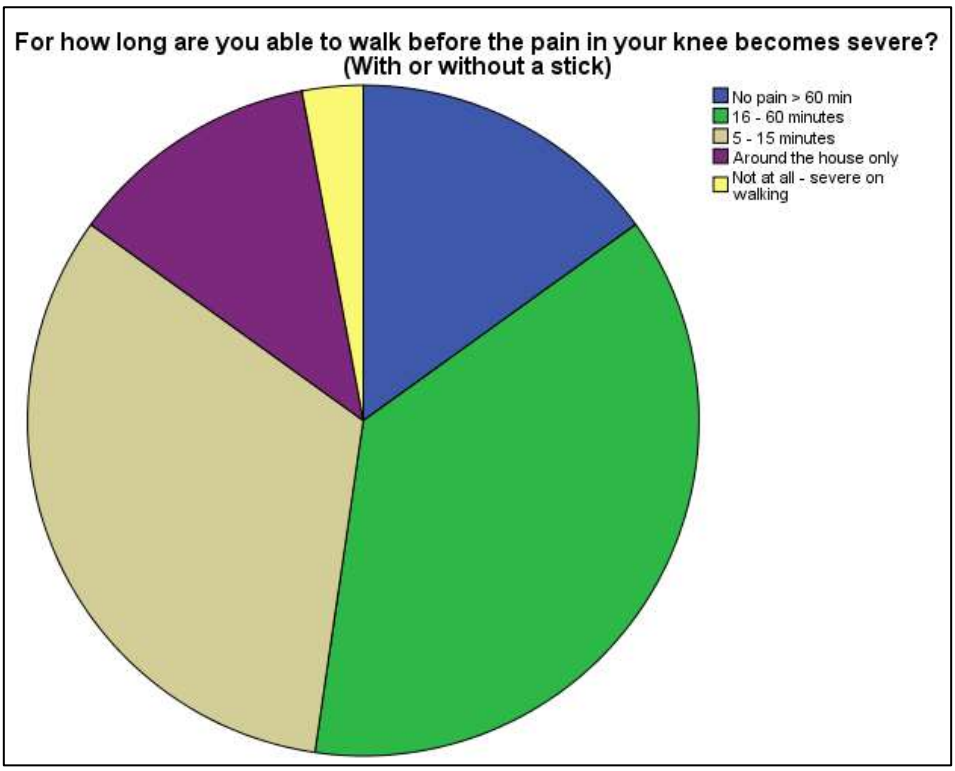
4.1.18.4 For how long are you able to walk before the pain in your knee becomes severe? (With or without a stick)

Table 23. For how long are you able to walk before the pain in your knee becomes severe? (With or without a stick)

	Frequency	Percent
No pain > 60 min	36	15.1%
16 - 60 minutes	89	37.2%
5 - 15 minutes	78	32.6%
Around the house only	29	12.2%
Not at all - severe on walking	7	2.9%
Total*	239	100.0%

**There are missing values on this variable (N=252)*

Graphic 21. For how long are you able to walk before the pain in your knee becomes severe? (With or without a stick)



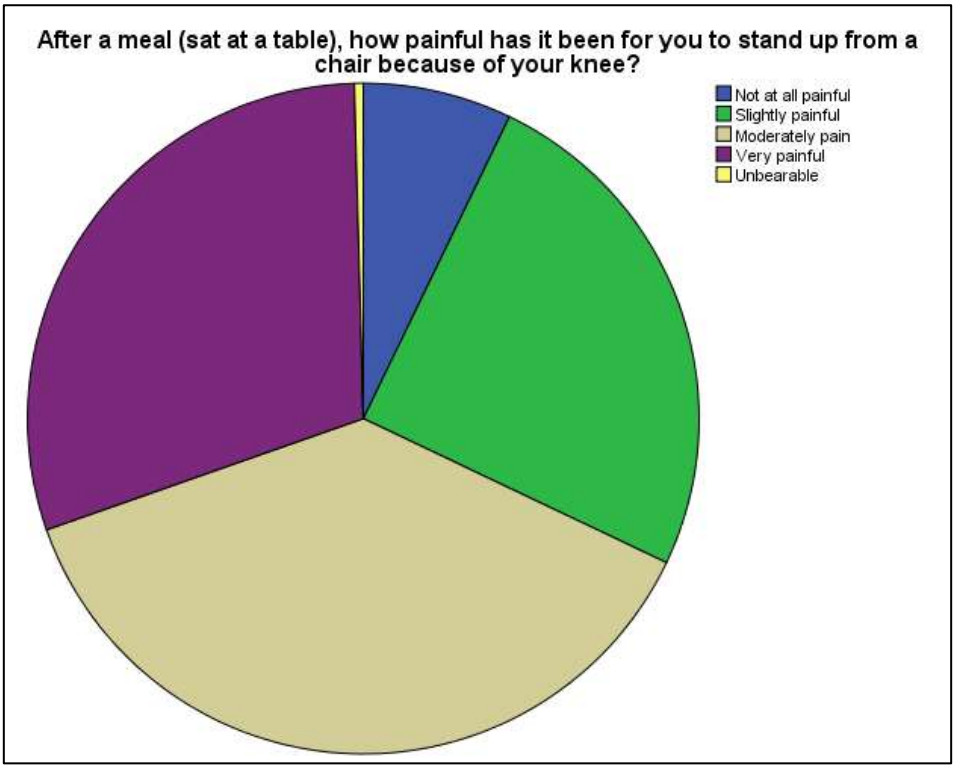
4.1.18.5 After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

Table 24. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

	Frequency	Percent
Not at all painful	17	7.2%
Slightly painful	59	24.8%
Moderately pain	89	37.6%
Very painful	71	30.0%
Unbearable	1	0.4%
Total*	237	100.0%

**There are missing values on this variable (N=252)*

Graphic 22. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?



4.1.18.6 Have you been limping when walking, because of your knee?

Table 25. Have you been limping when walking, because of your knee?

	Frequency	Percent
Rarely / never	32	13.4%
Sometimes or just at first	88	37.0%
Often, not just at first	36	15.1%
Most of the time	48	20.2%
All of the time	34	14.3%
Total*	238	100.0%

**There are missing values on this variable (N=252)*

Graphic 23. Have you been limping when walking, because of your knee?

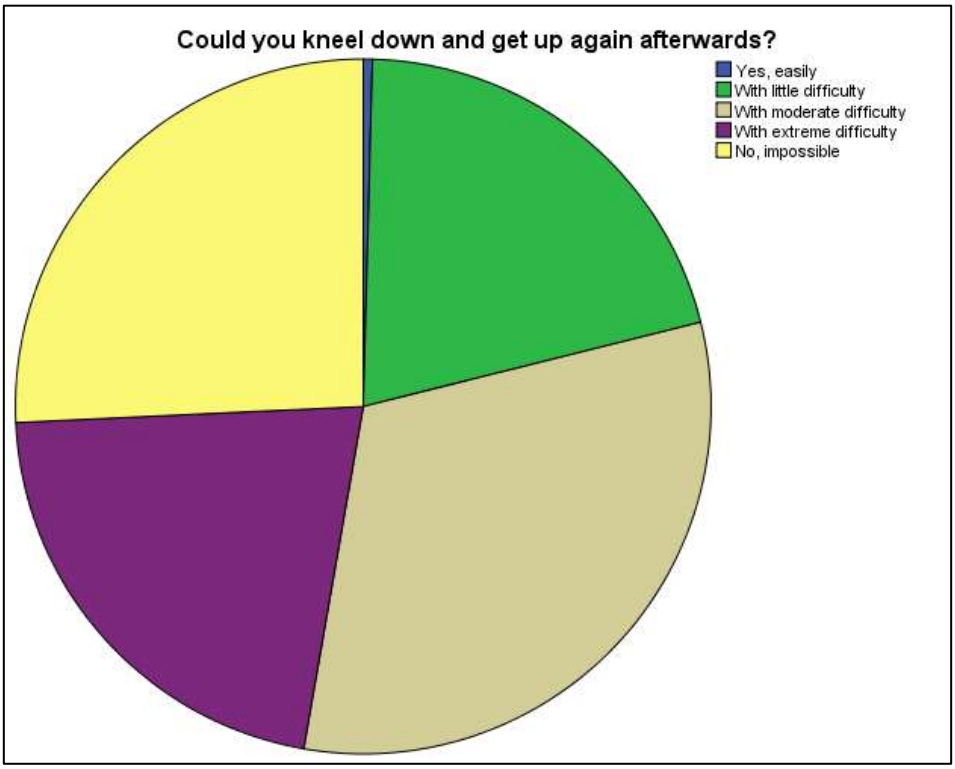
4.1.18.7 Could you kneel down and get up again afterwards?

Table 26. Could you kneel down and get up again afterwards?

	Frequency	Percent
Yes, easily	1	0.5%
With little difficulty	49	20.7%
With moderate difficulty	75	31.6%
With extreme difficulty	51	21.5%
No, impossible	61	25.7%
Total*	237	100.0%

**There are missing values on this variable (N=252)*

Graphic 24. Could you kneel down and get up again afterwards?



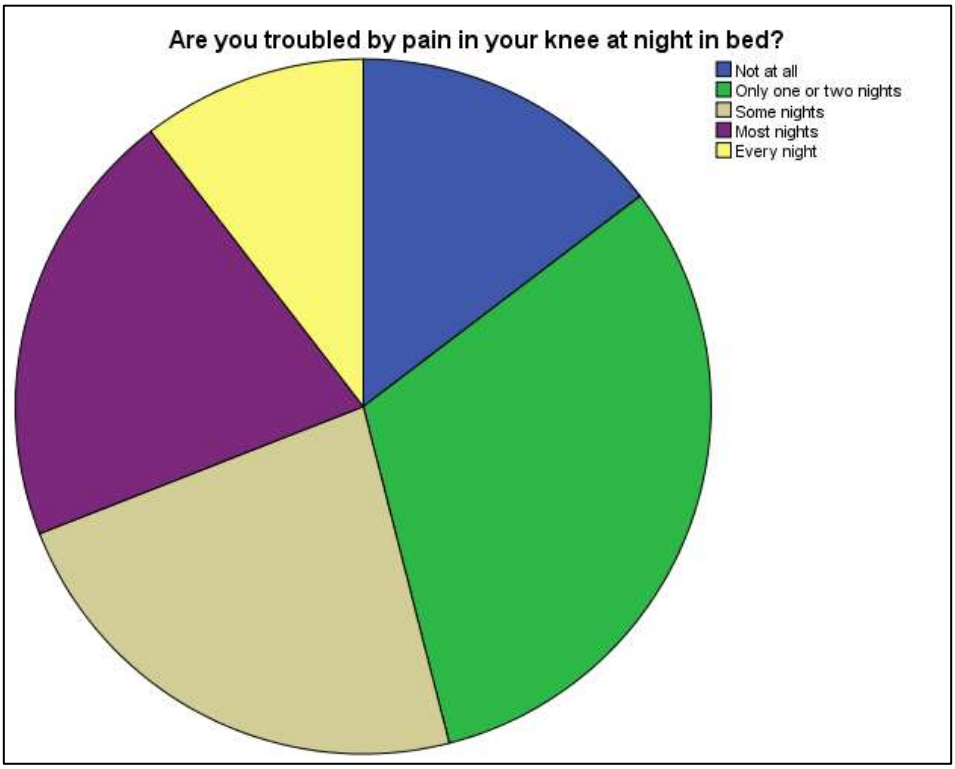
4.1.18.8 Are you troubled by pain in your knee at night in bed?

Table 27. Are you troubled by pain in your knee at night in bed?

	Frequency	Percent
Not at all	35	14.6%
Only one or two nights	75	31.4%
Some nights	55	23.0
Most nights	49	20.5%
Every night	25	10.5%
Total*	239	100.0%

**There are missing values on this variable (N=252)*

Graphic 25. Are you troubled by pain in your knee at night in bed?



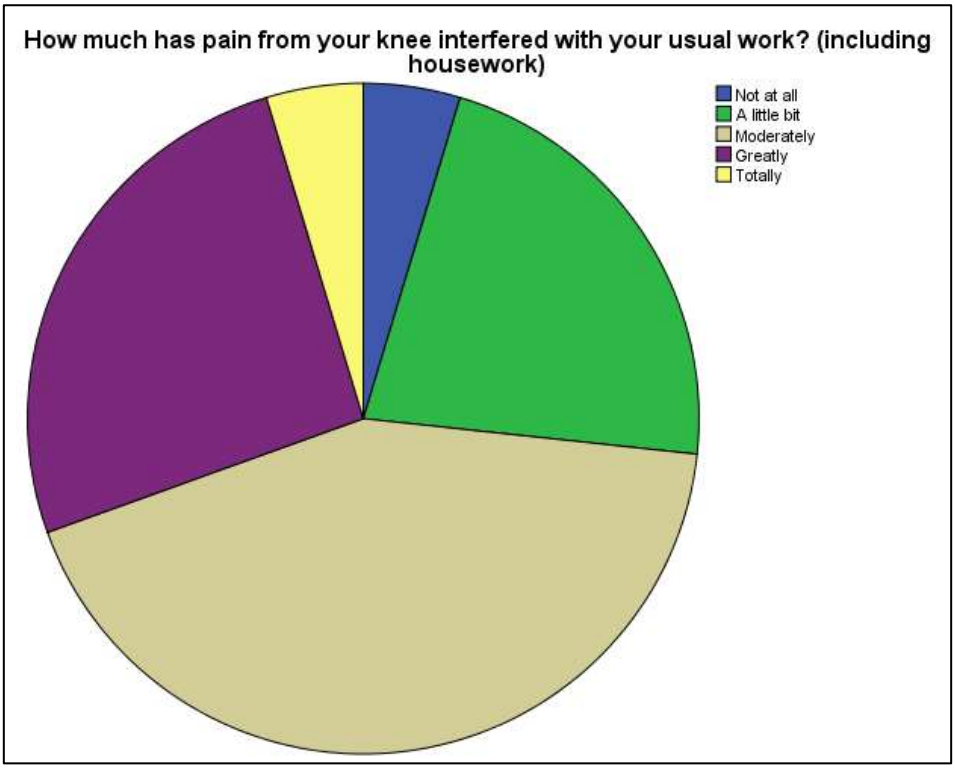
4.1.18.9 How much has pain from your knee interfered with your usual work? (including housework)

Table 28. How much has pain from your knee interfered with your usual work? (including housework)

	Frequency	Percent
Not at all	11	4.7%
A little bit	52	22.0
Moderately	101	42.8%
Greatly	61	25.8%
Totally	11	4.7%
Total*	236	100.0%

**There are missing values on this variable (N=252)*

Graphic 26. How much has pain from your knee interfered with your usual work? (including housework)



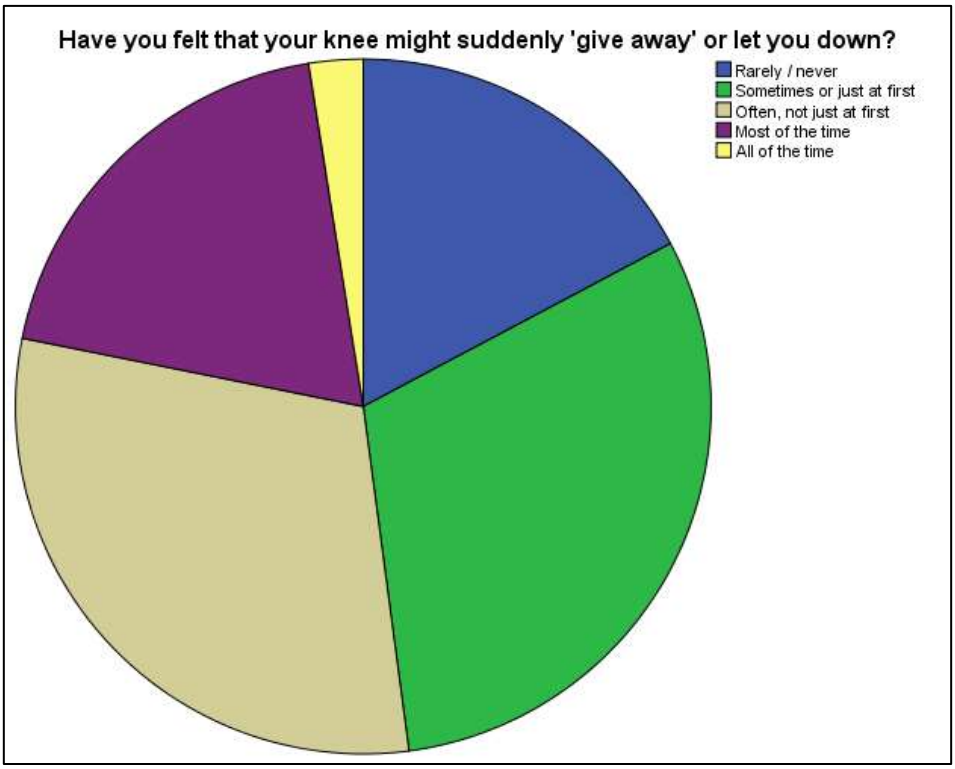
4.1.18.10 Have you felt that your knee might suddenly 'give away' or let you down?

Table 29. Have you felt that your knee might suddenly 'give away' or let you down?

	Frequency	Percent
Rarely / never	41	17.2%
Sometimes or just at first	73	30.7%
Often, not just at first	72	30.3%
Most of the time	46	19.3%
All of the time	6	2.5%
Total*	238	100.0%

**There are missing values on this variable (N=252)*

Graphic 27. Have you felt that your knee might suddenly 'give away' or let you down?



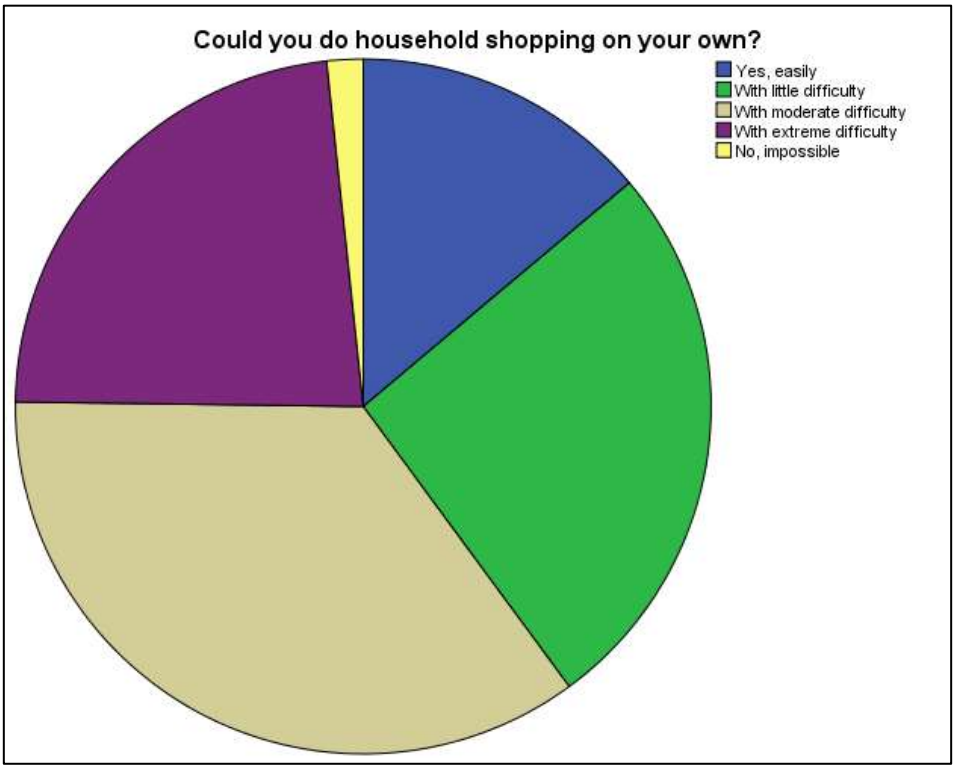
4.1.18.11 Could you do household shopping on your own?

Table 30. Could you do household shopping on your own?

	Frequency	Percent
Yes, easily	33	13.9%
With little difficulty	62	26.0%
With moderate difficulty	84	35.3%
With extreme difficulty	55	23.1%
No, impossible	4	1.7%
Total*	238	100.0%

**There are missing values on this variable (N=252)*

Graphic 28. Could you do household shopping on your own?



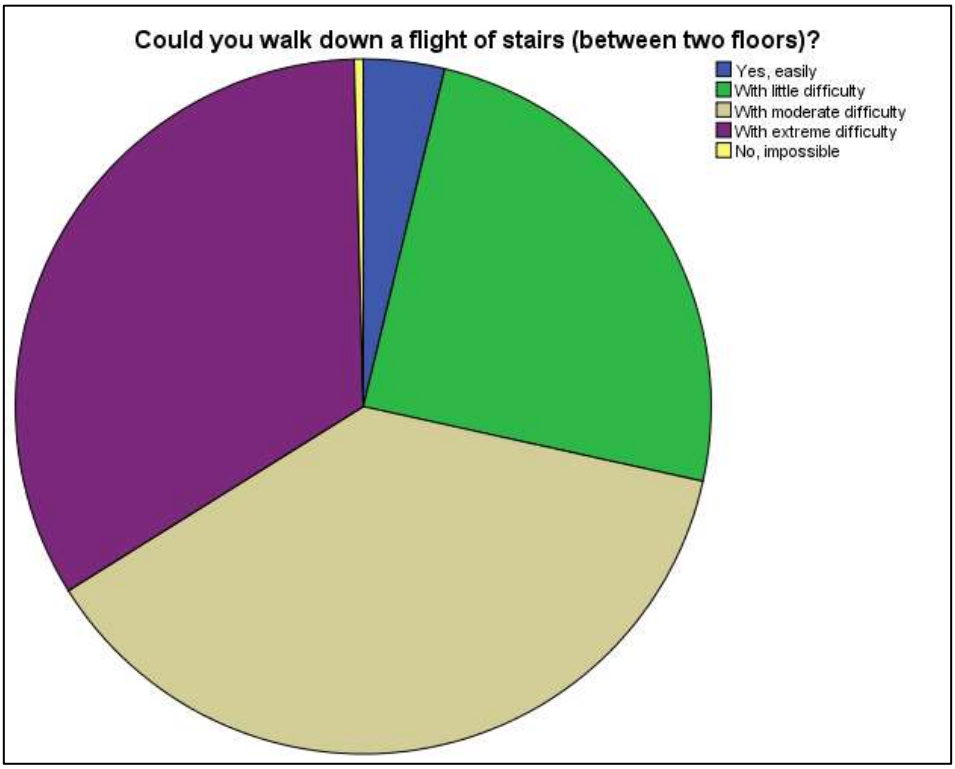
4.1.18.12 Could you walk down a flight of stairs (between two floors)?

Table 31. Could you walk down a flight of stairs (between two floors)?

	Frequency	Percent
Yes, easily	9	3.8%
With little difficulty	59	24.7%
With moderate difficulty	90	37.6%
With extreme difficulty	80	33.5%
No, impossible	1	0.4%
Total*	239	100.0%

**There are missing values on this variable (N=252)*

Graphic 29. Could you walk down a flight of stairs (between two floors)?



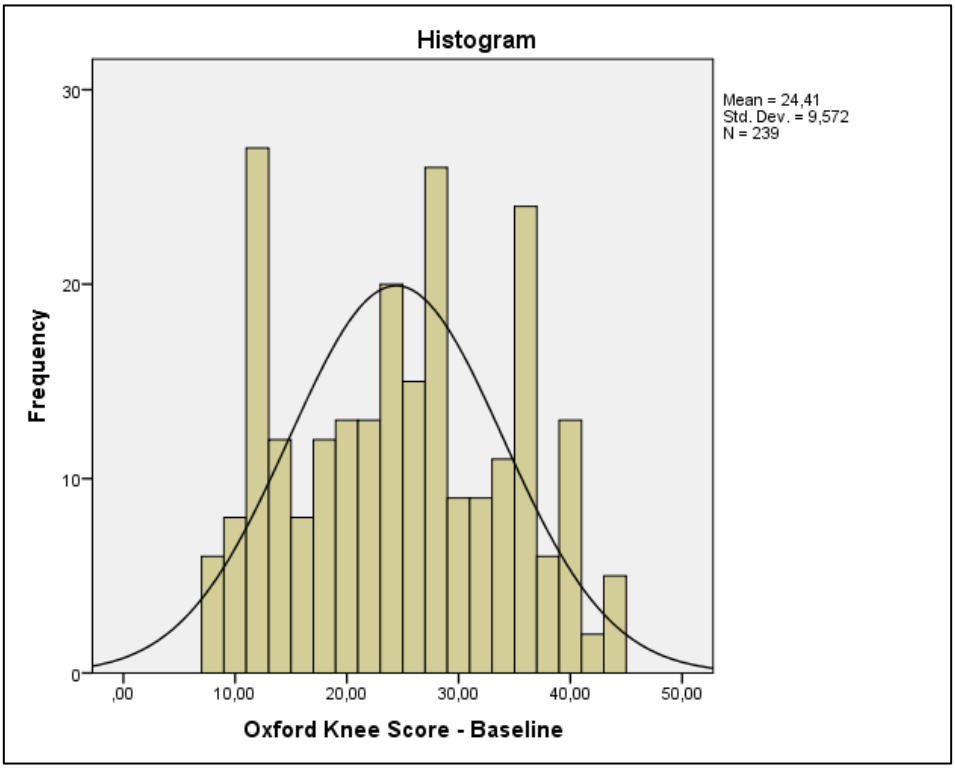
4.1.18.13 Oxford Knee Score

Table 32. Oxford Knee Score

N*	239
Mean	24.41
Median	25.00
Mode	35.00
Std. Deviation	9.572
Minimum	8.00
Maximum	44.00

**There are missing values on this variable (N=252)*

Graphic 30. Oxford Knee Score



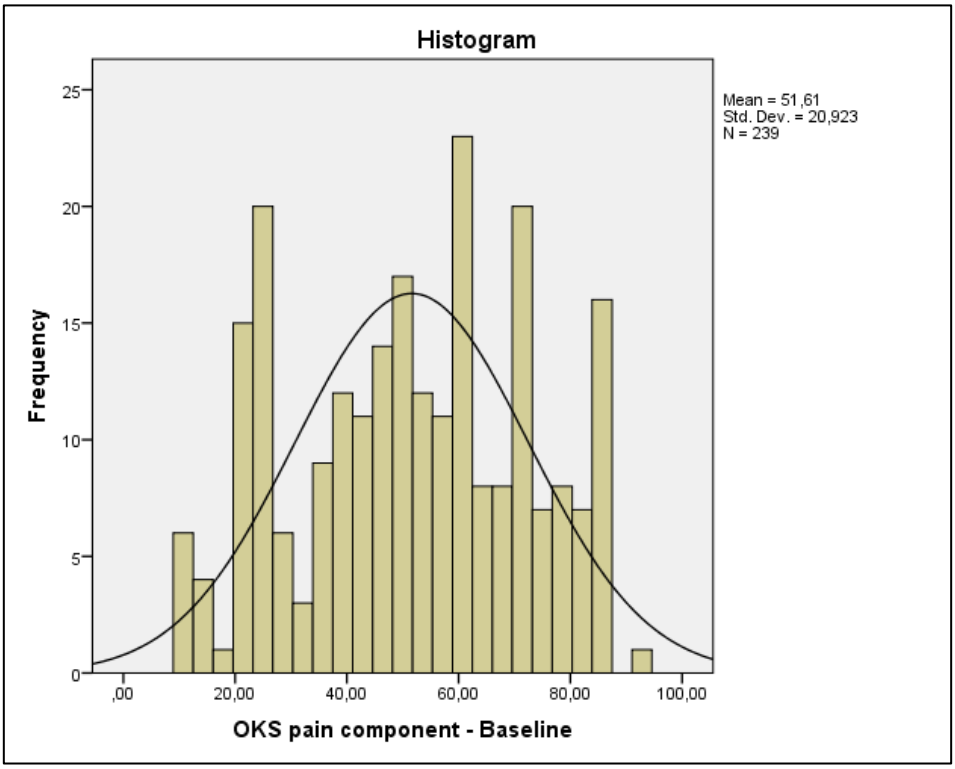
4.1.18.14 Oxford Knee Score Pain component

Table 33. Oxford Knee Score Pain component

N*	239
Mean	51.61
Median	53.55
Mode	60.69
Std. Deviation	20.923
Minimum	10.71
Maximum	92.82

**There are missing values on this variable (N=252)*

Graphic 31. Oxford Knee Score Pain component



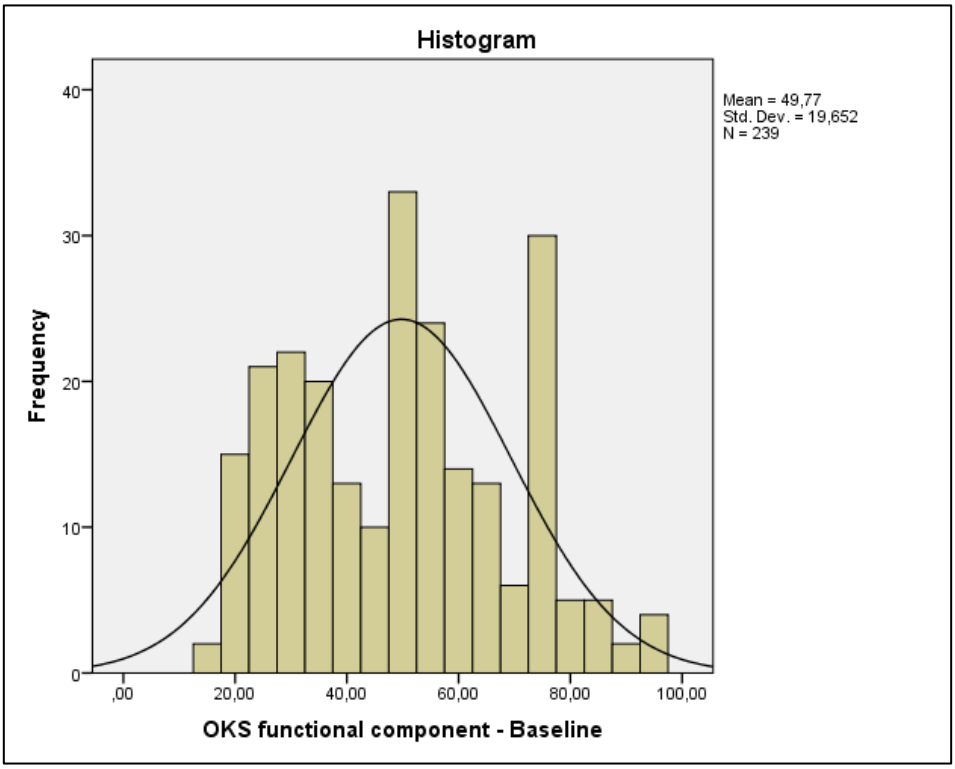
4.1.18.15 Oxford Knee Score Functional component

Table 34. Oxford Knee Score Functional component

N*	239
Mean	49.77
Median	50.00
Mode	50.00
Std. Deviation	19.652
Minimum	15.00
Maximum	95.00

**There are missing values on this variable (N=252)*

Graphic 32. Oxford Knee Score Functional component



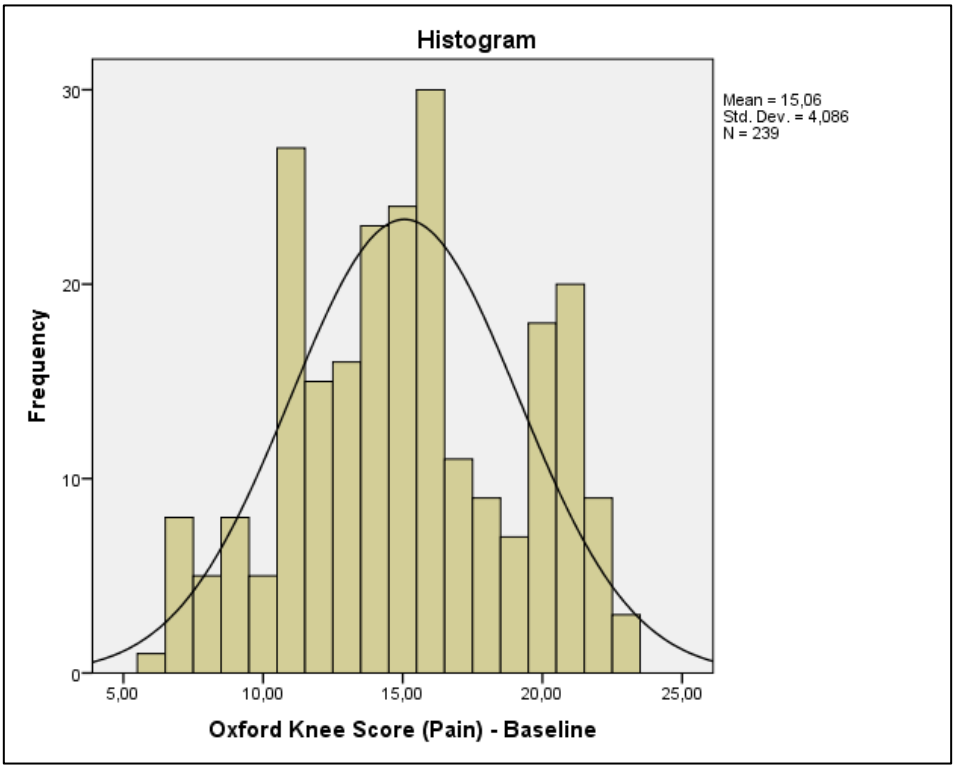
4.1.18.16 Oxford Knee Score Pain (Protocol)

Table 35. Oxford Knee Score Pain (Protocol)

N*	239
Mean	15.06
Median	15.00
Mode	16.00
Std. Deviation	4.086
Minimum	6.00
Maximum	23.00

**There are missing values on this variable (N=252)*

Graphic 33. Oxford Knee Score Pain (Protocol)



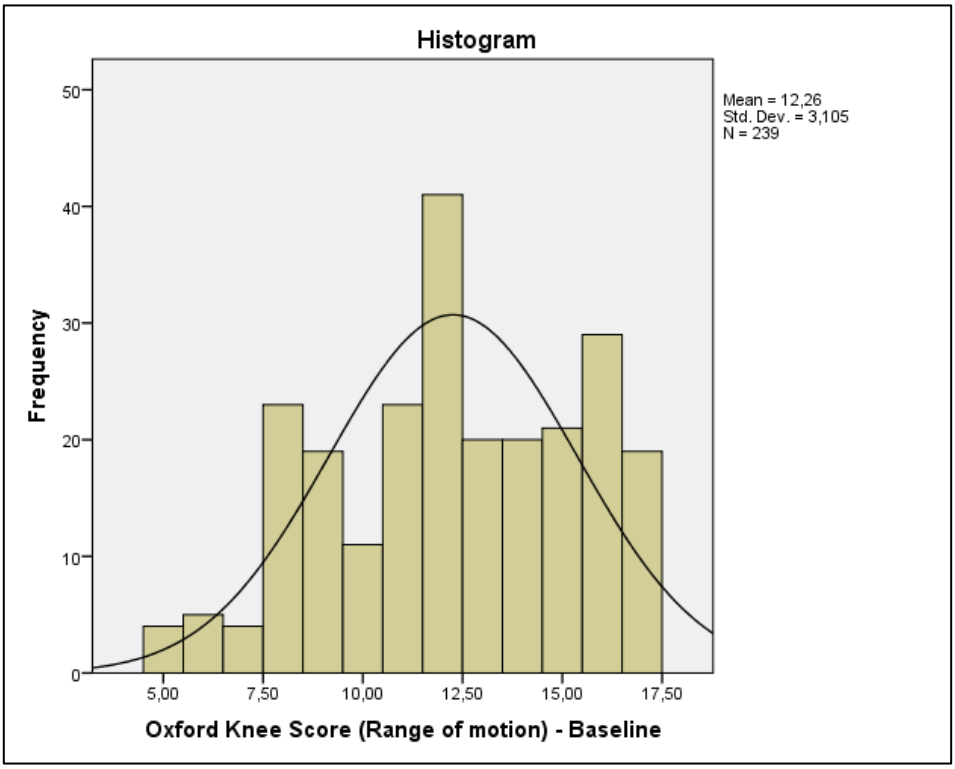
4.1.18.17 Oxford Knee Score Range of motion (Protocol)

Table 36. Oxford Knee Score Range of motion (Protocol)

N*	239
Mean	12.26
Median	12.00
Mode	12.00
Std. Deviation	3.105
Minimum	5.00
Maximum	17.00

**There are missing values on this variable (N=252)*

Graphic 34. Oxford Knee Score Range of motion (Protocol)



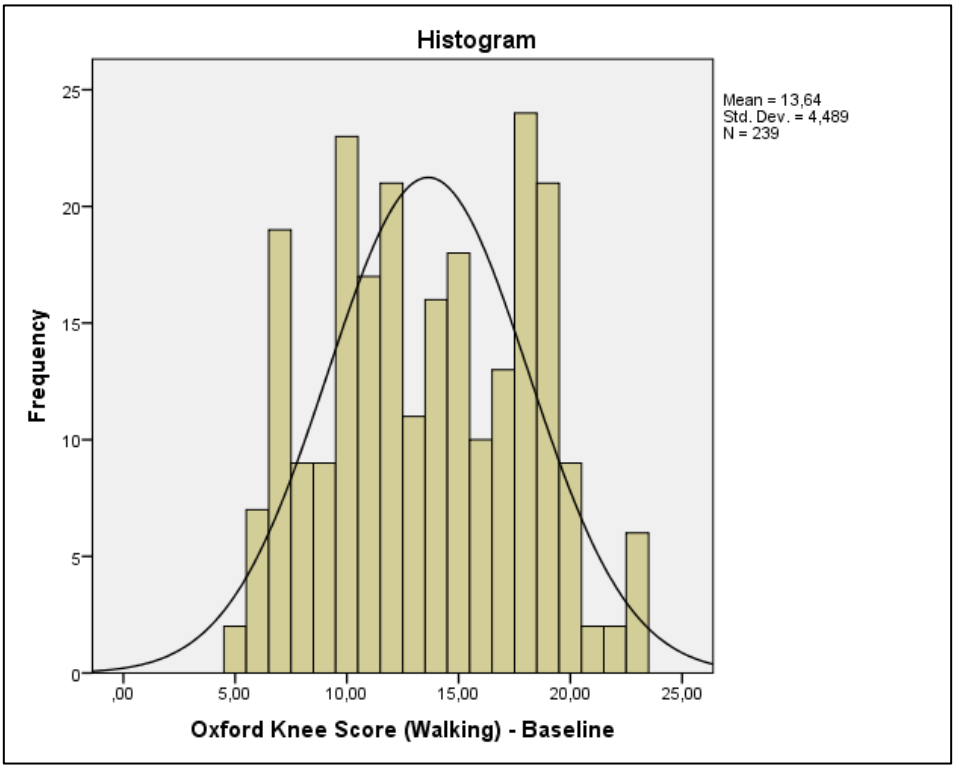
4.1.18.18 Oxford Knee Score Walking (Protocol)

Table 37. Oxford Knee Score Walking (Protocol)

N*	239
Mean	13.64
Median	14.00
Mode	18.00
Std. Deviation	4.489
Minimum	5.00
Maximum	23.00

**There are missing values on this variable (N=252)*

Graphic 35. Oxford Knee Score Walking (Protocol)



4.2 Visit 1 (one month after first injection) (N=237)

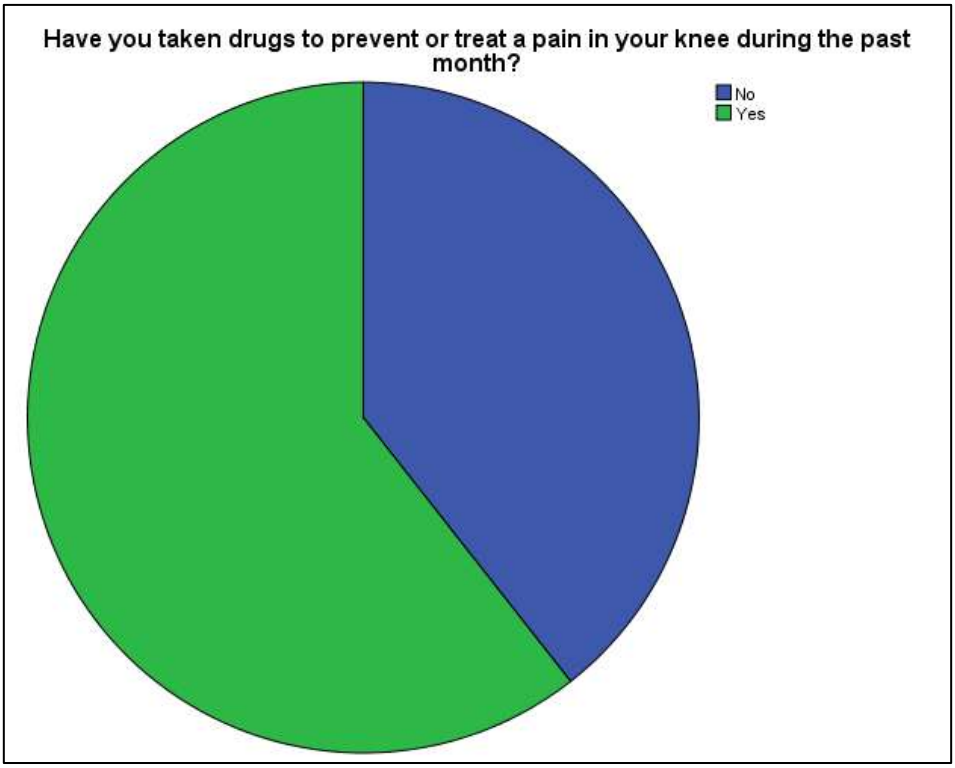
4.2.1 Have you taken drugs to prevent or treat a pain in your knee during the past month?

Table 38. Have you taken drugs to prevent or treat a pain in your knee during the past month?

	Frequency	Percent
No	93	39.4%
Yes	143	60.6%
Total*	236	100.0%

**There are missing values on this variable (N=237)*

Graphic 36. Have you taken drugs to prevent or treat a pain in your knee during the past month?



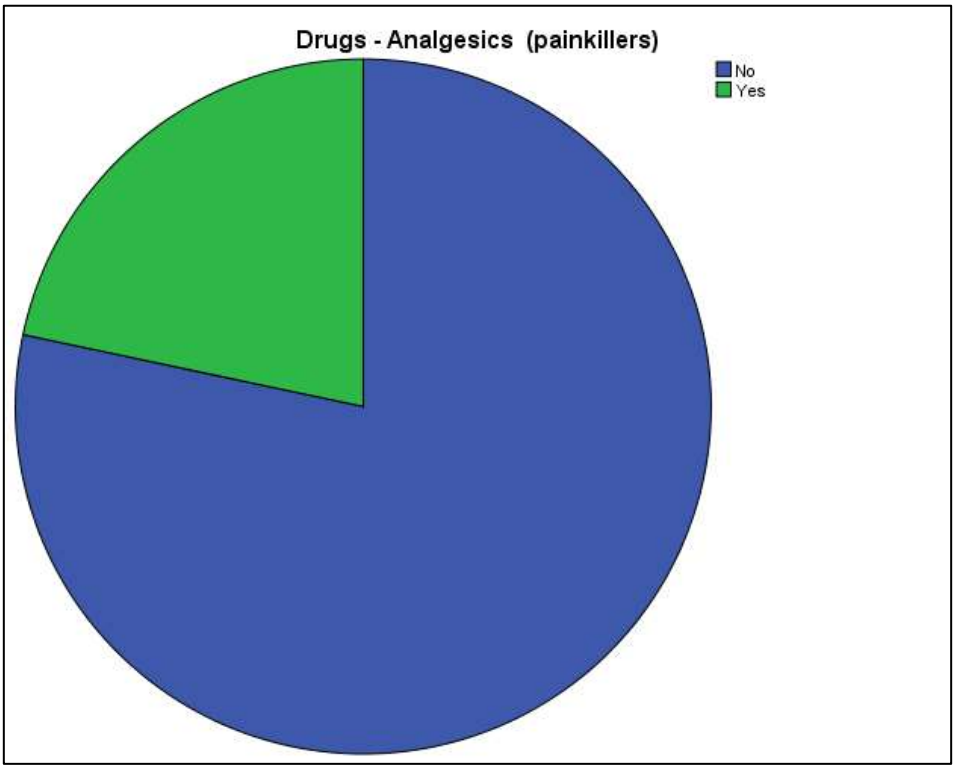
4.2.2 Analgesics (painkillers)

Table 39. Analgesics (painkillers)

	Frequency	Percent
No	177	78.3%
Yes	49	21.7%
Total*	226	100.0%

**There are missing values on this variable (N=237)*

Graphic 37. Analgesics (painkillers)



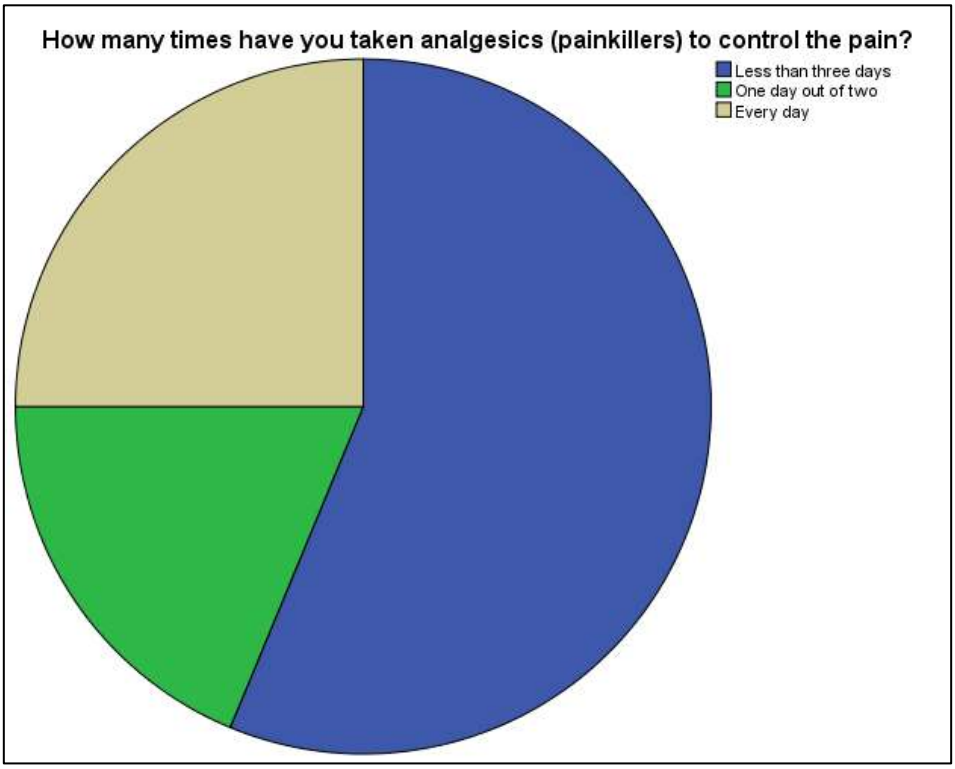
4.2.3 How many times have you taken analgesics (painkillers) to control the pain?

Table 40. How many times have you taken analgesics (painkillers) to control the pain?

	Frequency	Percent
Less than three days	27	56.3%
One day out of two	9	18.7%
Every day	12	25.0%
Total*	48	100.0%

**There are missing values on this variable (N=49)*

Graphic 38. How many times have you taken analgesics (painkillers) to control the pain?



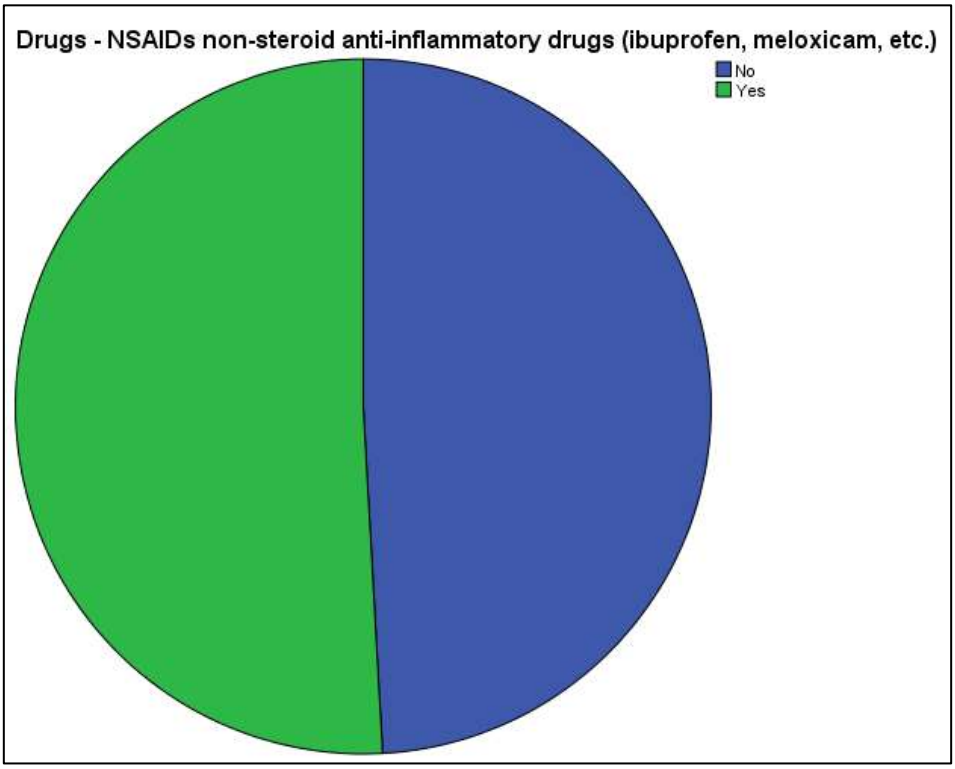
4.2.4 NSAIDs non-steroid anti-inflammatory drugs (ibuprofen, meloxicam, etc.)

Table 41. NSAIDs non-steroid anti-inflammatory drugs (ibuprofen, meloxicam, etc.)

	Frequency	Percent
No	111	49.1%
Yes	115	50.9%
Total*	226	100.0%

**There are missing values on this variable (N=237)*

Graphic 39. NSAIDs non-steroid anti-inflammatory drugs (ibuprofen, meloxicam, etc.)



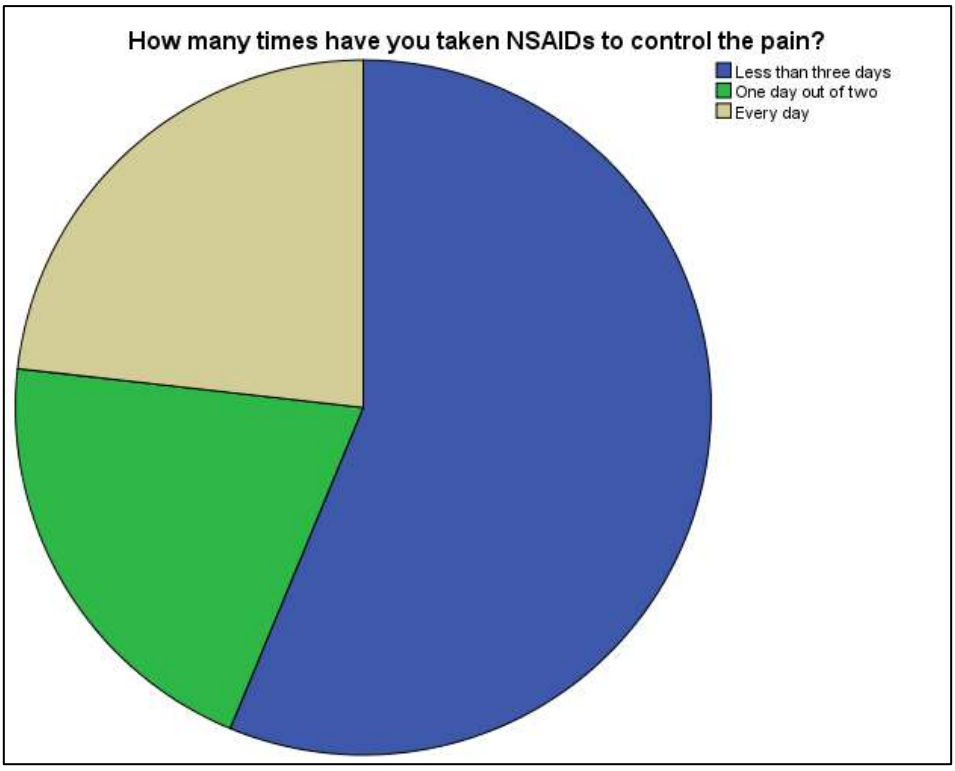
4.2.5 How many times have you taken NSAIDs to control the pain?

Table 42. How many times have you taken NSAIDs to control the pain?

	Frequency	Percent
Less than three days	63	56.3%
One day out of two	23	20.5%
Every day	26	23.2%
Total*	112	100.0%

**There are missing values on this variable (N=115)*

Graphic 40. How many times have you taken NSAIDs to control the pain?



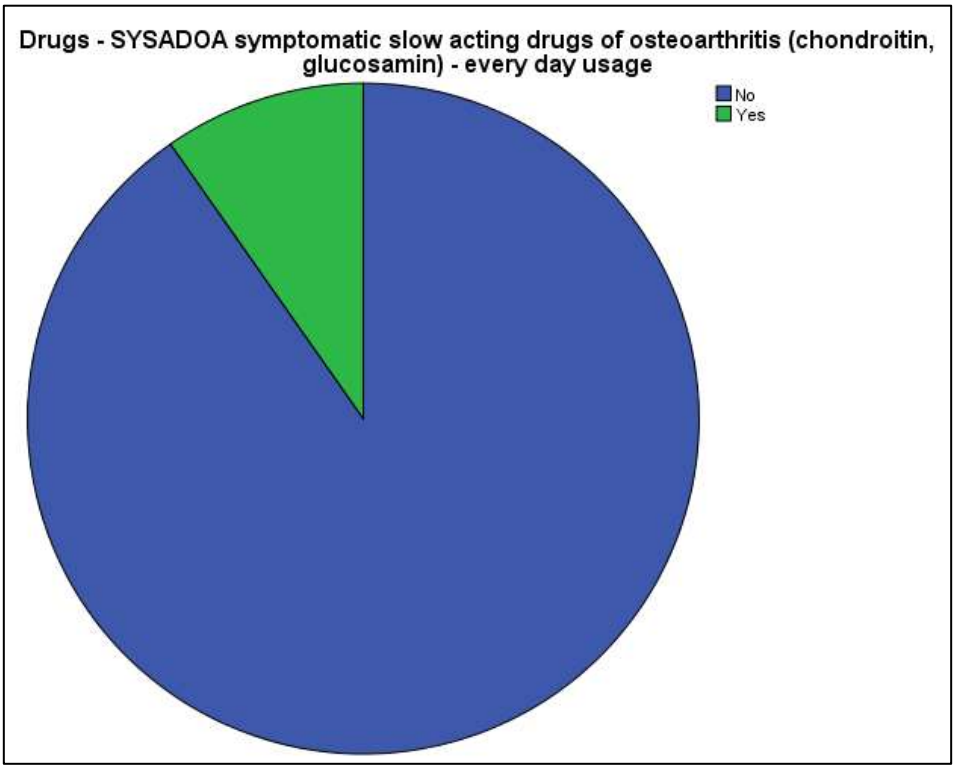
4.2.6 SYSADOA symptomatic slow acting drugs of osteoarthritis (chondroitin, glucosamine) - every day usage

Table 43. SYSADOA symptomatic slow acting drugs of osteoarthritis (chondroitin, glucosamine) - every day usage

	Frequency	Percent
No	204	90.3%
Yes	22	9.7%
Total*	226	100.0%

**There are missing values on this variable (N=237)*

Graphic 41. SYSADOA symptomatic slow acting drugs of osteoarthritis (chondroitin, glucosamine) - every day usage



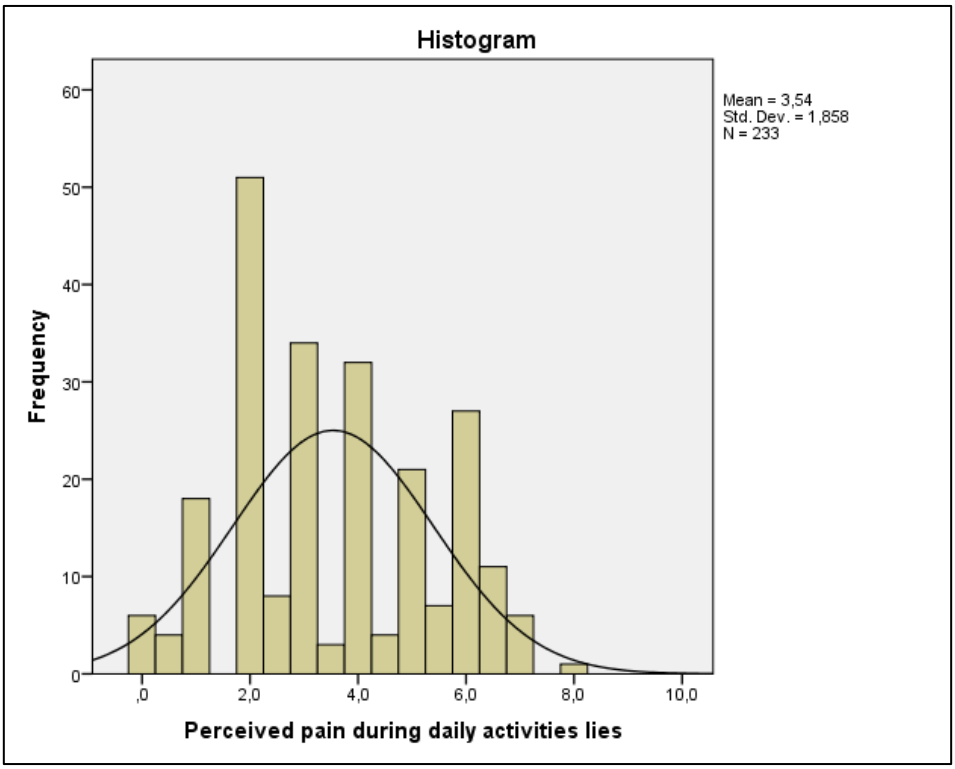
4.2.7 Perceived pain during daily activities lies

Table 44: Perceived pain during daily activities lies

N*	233
Mean	3.54
Median	3.00
Mode	2.0
Std. Deviation	1.858
Minimum	0.0
Maximum	8.0

**There are missing values on this variable (N=237)*

Graphic 42: Histogram: Perceived pain during daily activities lies



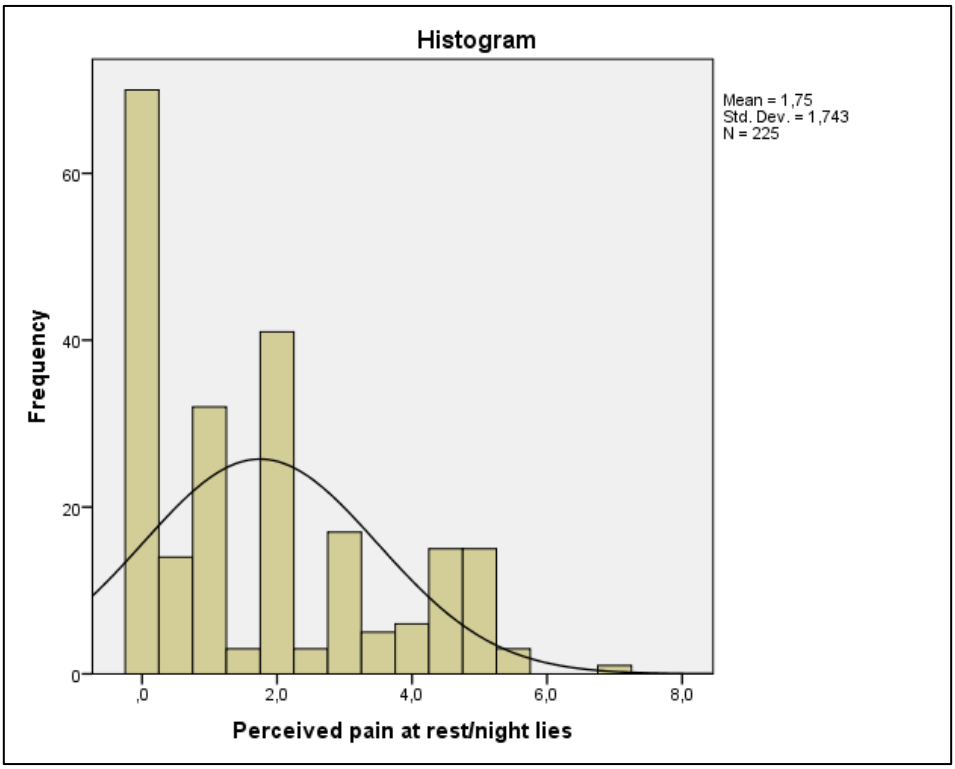
4.2.8 Perceived pain at rest/night lies

Table 45: Perceived pain at rest/night lies

N*	225
Mean	1.75
Median	1.00
Mode	.0
Std. Deviation	1.743
Minimum	0.0
Maximum	7.0

**There are missing values on this variable (N=237)*

Graphic 43: Histogram: Perceived pain at rest/night lies



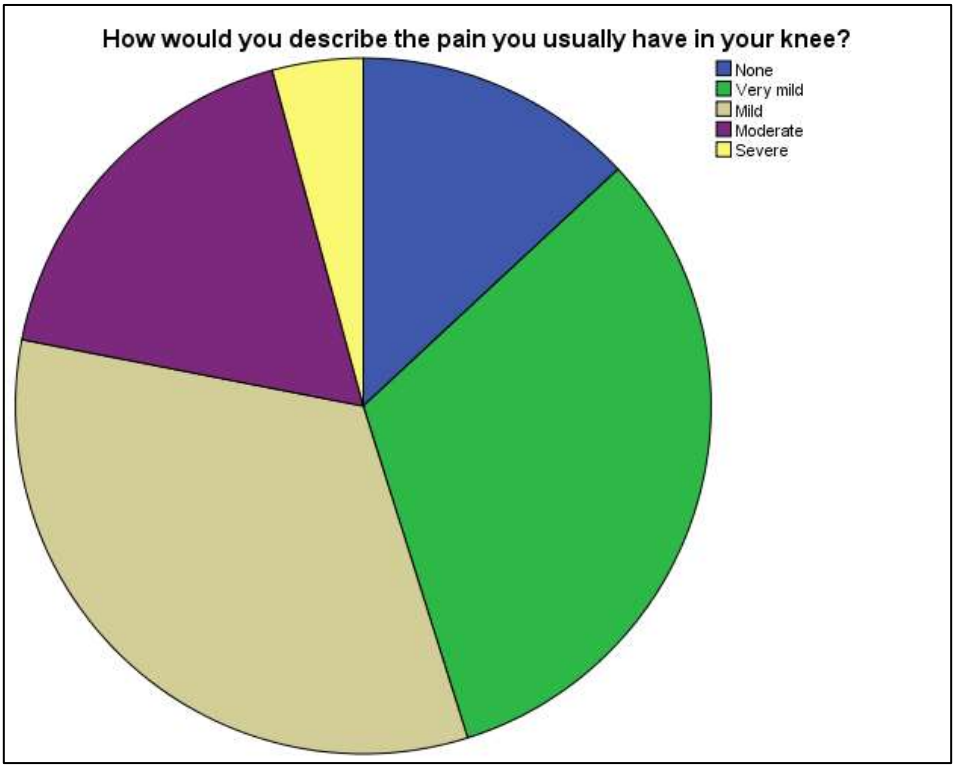
4.2.9 OKSQ. During the past 4 weeks...

4.2.9.1 How would you describe the pain you usually have in your knee?

Table 46. How would you describe the pain you usually have in your knee?

	Frequency	Percent
None	31	13.1%
Very mild	76	32.1%
Mild	78	32.9%
Moderate	42	17.7%
Severe	10	4.2%
Total	237	100.0%

Graphic 44. How would you describe the pain you usually have in your knee?



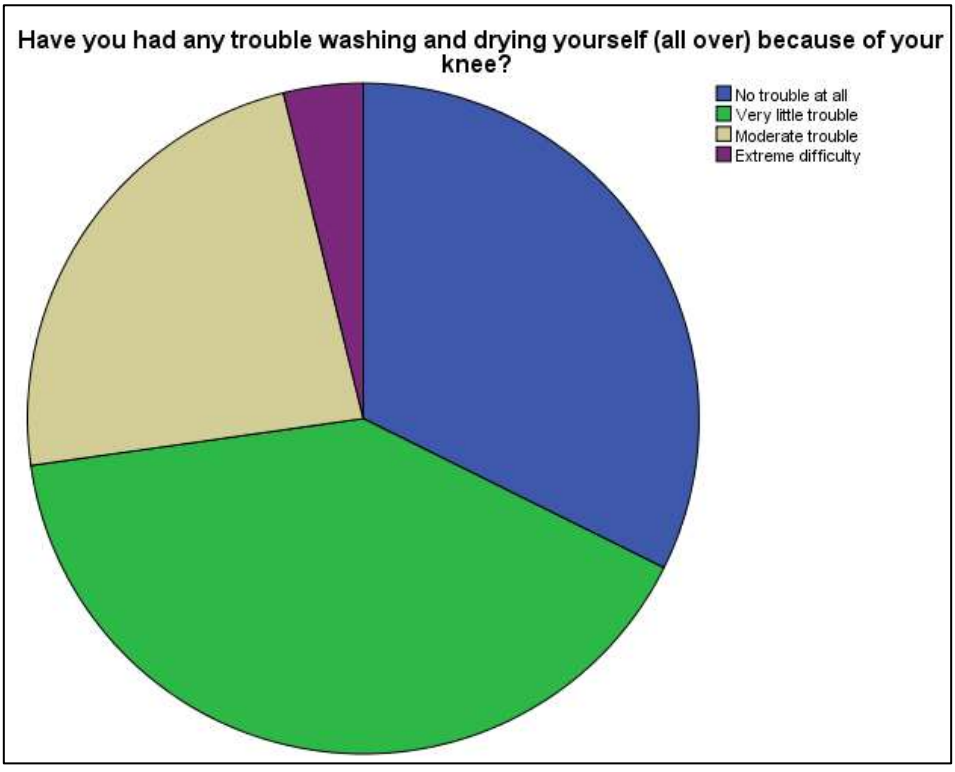
4.2.9.2 Have you had any trouble washing and drying yourself (all over) because of your knee?

Table 47. Have you had any trouble washing and drying yourself (all over) because of your knee?

	Frequency	Percent
No trouble at all	76	32.4%
Very little trouble	95	40.4%
Moderate trouble	55	23.4%
Extreme difficulty	9	3.8%
Total*	235	100.0%

**There are missing values on this variable (N=237)*

Graphic 45. Have you had any trouble washing and drying yourself (all over) because of your knee?



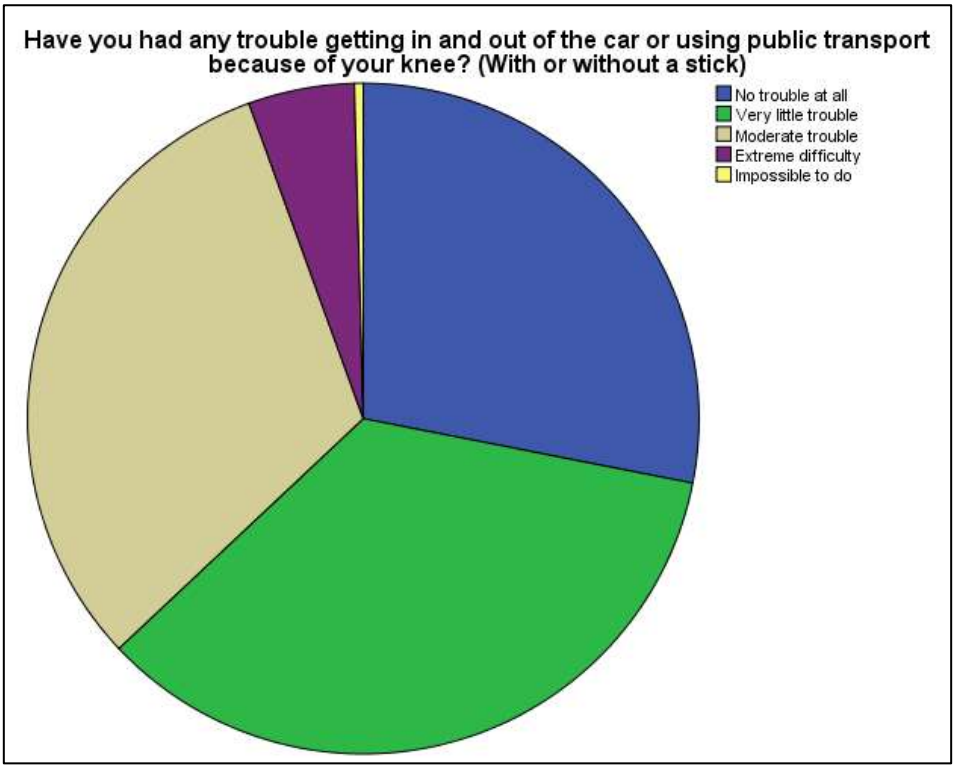
4.2.9.3 Have you had any trouble getting in and out of the car or using public transport because of your knee? (With or without a stick)

Table 48. Have you had any trouble getting in and out of the car or using public transport because of your knee? (With or without a stick)

	Frequency	Percent
No trouble at all	66	28.1%
Very little trouble	82	34.9%
Moderate trouble	74	31.5%
Extreme difficulty	12	5.1%
Impossible to do	1	0.4%
Total*	235	100.0%

**There are missing values on this variable (N=237)*

Graphic 46. Have you had any trouble getting in and out of the car or using public transport because of your knee? (With or without a stick)



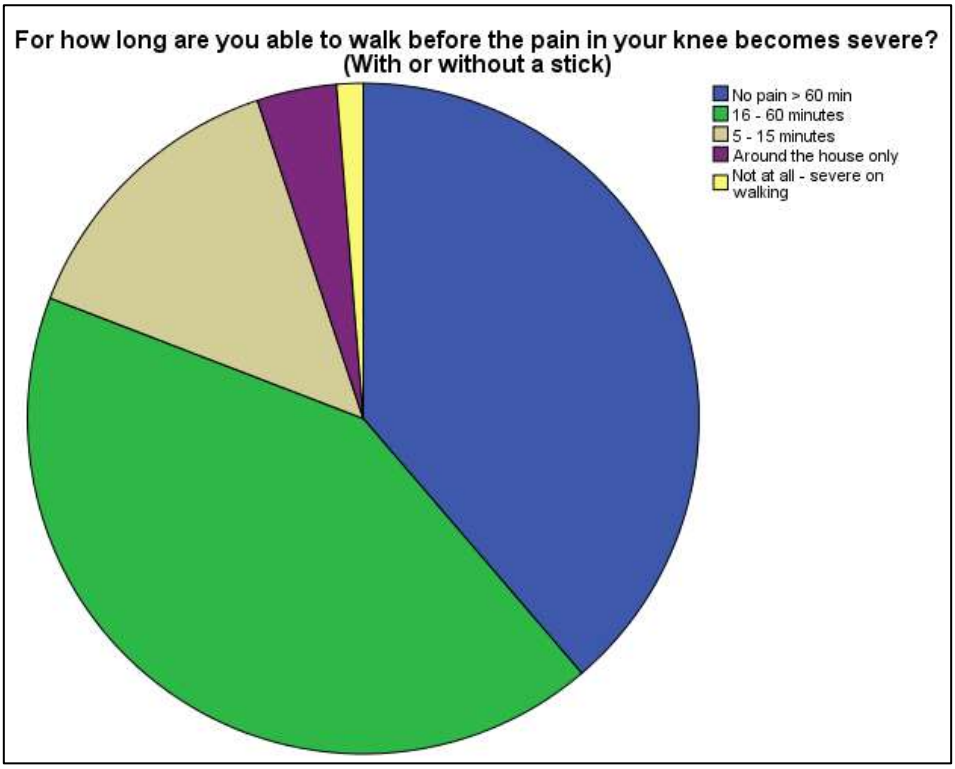
4.2.9.4 For how long are you able to walk before the pain in your knee becomes severe? (With or without a stick)

Table 49. For how long are you able to walk before the pain in your knee becomes severe? (With or without a stick)

	Frequency	Percent
No pain > 60 min	91	38.7%
16 - 60 minutes	99	42.1%
5 - 15 minutes	33	14.0
Around the house only	9	3.8%
Not at all - severe on walking	3	1.4%
Total*	235	100.0%

**There are missing values on this variable (N=237)*

Graphic 47. For how long are you able to walk before the pain in your knee becomes severe? (With or without a stick)

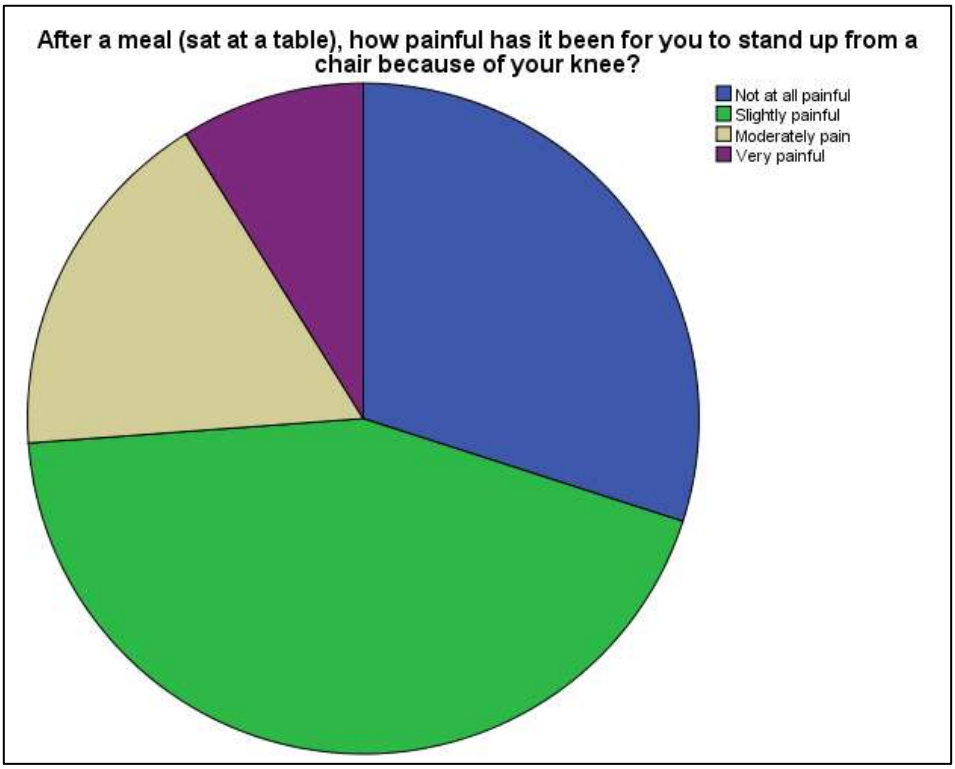


4.2.9.5 After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

Table 50. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

	Frequency	Percent
Not at all painful	71	30.0%
Slightly painful	104	43.9%
Moderately pain	41	17.2%
Very painful	21	8.9%
Total	237	100.0%

Graphic 48. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?



4.2.9.6 Have you been limping when walking, because of your knee?

Table 51. Have you been limping when walking, because of your knee?

	Frequency	Percent
Rarely / never	95	40.1%
Sometimes or just at first	78	32.9%
Often, not just at first	40	16.9%
Most of the time	13	5.5%
All of the time	11	4.6%
Total	237	100.0%

Graphic 49. Have you been limping when walking, because of your knee?

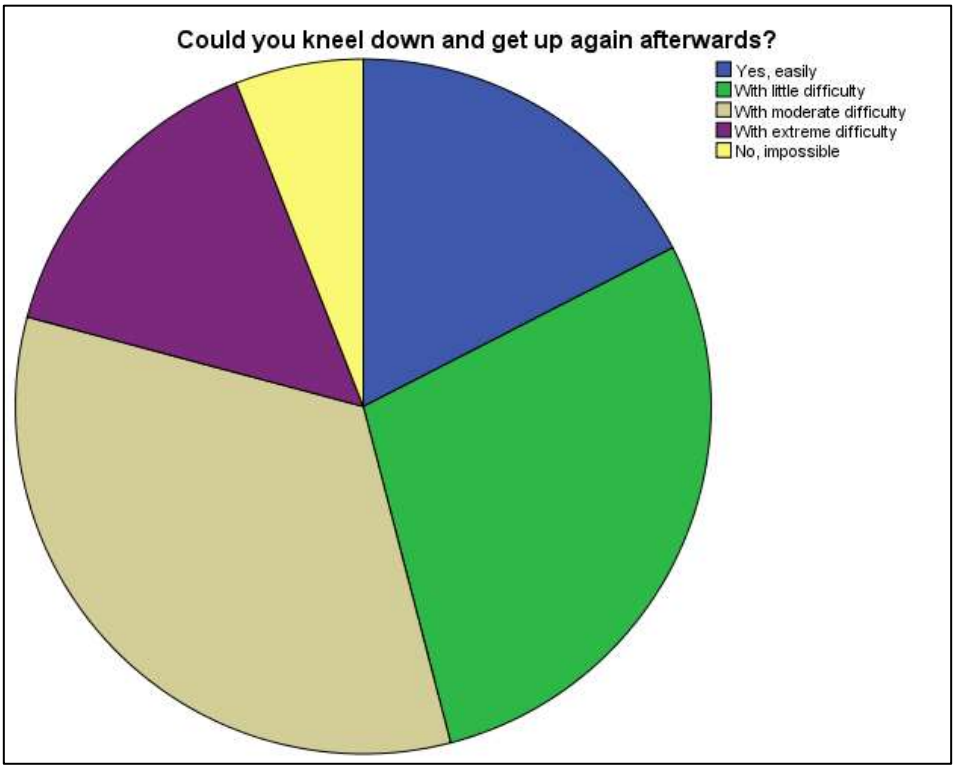
4.2.9.7 Could you kneel down and get up again afterwards?

Table 52. Could you kneel down and get up again afterwards?

	Frequency	Percent
Yes, easily	41	17.4%
With little difficulty	67	28.5%
With moderate difficulty	78	33.2%
With extreme difficulty	35	14.9%
No, impossible	14	6.0%
Total*	235	100.0%

**There are missing values on this variable (N=237)*

Graphic 50. Could you kneel down and get up again afterwards?

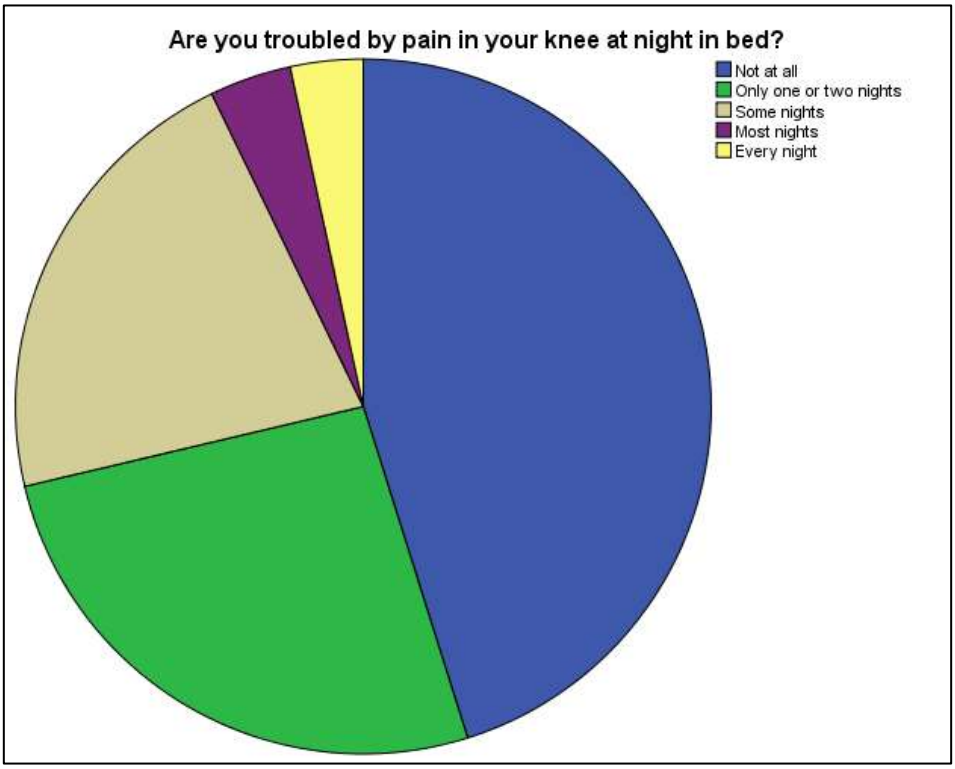


4.2.9.8 Are you troubled by pain in your knee at night in bed?

Table 53. Are you troubled by pain in your knee at night in bed?

	Frequency	Percent
Not at all	107	45.1%
Only one or two nights	62	26.2%
Some nights	51	21.5%
Most nights	9	3.8%
Every night	8	3.4%
Total	237	100.0%

Graphic 51. Are you troubled by pain in your knee at night in bed?



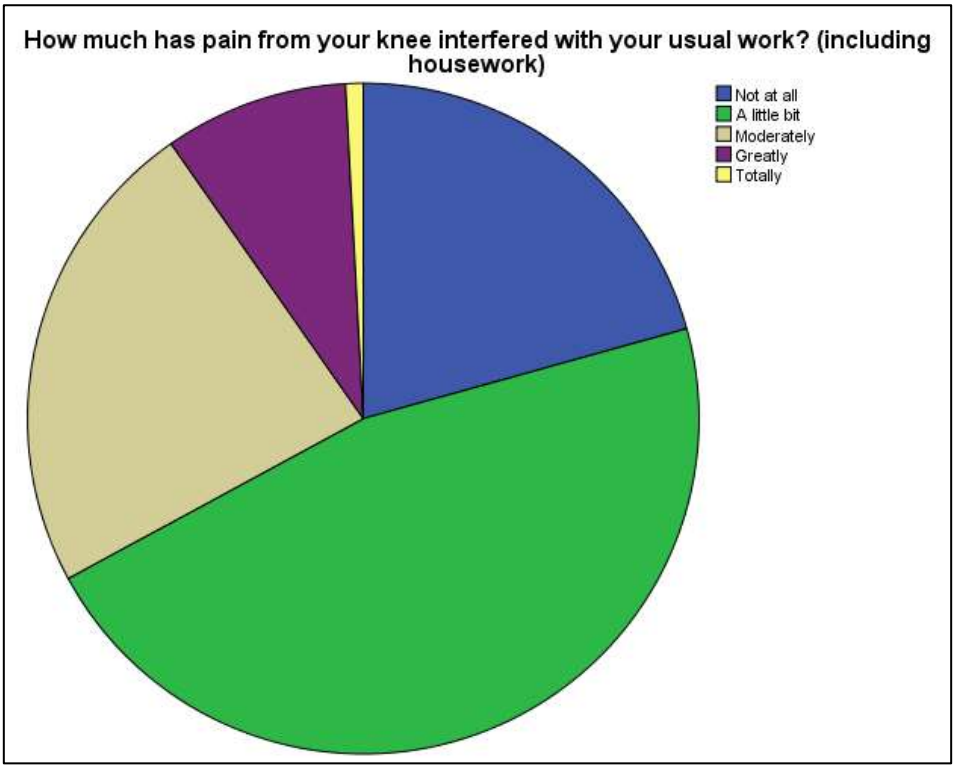
4.2.9.9 How much has pain from your knee interfered with your usual work? (including housework)

Table 54. How much has pain from your knee interfered with your usual work? (including housework)

	Frequency	Percent
Not at all	49	20.7%
A little bit	110	46.4%
Moderately	55	23.2%
Greatly	21	8.9%
Totally	2	0.8%
Total*	237	100.0%

**There are missing values on this variable (N=237)*

Graphic 52. How much has pain from your knee interfered with your usual work? (including housework)



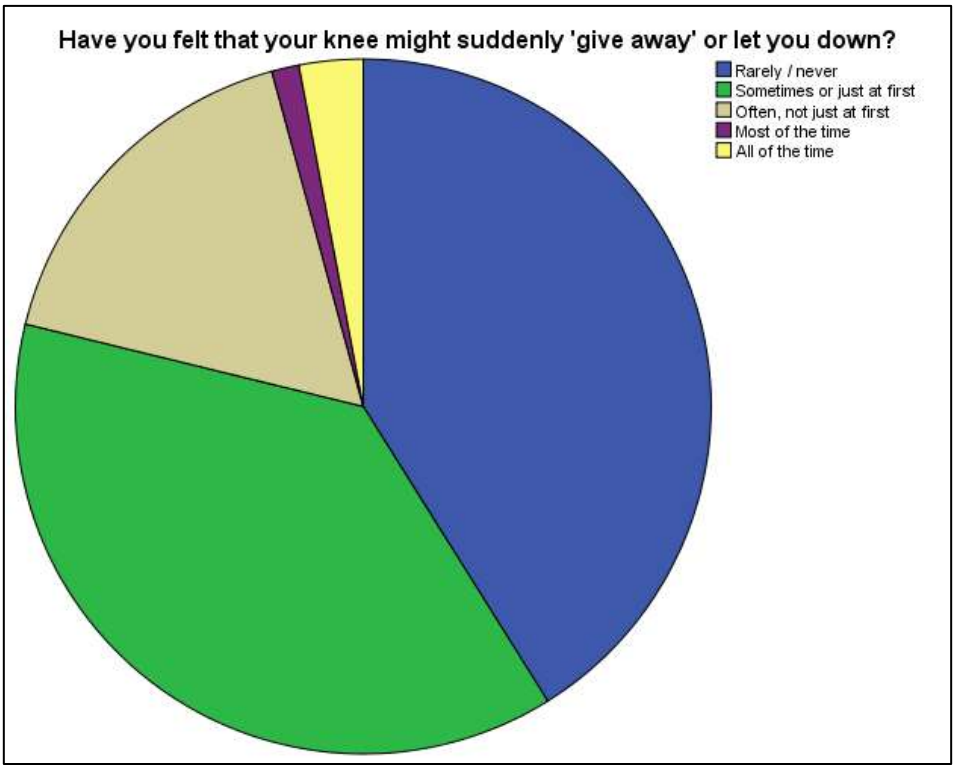
4.2.9.10 Have you felt that your knee might suddenly 'give away' or let you down?

Table 55. Have you felt that your knee might suddenly 'give away' or let you down?

	Frequency	Percent
Rarely / never	97	41.1%
Sometimes or just at first	89	37.7%
Often, not just at first	40	16.8%
Most of the time	3	1.3%
All of the time	7	3.0%
Total*	236	100.0%

**There are missing values on this variable (N=237)*

Graphic 53. Have you felt that your knee might suddenly 'give away' or let you down?

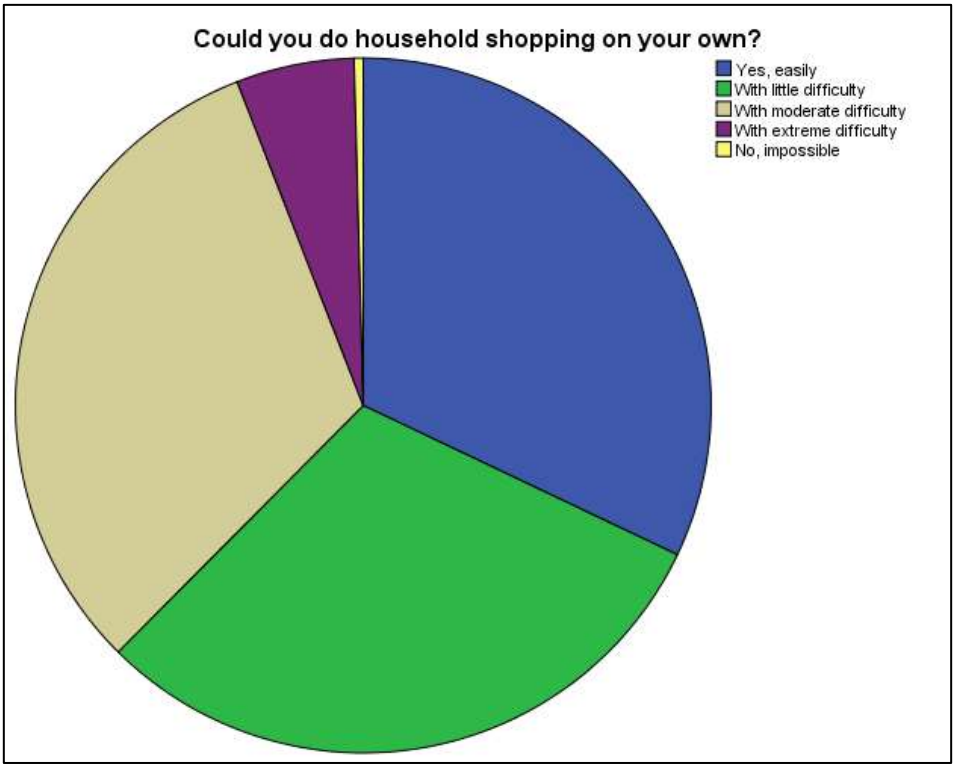


4.2.9.11 Could you do household shopping on your own?

Table 56. Could you do household shopping on your own?

	Frequency	Percent
Yes, easily	76	32.1%
With little difficulty	72	30.4%
With moderate difficulty	75	31.6%
With extreme difficulty	13	5.5%
No, impossible	1	0.4%
Total	237	100.0%

Graphic 54. Could you do household shopping on your own?



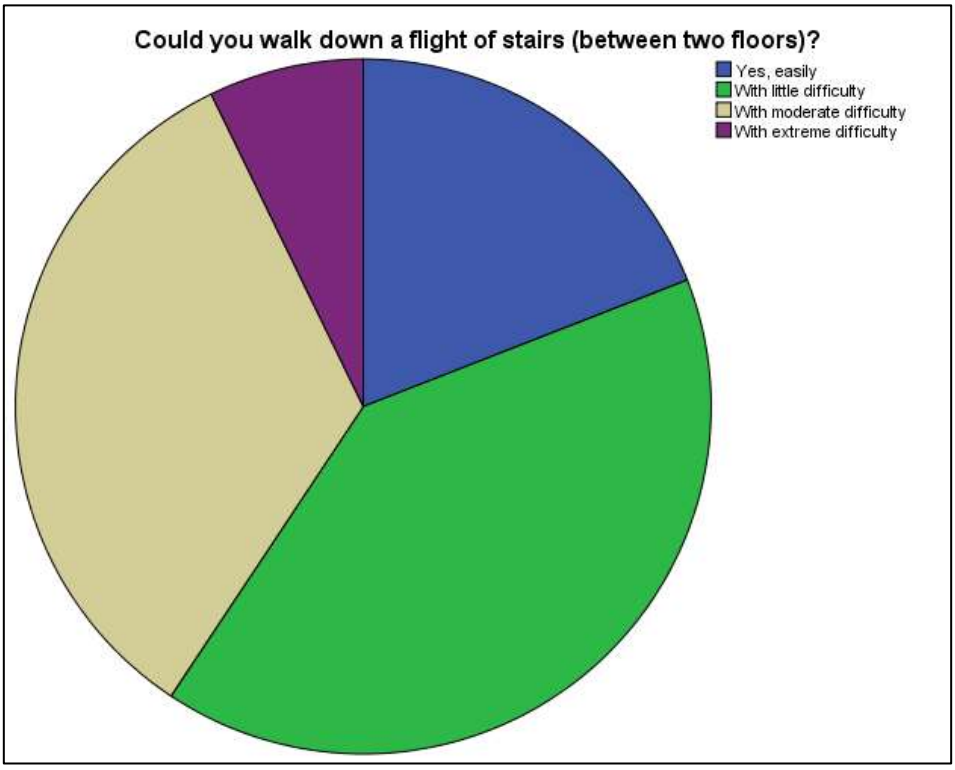
4.2.9.12 Could you walk down a flight of stairs (between two floors)?

Table 57. Could you walk down a flight of stairs (between two floors)?

	Frequency	Percent
Yes, easily	45	19.1%
With little difficulty	95	40.3%
With moderate difficulty	79	33.4%
With extreme difficulty	17	7.2%
Total*	236	100.0%

**There are missing values on this variable (N=237)*

Graphic 55. Could you walk down a flight of stairs (between two floors)?

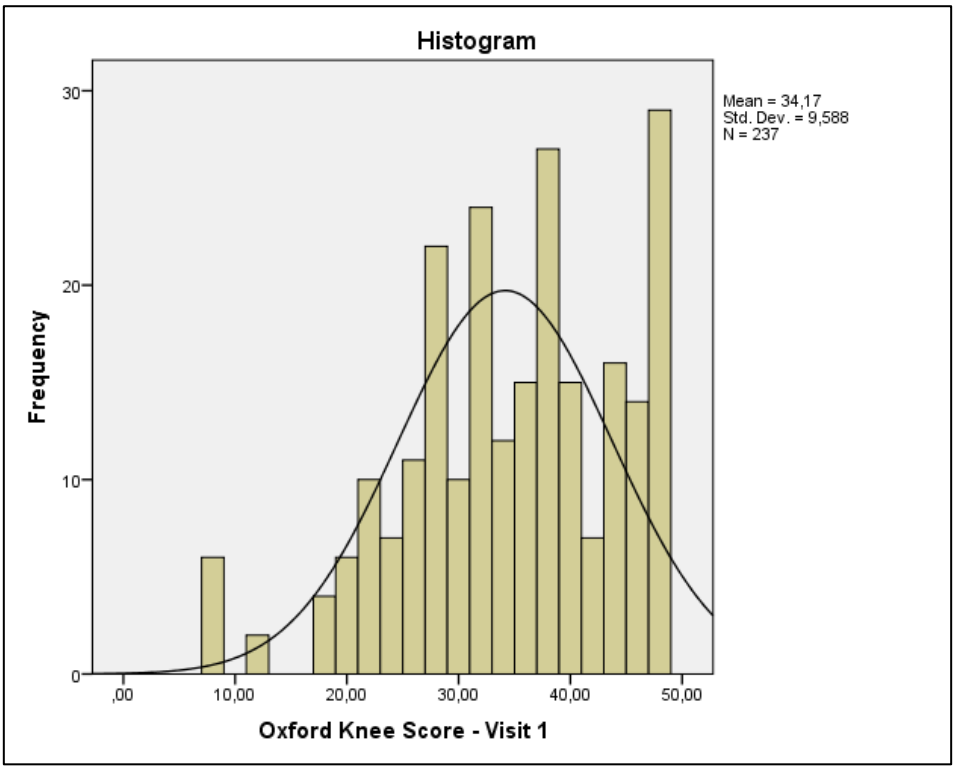


4.2.9.13 Oxford Knee Score

Table 58. Oxford Knee Score pain component

N	237
Mean	34.17
Median	35.00
Mode	37.00
Std. Deviation	9.588
Minimum	8.00
Maximum	48.00

Graphic 56. Oxford Knee Score pain component

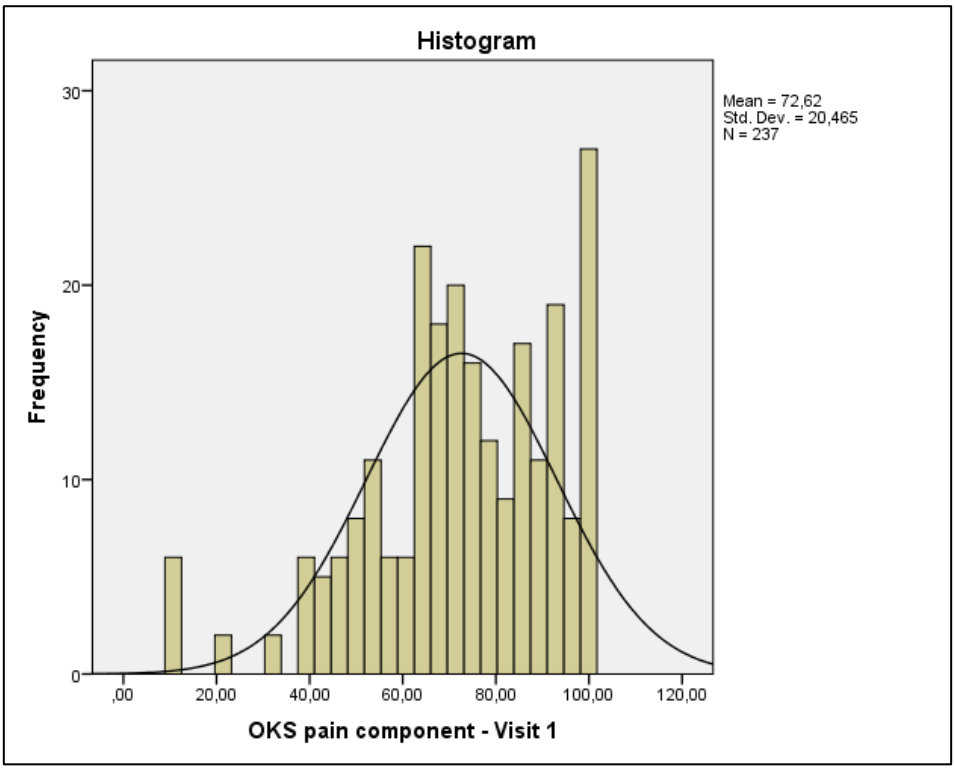


4.2.9.14 Oxford Knee Score Pain component

Table 59. Oxford Knee Score Pain component

N	239
Mean	72.62
Median	74.97
Mode	99.96
Std. Deviation	20.465
Minimum	10.71
Maximum	99.96

Graphic 57. Oxford Knee Score Pain component

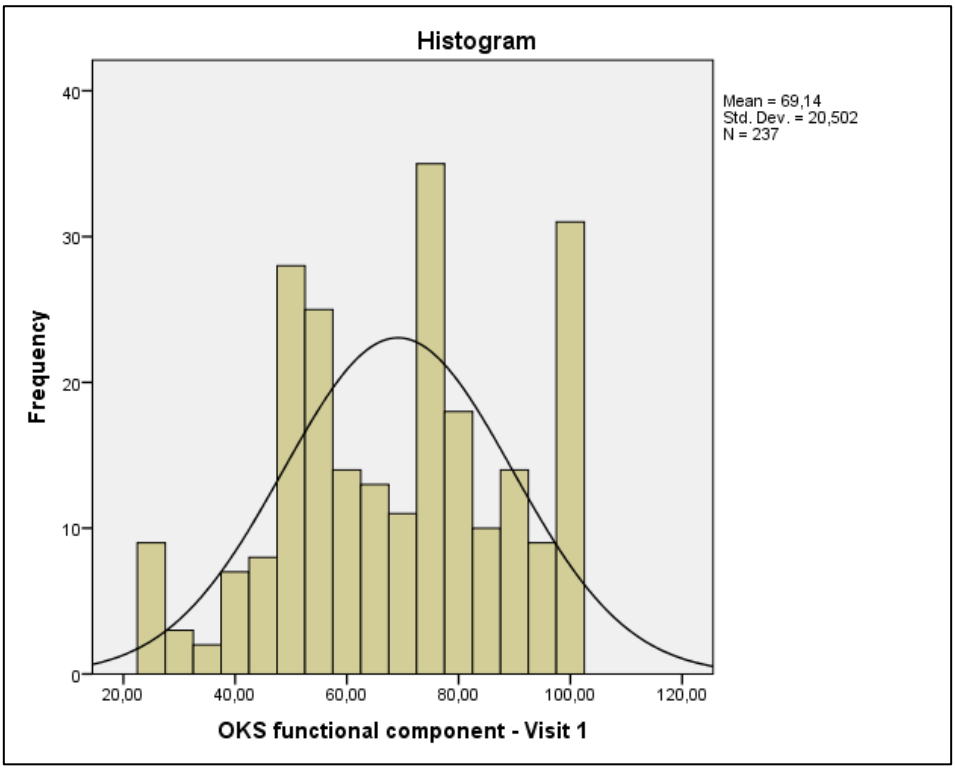


4.2.9.15 Oxford Knee Score Functional component

Table 60. Oxford Knee Score Functional component

N	239
Mean	69.14
Median	70.00
Mode	75.00
Std. Deviation	20.502
Minimum	25.00
Maximum	100.00

Graphic 58. Oxford Knee Score Functional component

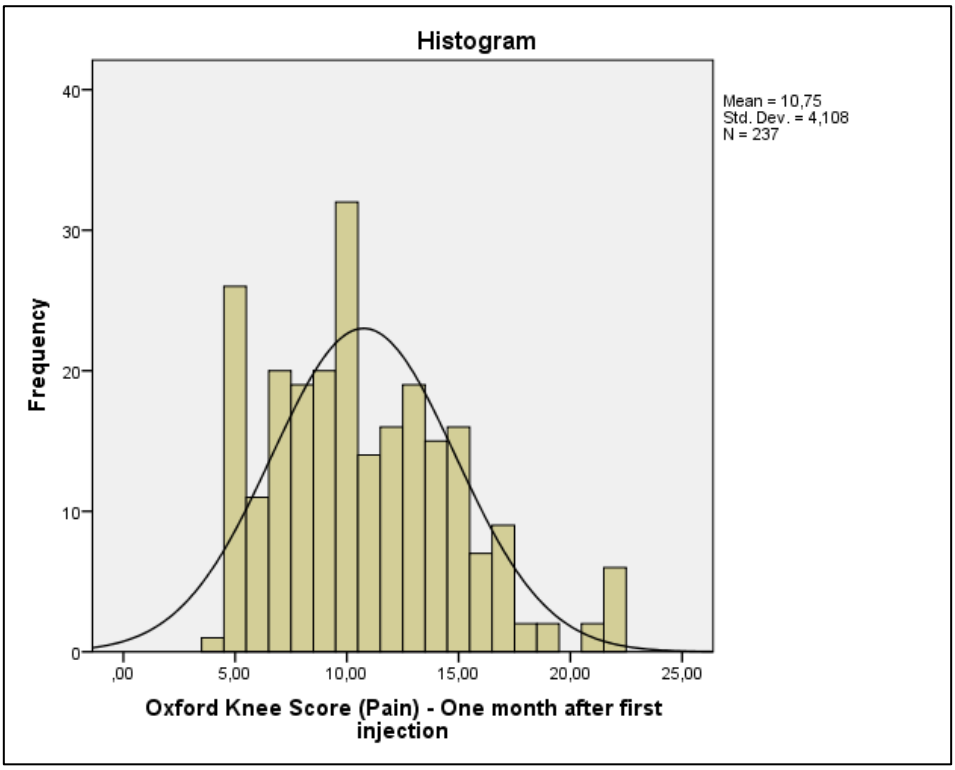


4.2.9.16 Oxford Knee Score Pain (Protocol)

Table 61. Oxford Knee Score Pain (Protocol)

N	237
Mean	10.75
Median	10.00
Mode	10.00
Std. Deviation	4.108
Minimum	4.00
Maximum	22.00

Graphic 59. Oxford Knee Score Pain (Protocol)

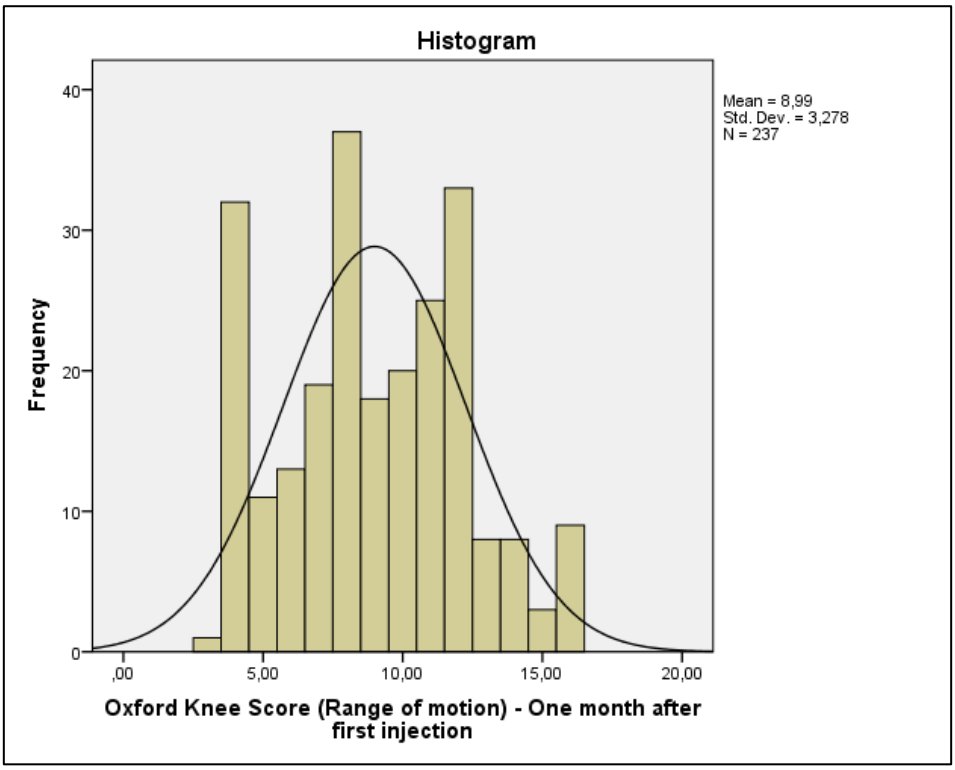


4.2.9.17 Oxford Knee Score Range of motion (Protocol)

Table 62. Oxford Knee Score Range of motion (Protocol)

N	237
Mean	8.99
Median	9.00
Mode	8.00
Std. Deviation	3.278
Minimum	3.00
Maximum	16.00

Graphic 60. Oxford Knee Score Range of motion (Protocol)

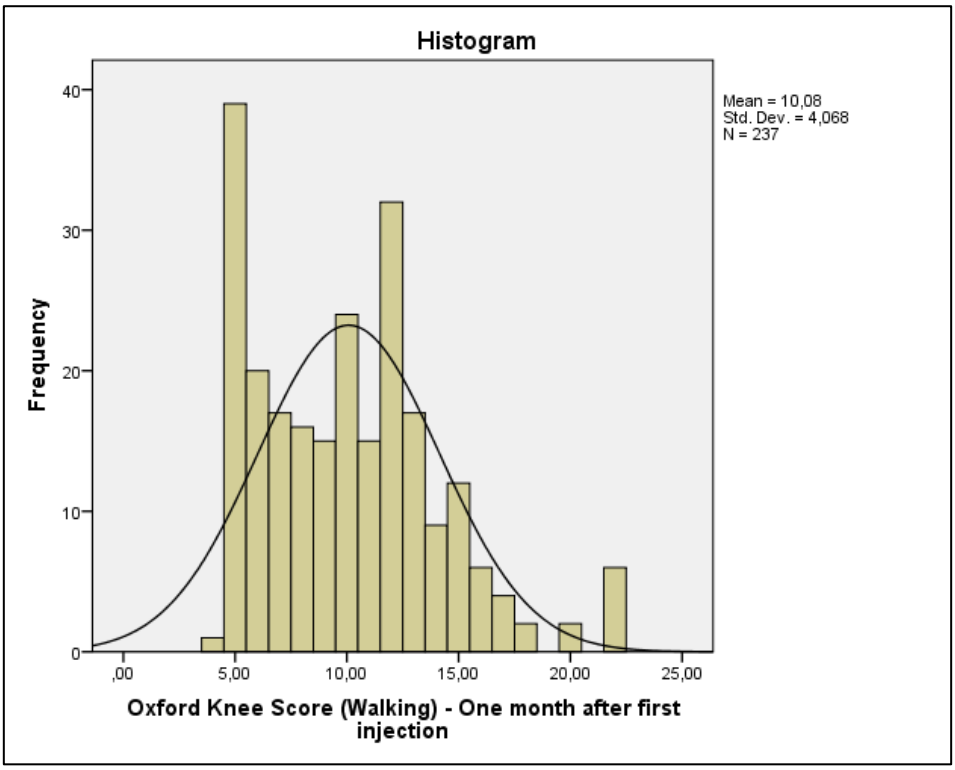


4.2.9.18 Oxford Knee Score Walking (Protocol)

Table 63. Oxford Knee Score Walking (Protocol)

N	237
Mean	10.08
Median	10.00
Mode	5.00
Std. Deviation	4.068
Minimum	4.00
Maximum	22.00

Graphic 61. Oxford Knee Score Walking (Protocol)



4.3 Visit 2 (six months after first injection) (N=230)

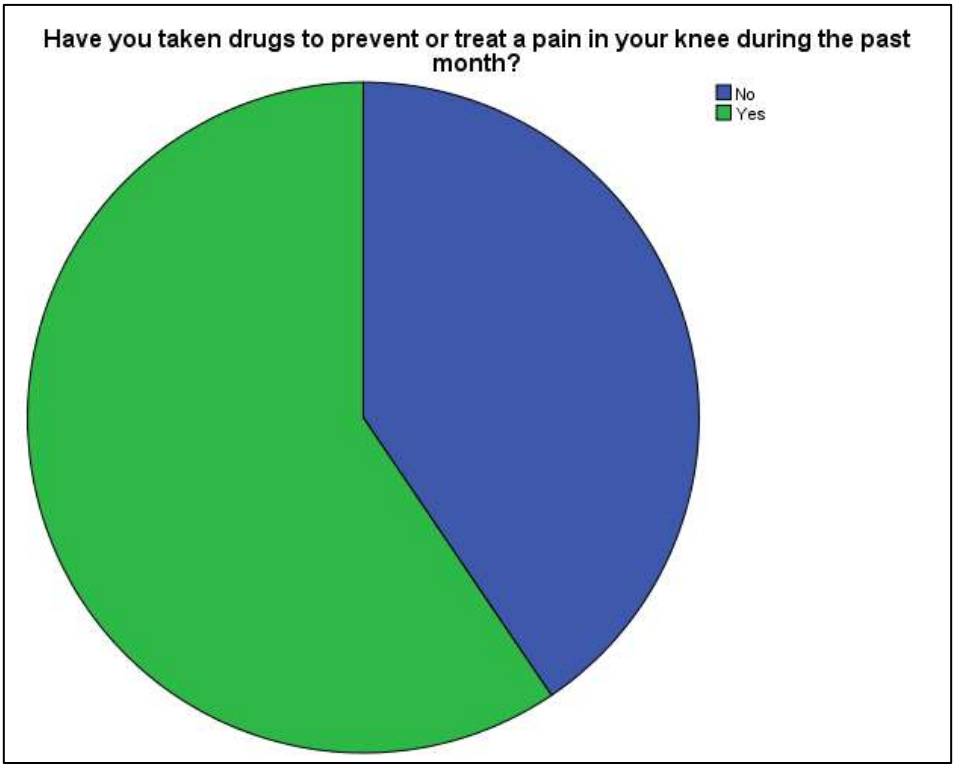
4.3.1 Have you taken drugs to prevent or treat a pain in your knee during the past month?

Table 64. Have you taken drugs to prevent or treat a pain in your knee during the past month?

	Frequency	Percent
No	92	40.5%
Yes	135	59.5%
Total*	227	100.0%

**There are missing values on this variable (N=230)*

Graphic 62. Have you taken drugs to prevent or treat a pain in your knee during the past month?



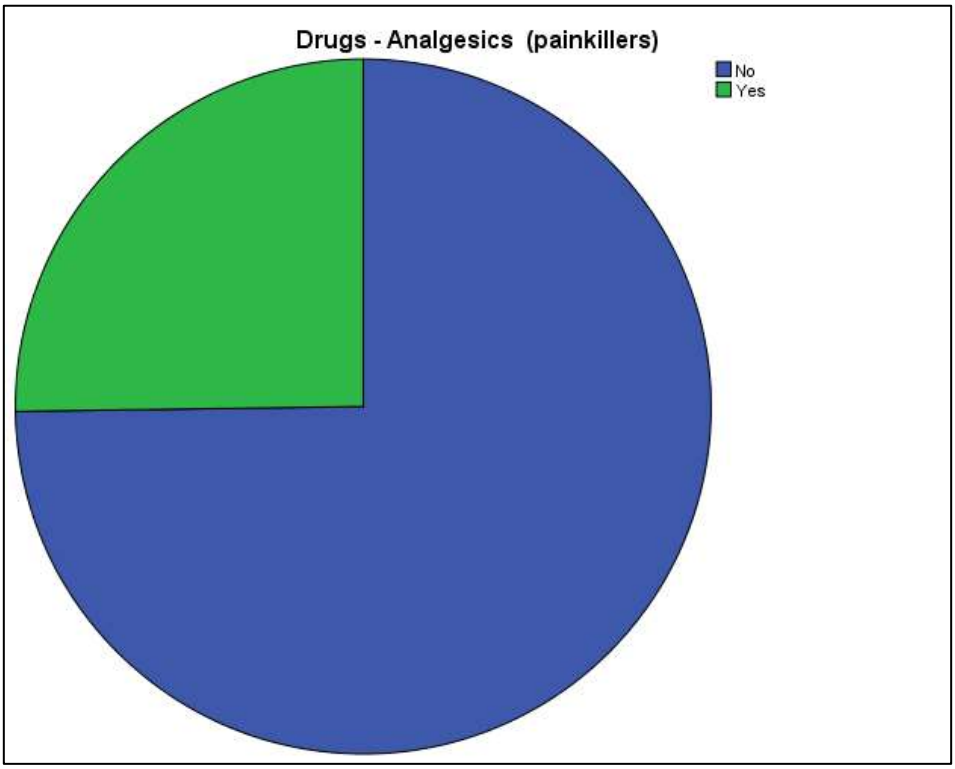
4.3.2 Analgesics (painkillers)

Table 65. Analgesics (painkillers)

	Frequency	Percent
No	166	74.8%
Yes	56	25.2%
Total*	222	100.0%

**There are missing values on this variable (N=230)*

Graphic 63. Analgesics (painkillers)



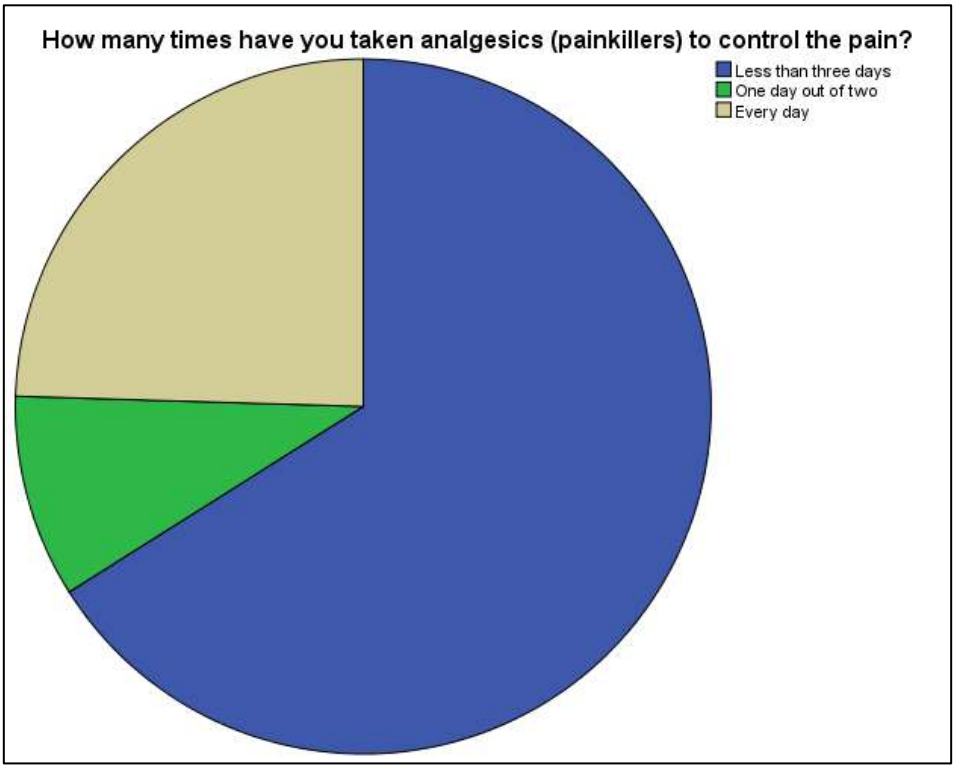
4.3.3 How many times have you taken analgesics (painkillers) to control the pain?

Table 66. How many times have you taken analgesics (painkillers) to control the pain?

	Frequency	Percent
Less than three days	35	66.0%
One day out of two	5	9.5%
Every day	13	24.5
Total*	53	100.0%

**There are missing values on this variable (N=56)*

Graphic 64. How many times have you taken analgesics (painkillers) to control the pain?



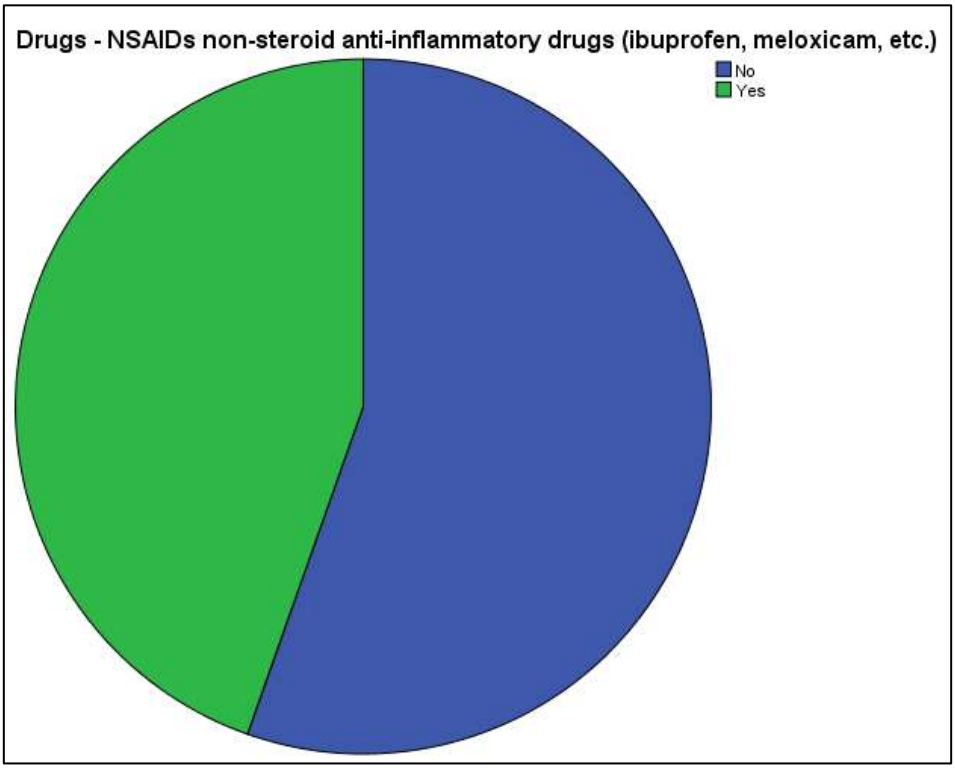
4.3.4 NSAIDs non-steroid anti-inflammatory drugs (ibuprofen, meloxicam, etc.)

Table 67. NSAIDs non-steroid anti-inflammatory drugs (ibuprofen, meloxicam, etc.)

	Frequency	Percent
No	123	55.4%
Yes	99	44.6%
Total*	222	100.0%

**There are missing values on this variable (N=230)*

Graphic 65. NSAIDs non-steroid anti-inflammatory drugs (ibuprofen, meloxicam, etc.)



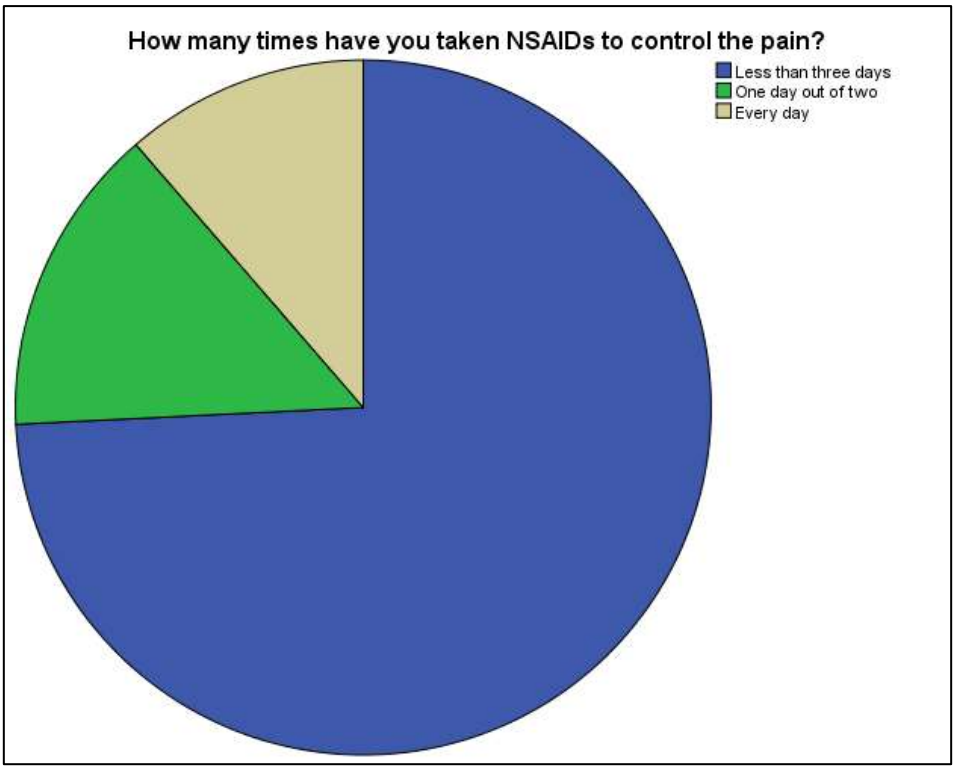
4.3.5 How many times have you taken NSAIDs to control the pain?

Table 68. How many times have you taken NSAIDs to control the pain?

	Frequency	Percent
Less than three days	72	74.3%
One day out of two	14	14.4%
Every day	11	11.3%
Total*	97	100.0%

**There are missing values on this variable (N=99)*

Graphic 66. How many times have you taken NSAIDs to control the pain?



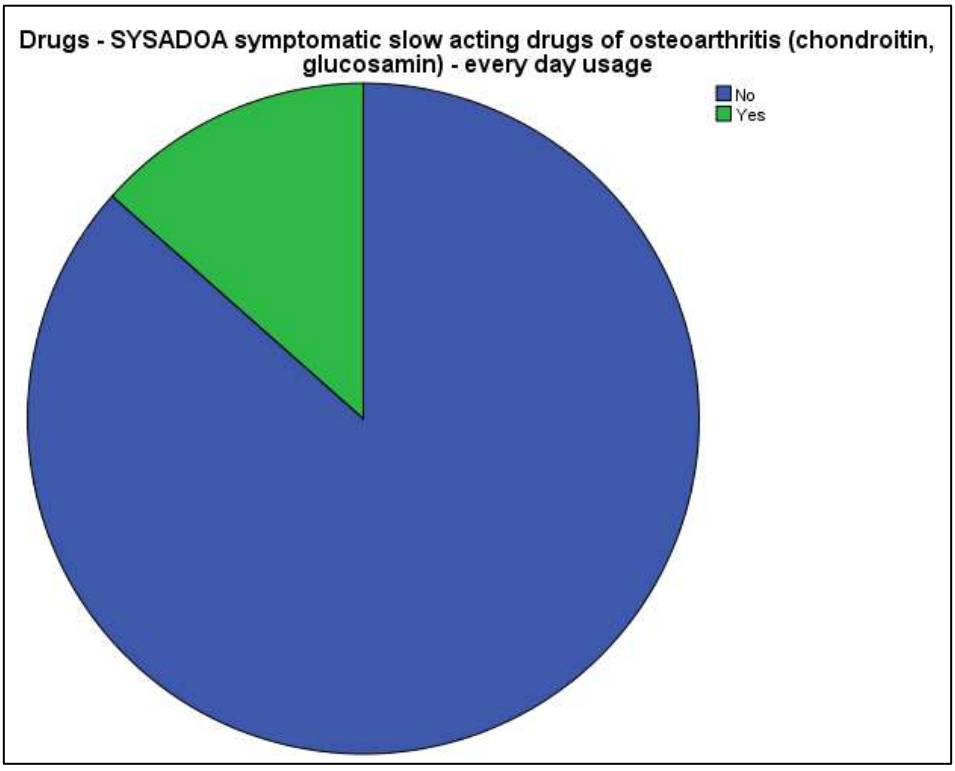
4.3.6 SYSADOA symptomatic slow acting drugs of osteoarthritis (chondroitin, glucosamine) - every day usage

Table 69. SYSADOA symptomatic slow acting drugs of osteoarthritis (chondroitin, glucosamine) - every day usage

	Frequency	Percent
No	193	86.5%
Yes	30	13.5%
Total*	223	100.0%

**There are missing values on this variable (N=230)*

Graphic 67. SYSADOA symptomatic slow acting drugs of osteoarthritis (chondroitin, glucosamine) - every day usage



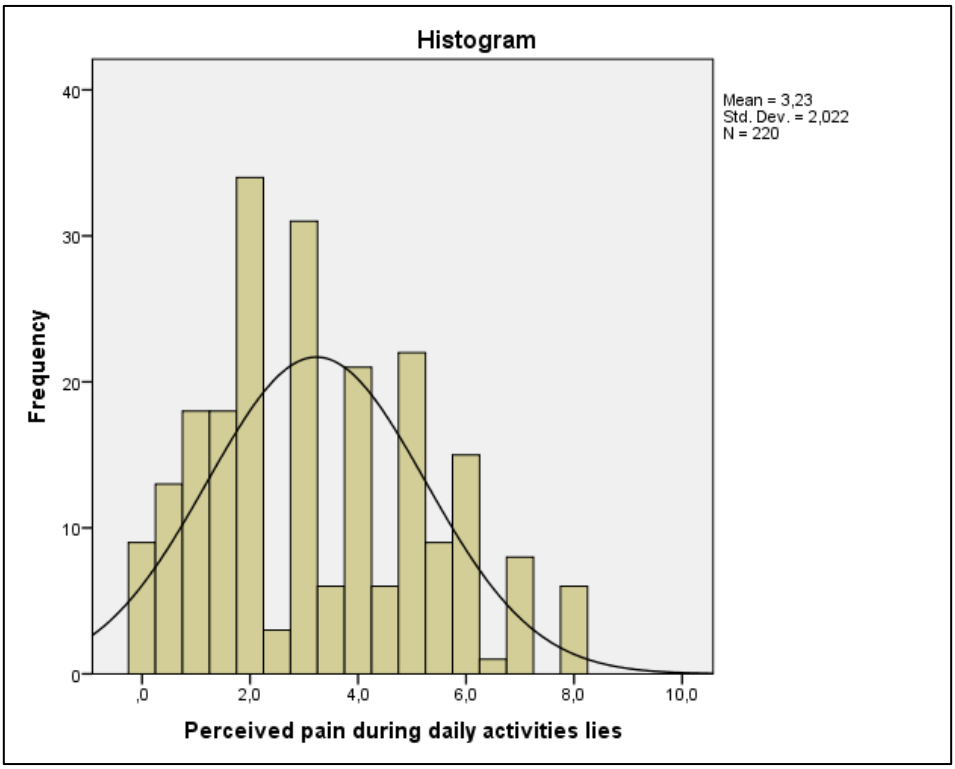
4.3.7 Perceived pain during daily activities lies

Table 70: Perceived pain during daily activities lies

N*	220
Mean	3.23
Median	3.00
Mode	2.0
Std. Deviation	2.022
Minimum	.0
Maximum	8.0

**There are missing values on this variable (N=230)*

Graphic 68: Histogram: Perceived pain during daily activities lies



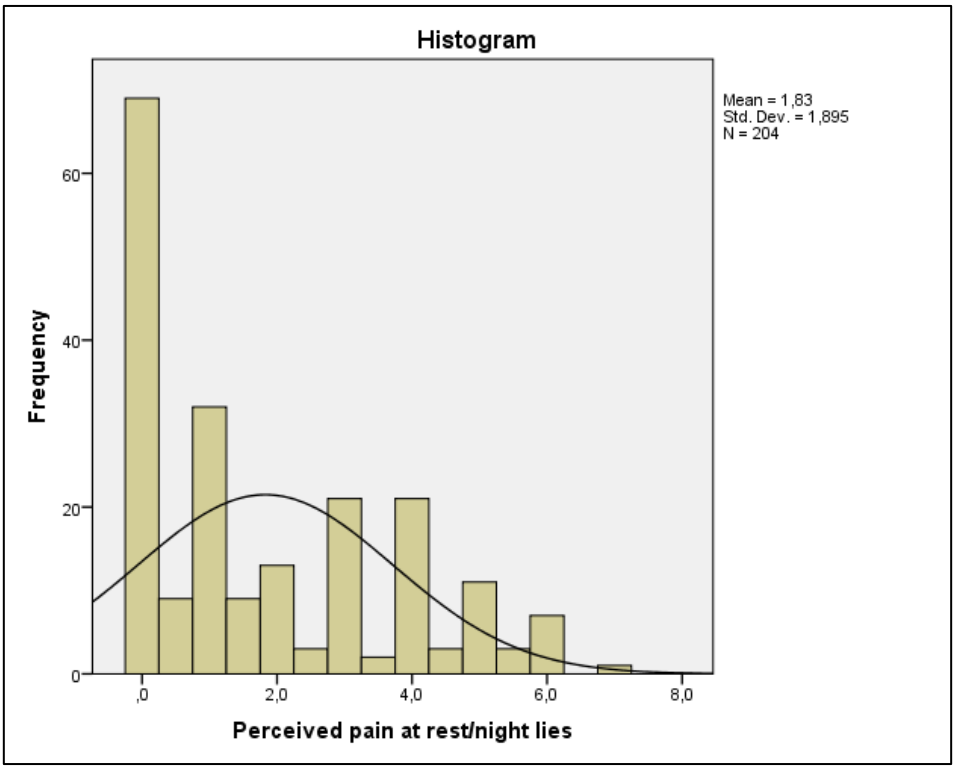
4.3.8 Perceived pain at rest/night lies

Table 71: Perceived pain at rest/night lies

N*	204
Mean	1.83
Median	1.00
Mode	.0
Std. Deviation	1.895
Minimum	0.0
Maximum	7.0

**There are missing values on this variable (N=230)*

Graphic 69: Histogram: Perceived pain at rest/night lies



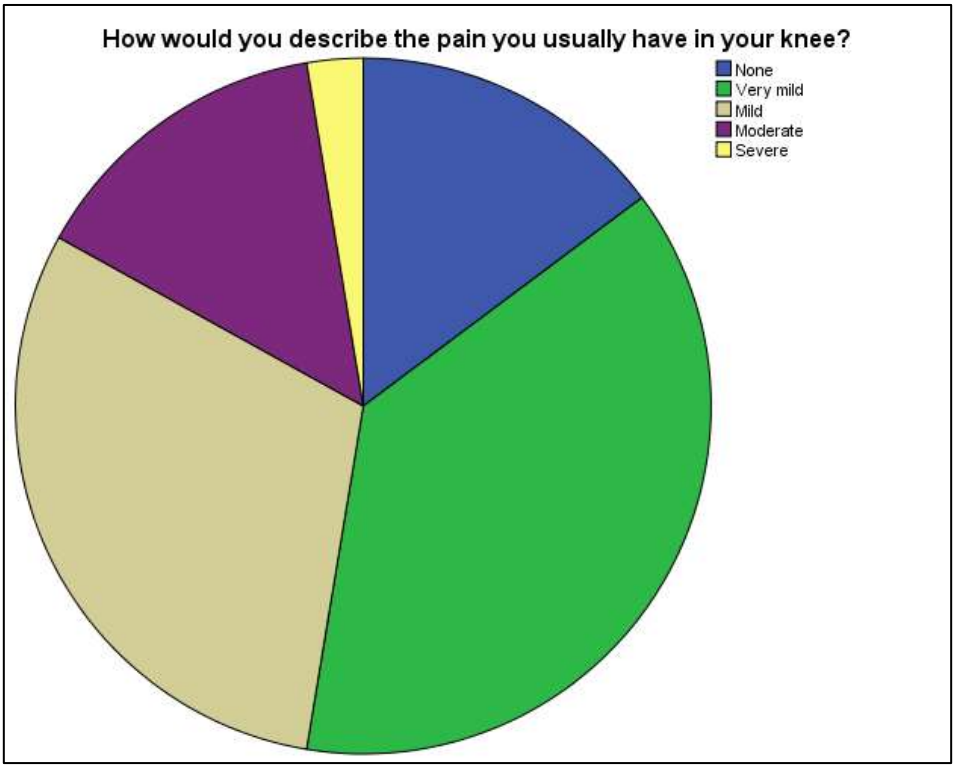
4.3.9 OKSQ. During the past 4 weeks...

4.3.9.1 How would you describe the pain you usually have in your knee?

Table 72. How would you describe the pain you usually have in your knee?

	Frequency	Percent
None	34	14.8%
Very mild	87	37.8%
Mild	70	30.4%
Moderate	33	14.4%
Severe	6	2.6%
Total	230	100.0%

Graphic 70. How would you describe the pain you usually have in your knee?

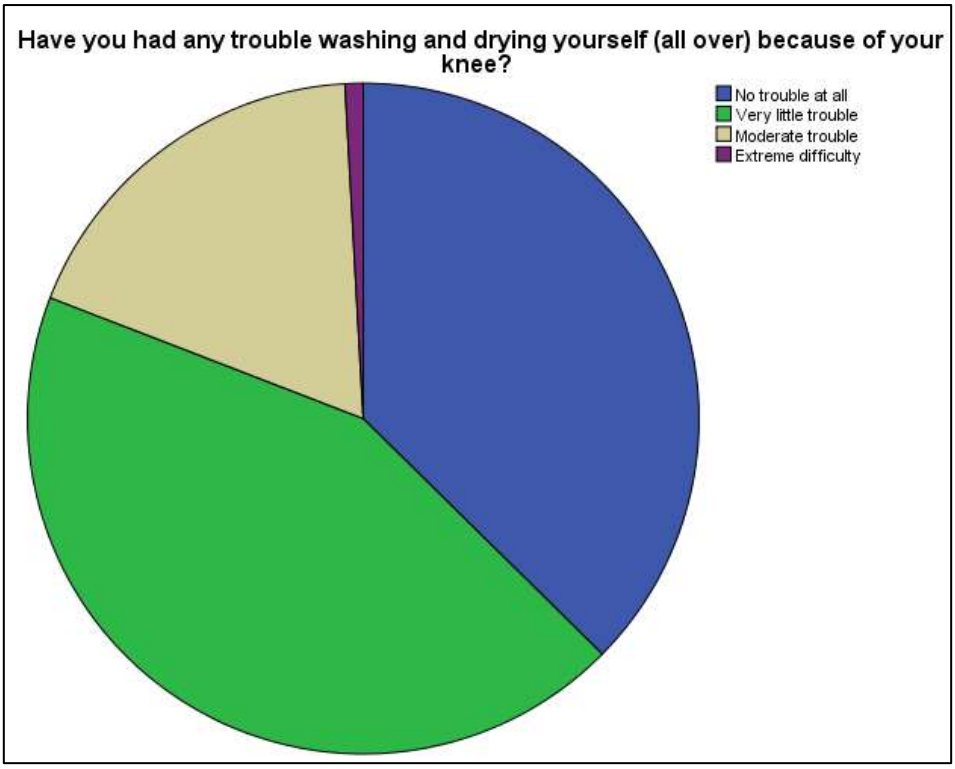


4.3.9.2 Have you had any trouble washing and drying yourself (all over) because of your knee?

Table 73. Have you had any trouble washing and drying yourself (all over) because of your knee?

	Frequency	Percent
No trouble at all	86	37.4%
Very little trouble	100	43.4%
Moderate trouble	42	18.3%
Extreme difficulty	2	0.9%
Total	230	100.0%

Graphic 71. Have you had any trouble washing and drying yourself (all over) because of your knee?



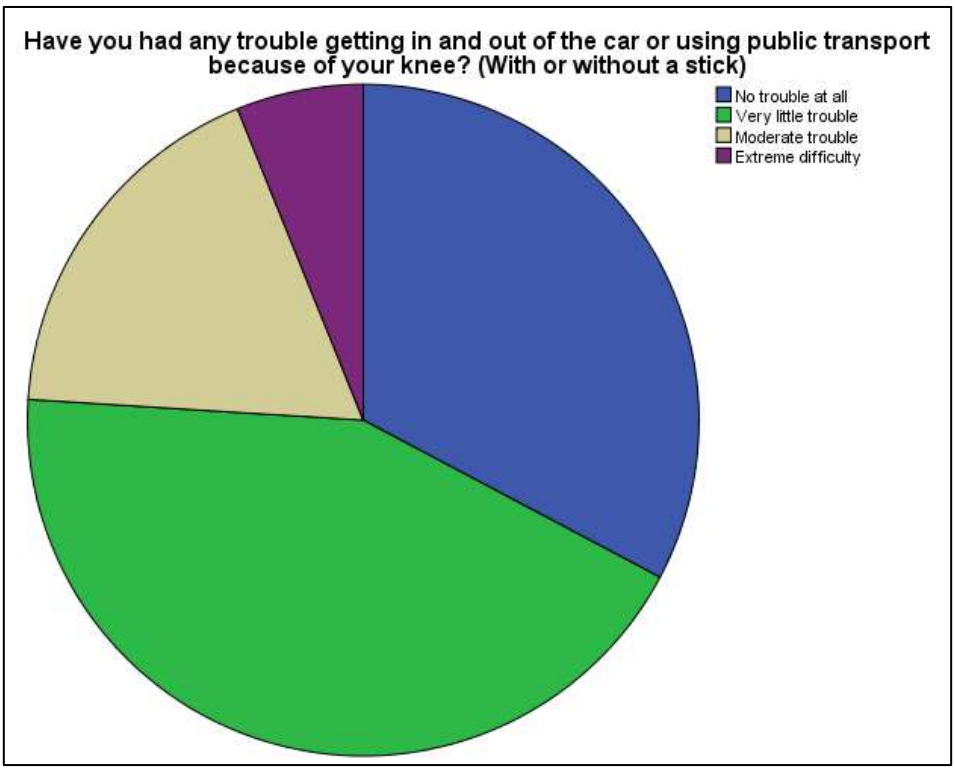
4.3.9.3 Have you had any trouble getting in and out of the car or using public transport because of your knee? (With or without a stick)

Table 74. Have you had any trouble getting in and out of the car or using public transport because of your knee? (With or without a stick)

	Frequency	Percent
No trouble at all	75	32.8%
Very little trouble	99	43.2%
Moderate trouble	41	17.9%
Extreme difficulty	14	6.1%
Total*	229	100.0%

**There are missing values on this variable (N=230)*

Graphic 72. Have you had any trouble getting in and out of the car or using public transport because of your knee? (With or without a stick)



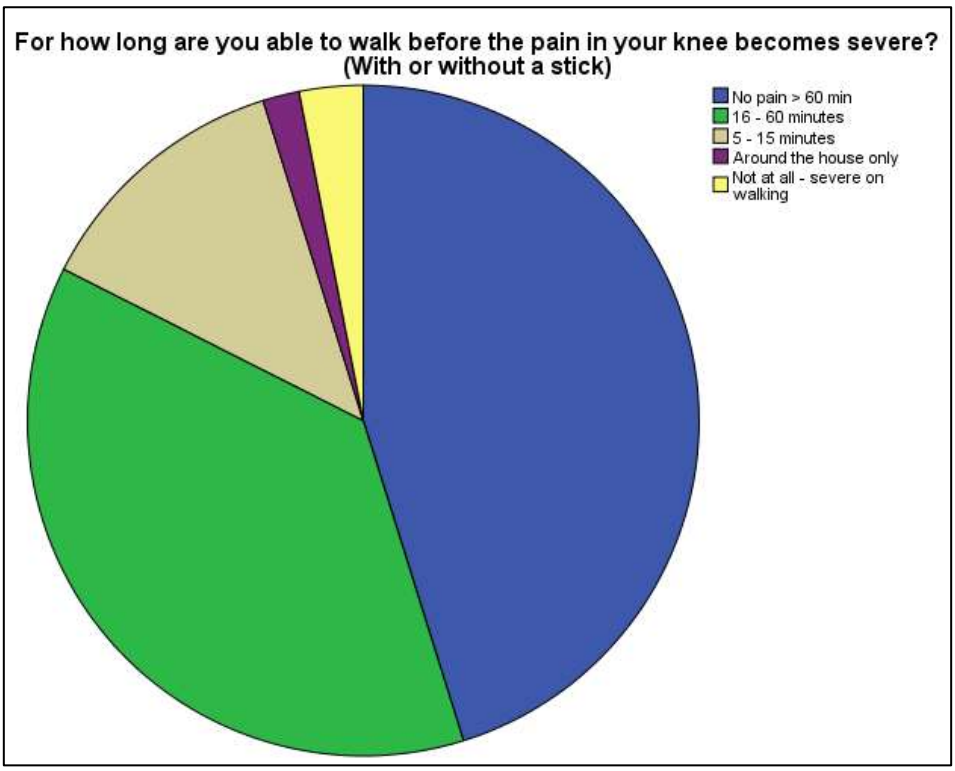
4.3.9.4 For how long are you able to walk before the pain in your knee becomes severe? (With or without a stick)

Table 75. For how long are you able to walk before the pain in your knee becomes severe? (With or without a stick)

	Frequency	Percent
No pain > 60 min	103	45.1%
16 - 60 minutes	85	37.3%
5 - 15 minutes	29	12.7%
Around the house only	4	1.8%
Not at all - severe on walking	7	3.1%
Total*	228	100.0%

**There are missing values on this variable (N=230)*

Graphic 73. For how long are you able to walk before the pain in your knee becomes severe? (With or without a stick)



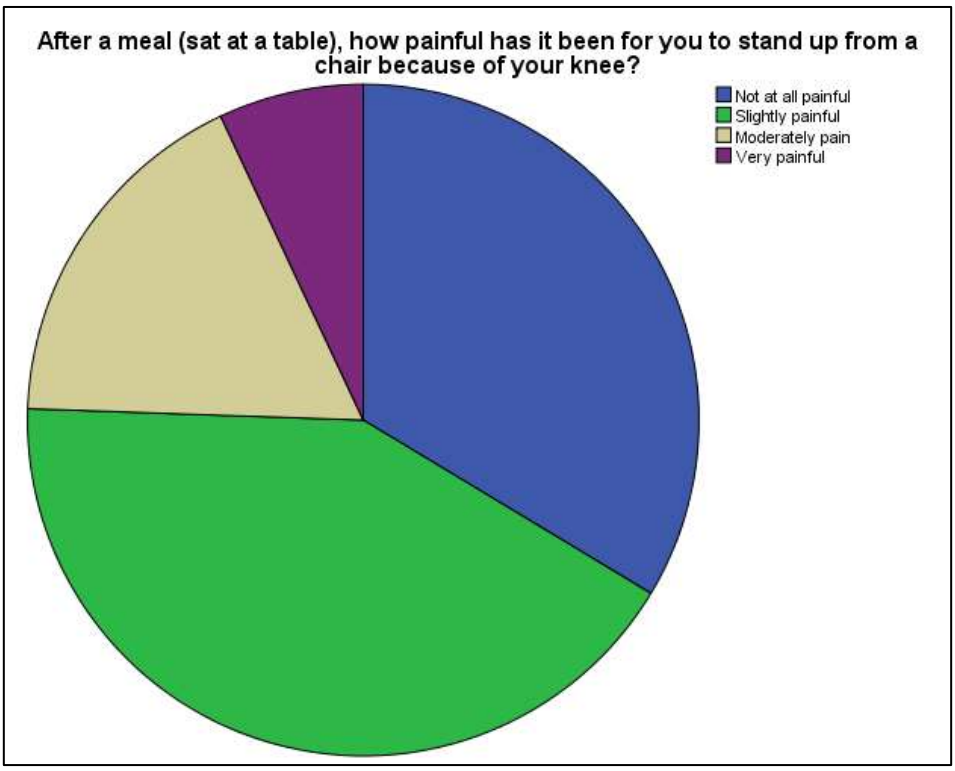
4.3.9.5 After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

Table 76. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

	Frequency	Percent
Not at all painful	77	33.6%
Slightly painful	96	41.9%
Moderately pain	40	17.5%
Very painful	16	7.0%
Total*	229	100.0%

**There are missing values on this variable (N=230)*

Graphic 74. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?



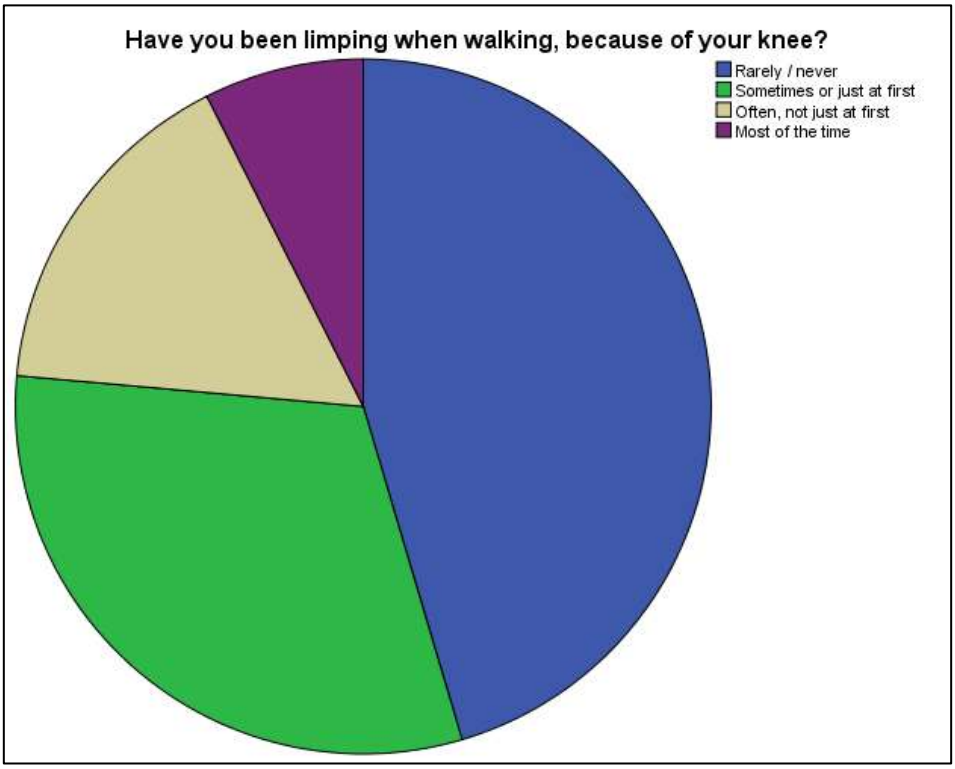
4.3.9.6 Have you been limping when walking, because of your knee?

Table 77. Have you been limping when walking, because of your knee?

	Frequency	Percent
Rarely / never	104	45.4
Sometimes or just at first	71	31.0
Often, not just at first	37	16.2
Most of the time	17	7.4
Total*	229	100.0%

**There are missing values on this variable (N=230)*

Graphic 75. Have you been limping when walking, because of your knee?

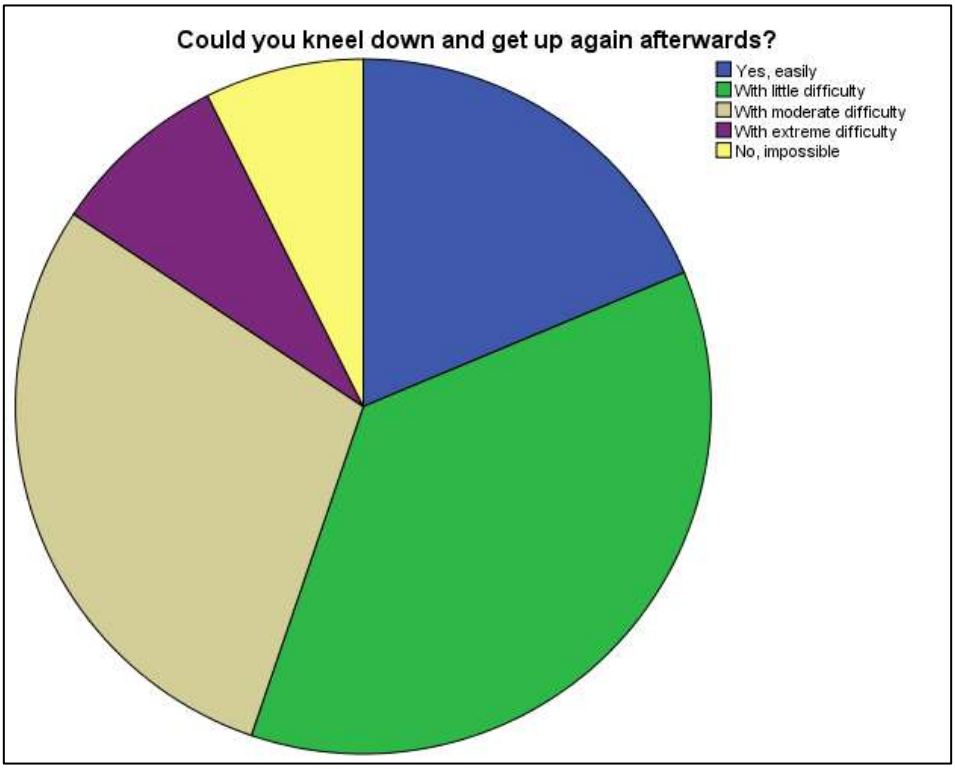


4.3.9.7 Could you kneel down and get up again afterwards?

Table 78. Could you kneel down and get up again afterwards?

	Frequency	Percent
Yes, easily	43	18.7%
With little difficulty	84	36.5%
With moderate difficulty	67	29.1%
With extreme difficulty	19	8.3%
No, impossible	17	7.4%
Total	230	100.0%

Graphic 76. Could you kneel down and get up again afterwards?



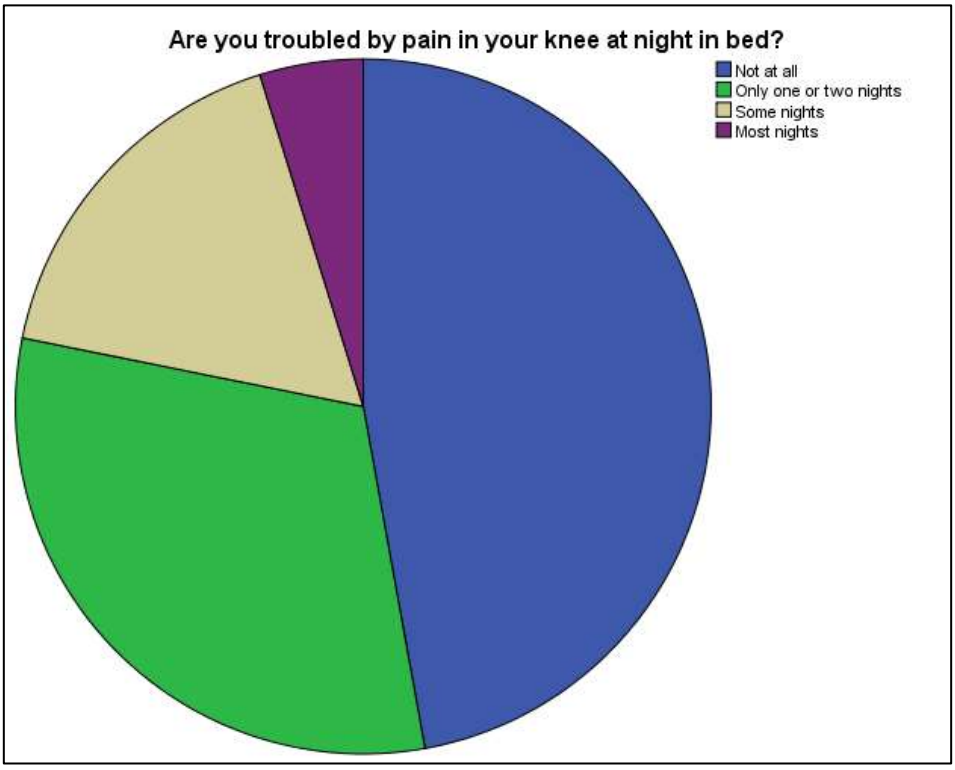
4.3.9.8 Are you troubled by pain in your knee at night in bed?

Table 79. Are you troubled by pain in your knee at night in bed?

	Frequency	Percent
Not at all	108	47.2%
Only one or two nights	71	31.0%
Some nights	39	17.0%
Most nights	11	4.8%
Total*	229	100.0%

**There are missing values on this variable (N=230)*

Graphic 77. Are you troubled by pain in your knee at night in bed?

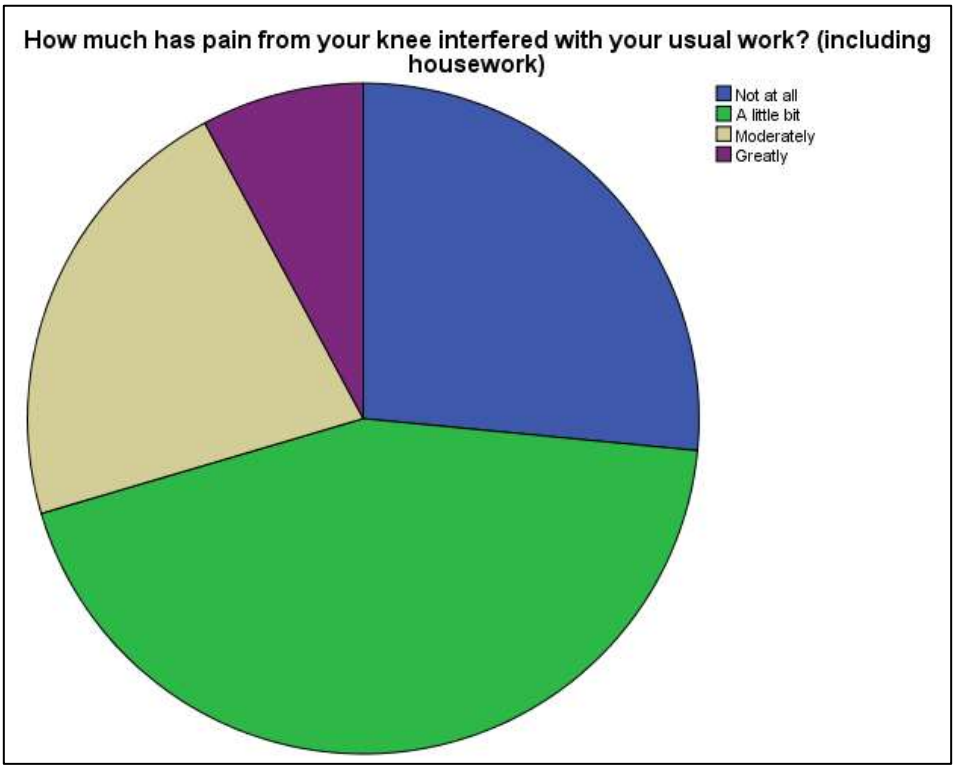


4.3.9.9 How much has pain from your knee interfered with your usual work? (including housework)

Table 80. How much has pain from your knee interfered with your usual work? (including housework)

	Frequency	Percent
Not at all	61	26.5%
A little bit	101	43.9%
Moderately	50	21.8%
Greatly	18	7.8%
Total	230	100.0%

Graphic 78. How much has pain from your knee interfered with your usual work? (including housework)



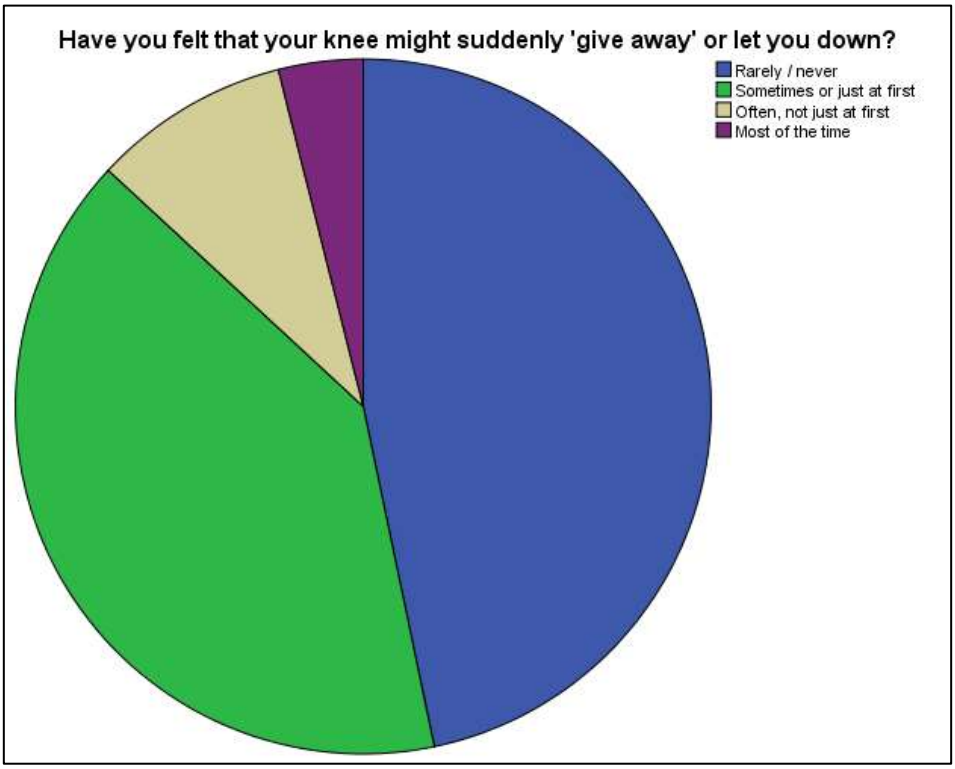
4.3.9.10 Have you felt that your knee might suddenly 'give away' or let you down?

Table 81. Have you felt that your knee might suddenly 'give away' or let you down?

	Frequency	Percent
Rarely / never	107	46.7%
Sometimes or just at first	92	40.2%
Often, not just at first	21	9.2%
Most of the time	9	3.9%
Total*	229	100.0%

**There are missing values on this variable (N=230)*

Graphic 79. Have you felt that your knee might suddenly 'give away' or let you down?



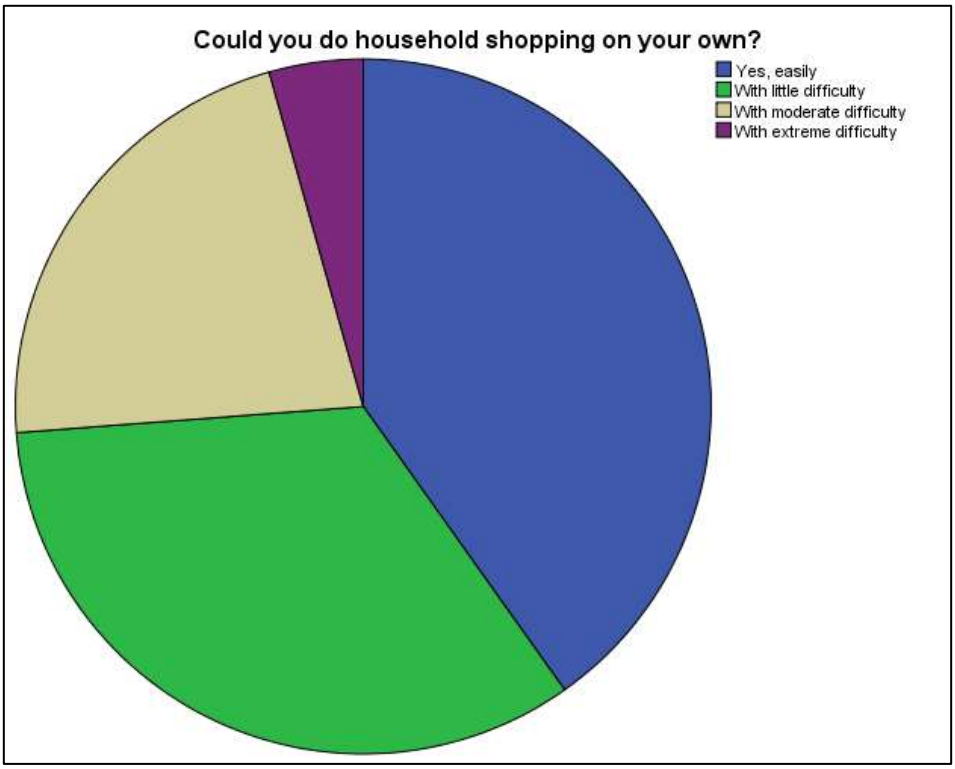
4.3.9.11 Could you do household shopping on your own?

Table 82. Could you do household shopping on your own?

	Frequency	Percent
Yes, easily	92	40.2%
With little difficulty	77	33.6%
With moderate difficulty	50	21.8%
With extreme difficulty	10	4.4%
Total*	229	100.0%

**There are missing values on this variable (N=230)*

Graphic 80. Could you do household shopping on your own?

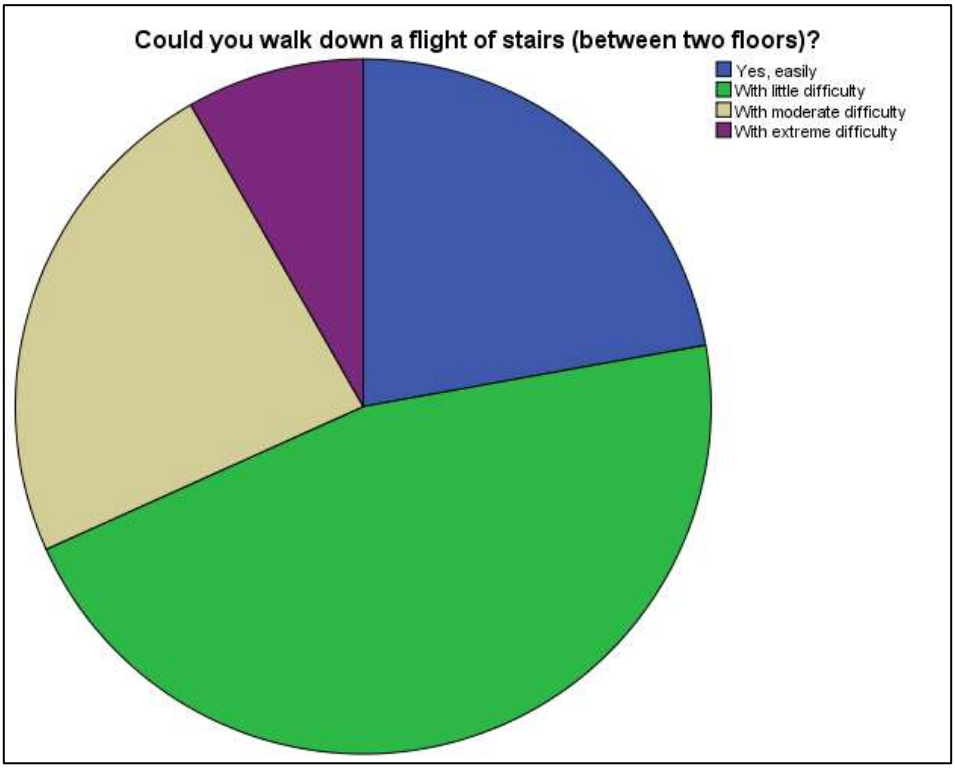


4.3.9.12 Could you walk down a flight of stairs (between two floors)?

Table 83. Could you walk down a flight of stairs (between two floors)?

	Frequency	Percent
Yes, easily	51	22.2
With little difficulty	106	46.1
With moderate difficulty	54	23.4
With extreme difficulty	19	8.3
Total	230	100.0%

Graphic 81. Could you walk down a flight of stairs (between two floors)?

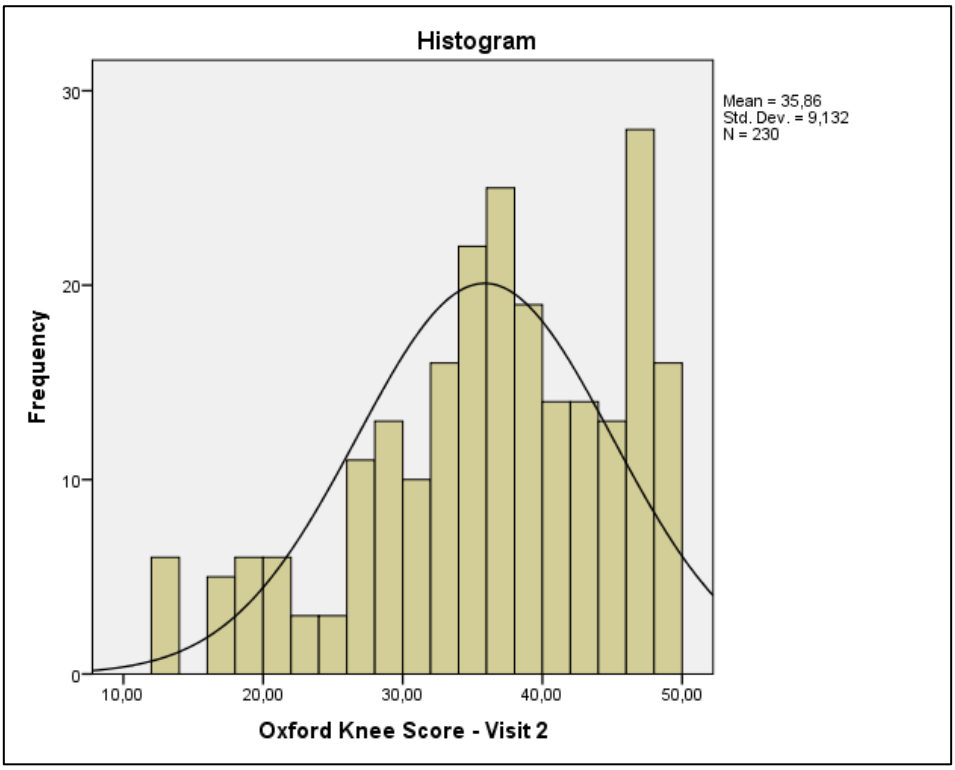


4.3.9.13 Oxford Knee Score

Table 84. Oxford Knee Score

N	230
Mean	35.86
Median	36.00
Mode	47.00
Std. Deviation	9.132
Minimum	13.00
Maximum	48.00

Graphic 82. Oxford Knee Score

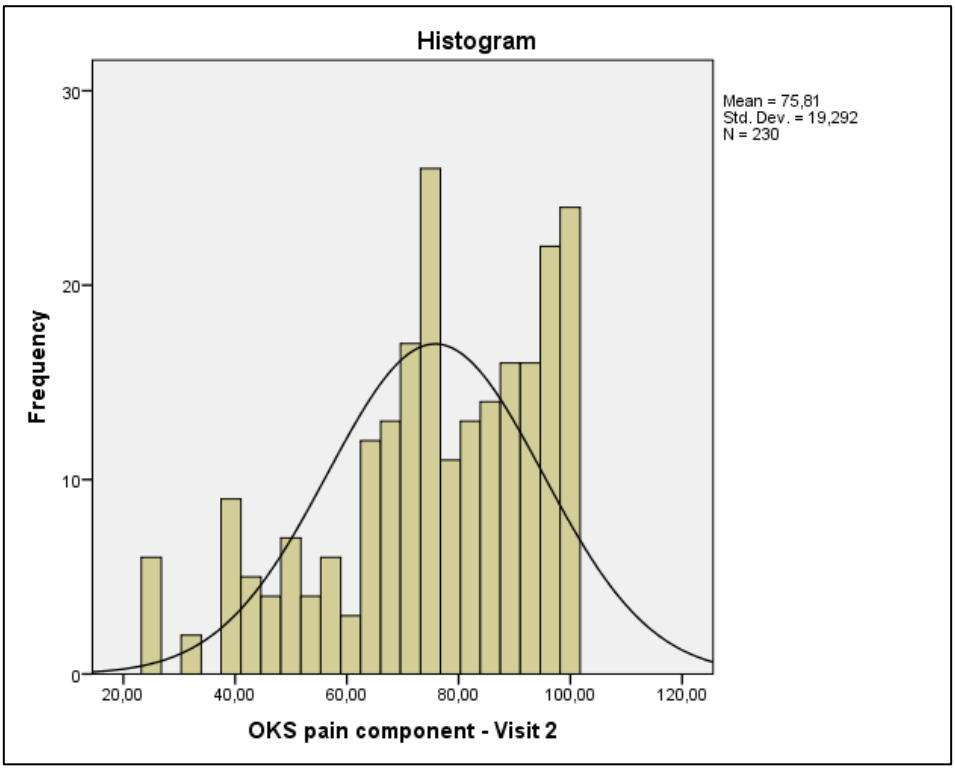


4.3.9.14 Oxford Knee Score Pain component

Table 85. Oxford Knee Score Pain component

N	239
Mean	75.81
Median	78.54
Mode	74.97
Std. Deviation	19.292
Minimum	24.99
Maximum	99.96

Graphic 83. Oxford Knee Score Pain component

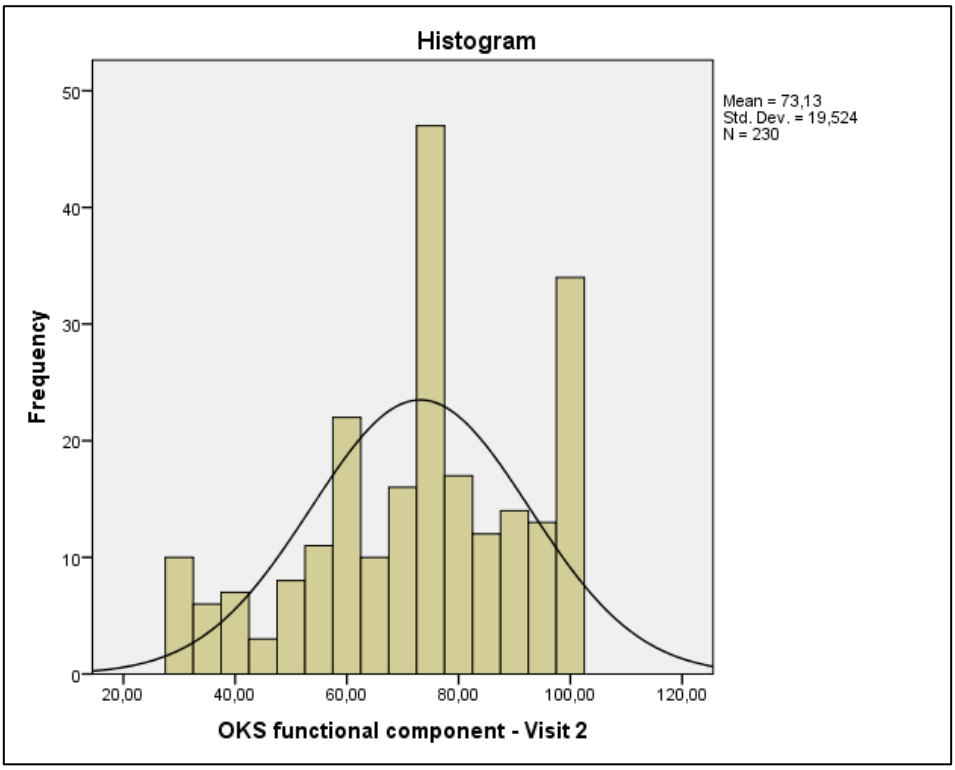


4.3.9.15 Oxford Knee Score functional component

Table 86. Oxford Knee Score functional component

N	230
Mean	73.13
Median	75.00
Mode	75.00
Std. Deviation	19.524
Minimum	30.00
Maximum	100.00

Graphic 84. Oxford Knee Score functional component

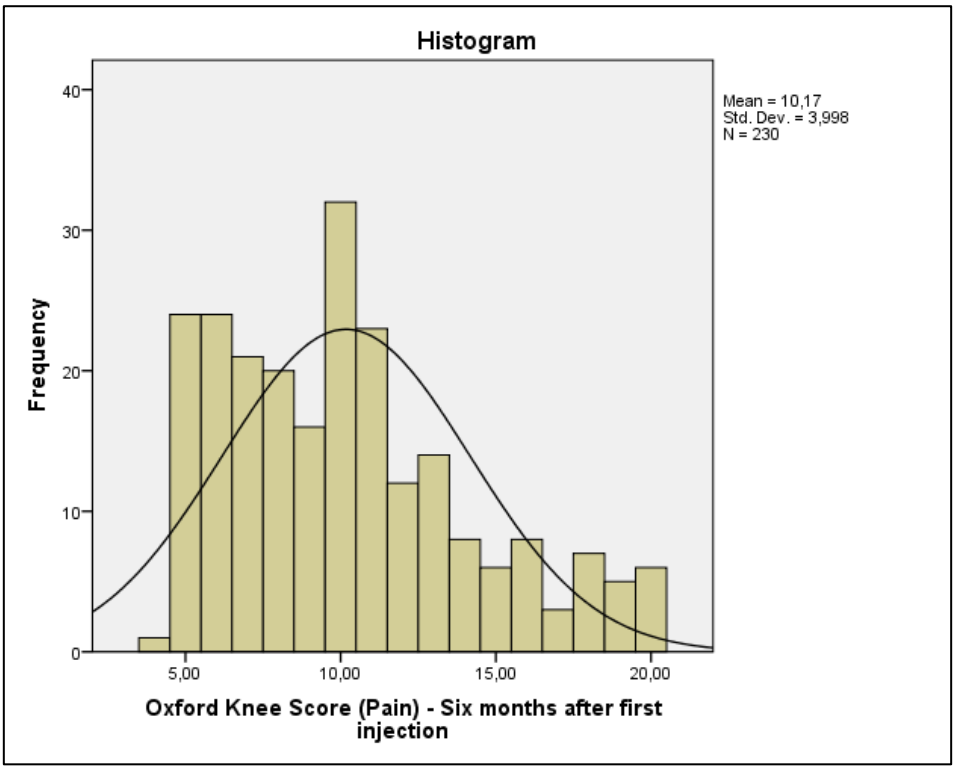


4.3.9.16 Oxford Knee Score Pain (Protocol)

Table 87. Oxford Knee Score Pain (Protocol)

N	230
Mean	10.17
Median	10.00
Mode	10.00
Std. Deviation	3.998
Minimum	4.00
Maximum	20.00

Graphic 85. Oxford Knee Score Pain (Protocol)

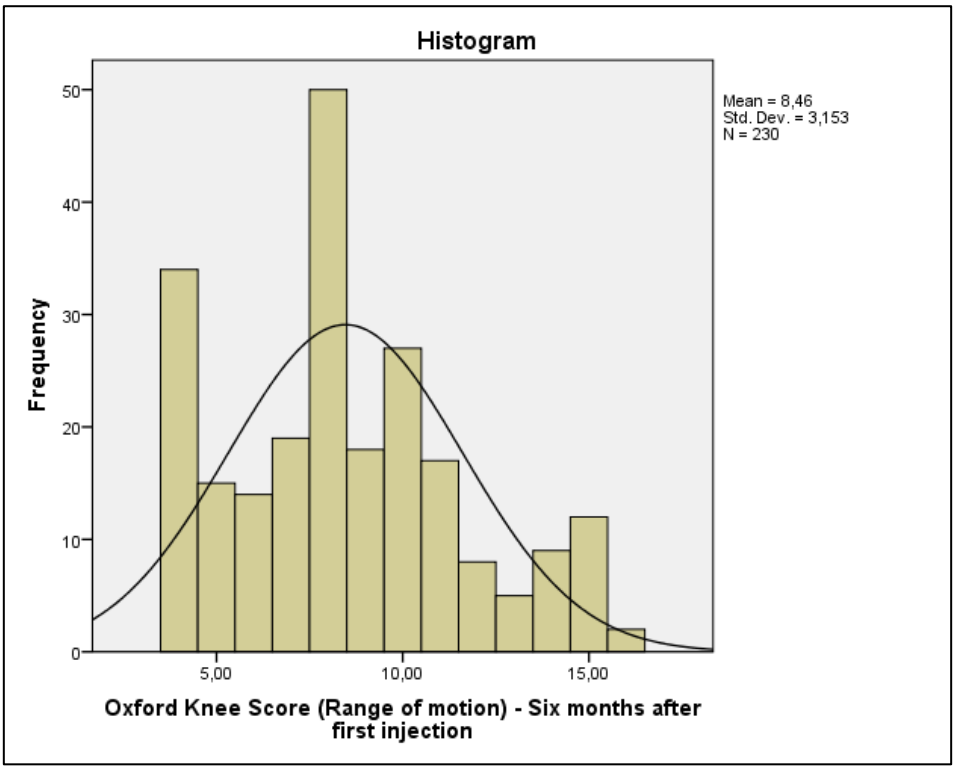


4.3.9.17 Oxford Knee Score Range of motion (Protocol)

Table 88. Oxford Knee Score Range of motion (Protocol)

N	230
Mean	8.46
Median	8.00
Mode	8.00
Std. Deviation	3.153
Minimum	4.00
Maximum	16.00

Graphic 86. Oxford Knee Score Range of motion (Protocol)

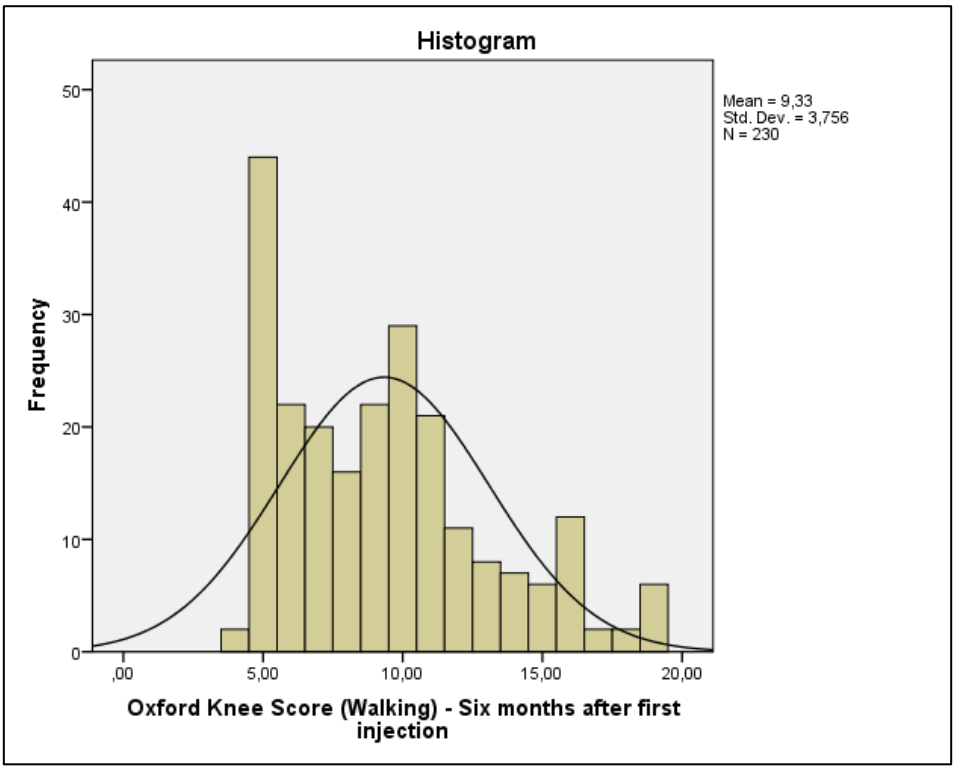


4.3.9.18 Oxford Knee Score Walking (Protocol)

Table 89. Oxford Knee Score Walking (Protocol)

N	230
Mean	9.33
Median	9.00
Mode	5.00
Std. Deviation	3.756
Minimum	4.00
Maximum	19.00

Graphic 87. Oxford Knee Score Walking (Protocol)



5 Homogeneity of the Sample

Table 90. Homogeneity of the sample (A)

Variable		Suplasyn			Suplasyn 1-shot			Sig.
		N	%	Mean ± SD	N	%	Mean ± SD	
Gender	Female	70	55.6%		71	56.3%		
	Male	56	44.4%		55	43.7%		
	Total	126	100.0%		126	100.0%		0.899
Age		126		61.6 ± 12.1	126		62.8 ± 10.2	ns
Radiological grade according to Kellgren–Lawrence	I	23	18.3%		18	14.3%		
	II	52	41.3%		55	43.7%		
	III	51	40.5%		53	42.1%		
	Total	126	100.0%		126	100.0%		0.693
Have you taken drugs to prevent or treat a pain in your knee during the past 3 months?	No	13	10.3%		9	7.1%		
	Yes	113	89.7%		117	92.9%		
	Total	126	100.0%		126	100.0%		0.372
Analgesics (painkillers)	No	65	51.6%		58	46.0%		
	Yes	61	48.4%		68	54.0%		
	Total	126	100.0%		126	100.0%		0.378
NSAIDs (ibuprofen, meloxicam, etc.)	No	42	33.3%		45	35.7%		
	Yes	84	66.7%		81	64.3%		
	Total	126	100.0%		126	100.0%		0.691
SYSADOA (chondroitin, glucosamin) - every day usage	No	87	69.0%		95	75.4%		
	Yes	39	31.0%		31	24.6%		
	Total	126	100.0%		126	100.0%		0.261
How many times have you taken analgesics (painkillers) to control the pain?	Less than three days	20	37.0%		27	43.5%		
	One day out of two	11	20.4%		11	17.7%		
	Every day	23	42.6%		24	38.7%		
	Total	54	100.0%		62	100.0%		0.773
How many times have you taken NSAIDs to control the pain?	Less than three days	37	44.0%		37	46.8%		
	One day out of two	14	16.7%		11	13.9%		
	Every day	33	39.3%		31	39.2%		
	Total	84	100.0%		79	100.0%		0.874
Previous intervention - Open surgery	No	126	100.0%		123	97.6%		
	Yes	0	0.0%		3	2.4%		
	Total	126	100.0%		126	100.0%		0.081
Previous intervention - Arthroscopy	No	117	92.9%		112	88.9%		
	Yes	9	7.1%		14	11.1%		
	Total	126	100.0%		126	100.0%		0.274
Previous intervention - Intraarticulare injections (HA, corticosteroids)	No	74	58.7%		80	63.5%		
	Yes	52	41.3%		46	36.5%		
	Total	126	100.0%		126	100.0%		0.438
Previous intervention - Arthrocentesis	No	123	97.6%		120	95.2%		
	Yes	3	2.4%		6	4.8%		
	Total	126	100.0%		126	100.0%		0.309

Intraarticulare injection type: Hyaluronic acid	No	111	88.1%		103	81.7%		
	Yes	15	11.9%		23	18.3%		
	Total	126	100.0%		126	100.0%		0.159
Intraarticulare injection type: Corticosteroids	No	97	77.0%		95	75.4%		
	Yes	29	23.0%		31	24.6%		
	Total	126	100.0%		126	100.0%		0.767
Perceived pain during daily activities lies		126		6, 6 ± 1.7	125		6, 6 ± 1.7	ns
Perceived pain at rest/night lies		119		3.8 ± 2.7	124		3.7 ± 2.4	ns
Oxford Knee Score - Baseline		116		23.5 ± 11.2	123		25.2 ± 7.7	ns
OKS Pain component - Baseline		116		49.5 ± 24.7	123		53.6 ± 16.4	ns
OKS Functional component - Baseline		116		48.4 ± 22.22	123		51.1 ± 17.1	ns
OKS Pain (Protocol) - Baseline		116		15.3 ± 4.9	123		14.8 ± 3.2	ns
OKS Range of motion (Protocol) - Baseline		116		12.4 ± 3.5	123		12.1 ± 2.7	ns
OKS Walking (Protocol) - Baseline		116		14.2 ± 5.2	123		13.1 ± 3.7	< 0.1
Oxford Knee Score - Visit 1		116		33.8 ± 11.5	121		34.5 ± 7.4	ns
OKS Pain component (Protocol)- Visit 1		116		71.7 ± 24.6	121		73.5 ± 15.5	ns
OKS Functional component (Protocol) - Visit 1		116		68.6 ± 23.9	121		69.7 ± 16.6	ns
OKS Pain (Protocol) - Visit 1		116		10.8 ± 4.9	121		10.7 ± 3.2	ns
OKS Range of motion (Protocol) - Visit 1		116		9.1 ± 3.8	121		8.9 ± 2.7	ns
OKS Walking (Protocol) - Visit 1		116		10.5 ± 4.8	121		9.7 ± 3.2	ns
Oxford Knee Score - Visit 2		116		36.1 ± 10.5	114		35.6 ± 7.6	ns
OKS Functional component - Visit 2		116		73.6 ± 22.22	114		72.6 ± 16.7	ns
OKS Pain component - Visit 2		116		76.3 ± 22.22	114		75.3 ± 16.2	ns
OKS Pain (Protocol) - Visit 2		116		10.10 ± 4.6	114		10.4 ± 3.3	ns
OKS Range of motion (Protocol) - Visit 2		116		8.3 ± 3.5	114		8.7 ± 2.8	ns
OKS Walking (Protocol) - Visit 2		116		9.4 ± 4.2	114		9.2 ± 3.3	ns

6 Statistical Inference

6.1 Pain evaluated with the Visual Analog Scale (VAS)

6.1.1 Paired data tests: Baseline Visit – Visit 1

Table 91. Paired data tests: Baseline Visit - Visit 1 – SUPLASYN

SUPLASYN	Baseline Visit		Visit 1		Paired differences			Cohen's d (IC95%)
	Mean (SD)	N	Mean (SD)	N	Mean (IC95%)	p t-test	p-Wilcoxon	
Perceived pain during daily activities lies	5.97 (1.72)	113	3.58 (2.17)	113	2.39 (2.02-2.77)	<0.001	<0.001	1,22 (0,94-1,51)
Perceived pain at rest/night lies	3.63 (2.85)	100	1.88 (2.03)	100	1.76 (1.33-2.18)	<0.001	<0.001	0,71 (0,42-1)

Table 92. Paired data tests: Baseline Visit – Visit 1 - SUPLASYN 1-SHOT

SUPLASYN 1-SHOT	Baseline Visit		Visit 1		Paired differences			Cohen's d (IC95%)
	Mean (SD)	N	Mean (SD)	N	Mean (IC95%)	p t-test	p-Wilcoxon	
Perceived pain during daily activities lies	6.04 (1.71)	120	3.5 (1.52)	120	2.53 (2.25-2.82)	<0.001	<0.001	1,57 (1,28-1,85)
Perceived pain at rest/night lies	3.71 (2.44)	117	1.73 (1.46)	117	1.98 (1.61-2.36)	<0.001	<0.001	0,99 (0,72-1,26)

6.1.2 Paired data tests: Baseline Visit – Visit 2

Table 93. Paired data tests: Baseline Visit - Visit 2 – SUPLASYN

SUPLASYN	Baseline Visit		Visit 2		Paired differences			Cohen's d (IC95%)
	Mean (SD)	N	Mean (SD)	N	Mean (IC95%)	p t-test	p-Wilcoxon	
Perceived pain during daily activities lies	5.96 (1.74)	109	3.25 (2.26)	109	2.71 (2.29-3.13)	<0.001	<0.001	1,34 (1,05-1,64)
Perceived pain at rest/night lies	3.93 (2.83)	88	1.96 (2.06)	88	1.97 (1.36-2.58)	<0.001	<0.001	0,79 (0,49-1,1)

Table 94. Paired data tests: Baseline Visit – Visit 2 - SUPLASYN 1-SHOT

SUPLASYN 1-SHOT	Baseline Visit		Visit 2		Paired differences			Cohen's d (IC95%)
	Mean (SD)	N	Mean (SD)	N	Mean (IC95%)	p t-test	p-Wilcoxon	
Perceived pain during daily activities lies	6.01 (1.67)	111	3.21 (1.77)	111	2.79 (2.43-3.16)	<0.001	<0.001	1,62 (1,32-1,93)
Perceived pain at rest/night lies	3.68 (2.47)	108	1.82 (1.76)	108	1.86 (1.49-2.23)	<0.001	<0.001	0,87 (0,59-1,14)

6.1.3 Paired data tests: Visit 1 – Visit 2

Table 95. Paired data tests: Visit 1 - Visit 2 – SUPLASYN

SUPLASYN	Visit 1		Visit 2		Paired differences			Cohen's d (IC95%)
	Mean (SD)	N	Mean (SD)	N	Mean (IC95%)	p t-test	p-Wilcoxon	
Perceived pain during daily activities lies	3.62 (2.19)	109	3.25 (2.26)	109	0.37 (0.15-0.59)	<0.001	<0.001	0,17 (-0,1-0,43)
Perceived pain at rest/night lies	1.86 (2.07)	95	1.82 (2.05)	95	0.05 (-0.33-0.42)	0.81	0,002	0,02 (-0,26-0,31)

Table 96. Paired data tests: Visit 1 – Visit 2 - SUPLASYN 1-SHOT

SUPLASYN 1-SHOT	Visit 1		Visit 2		Paired differences			Cohen's d (IC95%)
	Mean (SD)	N	Mean (SD)	N	Mean (IC95%)	p t-test	p-Wilcoxon	
Perceived pain during daily activities lies	3.47 (1.5)	111	3.21 (1.77)	111	0.26 (-0.03-0.55)	0.08	0,12	0,16 (-0,11-0,42)
Perceived pain at rest/night lies	1.7 (1.41)	106	1.84 (1.74)	106	-0.13 (-0.37-0.1)	0.25	0,29	-0,08 (-0,35-0,18)

6.1.4 **Comparison between SUPLASYN vs SUPLASYN 1-SHOT**

Table 97. Comparison between SUPLASYN vs SUPLASYN 1-SHOT: Baseline Visit

	SUPLASYN		SUPLASYN 1-SHOT		Total		Inferences	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	p-ANOVA	p-MW
Perceived pain during daily activities lies	6.02(1.67)	126	5.98(1.73)	125	6.00(1.70)	251	0.882	0.68
Perceived pain at rest/night lies	3.76(2.68)	119	3.72(2.39)	124	3.74(2.53)	243	0.91	0.83

Table 98. Comparison between SUPLASYN vs SUPLASYN 1-SHOT: Visit 1

	SUPLASYN		SUPLASYN 1-SHOT		Total		Inferences	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	p-ANOVA	p-MW
Perceived pain during daily activities lies	3.58(2.17)	113	3.50(1.52)	120	3.54(1.86)	233	0.76	0.96
Perceived pain at rest/night lies	1.76(2.02)	107	1.74(1.46)	118	1.75(1.74)	225	0.95	0.22

Table 99. Comparison between SUPLASYN vs SUPLASYN 1-SHOT: Visit 2

	SUPLASYN		SUPLASYN 1-SHOT		Total		Inferences	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	p-ANOVA	p-MW
Perceived pain during daily activities lies	3.25(2.26)	109	3.21(1.77)	111	3.23(2.02)	220	0.90	0.68
Perceived pain at rest/night lies	1.82(2.05)	95	1.84(1.76)	109	1.83(1.89)	204	0.95	0.39

6.1.5 **Friedman test: Perceived pain during daily activities lies**

Graphic 88. Perceived pain during daily activities lies.

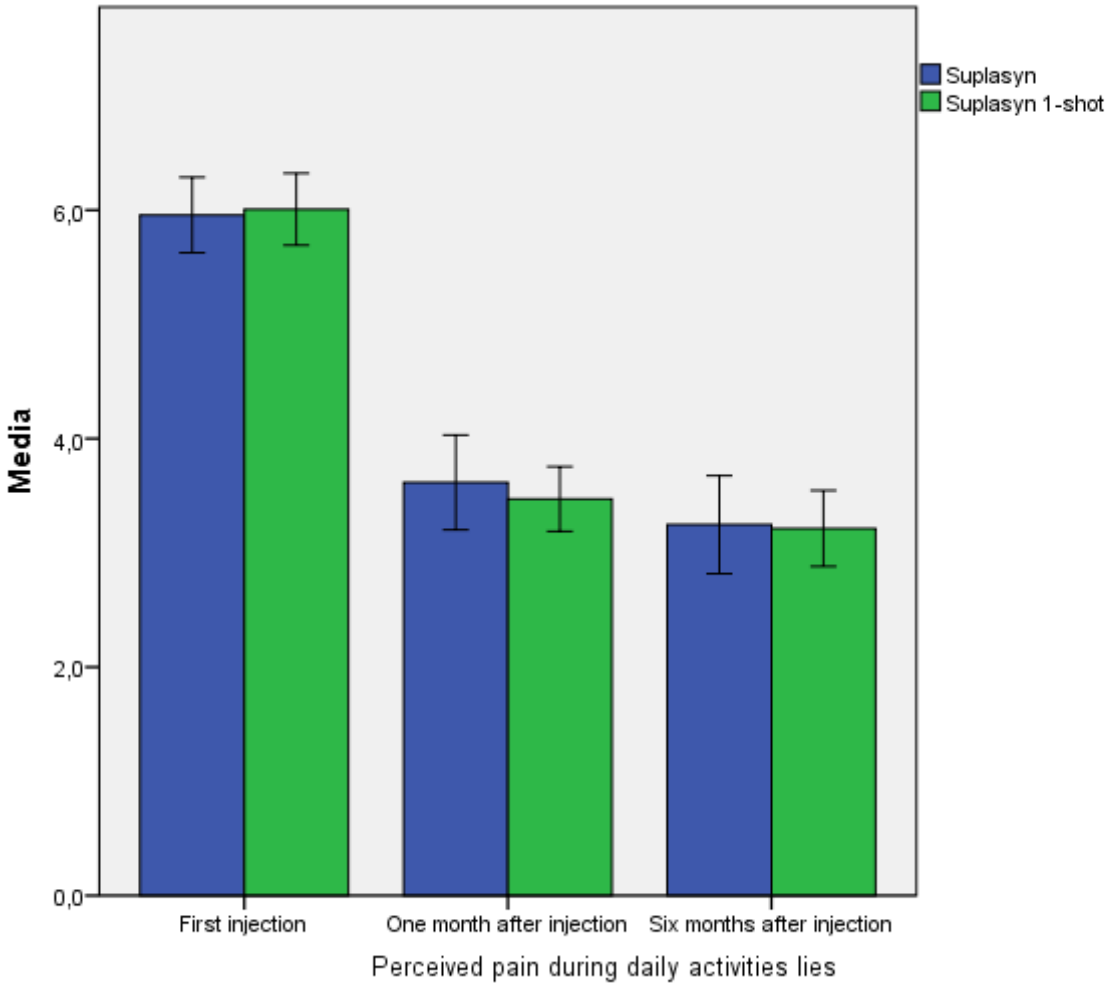


Table 100. Friedman test: Perceived pain during daily activities lies

SUPLASYN	**N**	109
	Asymp. Sig.	<0.001
SUPLASYN 1-SHOT	**N**	111
	Asymp. Sig.	<0.001

6.1.6 **Friedman test: Perceived pain at rest/night lies**

Graphic 89. Perceived pain during daily activities lies.

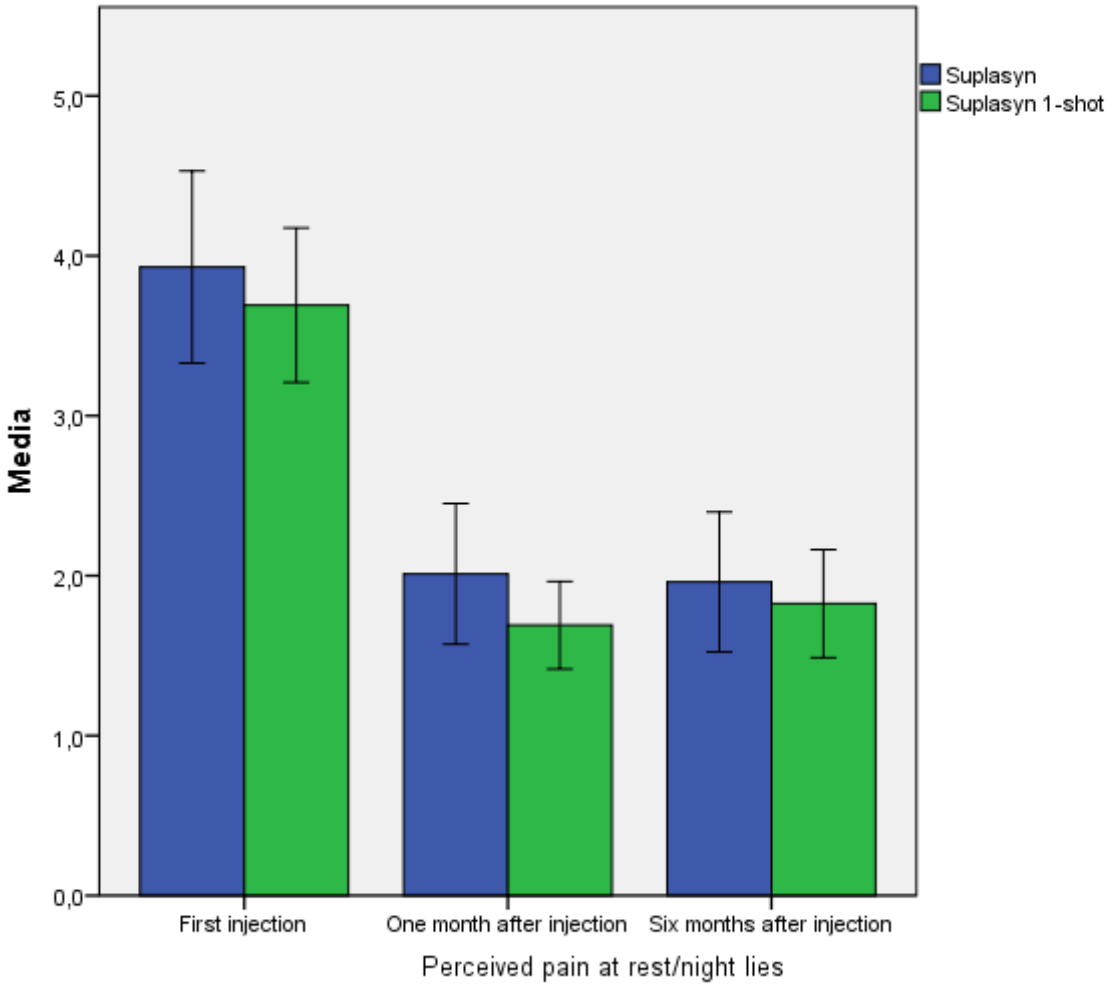


Table 101. Friedman test: Perceived pain during daily activities lies

SUPLASYN	**N**	88
	Asymp. Sig.	<0.001
SUPLASYN 1-SHOT	**N**	105
	Asymp. Sig.	<0.001

6.2 Oxford Knee Score

6.2.1 Paired data tests: Baseline Visit - Visit 1

Table 102. Paired data tests: Baseline Visit - Visit 1 – SUPLASYN

SUPLASYN	First injection		One month after injection		Paired differences			Cohen's d (IC95%)
	Mean (SD)	N	Mean (SD)	N	Mean (IC95%)	p t-test	p-Wilcoxon	
OKS	23.53 (1.04)	116	33.8 (1.07)	116	-10.28 (-11.64--8.91)	<0.001	<0.001	0,91 (0,64-1,18)
OKS – Pain component	49.46 (2.29)	116	71.71 (2.29)	116	-22.25 (-25.59--18.91)	<0.001	<0.001	0,9 (0,63-1,17)
OKS – Functional component	48.36 (2.05)	116	68.58 (2.22)	116	-20.22 (-22.75--17.68)	<0.001	<0.001	0,88 (0,61-1,15)
OKS – Pain (protocol)	15.29 (4.86)	116	10.78 (4.86)	116	4.51 (3.79-5.23)	<0.001	<0.001	0,93 (0,66-1,2)
OKS- Range of motion (protocol)	12.43 (3.5)	116	9.09 (3.82)	116	3.34 (2.9-3.79)	<0.001	<0.001	0,91 (0,64-1,18)
OKS – Walking (protocol)	14.16 (5.17)	116	10.46 (4.78)	116	3.71 (3.12-4.29)	<0.001	<0.001	0,74 (0,48-1,01)

Table 103. Paired data tests: Baseline Visit – Visit 1 - SUPLASYN 1-SHOT

SUPLASYN 1-SHOT	First injection		One month after injection		Paired differences			Cohen's d (IC95%)
	Mean (SD)	N	Mean (SD)	N	Mean (IC95%)	p t-test	p-Wilcoxon	
OKS	25.37 (0.7)	121	34.52 (0.67)	121	-9.15 (-10.25--8.05)	<0.001	<0.001	1,21 (0,94-1,49)
OKS – Pain component	53.93 (1.49)	121	73.49 (1.41)	121	-19.56 (-22.1--17.02)	<0.001	<0.001	1,23 (0,95-1,5)
OKS – Functional component	51.32 (1.55)	121	69.67 (1.51)	121	-18.35 (-20.76--15.93)	<0.001	<0.001	1,09 (0,82-1,36)
OKS – Pain (protocol)	14.81 (3.19)	121	10.72 (3.24)	121	4.09 (3.59-4.59)	<0.001	<0.001	1,27 (0,99-1,55)
OKS- Range of motion (protocol)	12.07 (2.68)	121	8.9 (2.68)	121	3.17 (2.81-3.52)	<0.001	<0.001	1,18 (0,91-1,46)
OKS – Walking (protocol)	13.08 (3.68)	121	9.72 (3.22)	121	3.36 (2.79-3.93)	<0.001	<0.001	0,97 (0,71-1,24)

6.2.2 Paired data tests: Baseline Visit - Visit 2

Table 104. Paired data tests: Baseline Visit - Visit 2 – SUPLASYN

SUPLASYN	First injection		Six month after injection		Paired differences			Cohen's d (IC95%)
	Mean (SD)	N	Mean (SD)	N	Mean (IC95%)	p t-test	p-Wilcoxon	
OKS	23.53 (1.04)	116	36.09 (0.97)	116	-12.57 (-14.03--11.1)	<0.001	<0.001	1,16 (0,88-1,44)
OKS – Pain component	49.46 (2.29)	116	76.29 (2.04)	116	-26.84 (-30.19--23.48)	<0.001	<0.001	1,15 (0,87-1,43)
OKS – Functional component	48.36 (2.05)	116	73.62 (2.04)	116	-25.26 (-28.18--22.34)	<0.001	<0.001	1,15 (0,87-1,42)
OKS – Pain (protocol)	15.29 (4.86)	116	9.99 (4.58)	116	5.3 (4.53-6.08)	<0.001	<0.001	1,12 (0,84-1,4)
OKS- Range of motion (protocol)	12.43 (3.5)	116	8.27 (3.49)	116	4.16 (3.65-4.68)	<0.001	<0.001	1,19 (0,91-1,47)
OKS – Walking (protocol)	14.16 (5.17)	116	9.43 (4.18)	116	4.73 (4.14-5.33)	<0.001	<0.001	1,01 (0,73-1,28)

Table 105. Paired data tests: Baseline Visit – Visit 2 - SUPLASYN 1-SHOT

SUPLASYN 1-SHOT	First injection		Six month after injection		Paired differences			Cohen's d (IC95%)
	Mean (SD)	N	Mean (SD)	N	Mean (IC95%)	p t-test	p-Wilcoxon	
OKS	25.71 (0.7)	114	35.62 (0.71)	114	-9.91 (-11.2--8.62)	<0.001	<0.001	1,32 (1,04-1,61)
OKS – Pain component	54.43 (1.48)	114	75.31 (1.52)	114	-20.89 (-23.57--18.2)	<0.001	<0.001	1,3 (1,02-1,59)
OKS – Functional component	52.32 (1.54)	114	72.63 (1.56)	114	-20.31 (-23.31--17.3)	<0.001	<0.001	1,23 (0,94-1,51)
OKS – Pain (protocol)	14.68 (3.05)	114	10.36 (3.31)	114	4.32 (3.76-4.89)	<0.001	<0.001	1,36 (1,07-1,65)
OKS- Range of motion (protocol)	11.9 (2.58)	114	8.66 (2.76)	114	3.25 (2.74-3.75)	<0.001	<0.001	1,21 (0,93-1,5)
OKS – Walking (protocol)	12.98 (3.6)	114	9.24 (3.28)	114	3.75 (3.17-4.32)	<0.001	<0.001	1,09 (0,81-1,36)

6.2.3 Paired data tests: Visit 1 - Visit 2

Table 106. Paired data tests: Baseline Visit 1 - Visit 2 – SUPLASYN

SUPLASYN	One month after injection		Six month after injection		Paired differences			Cohen's d (IC95%)
	Mean (SD)	N	Mean (SD)	N	Mean (IC95%)	p t-test	p-Wilcoxon	
OKS	33.8 (1.07)	116	36.09 (0.97)	116	-2.29 (-3.08--1.5)	<0.001	<0.001	0,21 (-0,05-0,47)
OKS – Pain component	71.71 (2.29)	116	76.29 (2.04)	116	-4.59 (-6.4--2.77)	<0.001	<0.001	0,2 (-0,06-0,45)
OKS – Functional component	68.58 (2.22)	116	73.62 (2.04)	116	-5.04 (-6.69--3.39)	<0.001	<0.001	0,22 (-0,04-0,48)
OKS – Pain (protocol)	10.78 (4.86)	116	9.99 (4.58)	116	0.79 (0.39-1.2)	<0.001	<0.001	0,17 (-0,09-0,43)
OKS- Range of motion (protocol)	9.09 (3.82)	116	8.27 (3.49)	116	0.82 (0.56-1.08)	<0.001	<0.001	0,22 (-0,03-0,48)
OKS – Walking (protocol)	10.46 (4.78)	116	9.43 (4.18)	116	1.03 (0.68-1.37)	<0.001	<0.001	0,23 (-0,03-0,49)

Table 107. Paired data tests: Visit 1 – Visit 2 - SUPLASYN 1-SHOT

SUPLASYN 1-SHOT	One month after injection		Six month after injection		Paired differences			Cohen's d (IC95%)
	Mean (SD)	N	Mean (SD)	N	Mean (IC95%)	p t-test	p-Wilcoxon	
OKS	34.96 (0.69)	113	35.74 (0.7)	113	-0.79 (-1.83-0.25)	0.14	0,23	0,11 (-0,15-0,37)
OKS – Pain component	74.31 (1.45)	113	75.6 (1.5)	113	-1.3 (-3.66-1.07)	0.28	0,42	0,08 (-0,18-0,34)
OKS – Functional component	70.71 (1.54)	113	72.83 (1.56)	113	-2.12 (-4.38-0.13)	0.06	0,12	0,13 (-0,13-0,39)
OKS – Pain (protocol)	10.57 (3.2)	113	10.32 (3.29)	113	0.25 (-0.26-0.75)	0.33	0,55	0,08 (-0,18-0,34)
OKS- Range of motion (protocol)	8.76 (2.66)	113	8.63 (2.76)	113	0.13 (-0.27-0.53)	0.51	0,65	0,05 (-0,21-0,31)
OKS – Walking (protocol)	9.52 (3.2)	113	9.18 (3.23)	113	0.35 (-0.14-0.83)	0.16	0,25	0,11 (-0,15-0,37)

6.2.4 Comparison between SUPLASYN vs SUPLASYN 1-SHOT

Table 108. Comparison between SUPLASYN vs SUPLASYN 1-SHOT: Baseline Visit

	SUPLASYN		SUPLASYN 1-SHOT		Total		Inferences	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	p-ANOVA	p-MW
OKS	23.53 (11.17)	116	25.24 (7.73)	123	24.41 (9.57)	239	0.17	0.15
OKS – Pain component	49.46 (24.71)	116	53.64 (16.43)	123	51.61 (20.92)	239	0.12	0.21
OKS – Functional component	48.36 (22.04)	116	51.1 (17.09)	123	49.77 (19.65)	239	0.28	0.15
OKS – Pain (protocol)	15.29 (4.86)	116	14.85 (3.19)	123	15.06 (4.09)	239	0.40	0.48
OKS- Range of motion (protocol)	12.43 (3.5)	116	12.1 (2.68)	123	12.26 (3.1)	239	0.41	0.27
OKS – Walking (protocol)	14.16 (5.17)	116	13.15 (3.69)	123	13.64 (4.49)	239	0.08	0.09

Table 109. Comparison between SUPLASYN vs SUPLASYN 1-SHOT: Visit 1

	SUPLASYN		SUPLASYN 1-SHOT		Total		Inferences	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	p-ANOVA	p-MW
OKS	33.8 (11.48)	116	34.52 (7.37)	121	34.17 (9.59)	237	0.57	0.86
OKS – Pain component	71.71 (24.61)	116	73.49 (15.54)	121	72.62 (20.47)	237	0.50	0.71
OKS – Functional component	68.58 (23.94)	116	69.67 (16.64)	121	69.14 (20.5)	237	0.68	0.86
OKS – Pain (protocol)	10.78 (4.86)	116	10.72 (3.24)	121	10.75 (4.11)	237	0.9	0.42
OKS- Range of motion (protocol)	9.09 (3.82)	116	8.9 (2.68)	121	8.99 (3.28)	237	0.66	0.81
OKS – Walking (protocol)	10.46 (4.78)	116	9.72 (3.22)	121	10.08 (4.07)	237	0.16	0.48

Table 110. Comparison between SUPLASYN vs SUPLASYN 1-SHOT: Visit 2

	SUPLASYN		SUPLASYN 1-SHOT		Total		Inferences	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	p-ANOVA	p-MW
OKS	36.09 (10.47)	116	35.62 (7.57)	114	35.86 (9.13)	230	0.70	0.2
OKS – Pain component	76.29 (21.97)	116	75.31 (16.2)	114	75.81 (19.29)	230	0.70	0.14
OKS – Functional component	73.62 (22.02)	116	72.63 (16.69)	114	73.13 (19.52)	230	0.70	0.47
OKS – Pain (protocol)	9.99 (4.58)	116	10.36 (3.31)	114	10.17 (4)	230	0.49	0.07
OKS- Range of motion (protocol)	8.27 (3.49)	116	8.66 (2.76)	114	8.46 (3.15)	230	0.35	0.2
OKS – Walking (protocol)	9.43 (4.18)	116	9.24 (3.28)	114	9.33 (3.76)	230	0.70	0.80

6.2.5 Friedman test: Oxford Knee Score

Graphic 90. Oxford Knee Score

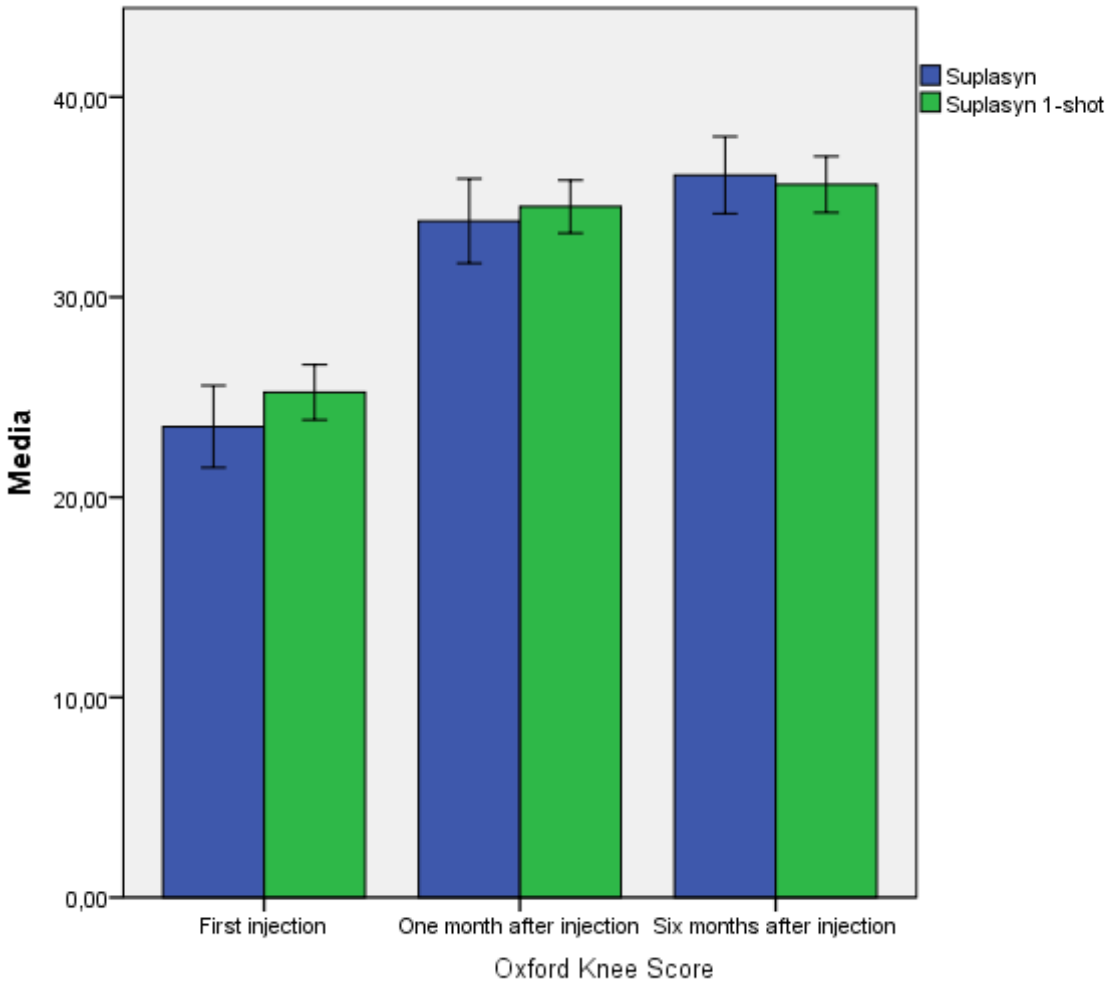


Table 111. Oxford Knee Score

SUPLASYN	**N**	116
	Asymp. Sig.	<0.001
SUPLASYN 1-SHOT	**N**	113
	Asymp. Sig.	<0.001

6.2.6 Friedman test: Oxford Knee Score – Pain component

Graphic 91. Oxford Knee Score – Pain component

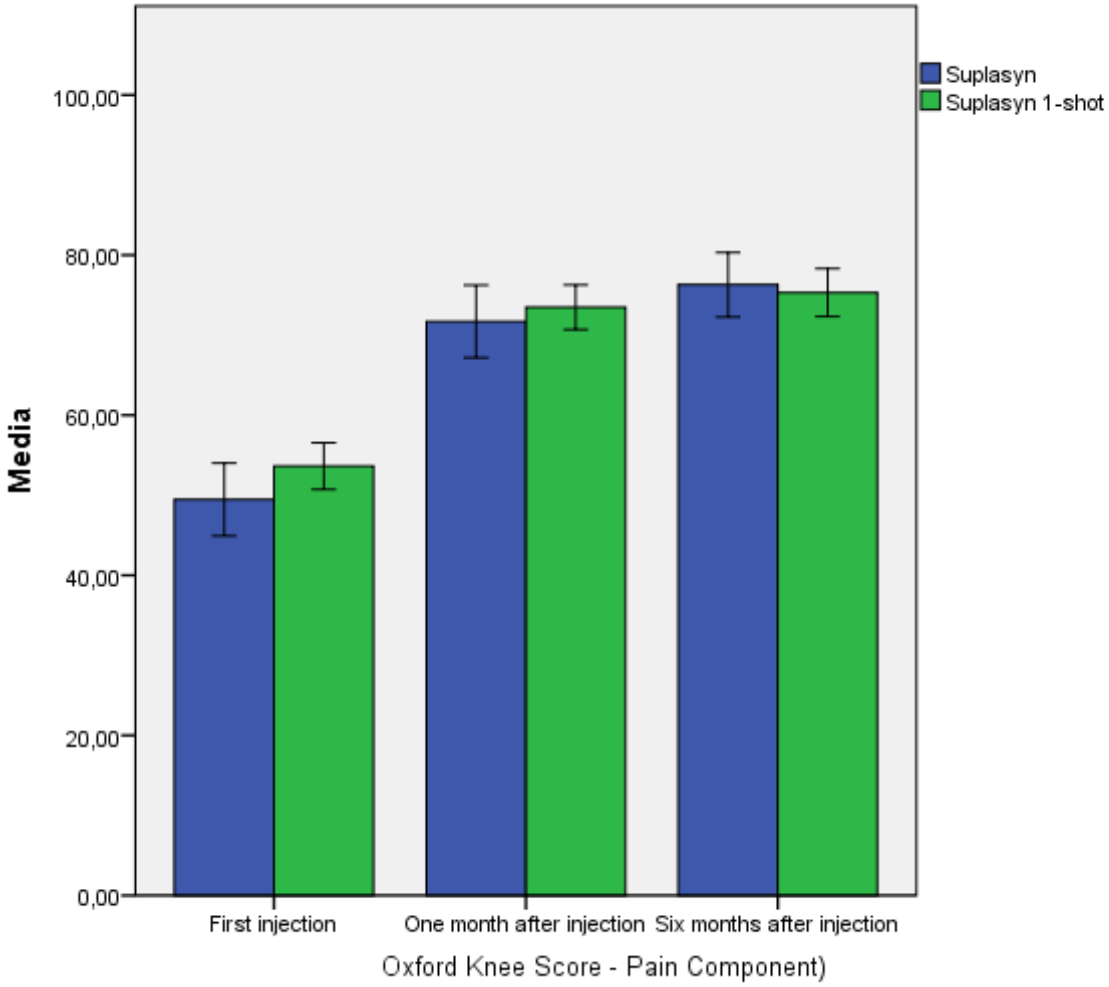


Table 112. Oxford Knee Score – Pain component

SUPLASYN	**N**	116
	Asymp. Sig.	<0.001
SUPLASYN 1-SHOT	**N**	113
	Asymp. Sig.	<0.001

6.2.7 Friedman test: Oxford Knee Score – Functional component

Graphic 92. Oxford Knee Score – Functional component

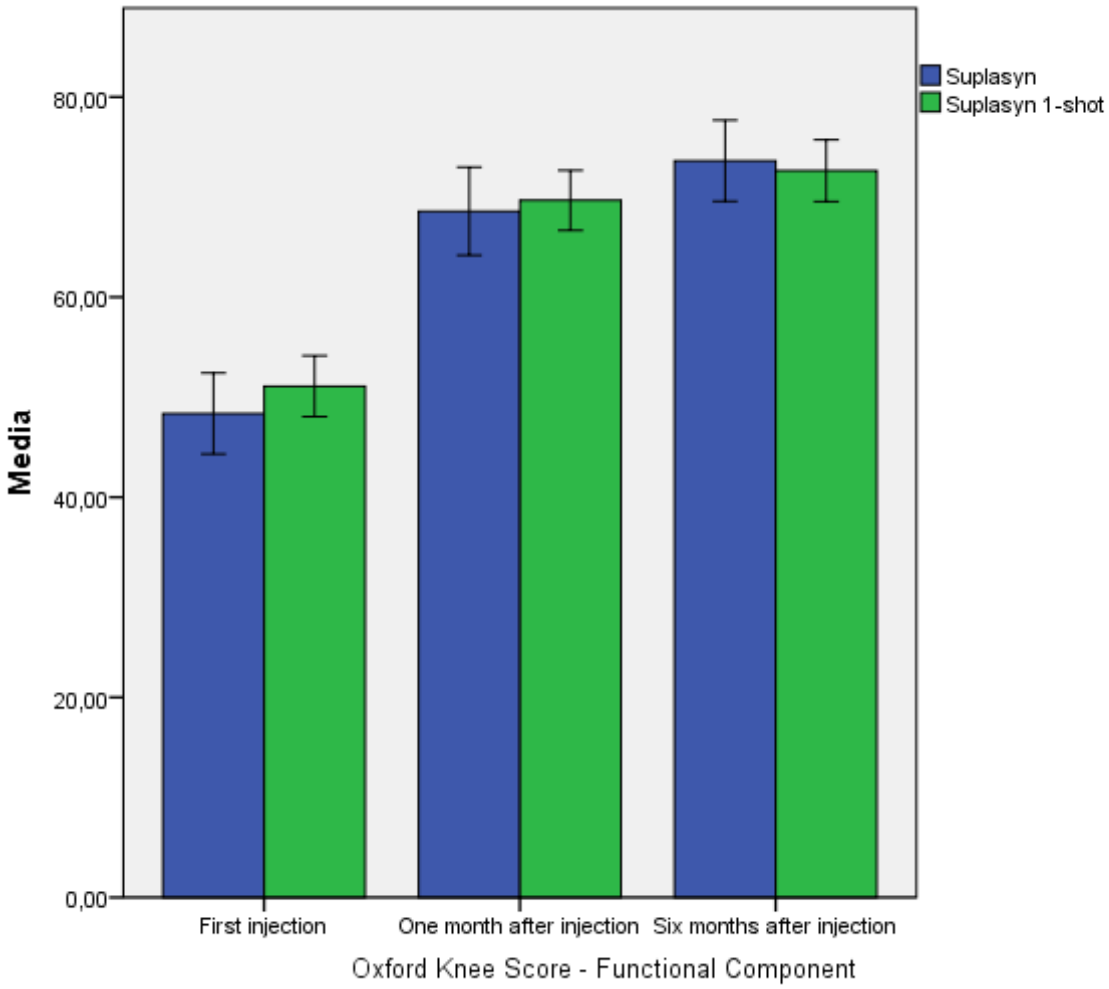


Table 113. Oxford Knee Score – Functional component

SUPLASYN	**N**	116
	Asymp. Sig.	<0.001
SUPLASYN 1-SHOT	**N**	113
	Asymp. Sig.	<0.001

6.4.8 Friedman test: Oxford Knee Score – Pain (protocol)

Graphic 93. Oxford Knee Score - Pain

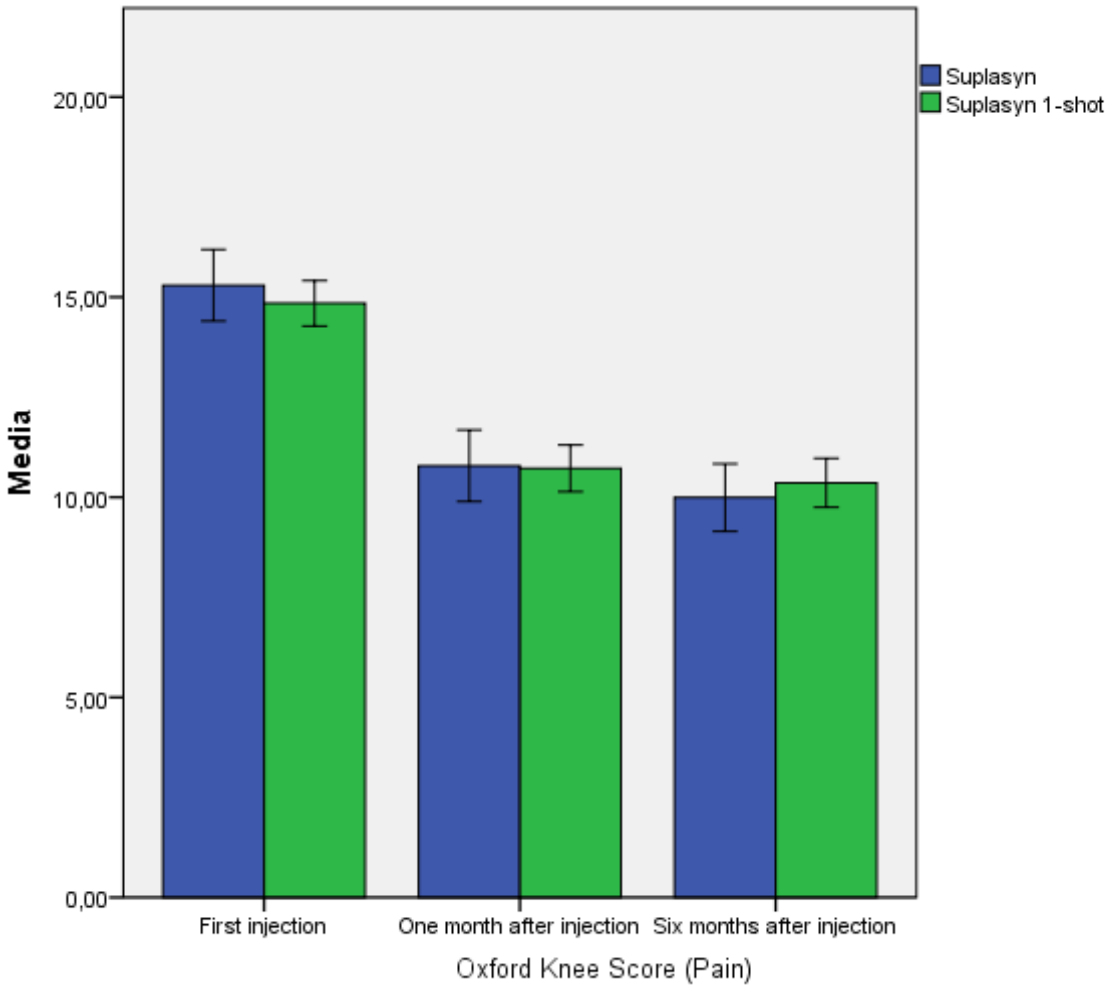


Table 114. Oxford Knee Score - Pain

SUPLASYN	**N**	116
	Asymp. Sig.	<0.001
SUPLASYN 1-SHOT	**N**	113
	Asymp. Sig.	<0.001

6.4.9 Friedman test: Oxford Knee Score – Range of Motion (protocol)

Graphic 94. Oxford Knee Score – Range of motion

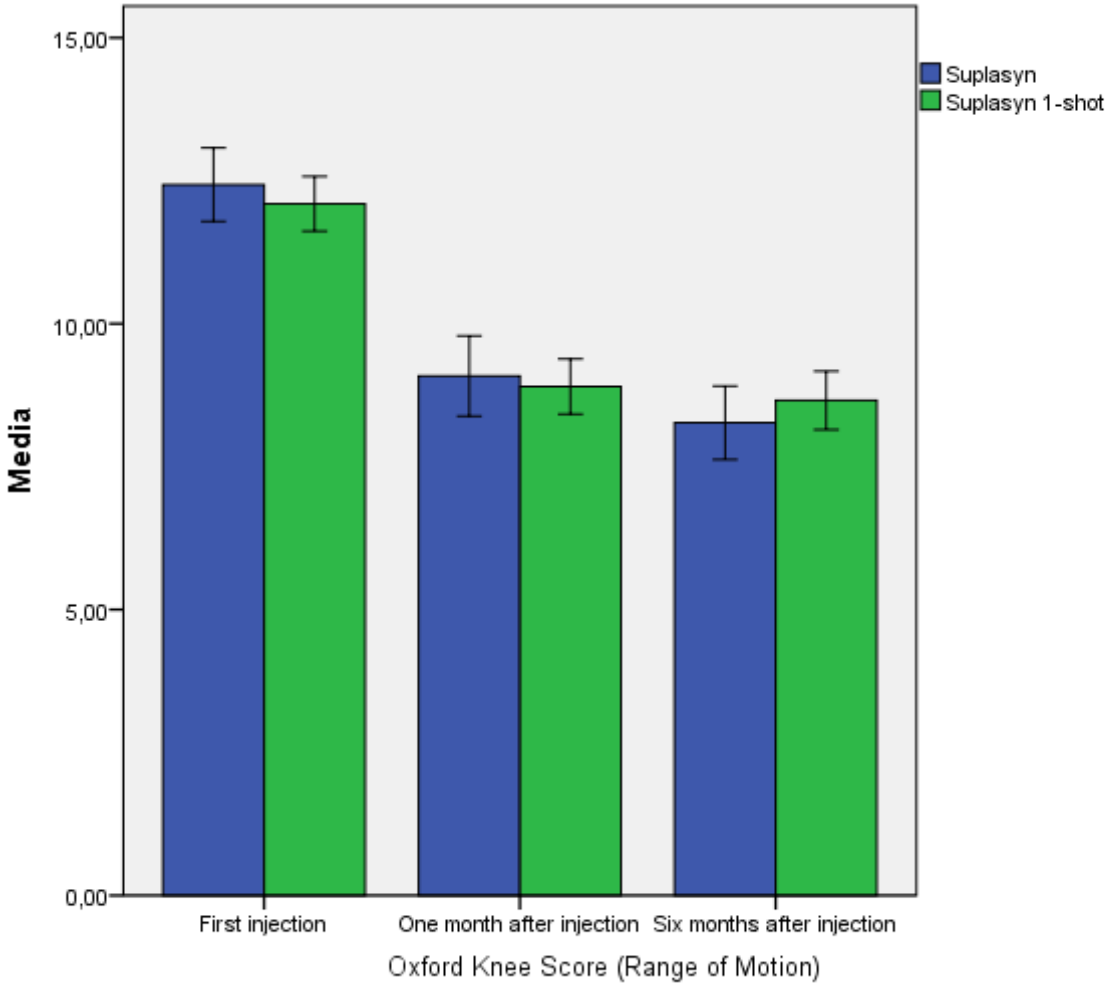


Table 115. Oxford Knee Score - Range of Motion

SUPLASYN	**N**	116
	Asymp. Sig.	<0.001
SUPLASYN 1-SHOT	**N**	113
	Asymp. Sig.	<0.001

6.4.10 Friedman test: Oxford Knee Score – Walking (protocol)

Graphic 95. Oxford Knee Score – Walking

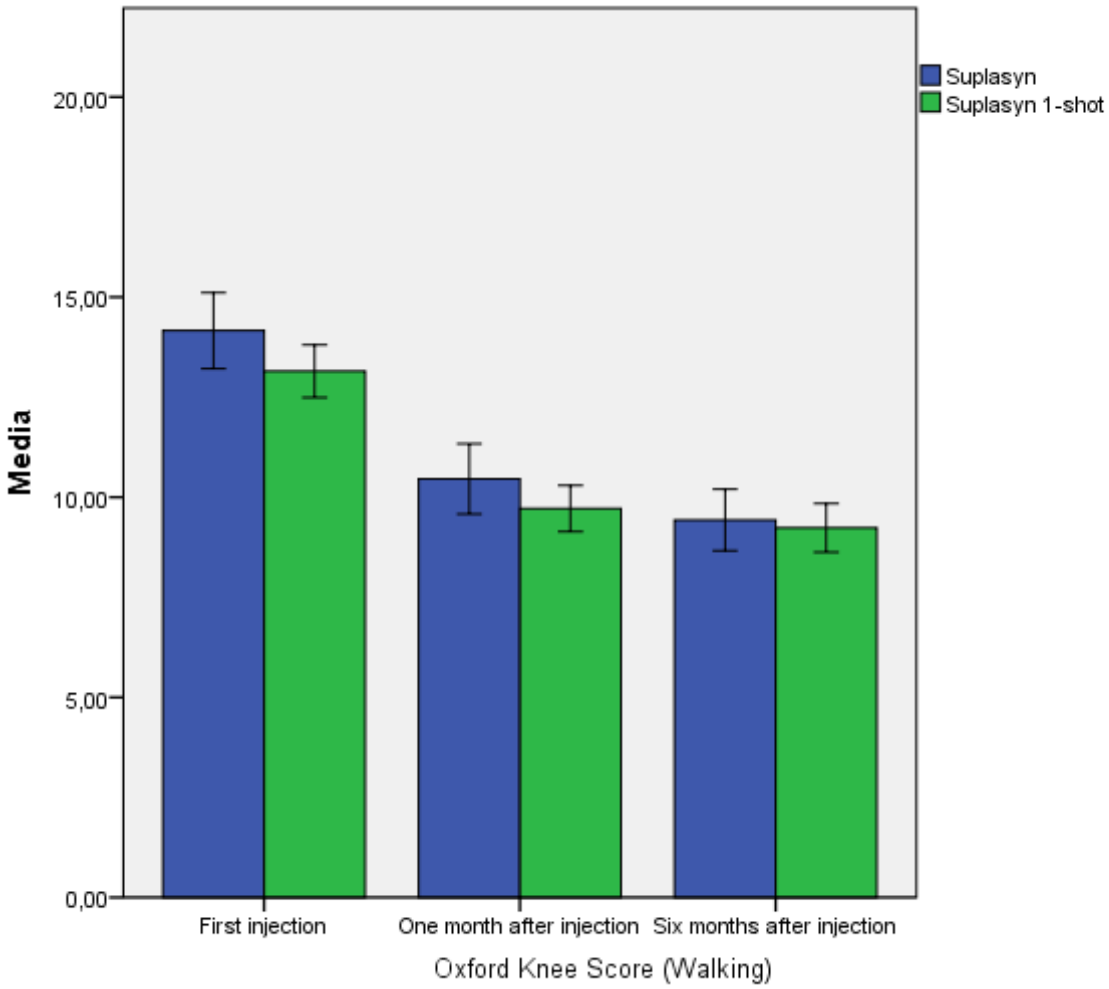


Table 116. Oxford Knee Score - Walking

SUPLASYN	**N**	116
	Asymp. Sig.	<0.001
SUPLASYN 1-SHOT	**N**	113
	Asymp. Sig.	<0.001

7 Non-Inferiority– Equivalence Analysis

7.1 Non-Inferiority– Equivalence Table

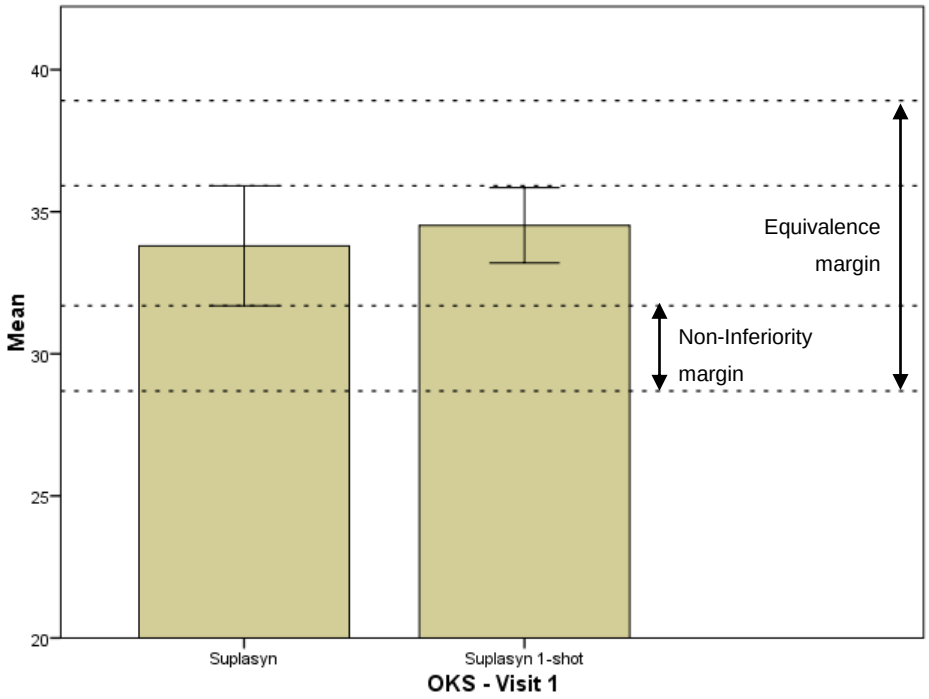
Table 117. Non-Inferiority– Equivalence

		N	Mean (SD)	95% Confidence Interval for Mean		p	Non-Inferiority	Equivalence
				Lower Bound	Upper Bound			
Oxford Knee Score - One month after first injection	**SUPLASYN**	116	33.8 (11.48)	31.69	35.91	0.56	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	121	34.52 (7.37)	33.19	35.85			
	Total	237	34.17 (9.59)	32.94	35.40			
Oxford Knee Score - Six months after first injection	**SUPLASYN**	116	36.09 (10.47)	34.17	38.02	0.70	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	114	35.62 (7.57)	34.22	37.03			
	Total	230	35.86 (9.13)	34.67	37.05			
OKS pain component - One month after first injection	**SUPLASYN**	116	71.71 (24.61)	67.18	76.23	0.50	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	121	73.49 (15.54)	70.70	76.29			
	Total	237	72.62 (20.47)	70.00	75.24			
OKS pain component - Six months after first injection	**SUPLASYN**	116	76.29 (21.97)	72.25	80.33	0.70	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	114	75.31 (16.2)	72.31	78.32			
	Total	230	75.81 (19.29)	73.30	78.31			
OKS functional component - One month after first injection	**SUPLASYN**	116	68.58 (23.94)	64.18	72.98	0.68	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	121	69.67 (16.64)	66.67	72.66			
	Total	237	69.14 (20.5)	66.51	71.76			
OKS functional component - Six months after first injection	**SUPLASYN**	116	73.62 (22.02)	69.57	77.67	0.70	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	114	72.63 (16.69)	69.54	75.73			
	Total	230	73.13 (19.52)	70.59	75.67			
Oxford Knee Score (Pain) - One month after first injection	**SUPLASYN**	116	10.78 (4.86)	9.89	11.68	0.90	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	121	10.72 (3.24)	10.14	11.30			
	Total	237	10.75 (4.11)	10.23	11.28			
Oxford Knee Score (Pain) - Six months after first injection	**SUPLASYN**	116	9.99 (4.58)	9.15	10.83	0.49	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	114	10.36 (3.31)	9.75	10.97			
	Total	230	10.17 (4)	9.65	10.69			

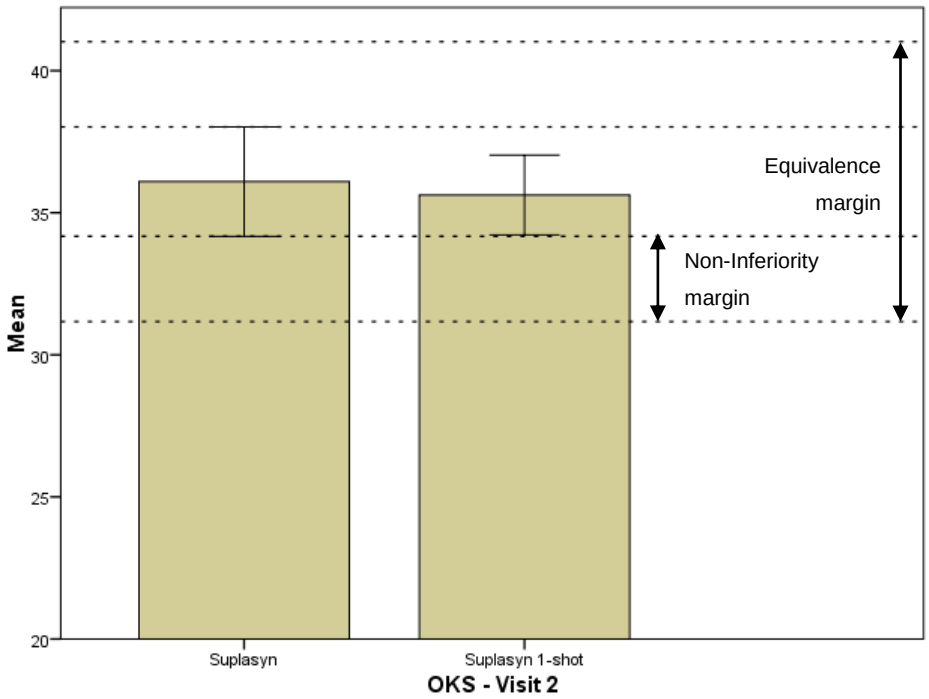
Oxford Knee Score (Walking) - One month after first injection	**SUPLASYN**	116	10.46 (4.78)	9.58	11.34	0.16	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	121	9.72 (3.22)	9.14	10.30			
	Total	237	10.08 (4.07)	9.56	10.60			
Oxford Knee Score (Walking) - Six months after first injection	**SUPLASYN**	116	9.43 (4.18)	8.66	10.20	0.70	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	114	9.24 (3.28)	8.63	9.85			
	Total	230	9.33 (3.76)	8.85	9.82			
Oxford Knee Score (Range of motion) - One month after first injection	**SUPLASYN**	116	9.09 (3.82)	8.38	9.79	0.66	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	121	8.9 (2.68)	8.42	9.38			
	Total	237	8.99 (3.28)	8.57	9.41			
Oxford Knee Score (Range of motion) - Six months after first injection	**SUPLASYN**	116	8.27 (3.49)	7.62	8.91	0.35	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	114	8.66 (2.76)	8.14	9.17			
	Total	230	8.46 (3.15)	8.05	8.87			
Perceived pain during daily activities lies - One month after first injection	**SUPLASYN**	113	3.58 (2.17)	3.17	3.98	0.76	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	120	3.5 (1.52)	3.23	3.78			
	Total	233	3.54 (1.86)	3.30	3.78			
Perceived pain during daily activities lies - Six months after first injection	**SUPLASYN**	109	3.25 (2.26)	2.82	3.68	0.90	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	111	3.21 (1.77)	2.88	3.55			
	Total	220	3.23 (2.02)	2.96	3.50			
Perceived pain at rest/night lies - One month after first injection	**SUPLASYN**	107	1.76 (2.01)	1.37	2.14	0.95	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	118	1.74 (1.46)	1.47	2.01			
	Total	225	1.75 (1.74)	1.52	1.98			
Perceived pain at rest/night lies - Six months after first injection	**SUPLASYN**	95	1.82 (2.05)	1.40	2.23	0.95	**Non-Inferior**	**Equivalent**
	SUPLASYN 1-SHOT	109	1.83 (1.76)	1.50	2.17			
	Total	204	1.83 (1.89)	1.56	2.09			

7.3 Non-Inferiority– Equivalence Graphics

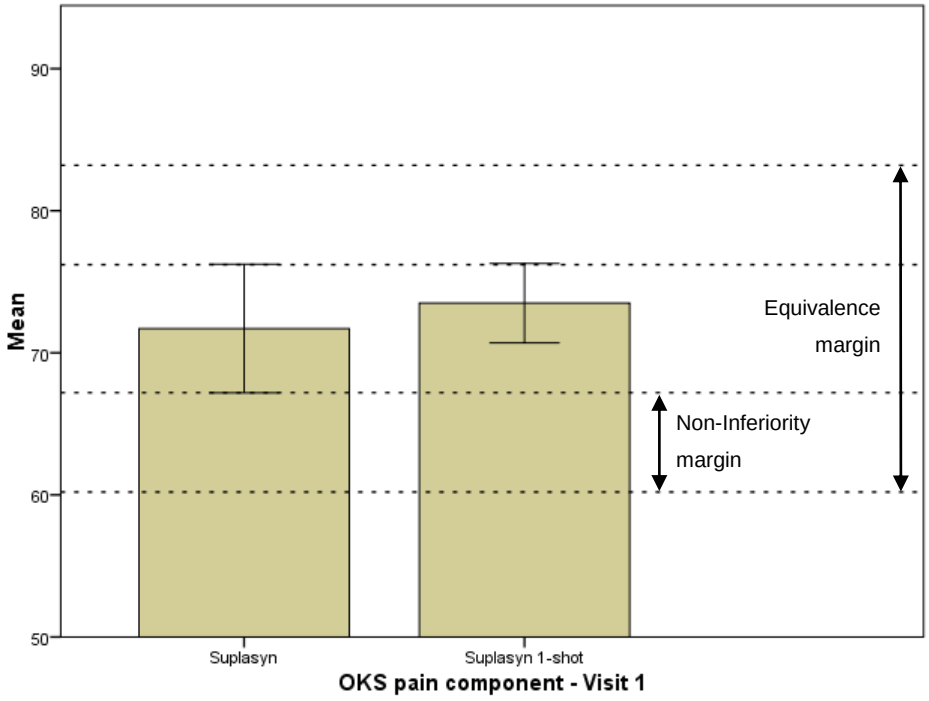
Graphic 96: Oxford Knee Score Visit 1



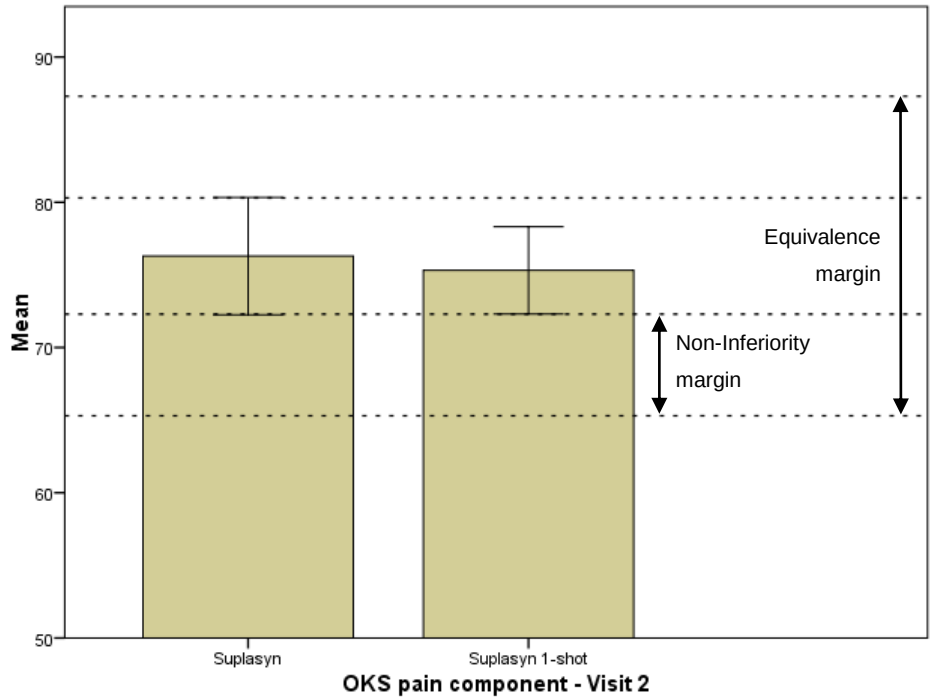
Graphic 97: Oxford Knee Score Visit 2



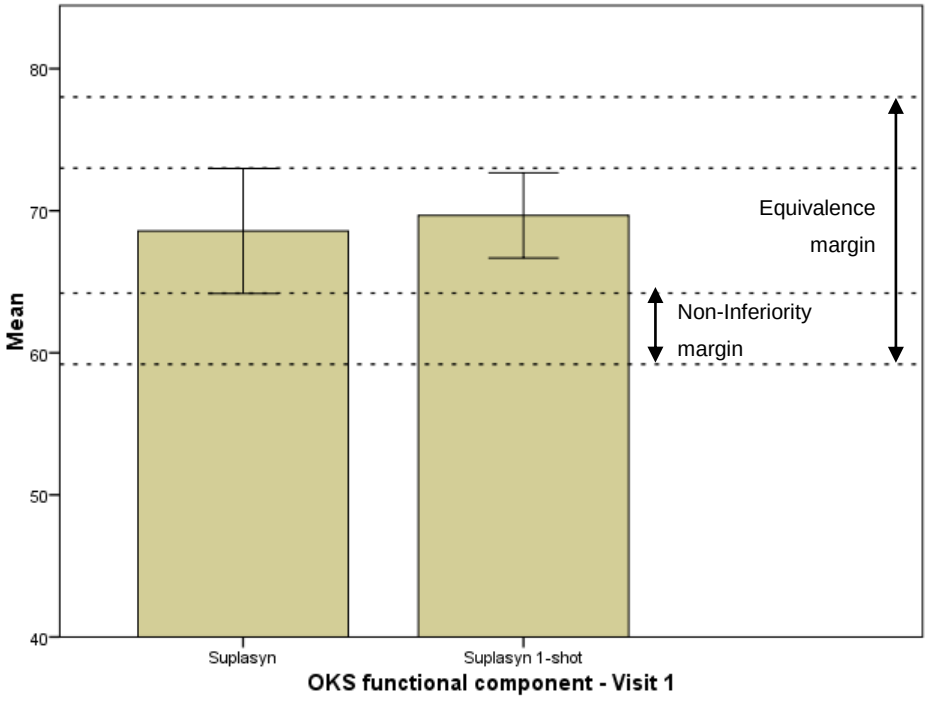
Graphic 98: Oxford Knee Score Pain component - Visit 1



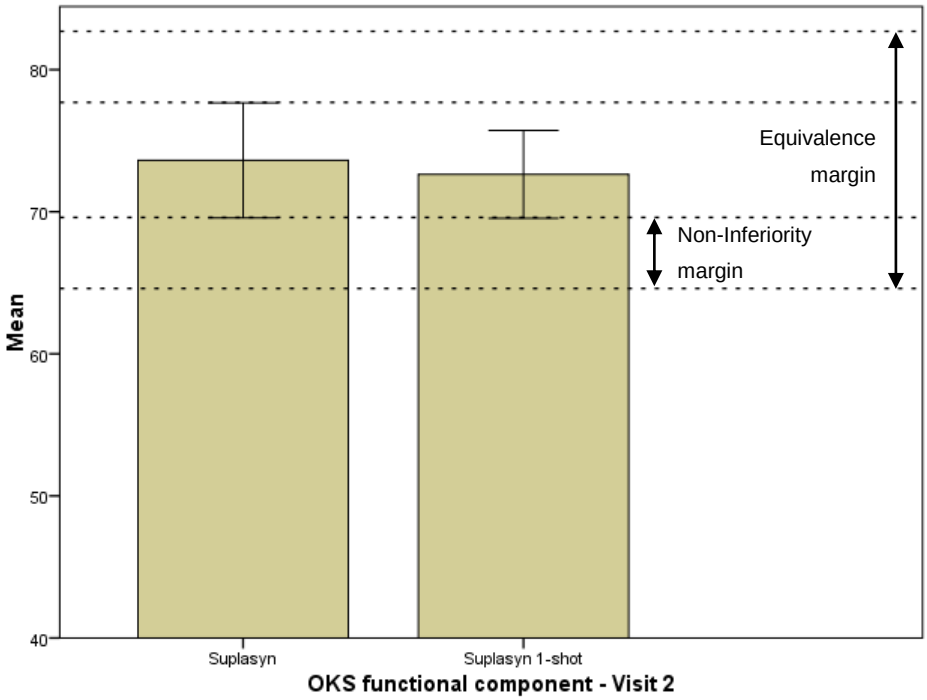
Graphic 99: Oxford Knee Score Pain component - Visit 2



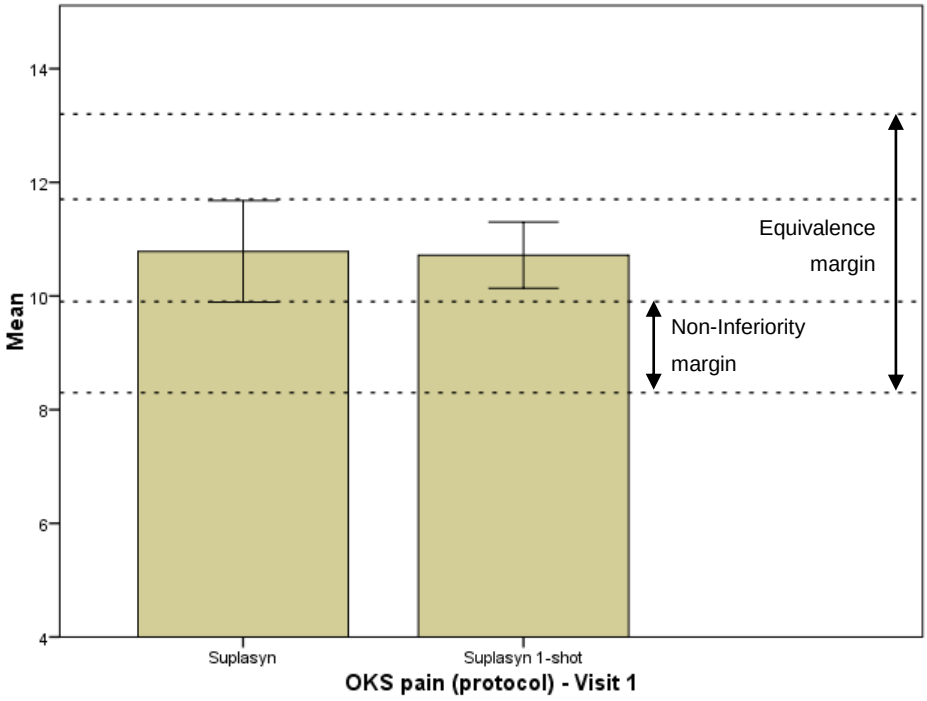
Graphic 100: Oxford Knee Score Functional component - Visit 1



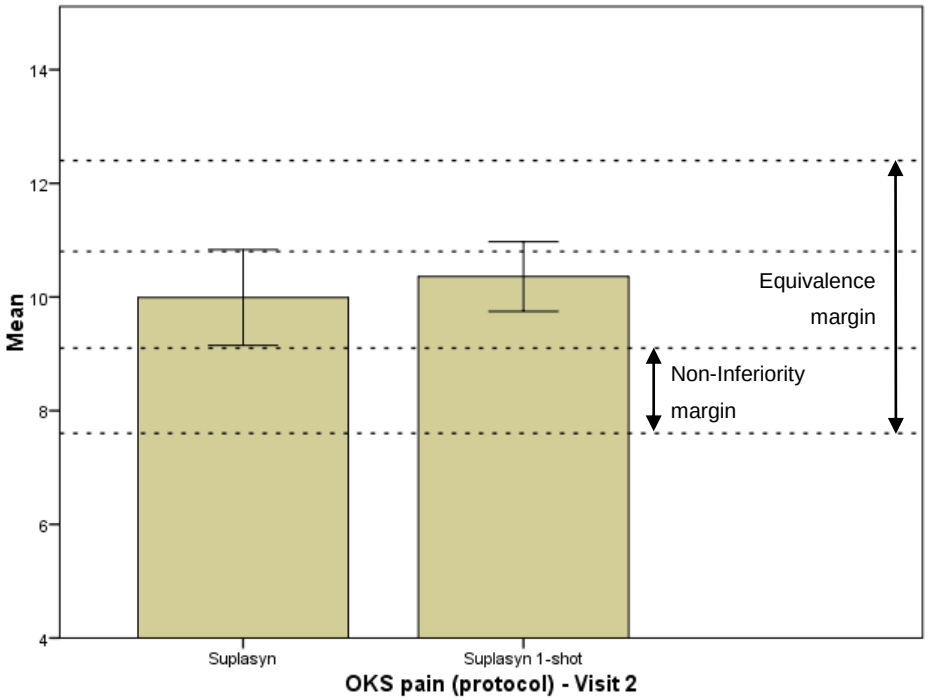
Graphic 101: Oxford Knee Score Functional component - Visit 2



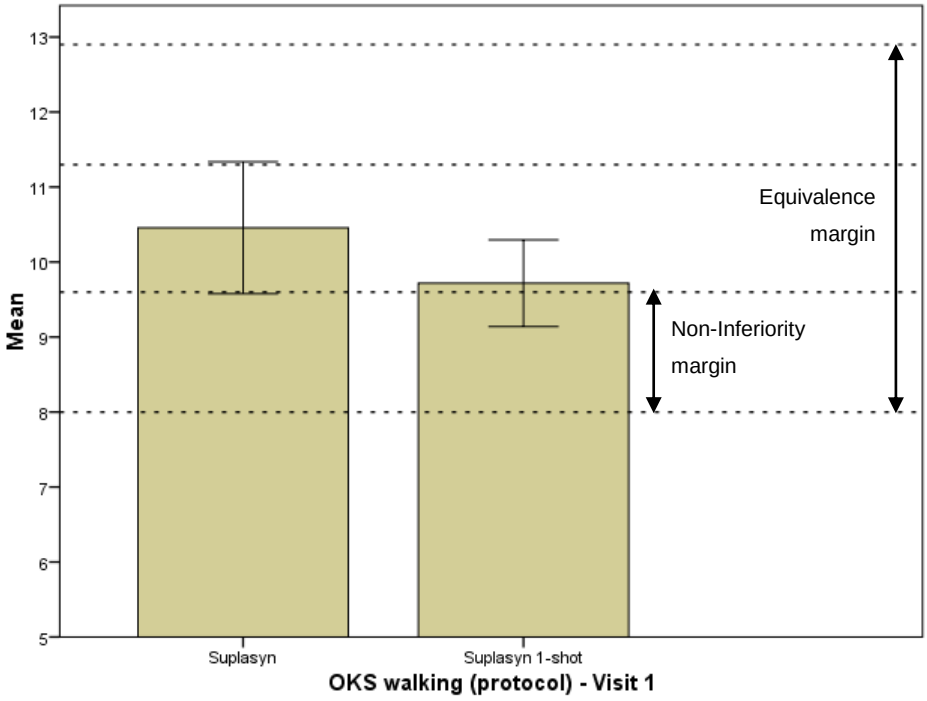
Graphic 102: Oxford Knee Score Pain (protocol) - Visit 1



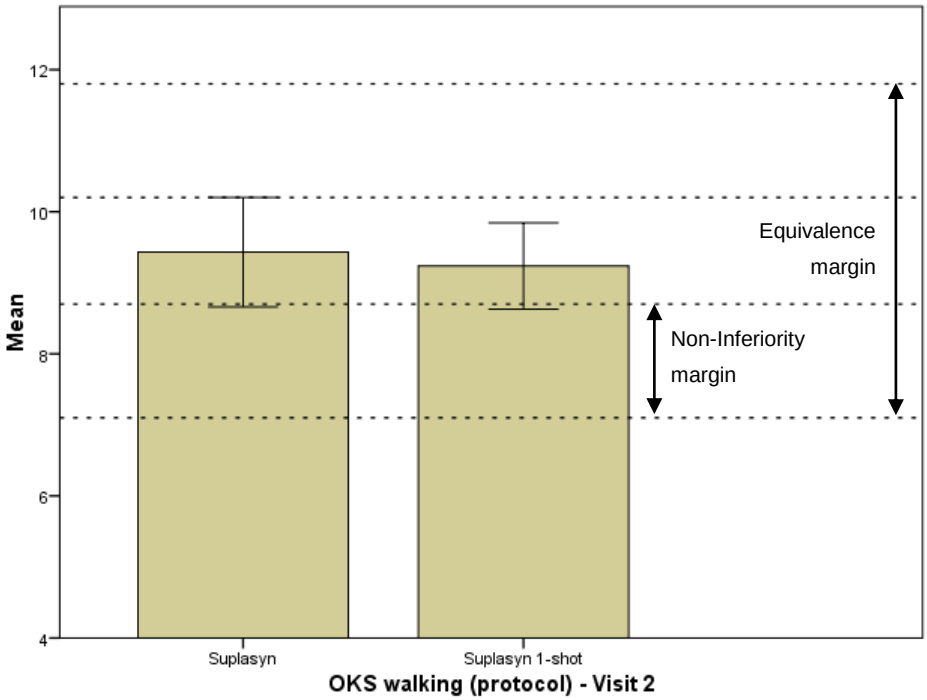
Graphic 103: Oxford Knee Score Pain (protocol) - Visit 2



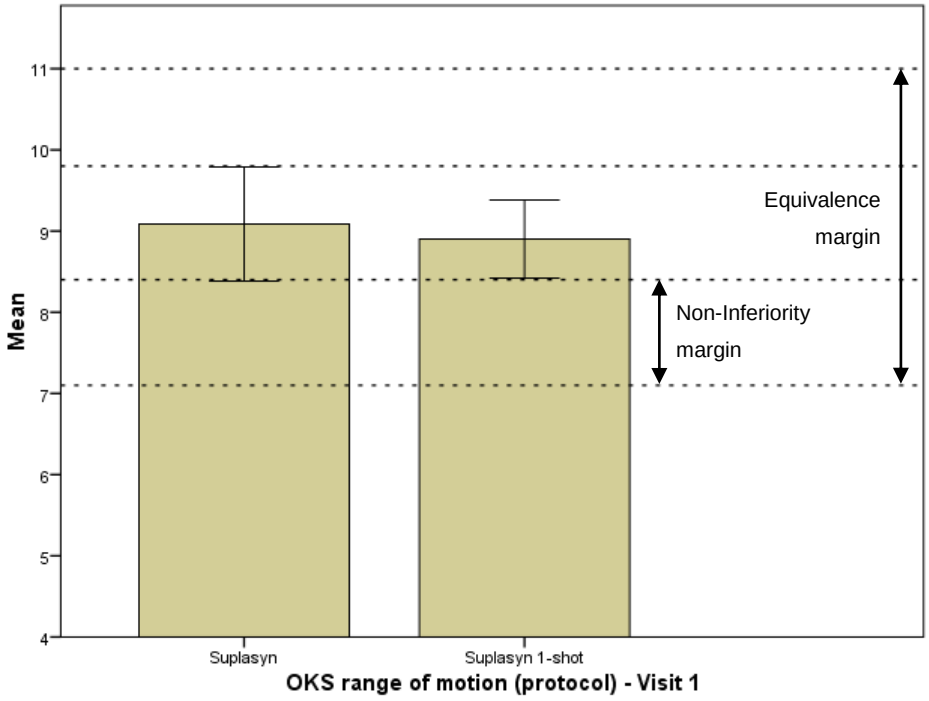
Graphic 104: Oxford Knee Score Walking (protocol) - Visit 1



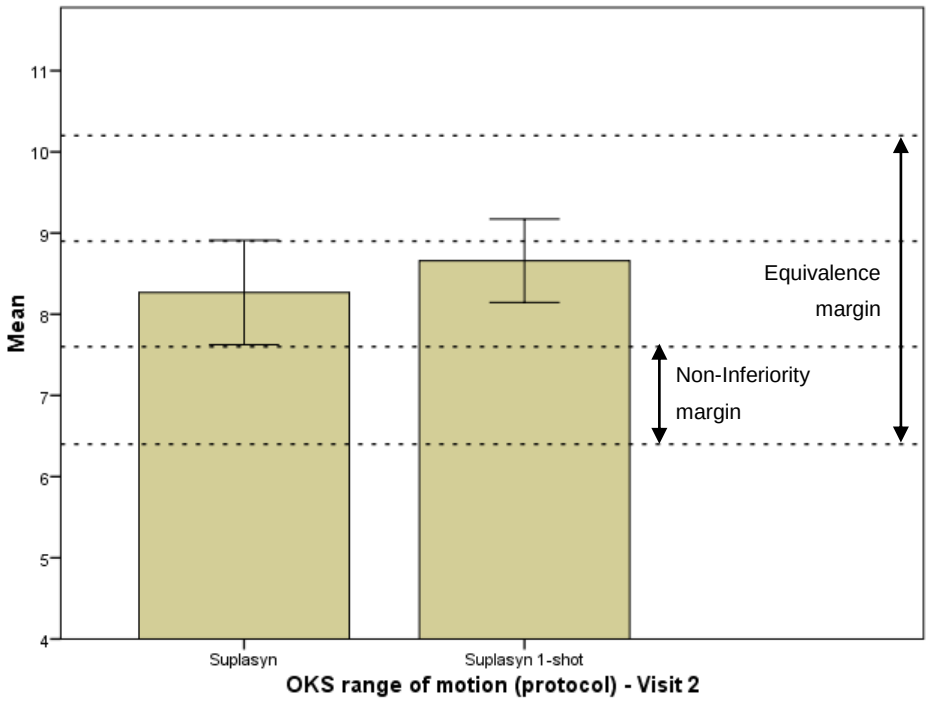
Graphic 105: Oxford Knee Score Walking (protocol) - Visit 2



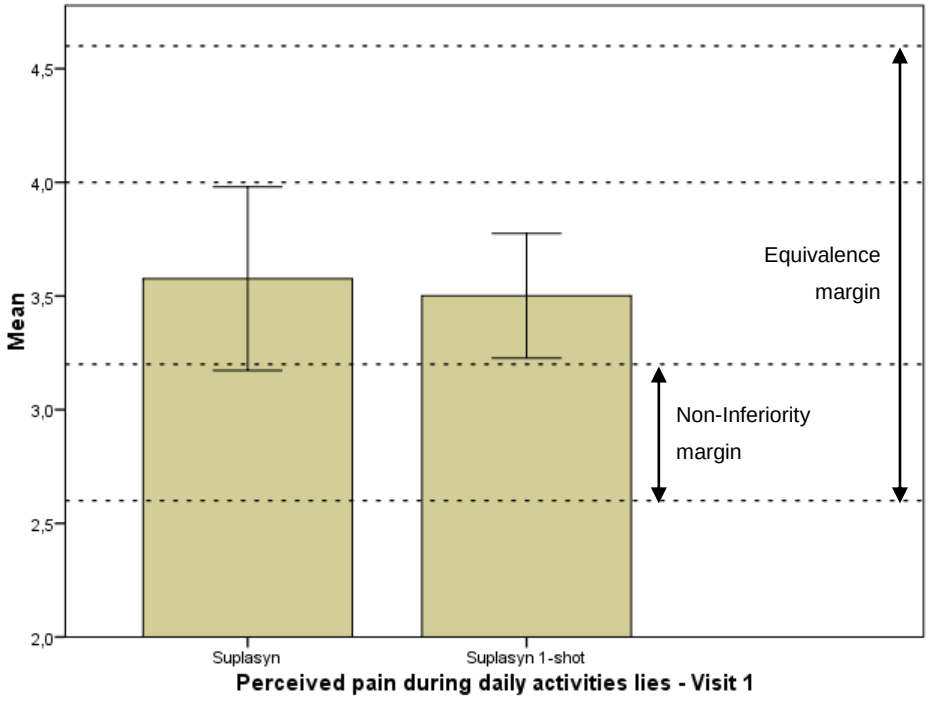
Graphic 106: Oxford Knee Score Range of motion (protocol) - Visit 1



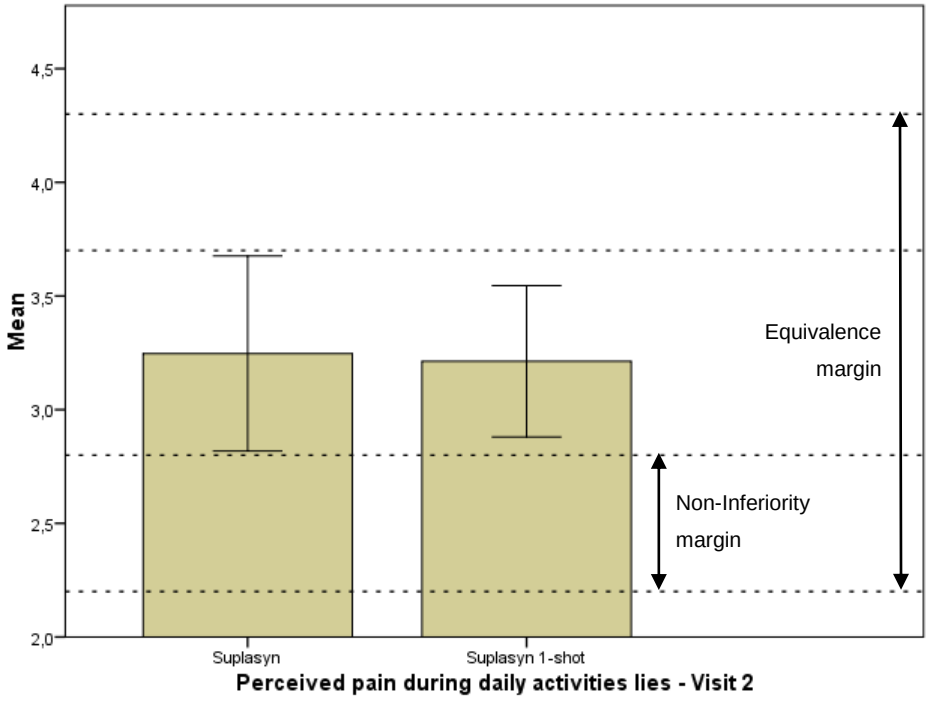
Graphic 107: Oxford Knee Score Range of motion (protocol) - Visit 2



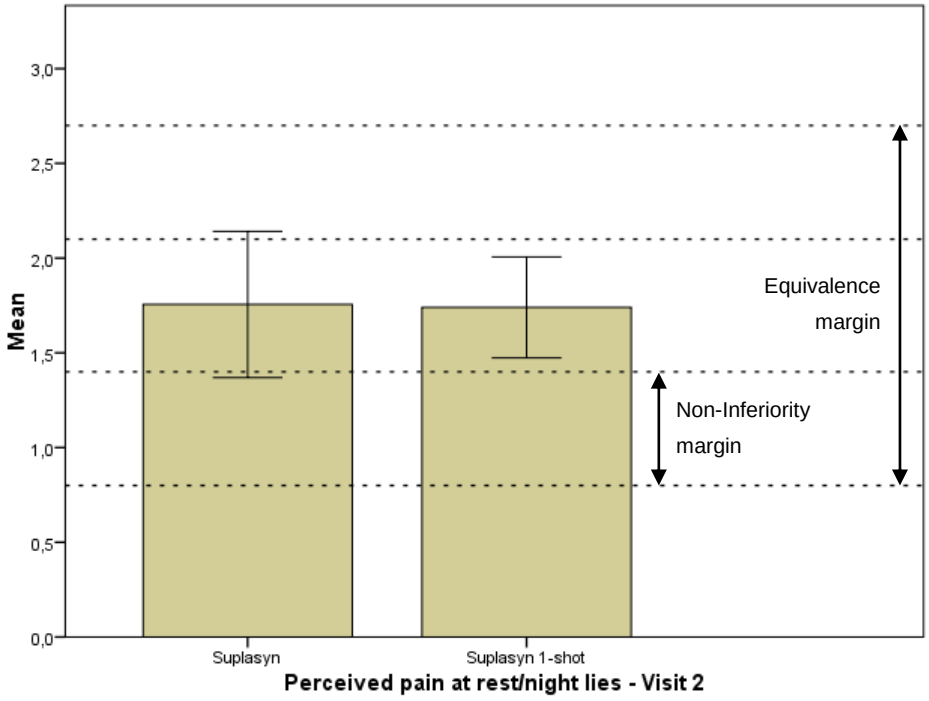
Graphic 108: Perceived pain during activities lies - Visit 1



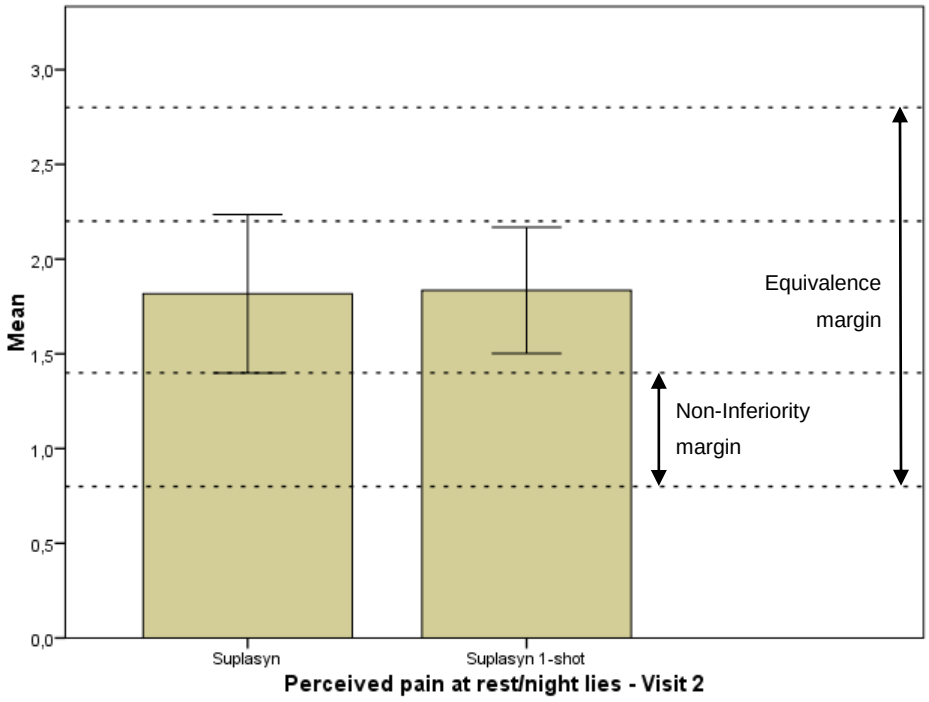
Graphic 109: Perceived pain during activities lies - Visit 2



Graphic 110: Perceived pain at rest/night lies - Visit 1



Graphic 111: Perceived pain at rest/night lies - Visit 2



8 Conclusions

Samples were found to be homogeneous at baseline with no significant differences between groups in patients' characteristics.

Both treatment groups showed to be notably effective in pain reduction and functional improvement, with large effect sizes (Cohen's d) between 0.9 and 1.2.

When performing the analysis of non-inferiority and equivalence, we found equivalence between the two products in each variable studied, concluding that the two tratments are equivalent and not inferior to each other.

9 Bibliography

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10 Anex

10.1 ESTIK Protocol

CONFIDENCIAL

The Effectiveness and Safety of Triple 2ml Hyaluronic Acid Intra-articular Injection (Suplasyn®) in Managing Symptomatic Primary Osteoarthritis of the Knee in Real-life Practice: ESTIK Survey.

STUDY PROTOCOL

Main Investigator:
Pavel Martinek, MD

SUMMARY

Official Title

The Effectiveness and Safety of Triple 2ml Hyaluronic Acid Intra-articular Injection (Suplasyn®) in Managing Symptomatic Primary Osteoarthritis of the Knee in Real-life Practice: ESTIK Survey.

Responsible Party/Sponsor

Mylan Institutional International
Thurgauerstrasse 40
8050 Zürich, Switzerland

Main investigator/Study Coordinator

Pavel Martinek, MD
Krnov Hospital (Czech Republic)

Study Officials/Investigators

Orthopeadists/Traumatologists

Review Board

All study materials have been approved by the Ethical Committee for Clinical Investigation of the Krnov Hospital (The Czech Republic).

Primary Outcome

To assess changes in clinical outcome of patients with OA recommended with a triple Suplasyn® 2ml injection for viscosupplementation.

Intended Intervention:

Suplasyn® 2ml during 3 weeks for the viscosupplementation of the knee.

Study Type:

Observational, non-interventional, international and multicenter study.

Study Design

Observational Model: Case-Only; Time Perspective: Prospective study

Condition for Study

Osteoarthritis of the Knee.

Study sample

Patients over 18 years old with Primary Knee Osteoarthritis (Kellgren's grades I to III) without effusion.

Data Monitoring

Clever Instruments S.L. will be in charge of logistic and clinical trial monitoring.

Calendar

Study Start Date: June, 2014 – September, 2014

Study Completion Date: December, 2014 - March, 2015

Overall study period will be of 6 months, approximately.

INDEX

1 GENERAL INFORMATION

Official Title

The Effectiveness and Safety of Triple 2ml Hyaluronic Acid Intra-articular Injection (Suplasyn®) in Managing Symptomatic Primary Osteoarthritis of the Knee in Real-life Practice: **ESTIK Survey**.

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Study Officials/Investigators

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Duration of the Study

Intended duration: 6-9 months

Data will be provided by investigators from retrospectively results observed in patients who were previously recommended with viscosupplementation with Suplasyn® between June-September 2014 and December2014-March 2015.

The assignment of the patient to a particular therapeutic strategy should not be decided in advance by this protocol but falls within current practice and the use Suplasyn® was clearly separated from the decision to include the patient's data in this study.

2 BACKGROUND

Osteoarthritis (OA) of the knee is a painful and disabling condition that is becoming more prevalent in patients over 50 years of age that results in symptoms in 10% of people older than 55 years which severely impair up to a quarter overall these patients. (1)

OA is generally treated using conservative measures at initial phases of the disease (2), more frequently with analgesics, topical and oral non-steroidal anti-inflammatory drugs (NSAIDs). However, their long-term use of these agents might different organic risks such as complications in hepatic, cardiovascular, gastrointestinal or renal systems.

In recent years, viscosupplementation has been more often used as a therapeutic modality for the management of knee OA (3,4). Intra-articular injections of Hyaluronic Acid (HA) have shown good safety profiles and efficacy for treating knee OA pain. Recent clinical data have demonstrated that anti-inflammatory and chondroprotective effects of HA viscosupplementation are associated with a significant and maintained reduction on pain up to 14-26 weeks after injection while improving patients' function (5-7), results which show a clear difference compared to the short-term effect of other interventions such as pharmacological treatment with NSAIDs and/or corticosteroid injections.

Viscosupplementation

Viscosupplementation is intended as an alternative of HA's degradation in the synovial fluid of patients affected with knee osteoarthritis by the administration of exogenous HA through intra-articular injection. Viscosupplementation is recommended (6) for the treatment of knee OA by the current Osteoarthritis Research Society International (OARSI) Guidelines and previous practice guidelines (4,8-11) and despite that in other reference documents such as current Clinical Practice Guidelines (CPG) of the American Academy of Orthopaedic Surgeons (AAOS) is not included as a main recommendation(12), this makes reference to published evidence reporting significant improvements on OA symptoms after viscosupplementation. Because of the lack of evidence and the possible discrepancies across studies, conclusion should be as that viscosupplementation may be of significant benefit for *some* patients (13).

Administration of an exogenous HA cannot explain long-term reduction of symptoms, considering that HA has short half-life. HA has biological effects on the inflammatory cells and

stimulates HA production by synovial cells. Its key molecular role in joints' biomechanics explains how a reduction in its concentration and molecular weight greatly alters the properties of synovial fluid, causing cartilage damage and worsening osteoarthritis symptoms (14). Treatment with exogenous HA attempts to restore the elasticity and viscosity of synovial fluid to normal levels, resulting in pain reduction and functional improvement. Different studies have also confirmed that HA interacts with mediators of inflammation and matrix turnover in joint cells. HA has also a biosynthetic chondroprotective effect (15-20).

Identification of CD44, a glycoprotein expressed on the cell surface of chondrocytes, may explain HA interaction with chondrocytes since CD44 is considered a HA's receptor at the chondrocyte cell surface so the provision of exogenous HA into articular cartilage is facilitated through this receptors (21,22).

Triple versus Single Injection

Study assessing five different dosing regimens of viscosupplementation suggests that 3 x 2ml injections one week apart are efficacious and well tolerated (25). Multidosage viscosupplementation (3-6 injections) still remains a golden standard if choosing the viscosupplementation as a treatment for knee OA.

The single injection represents a new alternative to the three injections treatment regimen with documented statistically and clinically significant improvements (30) both in pain and physical function in patients with knee OA (23), however its efficacy, safety and long-term effect should be studied in order to establish if this newly introduced approach is comparable with the proven triple injections regimen (26).

Suplasyn® 2ml and 1-shot (6ml)

Suplasyn® is a low-intermediate molecular weight HA (500-1000 kDa) product which is safe and well tolerated (24). Suplasyn® is a CE marked Medical Device (CE0473) and is approved by in several countries for the treatment of pain associated with knee osteoarthritis. The recommended treatment regimen for the treatment of knee osteoarthritis pain is one 2 ml intra-articular injection per week for three consecutive weeks (28) or a single injection of 6ml (33,34).

Both presentations are supplied as pre-filled syringes containing 20mg/2ml of sodium hyaluronate which is administered according to a dosing regimen of one injection per week for three to six consecutive weeks.

Suplasyn® has shown to be more effective than placebo on pain and function in knee osteoarthritis (24) with similar efficacy when compared to NSAIDs (27) and with maintained effects over the long term (28). These studies also demonstrated its excellent safety profile.

Suplasyn® has also demonstrated useful health economic benefits with a reduction in the costs of management of knee OA during the 26-weeks following the course of viscosupplementation (29).

Study Rationale

The current study is designed to assess the effectiveness and safety of Suplasyn® 2ml injections in a 26-week, international, multicenter, non-interventional observational study of patients recommended with one 2 ml intra-articular injection of Suplasyn® per week for three consecutive weeks with for the treatment of knee osteoarthritis. The intention is to assess the efficacy and safety of the treatment in real-life practice. Our primary target is to obtain and verify long-term outcomes from a naturalistic primary care experience.

Rationale for using viscosupplementation is to restore the protective viscoelasticity of synovial hyaluronic acid, decrease pain and improve mobility. Immediate benefit of viscosupplementation is the relief of pain while long-term benefits results are believed to include the return of joint mobility by the restoration of trans-synovial flow and the metabolic and rheological homeostasis of the joint (31). Short duration of HA within the joint does not fully explain the indisputable long-term clinical efficacy seen in practice (32).

In this case, it is appropriate to evaluate, under real-life conditions, the short-term and long-term effectiveness of triple Suplasyn® 2ml intra-articular injections and to how the extended treatment regime may impact patient satisfaction or treatment safety.

3 OBJECTIVES

3.1 Main Objective

To assess changes in clinical outcome of patients with OA recommended with a triple Suplasyn® 2ml injection for viscosupplementation.

3.2 Secondary Objectives

- To evaluate the safety profile and adverse events (AEs) of Suplasyn® 2ml injections.
- To evaluate the concomitant consumption of permitted rescue medications (analgesics, NSAIDS) throughout the study.
- To evaluate characteristics of the beneficiary population (Intended to treat).

4 SOURCE OF INFORMATION

All data will be provided by the researcher and by the patients who assist to the orthopedist/traumatologist with a symptomatic knee OA and according to physician criteria could be recommended with viscosupplementation with Suplasyn®.

5 STUDY DESIGN

5.1 Study Type:

Observational, non-interventional, international and multicenter study.

5.2 Study Design

Observational Model: Case-Only; Time Perspective: Prospective study

5.3 Study population

Main Selection Criteria:

Patients consulting to the orthopedist/traumatologist to primary care centers and according to specialist evaluation are susceptible of been recommended with viscosupplementation through a intraarticular

injection of Hyaluronic Acid (Suplasyn®) once per week during a 3 three weeks period. All patients who received the specific recommendation are includable for study.

Eligible patients:

- Ages: 18 years to 85 years
- Genders: Both
- Accepts Healthy Volunteers: No
- Study Population: Patients with symptomatic primary knee OA, with radiological grades I to III (according Kellgren-Lawrence Score) and without clinical effusion at time of inclusion.

All patients whose data will be recorded should have been informed by the researcher of the nature of the study and that his/her participation is voluntary. Registration of their data has to be started as long as he/she has signed the consent form and has clearly understood all the study procedures. Consent form could be obtained orally as long as the researcher asks for a witness to sign (i.e. nurse or patients' relative).

Inclusion Criteria:

- Age between 18 and 85 years old
- Primary osteoarthritic degeneration of the knee (patients with documented knee osteoarthritis)
- Patients fulfilling criteria for primary knee osteoarthritis, radiological grades I–III (Kellgren–Lawrence) (35) and joint space width ≥2 mm
- Patients without clinical effusion at baseline
- Fully aware of study procedures
- Willing to participate in all study processes and assessments

Exclusion Criteria:

- Allergic reactivity to hyaluronic acid
- Current knee infection, infection around injection site or any skin disease
- Pregnancy or lactation
- Participating in other clinical trial
- Any reason that may jeopardize the collection of data (patient likely to be lost-to-follow up)

5.4 Duration of Study Period and Follow-up

All patients will be followed during 26 weeks after the first injection with Suplasyn®. The study end date will be considered when the last patient has completed the observation period.

5.5 Intended Intervention

- 2ml of Hyaluronic Acid Intra-articular Injection (Suplasyn®) on the affected knee at baseline (Day 1), one week (Week1) and two weeks (Week 2) after initiation of the viscosupplementation VS treatment.
- Paracetamol, NSAID or analgesics are allowed as a rescue medication if unbearable pain had not improved after at least 1 hour rest.
- Glucosamines and chondroitines or other slow-acting drugs for osteoarthritis (i.e. diacerhein or avocado/soybean unsaponifiables) are allowed if at a stable dosage for 3 months or more. Consumption of rescue or other medication is recorded in a patients data form.

5.6 Sample size calculation

As it is an observational study of descriptive nature, a minimum margin to obtain statistical significance has not been settled. An estimated sample of 300 patients that have could be recommended during the established period for inclusion of data is considered.

6 MAIN VARIABLES

6.1 Main Variables for Evaluation

- Knee pain symptoms
- Physical function
- Quality of Life (QoL)
- Safety (Adverse Events)
- Compliance with treatment

6.2 Measures

The quality-of-life questionnaires that are completed by the patient with no input from the healthcare personnel may be more objective, because they more faithfully reflect the experience of the patient. In

knee osteoarthritis treatment, the self-assessed Oxford Knee Score (OKS) and Visual Analog Scale (VAS) are widely used.

☑ **Patients Outcome assessed with the Oxford Knee Score (OKS)** (39). Describes any changes from baseline over a period of 6 months; the study subjects will complete personally the (OKS) questionnaire at baseline, 1 and 6 months following the viscosupplementation of the knee.

This is a "self-administered" questionnaire. It has 12 items on daily activities, which the patient must answer without help from healthcare personnel. Each item is scored from 1 (normal function) to 5 (extreme difficulty). The global score is the sum of the 12 item scores. Therefore, the best possible score is 12 and the worst possible score is 60. Partial scores have also been defined, for pain (questions 1, 4, 5, 8 and 9) (5–25 points), range of motion (questions 2, 3, 7 and 12) (4 – 20 points) and walking (questions 4, 6, 9, 10 and 11) (5–25 points).

The OKS is a disease-specific, purpose built, high performance instrument for evaluative research in knee osteoarthritis clinical trials. It assesses the outcome, as judged by the patient. This is of value in the large multicenter trials. (40-42) **The OKS** questionnaire may be compared with others that have been successfully applied to the treatment of osteoarthritis, but it has the advantage over assessments such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Arthritis Impact Measurement Scales (AIMS), in that it is intended specifically for use with knee surgery and knee OA treatment alone, and is simpler and quicker to process (37,38).

☑ **Pain evaluated with the Visual Analog Scale (VAS)**

The (VAS) will describe the change in the level of knee pain from baseline following viscosupplementation of the knee. (Time Frame: The study subjects will complete the (VAS) at baseline, 1 and 6 months following the viscosupplementation of the knee.)

The (VAS) responses are expressed on a 100 mm line, with 0 representing no pain and 100 mm representing the worst pain possible. (43,44) The patient places a mark across the line representing where their perceived pain lies, from no pain to severe pain; measured at rest (night) and during daily activities.

☑ **Safety assessment**

Adverse events observed by the doctors or reported by the patients spontaneously or following a non-leading questions, will be collected on patient data form. Particular attention will be paid to local painful

reactions at the injection site, post-injection reactions (i.e. effusion, skin rush, swelling, warmth) and acute pseudoseptic arthritis (36).

☑ **Compliance** will considered based on the a posteriori analysis of the number of visits and number of doses applied for each patient. A discontinuation is defined as an interruption of recommended regimen of three weekly doses at any point of that period.

7 STATISTICAL ANALYSIS

All data will be analyzed with the statistical software SPSS-Windows.

7.1 Descriptive Statistics

All variables recorded will be descriptively analyzed. Categorical variables will be presented as frequencies and proportions. Quantitative factors (continuous/ordinals) will be also presented as central tendencies indexes (mean, median) and dispersion measures (standard deviation, minimum and maximum values).

7.2 Study Objectives

Primary outcome is to assess in real-life practice the effectiveness of viscosupplementation treatment using triple Suplasyn® 2ml injections (20 mg/2ml sodium hyaluronate, 500-1000kDa MW). The primary efficacy endpoint is the change from baseline in the Oxford knee score assessing the **function** of the OA knee at 4 and 26 weeks and the change from baseline in the patient-rated knee OA **pain** assessment (100 mm visual analogue scale/VAS) at 4 and 26 weeks.

Both scores obtained with the Oxford Knee Score and Pain VAS will be registered at 1 and 6 months following viscosupplementation of the knee.

Secondary objectives correspond to the evaluation of the **safety profile and adverse events** (AEs) of Suplasyn® 2ml injections, assessment of **concomitant consumption of permitted rescue medications** (analgesics, NSAIDs) throughout the study and the known the **characteristics of the beneficiary population** (intend-to-treat).

Continuous variables will be expressed as mean ± Standard Deviation (SD) while categorical binary variables will be presented as percentages.

Both primary and secondary objectives will be analyzed with tests for repeated measures to determinate the evolution of the variables throughout study visits. P values <0.05 will be considered as statistically significant.

7.3 Sample stratification

Sample could be stratified based on factors such as patients' characteristics (gender, age), Knee OA radiological characteristics, use of conventional medication (NSAIDS, corticosteroid injections), history of interventional treatment in the affected knee (open surgery, arthroscopy, arthrocentesis) and impairment associated with the perceived pain caused by the OA. These variables will be analyzed through statistic tests for independent measures.

8 ETHICAL CONSIDERATIONS

8.1 General Considerations

The present protocol will be conducted in full concordance with principles of the "Declaration of Helsinki" (Helsinki, 1964) amended by the 64th World Medical Assembly (Fortaleza, 2013), the Good Clinical Practice.

The ESTIK survey correspond to Post-Market Clinical Follow-up (PMCF) studies conducted using CE marked devices according to the Council Directive 93/42/EEC concerning Medical Devices (June 14th, 1993, last amended by Directive 2007/47/EC of the European Parliament and of the Council of on September 5th, 2007) which represents that Suplasyn® should be recommended following the Good Clinical Practice principles, thus to be use in the usual manner in accordance with the instructions for use (leaflet) supplied with the marketed products.

8.2 Evaluation of benefit-risk for patients during study

The participation in this study does not involve or represent an increased risk for patients and does not modify the usual therapeutic practices. Participants will be not subjected to additional or extraordinary diagnostic tests other than those normally indicated for these patients.

8.3 Safety Assessment

Adverse events observed by the doctors or reported by the patients spontaneously or following a non-leading questions, will be collected on patient data form. Particular attention will be paid to local painful reactions at the injection site, post-injection reactions (i.e. effusion, skin rush, swelling, warmth) and acute pseudoseptic arthritis. (36)

8.4 Patients Information Sheet and Consent Form

All patients will receive an information sheet with a description of the study and its procedures as well as a consent form to be signed. It is important to remark that all patients whose data will be recorded should be informed of the nature of the study and have to give their informed consent (or oral consent with signature of a witness, i.e. nurse or relative) for the collection of their data, since this project is an observational study thus the decision to include a patients in it must be considered after the recommendation of Suplasyn®.

8.5 Ethical Committee Evaluation

All study materials, including protocols and surveys, have been developed by Dr. Martinek, and have been approved by the Ethics Committee for Clinical Research of the Krnov Hospital (Czech Republic).

8.6 Data Protection

Researchers will guarantee the anonymity of each patients participating in the study and will protect his/her identity from third-parties or non-authorized figures.
No personal information which may allow identifying patients will be recorded. Patients' identity will be codified in the CRFs and only each researcher will have access to this data in cases of verification or clarifications.
All the data recorded in the surveys will be hosted in secured servers with restricted access, which are also subjected to Spanish Data Protection laws (database files are notified and registered at the Spanish Data Protection Agency) according the "Ley Orgánica 15/1999, 13 de diciembre de 1999".

8.7 Interference with researcher prescription habits

Suplasyn® should be recommended following the Good Clinical Practice principles, thus to be use in the usual manner in accordance with the instructions for use (leaflet) supplied with the marketed products.

The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the use of the medical device is clearly separated from the decision to include the patient in the study.

No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.

9 PRACTICAL CONSIDERATIONS

9.1 Work plan

All researches will have to register to be assigned with a personal id and password for access to study online surveys. Once the researcher has signed the *researcher commitment form* and have received a confirmation of his/her registration can proceed to the inclusion of data.

Patients will be selected from those who accomplish inclusion criteria, based on the consecutive sampling technique. Researcher will proceed to explain patient about the study and ask for a signature on the *consent form* prior to the inclusion.

It is important to keep in mind that the recommendation with Suplasyn® for the viscosupplementation of the affected knee is not conditioned to the development of the study or the inclusion of a specific patient in this study.

Data will be recorded by the researcher in an online electronic Case Report Form (eCRF) to which will access with their id and password. The online platform will assign to each patient an automatic and unique code which will allow registering his/her clinical information throughout all study visits for the later generation of a database and an analysis of the final results. The eCRF does not contain any patients' personal information and the researcher is committed to keep the access information and the content of the eCRFs in complete anonymity, besides the obligation to accomplish with the principles and laws applicable in his/her local context, being fully responsible for the truthful of the provided data.

- On **visit 1 (baseline)** patient will receive the first intraarticular injection of 2ml of Hyaluronic Acid - Suplasyn® in the affected knee following the product instructions leaflet and according to standard measures for these types of procedures. In this visit, patient will also have to complete the Patient eCRF which includes the OKS.
- On **visit 2 (administration of the second HA injection, one week after first injection)** and **Visit 3 (administration of the third HA injection, one week after second injection)** adverse events should be investigated. In case the researcher obtains as a response to the question

"How did you feel since your last visit" any adverse event since prior visit, the *Adverse Event Form* should be completed and sent to the study coordinator.

- **Visit 4 (1 month after injection):** Researcher will complete the eCRF corresponding to that visit by recording data on patient's consumption of any pharmacological treatment for pain during the previous month, recording data on frequency, dose and type of drug used. In this visit patient will have to assess his/her perceived pain with the VAS, grading the intensity of this symptom "during daily activities" and "at rest/at night".
- **Visit 5 (6 months after injection):** The procedure will be the same that on visit 4.

9.2 Interim and Final Reports

A final report will be developed based on the final results.

9.3 Dissemination of results

All data collected during this study will be used globally and not individually. Researchers who participated in the project will receive a copy of the final study report with the results obtained and this document shall be confidential.

Scientific publications and/or materials including conference presentations will be considered, always making explicit reference to the study.

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10.2 ESSIK Protocol

CONFIDENCIAL

The Effectiveness and Safety of Single 6ml Hyaluronic Acid Intra-articular Injection (Suplasyn® 1-shot) in Managing Symptomatic Primary Osteoarthritis of the Knee in Real-life Practice: ESSIK Survey.

STUDY PROTOCOL

Main Investigator:
Pavel Martinek, MD

SUMMARY

Official Title

The Effectiveness and Safety of Single 6ml Hyaluronic Acid Intra-articular Injection (Suplasyn® 1-shot) in Managing Symptomatic Primary Osteoarthritis of the Knee in Real-life Practice: ESSIK Survey.

Responsible Party/Sponsor

Mylan Institutional International
Thurgauerstrasse 40
8050 Zürich, Switzerland

Main Investigator/Study Coordinator

Pavel Martinek, MD
Krnov Hospital (Czech Republic)

Study Officials/Investigators

Orthopeadists/Traumatologists

Review Board

All study materials have been approved by the Ethical Committee for Clinical Investigation of the Krnov Hospital (The Czech Republic).

Primary Outcome

To assess changes in clinical outcome of patients with OA recommended with a single Suplasyn® 1-shot 6ml injection for viscosupplementation.

Intended Intervention:

A single dose of Suplasyn®1-shot (6ml) for the viscosupplementation of the knee.

Study Type:

Observational, non-interventional, international and multicenter study.

Study Design

Observational Model: Case-Only; Time Perspective: Prospective study

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Condition for Study

Osteoarthritis of the Knee.

Study sample

Patients over 18 years old with Primary Knee Osteoarthritis (Kellgren's grades I to III) without effusion.

Data Monitoring

Clever Instruments S.L. will be in charge of logistic and clinical trial monitoring.

Calendar

Study Start Date: June, 2014 – September, 2014

Study Completion Date: December, 2014 - March, 2015

Overall study period will be of 6 months, approximately.

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1 GENERAL INFORMATION

Official Title

The Effectiveness and Safety of Single 6ml Hyaluronic Acid Intra-articular Injection (Suplasyn® 1-shot) in Managing Symptomatic Primary Osteoarthritis of the Knee in Real-life Practice: ESSIK Survey

Responsible Party/Sponsor

Mylan Institutional International
Thurgauerstrasse 40
8050 Zürich, Switzerland

Main Investigator

Pavel Martinek, MD
Krnov Hospital (Czech Republic)

Study Officials/Investigators

Orthopeadists/Traumatologists

Duration of the Study

Intended duration: 6-9 months

Data will be provided by investigators from the clinical results observed in patients who were recommended with viscosupplementation with Suplasyn® 1-shot between June-September 2014 and December2014-March 2015.

The assignment of the patient to a particular therapeutic strategy should not be decided in advance by this protocol but falls within current practice and the use Suplasyn® 1-shot was clearly separated from the decision to include the patient's data in this study.

2 BACKGROUND

Osteoarthritis (OA) of the knee is a painful and disabling condition that is becoming more prevalent in patients over 50 years of age that results in symptoms in 10% of people older than 55 years which severely impair up to a quarter overall these patients. (1)

OA is generally treated using conservative measures at initial phases of the disease (2), more frequently with analgesics, topical and oral non-steroidal anti-inflammatory drugs (NSAIDs). However, their long-term use of these agents might different organic risks such as complications in hepatic, cardiovascular, gastrointestinal or renal systems.

In recent years, viscosupplementation has been more often used as a therapeutic modality for the management of knee OA (3,4). Intra-articular injections of Hyaluronic Acid (HA) have shown good safety profiles and efficacy for treating knee OA pain. Recent clinical data have demonstrated that anti-inflammatory and chondroprotective effects of HA viscosupplementation are associated with a significant and maintained reduction on pain up to 14-26 weeks after injection while improving patients' function (5-7), results which show a clear difference compared to the short-term effect of other interventions such as pharmacological treatment with NSAIDs and/or corticosteroid injections.

Viscosupplementation

Viscosupplementation is intended as an alternative of HA's degradation in the synovial fluid of patients affected with knee osteoarthritis by the administration of exogenous HA through intra-articular injection. Viscosupplementation is recommended (6) for the treatment of knee OA by the current Osteoarthritis Research Society International (OARSI) Guidelines and previous practice guidelines (4,8-11) and despite that in other reference documents such as current Clinical Practice Guidelines (CPG) of the American Academy of Orthopaedic Surgeons (AAOS) is not included as a main recommendation(12), this makes reference to published evidence reporting significant improvements on OA symptoms after viscosupplementation. Because of the lack of evidence and the possible discrepancies across studies, conclusion should be as that viscosupplementation may be of significant benefit for *some* patients (13).

Administration of an exogenous HA cannot explain long-term reduction of symptoms, considering that HA has short half-life. HA has biological effects on the inflammatory cells and

stimulates HA production by synovial cells. Its key molecular role in joints' biomechanics explains how a reduction in its concentration and molecular weight greatly alters the properties of synovial fluid, causing cartilage damage and worsening osteoarthritis symptoms (14). Treatment with exogenous HA attempts to restore the elasticity and viscosity of synovial fluid to normal levels, resulting in pain reduction and functional improvement. Different studies have also confirmed that HA interacts with mediators of inflammation and matrix turnover in joint cells. HA has also a biosynthetic chondroprotective effect (15-20).

Identification of CD44, a glycoprotein expressed on the cell surface of chondrocytes, may explain HA interaction with chondrocytes since CD44 is considered a HA's receptor at the chondrocyte cell surface so the provision of exogenous HA into articular cartilage is facilitated through this receptors (21,22).

Single Injection

In order to reduce the number of intra-articular injections (and potential related side effects) a randomized, double-blind study was conducted, and the results demonstrated the efficacy, safety and long-term effects (up to 26 weeks) of a single-dose injection of visco-supplementation (26). Study assessing five different dosing regimens of viscosupplementation suggests that a single 6 ml injection of HA may be as efficacious, and as well tolerated, as 3 x 2 ml one week apart (25).

Single injection of HA offers statistically significant and clinically meaningful improvements (30) both in pain and physical function in patients with knee OA, thereby demonstrating the multi-dimensional effectiveness of this therapy (23).

The single injection represents an attractive alternative to the three injections treatment regimen with documented statistically and clinically significant improvements (30) both in pain and physical function in patients with knee OA (23), reducing the number of intra-articular injections required and thereby offering potential comfort and safety benefits to patients.

Suplasyn® 2ml and 1-shot (6ml)

Suplasyn® is a low-intermediate molecular weight HA (500-1000 kDa) product which is safe and well tolerated (24). Suplasyn® is a CE marked Medical Device (CE0473) and is approved by in several countries for the treatment of pain associated with knee osteoarthritis.

Suplasyn® 1-shot is supplied in the form of a prefilled syringe containing 60 mg/ 6ml of sodium hyaluronate in a viscoelastic solution administered as a single injection. It is marketed jointly with the

2ml Suplasyn® (prefilled syringe containing 20 mg/2ml sodium hyaluronate) which is administered according to a dosing regimen of one injection per week for three to six weeks.

Suplasyn® has shown to be more effective than placebo on pain and function in knee osteoarthritis (24) with similar efficacy when compared to NSAIDs (27) and with maintained effects over the long term (28). These studies also demonstrated its excellent safety profile.

Suplasyn® has also demonstrated useful health economic benefits with a reduction in the costs of management of knee OA during the 26-weeks following the course of viscosupplementation (29).

Study Rationale

The current study is designed to assess the effectiveness and safety of one 6ml injection of Suplasyn® 1-shot in a 26-week, international, multicenter, non-interventional observational study of patients recommended with a single intra-articular 6ml injection for the treatment of knee osteoarthritis. The intention is to assess the efficacy and safety of the treatment in real-life practice. Our primary target is to obtain and verify long-term outcomes from a naturalistic primary care experience.

Rationale for using viscosupplementation is to restore the protective viscoelasticity of synovial hyaluronic acid, decrease pain and improve mobility. Immediate benefit of viscosupplementation is the relief of pain while long-term benefits results are believed to include the return of joint mobility by the restoration of trans-synovial flow and the metabolic and rheological homeostasis of the joint (31). Short duration of HA within the joint does not fully explain the indisputable long-term clinical efficacy seen in practice (32).

In this case, it is appropriate to evaluate, under real-life conditions, the short-term and long-term effectiveness of a single injection of Suplasyn® 1-shot 6ml intra-articular injections and to how the extended treatment regime may impact patient satisfaction or treatment safety.

3 OBJECTIVES

3.1 Main Objective

To assess changes in clinical outcome of patients with OA recommended with a single injection with Suplasyn® 1-shot viscosupplementation for knee OA during a 26 weeks follow-up.

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3.2 Secondary Objectives

- To evaluate the safety profile and adverse events (AEs) of Suplasyn® 1-shot injection.
- To evaluate the concomitant consumption of permitted rescue medications (analgesics, NSAIDS) throughout the study.
- To evaluate characteristics of the beneficiary population (Intended to treat).

4 SOURCE OF INFORMATION

All data will be provided by the researcher and by the patients who assist to the orthopedist/traumatologist with a symptomatic knee OA and according to physician criteria could be recommended with viscosupplementation with Suplasyn® 1-shot.

5 STUDY DESIGN

5.1 Study Type:

Observational, non-interventional, international and multicenter study.

5.2 Study Design

Observational Model: Case-Only; Time Perspective: Prospective study

5.3 Study population

Main Selection Criteria:

Patients consulting to the orthopedist/traumatologist to primary care centers and according to specialist evaluation are susceptible of been recommended with viscosupplementation through a single intraarticular injection of Hyaluronic Acid (Suplasyn® 1-shot). All patients who received the specific recommendation are includable for study.

Eligible patients:

- Ages: 18 years to 85 years
- Genders: Both

- Accepts Healthy Volunteers: No
- Study Population: Patients with symptomatic primary knee OA, with radiological grades I to III (according Kellgren-Lawrence Score) and without clinical effusion at time of inclusion.

All patients whose data will be recorded should have been informed by the researcher of the nature of the study and that his/her participation is voluntary. Registration of their data has to be started as long as he/she has signed the consent form and has clearly understood all the study procedures. Consent form could be obtained orally as long as the researcher asks for a witness to sign (i.e. nurse or patients' relative).

Inclusion Criteria:

- Age between 18 and 85 years old
- Primary osteoarthritic degeneration of the knee (patients with documented knee osteoarthritis)
- Patients fulfilling criteria for primary knee osteoarthritis, radiological grades I–III (Kellgren–Lawrence) (35) and joint space width ≥2 mm
- Patients without clinical effusion at baseline
- Fully aware of study procedures
- Willing to participate in all study processes and assessments

Exclusion Criteria:

- Allergic reactivity to hyaluronic acid
- Current knee infection, infection around injection site or any skin disease
- Pregnancy or lactation
- Participating in other clinical trial
- Any reason that may jeopardize the collection of data (patient likely to be lost-to-follow up)

5.4 Duration of Study Period and Follow-up

All patients will be followed during 26 weeks after the injection with Suplasyn® 1-shot. The study end date will be considered when the last patient has completed the observation period.

5.5 Intended Intervention

- 6ml of Hyaluronic Acid Intra-articular Injection (Suplasyn® 1-shot) on the affected knee at baseline (Day 1).

- Paracetamol, NSAID or analgesics are allowed as a rescue medication if unbearable pain had not improved after at least 1 hour rest.
- Glucosamines and chondroitines or other slow-acting drugs for osteoarthritis (i.e. diacerhein or avocado/soybean unsaponifiables) are allowed if at a stable dosage for 3 months or more. Consumption of rescue or other medication is recorded in a patients data form.

5.6 Sample size calculation

As it is an observational study of descriptive nature, a minimum margin to obtain statistical significance has not been settled. An estimated sample of 300 patients that have could be recommended during the established period for inclusion of data is considered.

6 MAIN VARIABLES

6.1 Main Variables for Evaluation

- Knee pain symptoms
- Physical function
- Quality of Life (QoL)
- Safety (Adverse Events)

6.2 Measures

The quality-of-life questionnaires that are completed by the patient with no input from the healthcare personnel may be more objective, because they more faithfully reflect the experience of the patient. In knee osteoarthritis treatment, the self-assessed Oxford Knee Score (OKS) and Visual Analog Scale (VAS) are widely used.

☑ **Patients Outcome assessed with the Oxford Knee Score (OKS)** (39). Describes any changes from baseline over a period of 6 months; the study subjects will complete personally the (OKS) questionnaire at baseline, 1 and 6 months following the viscosupplementation of the knee.

This is a "self-administered" questionnaire. It has 12 items on daily activities, which the patient must answer without help from healthcare personnel. Each item is scored from 1 (normal function) to 5 (extreme difficulty). The global score is the sum of the 12 item scores. Therefore, the best possible score is 12 and the worst possible score is 60. Partial scores have also been defined, for pain

(questions 1, 4, 5, 8 and 9) (5–25 points), range of motion (questions 2, 3, 7 and 12) (4 – 20 points) and walking (questions 4, 6, 9, 10 and 11) (5–25 points).

The OKS is a disease-specific, purpose built, high performance instrument for evaluative research in knee osteoarthritis clinical trials. It assesses the outcome, as judged by the patient. This is of value in the large multicenter trials. (40-42) **The OKS** questionnaire may be compared with others that have been successfully applied to the treatment of osteoarthritis, but it has the advantage over assessments such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Arthritis Impact Measurement Scales (AIMS), in that it is intended specifically for use with knee surgery and knee OA treatment alone, and is simpler and quicker to process (37,38).

☑ **Pain evaluated with the Visual Analog Scale (VAS)**

The (VAS) will describe the change in the level of knee pain from baseline following viscosupplementation of the knee. (Time Frame: The study subjects will complete the (VAS) at baseline, 1 and 6 months following the viscosupplementation of the knee)

The (VAS) responses are expressed on a 100 mm line, with 0 representing no pain and 100 mm representing the worst pain possible. (43,44) The patient places a mark across the line representing where their perceived pain lies, from no pain to severe pain; measured at rest (night) and during daily activities.

☑ **Safety assessment**

Adverse events observed by the doctors or reported by the patients spontaneously or following a non-leading questions, will be collected on patient data form. Particular attention will be paid to local painful reactions at the injection site, post-injection reactions (i.e. effusion, skin rush, swelling, warmth) and acute pseudoseptic arthritis (36).

7 STATISTICAL ANALYSIS

All data will be analyzed with the statistical software SPSS-Windows.

7.1 Descriptive Statistics

All variables recorded will be descriptively analyzed. Categorical variables will be presented as frequencies and proportions. Quantitative factors (continuous/ordinals) will be also presented as central

tendencies indexes (mean, median) and dispersion measures (standard deviation, minimum and maximum values).

7.2 Study Objectives

Primary outcome is to assess in real-life practice the effectiveness of viscosupplementation treatment using Suplasyn® 1-shot 6ml injection (60 mg/6ml sodium hyaluronate, 500-1000kDa MW). The primary efficacy endpoint is the change from baseline in the Oxford knee score assessing the **function** of the OA knee at 4 and 26 weeks and the change from baseline in the patient-rated knee OA **pain** assessment (100 mm visual analogue scale/VAS) at 4 and 26 weeks.

Both scores obtained with the Oxford Knee Score and Pain VAS will be registered at 1 and 6 months following viscosupplementation of the knee.

Secondary objectives correspond to the evaluation of the **safety profile and adverse events** (AEs) of Suplasyn® 1-shot 6ml injection, assessment of **concomitant consumption of permitted rescue medications** (analgesics, NSAIDs) throughout the study and the known the **characteristics of the beneficiary population** (intend-to-treat).

Continuous variables will be expressed as mean ± Standard Deviation (SD) while categorical binary variables will be presented as percentages.

Both primary and secondary objectives will be analyzed with tests for repeated measures to determinate the evolution of the variables throughout study visits. P values <0.05 will be considered as statistically significant.

7.3 Sample stratification

Sample could be stratified based on factors such as patients' characteristics (gender, age), Knee OA radiological characteristics, use of conventional medication (NSAIDS, corticosteroid injections), history of interventional treatment in the affected knee (open surgery, arthroscopy, arthrocentesis) and impairment associated with the perceived pain caused by the OA. These variables will be analyzed through statistic tests for independent measures.

8 ETHICAL CONSIDERATIONS

8.1 General Considerations

The present protocol will be conducted in full concordance with principles of the "Declaration of Helsinki" (Helsinki, 1964) amended by the 64th World Medical Assembly (Fortaleza, 2013), the Good Clinical Practice.

The ESTIK survey correspond to Post-Market Clinical Follow-up (PMCF) studies conducted using CE marked devices according to the Council Directive 93/42/EEC concerning Medical Devices (June 14th, 1993, last amended by Directive 2007/47/EC of the European Parliament and of the Council of on September 5th, 2007) which represents that Suplasyn® 1-shot should be recommended following the Good Clinical Practice principles, thus to be use in the usual manner in accordance with the instructions for use (leaflet) supplied with the marketed products.

8.2 Evaluation of benefit-risk for patients during study

The participation in this study does not involve or represent an increased risk for patients and does not modify the usual therapeutic practices. Participants will be not subjected to additional or extraordinary diagnostic tests other than those normally indicated for these patients.

8.3 Safety Assessment

Adverse events observed by the doctors or reported by the patients spontaneously or following a non-leading questions, will be collected on patient data form. Particular attention will be paid to local painful reactions at the injection site, post-injection reactions (i.e. effusion, skin rush, swelling, warmth) and acute pseudoseptic arthritis. (36)

8.4 Patients Information Sheet and Consent Form

All patients will receive an information sheet with a description of the study and its procedures as well as a consent form to be signed. It is important to remark that all patients whose data will be recorded should be informed of the nature of the study and have to give their informed consent (or oral consent with signature of a witness, i.e. nurse or relative) for the collection of their data, since this project is an observational study thus the decision to include a patients in it must be considered after the recommendation of Suplasyn® 1-shot.

8.5 Ethical Committee Evaluation

All study materials, including protocols and surveys, have been developed by Dr. Martinek, and have been approved by the Ethics Committee for Clinical Research of the Krnov Hospital (Czech Republic).

8.6 Data Protection

Researchers will guarantee the anonymity of each patients participating in the study and will protect his/her identity from third-parties or non-authorized figures.

No personal information which may allow identifying patients will be recorded. Patients' identity will be codified in the Case Data Forms and only each researcher will have access to this data in cases of verification or clarifications.

All the data recorded in the surveys will be hosted in secured servers with restricted access, which are also subjected to Spanish Data Protection laws (database files are notified and registered at the Spanish Data Protection Agency) according the "Ley Orgánica 15/1999, 13 de diciembre de 1999".

8.7 Interference with researcher prescription habits

Suplasyn® 1-shot should be recommended following the Good Clinical Practice principles, thus to be use in the usual manner in accordance with the instructions for use (leaflet) supplied with the marketed products. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the use of the medical device is clearly separated from the decision to include the patient in the study.

No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.

9 PRACTICAL CONSIDERATIONS

9.1 Work plan

All researches will have to register to be assigned with an personal id and password for access to study online surveys. Once the researcher has signed the *researcher commitment form* and have received a confirmation of his/her registration can proceed to the inclusion of data.

Patients will be selected from those who accomplish inclusion criteria, based on the consecutive sampling technique. Researcher will proceed to explain patient about the study and ask for a signature on the *consent form* prior to the inclusion.

It is important to keep in mind that the recommendation with Suplasyn® 1-shot for the viscosupplementation of the affected knee is not conditioned to the development of the study or the inclusion of a specific patient in this study.

Data will be recorded by the researcher in an online electronic Case Report Form (eCRF) to which will access with their id and password. The online platform will assign to each patient an automatic and unique code which will allow registering his/her clinical information throughout all study visits for the later generation of a database and an analysis of the final results. The eCRF does not contain any patients'

personal information and the researcher is committed to keep the access information and the content of the eCRFs in complete anonymity, besides the obligation to accomplish with the principles and laws applicable in his/her local context, being fully responsible for the truthful of the provided data.

- On **visit 1 (baseline)** patient will receive the single intraarticular injection of 6ml of Hyaluronic Acid - Suplasyn® 1-shot in the affected knee following the product instructions leaflet and according to standard measures for these types of procedures. In this visit, patient will also have to complete the Patient eCRF which includes the OKS.
- **Visit 2 (1 month after injection):** Researcher will complete the eCRF corresponding to that visit by recording data on patient's consumption of any pharmacological treatment for pain during the previous month, recording data on frequency, dose and type of drug used. In this visit patient will have to assess his/her perceived pain with the VAS, grading the intensity of this symptom "during daily activities" and "at rest/at night".
  Adverse events should be investigated. In case the researcher obtains as a response to the question "How did you feel since your last visit" any adverse event since prior visit, the *Adverse Event Form* should be completed and sent to the study coordinator.
- **Visit 3 (6 months after injection):** The procedure will be the same that on visit 2.

9.2 Interim and Final Reports

A final report will be developed based on the final results.

9.3 Dissemination of results

All data collected during this study will be used globally and not individually. Researchers who participated in the project will receive a copy of the final study report with the results obtained and this document shall be confidential.

Scientific publications and/or materials including conference presentations will be considered, always making explicit reference to the study.

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