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## Responsiveness of the OARSI-OMERACT osteoarthritis pain and function measures

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**TITLE:** RESPONSIVENESS OF THE OARSI-OMERACT OSTEOARTHRITIS PAIN AND FUNCTION MEASURES

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## **ABSTRACT**

*Objective:* To assess the responsiveness of the Intermittent and Constant Osteoarthritis Pain measure (ICOAP), Hip Disability and Osteoarthritis Outcome Score Physical Function Short Form (HOOS-PS), and the Knee Disability and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS) in a pharmacological trial.

*Methods:* Data were obtained from a randomized double-blind trial comparing naproxinod with naproxen and ibuprofen in individuals with hip or knee osteoarthritis (OA) (NCT00662896). Participants completed the ICOAP, HOOS-PS/KOOS-PS, and WOMAC Likert version 3.0 before and 13 weeks after treatment. In hip and knee OA participants separately, the mean pre-post treatment change in scores, effect size (ES) and standardized response mean (SRM) were determined for each measure by treatment arm, and for all arms combined.

*Results:* Of 349 trial participants, 156 with knee OA and 48 with hip OA completed all measures at both time-points and were included (mean age 61 years; two-thirds female). Although there was both within treatment and between treatment variability in response, among knee OA participants, ICOAP intermittent, constant, and total scores and KOOS-PS scores showed, on average, moderate effects, with ESs ranging from 0.46 to 0.54 and SRMs from 0.49 to 0.56. Similar changes were seen for the WOMAC pain and function subscales (0.58 and 0.58, respectively). In those with hip OA, no significant improvement in symptoms was seen for any measure.

*Conclusion:* Responsiveness to pharmaceutical intervention was demonstrated for ICOAP and KOOS-PS among participants with knee OA. Absence of treatment response precluded assessment of responsiveness in hip OA.

**KEY WORDS:** Intermittent and Constant Osteoarthritis Pain (ICOAP) Measure; Hip Disability and Osteoarthritis Outcome Score Physical Function - Short form (HOOS-PS); Knee Disability and Osteoarthritis Outcome Score Physical Function Short form (KOOS-PS); Responsiveness.

**RUNNING HEADLINE:** *RESPONSIVENESS of OARSI-OMERACT MEASURES*

## Introduction

Osteoarthritis (OA) is the leading cause of joint pain and physical disability with substantial effects on quality of life and use of health care services<sup>1</sup>. Current treatment for OA focuses on achieving pain relief, with downstream benefits on functional limitations, sleep<sup>2</sup>, fatigue<sup>3</sup>, and mood<sup>4,5</sup>, using a variety of pharmacological and non-pharmacological therapies<sup>6</sup>. A number of patient-reported outcome measures have been used to evaluate changes in pain and physical disability in hip and knee OA as a result of pharmacologic interventions. Perhaps most widely used has been the Western Ontario McMaster Universities OA Index (WOMAC)<sup>7</sup>, comprised of 3 subscales, one each for pain, stiffness, and physical function. An 11-item short-form version of the WOMAC function scale has also been developed and assessed for reliability, validity and responsiveness<sup>8,9</sup>. However, recognized limitations of the WOMAC include the high correlation between pain and physical function subscale scores (pain items largely evaluate pain severity on specified activities), which may preclude the assessment of pain and disability as independent constructs<sup>10,11</sup>. Studies have consistently failed to demonstrate the factorial validity of the WOMAC<sup>12,13</sup>. Finally, qualitative research has raised concerns about the adequacy of existing OA pain measures, including the WOMAC, to comprehensively evaluate the pain experience in OA<sup>14</sup>.

To address these issues, under the auspices of an OARSI-OMERACT initiative, three new measures have been developed to evaluate pain and function in hip and knee OA: The Intermittent and Constant Osteoarthritis Pain Score (ICOAP)<sup>14</sup>, the Hip Disability and Osteoarthritis Outcome Score Physical Function short form (HOOS-PS)<sup>15</sup>, and the Knee Disability and Osteoarthritis Outcome Score Physical Function short form (KOOS-PS)<sup>16</sup>. The ICOAP is an 11-item scale for assessment of hip or knee OA pain, which was developed from content analysis of qualitative interviews in individuals with painful hip or knee OA<sup>14,17</sup>. ICOAP evaluates two pain domains: a 5-item scale evaluates constant pain (intensity and impact on mood – 2 items, sleep and quality of life); and a 6-item scale evaluates intermittent pain or

“pain that comes and goes” (same items as for constant subscale plus an item assessing pain frequency). Item responses are from ‘not at all’ (0) to ‘extremely’ (4) or ‘never’ (0) to ‘very often’ (4)<sup>17</sup>. Subscale scores are created by summing item scores and normalizing from 0 (no pain) to 100 (extreme pain). A total ICOAP score is calculated by summing the subscale scores. In a hip/knee OA cohort aged 40+ , ICOAP was found to be internally consistent (Chronbach’s alpha 0.93) and reliable (test-retest reliability intraclass correlation coefficient 0.85)<sup>17</sup>. Descriptive analyses demonstrated good distribution of response options across all items and discrimination of the two types of pain<sup>17</sup>. Total and subscale ICOAP scores were significantly correlated with scores on the WOMAC pain scale, the Knee Injury and OA Outcome Score (KOOS) symptoms scale, and self-rated effect of hip/knee problems on quality of life, with Spearman correlation coefficients ranged in magnitude from 0.60 (KOOS symptoms) to 0.81 (WOMAC pain scale)<sup>17</sup>. Correlations between ICOAP scores and WOMAC function were lower than those for WOMAC pain with WOMAC function, indicating that the two measures are evaluating different constructs.

The Hip disability and Osteoarthritis Outcome Score-Physical Function Short-form (HOOS-PS) and Knee injury and Osteoarthritis Outcome Score-Physical Function Short-form (KOOS-PS) were developed from the Activities of Daily Living subscale (which subsumes the 17 physical function items of the WOMAC Likert 3.0) and the Sport and Recreation subscale of the HOOS and the KOOS, respectively<sup>18,19</sup>. The latter were designed to evaluate a broader spectrum of physical function impairments in people with hip and knee OA than has been previously demonstrated using the WOMAC. The short-form versions were derived from Rasch analysis of data from individuals aged 19-96 years with hip and knee OA, respectively, from multiple countries across a breadth of disease severity ranging from community to pre-total joint replacement samples. The short-form HOOS is comprised of 5 items, which assess level of difficulty performing the following activities: sitting, descending stairs, getting in/out of bath or shower,

twisting/pivoting on loaded leg, and running. The short-form KOOS is comprised of 7 items, which assess level of difficulty with rising from bed, putting on socks/stockings, rising from sitting, bending to the floor, twisting/pivoting on your injured knee, kneeling and squatting. In joint replacement recipients, internal consistency using Cronbach's alpha was 0.79 and 0.89 for the HOOS-PS and KOOS-PS, respectively. Correlations of the HOOS-PS and KOOS-PS with the WOMAC 17-item physical function subscale were both 0.90 and 0.85 with the WOMAC physical function excluding items common to the short measures<sup>20</sup>.

The current study evaluated the responsiveness of these measures in the context of a double-blind, randomized, controlled clinical trial comparing the effects of naproxinod 750 and 375 mg bid, equimolar amounts of naproxen (500 mg and 250 mg bid, respectively), and ibuprofen 600 mg tid on blood pressure, pain and disability in patients with hip and knee OA. Naproxinod is a cyclooxygenase-inhibiting nitric-oxide (NO) donator with analgesic, anti-inflammatory, antipyretic and NO-donating properties<sup>21</sup>; prior studies have found naproxinod to be non-inferior to naproxen and ibuprofen in relieving pain and improving physical function in OA as measured using the WOMAC<sup>21-23</sup>. The current study evaluated the responsiveness of the ICOAP, HOOS-PS, and KOOS-PS to changes in pain and disability following pharmacologic intervention.

## **Methods**

Study subjects were participants in a 13-week, phase I double-blind, randomized, naproxen- and ibuprofen-controlled parallel group, multicenter trial, conducted in the United States, that compared the effects of naproxinod to naproxen and ibuprofen on blood pressure, pain and disability in individuals with painful hip and knee OA and well-controlled hypertension (NCT00662896). Participants

were randomly allocated to one of five study arms; naproxinod 750mg, naproxinod 375mg, naproxen 500mg, naproxen 250mg, or ibuprofen 600mg in a 1:1:1:1:1 ratio for 13 weeks duration. Eligible participants were individuals aged 40+ years with diagnosed hip or knee OA and OA-related pain for at least three months. All participants had controlled essential hypertension on one antihypertensive medication (diuretic, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker or beta-blocker) and were current chronic users of non-steroidal anti-inflammatory drugs or acetaminophen. Participants discontinued all prior analgesic therapy at screening. Individuals with uncontrolled diabetes, prior gastric or duodenal ulceration or history of gastro-duodenal bleeding, hepatic or renal impairment, drug/alcohol abuse, congestive heart failure, clinically relevant abnormal electrocardiogram, current or expected use of anticoagulants and/or participating in another investigational study within 30 days of pre-screening were excluded. The pre-specified primary trial outcome was the mean change from baseline in 24-hour arterial blood pressure as measured using ambulatory blood pressure monitoring. The WOMAC, ICOAP, HOOS-PS (hip OA patients) and KOOS-PS (knee OA patients) were included as exploratory endpoints. Participants were assessed by interview prior to and at 13 weeks post-randomization. Participants were asked to complete relevant data for only their most painful hip or knee, as determined at the initial visit. For all measures, scores were standardized to 0 to 100 with higher scores indicating greater pain or disability.

### *Statistical Analysis*

Statistical analyses were restricted to participants with complete data for all measures at both the initial and 13-week assessments, conducted separately for hip and knee OA participants, and performed by treatment group as well as for the five study arms combined. Descriptive data for the hip and knee samples were calculated, separately, using means, medians and proportions, as appropriate. Pearson correlations between baseline scores for all measures (ICOAP subscale and total scores, HOOS-PS, KOOS-



PS, and WOMAC Likert-type version 3.0 pain and function subscale scores) were calculated. For each measure we also calculated: the mean and standard deviation of change in scores from baseline to follow-up; the effect size (ES; mean change in scores divided by the standard deviation of baseline scores); and the standardized response mean (SRM; mean change in scores divided by the standard deviation of the mean change). The 95% confidence intervals for the ES and SRM were determined using bootstrapping, with 1000 bootstrap samples used for each confidence interval<sup>24</sup>. For the present study, ES was considered low if values were  $\leq 0.3$ , large for values  $\geq 0.8$  and moderate for intermediate values. Differences in mean pre-post treatment scores were assessed using paired t tests. Variability in response by treatment arm was assessed using analysis of variance.

## Results

**Sample Characteristics:** Of 349 individuals who were randomized, 204 had complete data for all measures at both time points and were included in these analyses. Of these 204 participants, the most painful joint was a knee for 156 (76.5%) and a hip for 48 (23.5%). The characteristics of hip and knee participants were similar; mean age was 61.2 and 60.3 years, respectively; more than two-thirds were female (68.6% and 68.8%, respectively) and Caucasian (82.7% and 83.3%, respectively). (**Table 1**)

### **Correlations between Measures:**

All measures were significantly correlated ( $p < 0.001$ ). However, for both hip and knee OA participants, the correlations between WOMAC pain and function subscale scores were higher (0.91 for knees; 0.89 for hips) than were the correlations between ICOAP subscale or total scores with KOOS-PS (Pearson's  $r$  0.57-0.62), HOOS-PS ( $r = 0.51$ -0.62), or WOMAC function ( $r = 0.76$  -0.81 for knees;  $r = 0.75$ -0.79 for hips). (**Table 2**).

### **Responsiveness of the Measures:**

*Knee OA Participants:* Pooling all treatment arms, there was a significant improvement in both pain and function measures following treatment ( $p < 0.0001$ ). (**Table 3**) However, significant within and between-treatment group variability in response was observed. This reached statistical significance only for knee function measures (WOMAC function,  $p = 0.008$ ; KOOS-PS,  $p = 0.02$ ). ICOAP intermittent, constant, and total scores showed moderate effect sizes (0.46 to 0.54), with SRMs between 0.49 and 0.56, overall. Across treatment groups, effect sizes ranged from 0.24-0.61 (constant scale), 0.19-0.96 (intermittent scale) and 0.22-0.81 (total score). SRMs varied similarly. The WOMAC pain subscale showed a similar moderate ES (0.55) and SRM of 0.58, overall, and similar variability across treatment arms, with ES values from 0.26-0.79 and SRM values from 0.30-0.94. Physical function scores using the KOOS-PS and WOMAC physical function subscale showed comparable results with, on average, moderate ESs (0.53 and 0.52, respectively) and SRMs of 0.52 and 0.58, respectively, but with significant variability across treatment groups as noted above.

*Hip OA Participants:* Non-significant changes were seen for all measures following treatment among hip OA participants, both overall and across treatment groups. (**Table 2**) The corresponding ESs and SRMs were non-significant for all measures, but once again varied substantially across treatment arms.

### **Discussion**

In a five arm randomized trial comparing three active pharmacologic agents on blood pressure in individuals with hip and knee OA, the new OARSI-OMERACT pain and function measures were found to be responsive to pre-post treatment changes in pain and disability in participants with knee but not hip OA. For both the new measures and WOMAC pain and function subscale scores, no significant treatment

response was observed among hip OA patients overall, or by treatment arm. However, sample size per treatment arm was small within the hips OA group, potentially limiting power to detect significant pre-post change in symptoms. These findings complement those of previous studies, which documented the responsiveness of ICOAP and HOOS-PS/KOOS-PS to changes in pain and function, respectively, following total joint replacement surgery<sup>20,25</sup>.

As noted earlier, ICOAP was developed to evaluate, separately, the two distinct types of pain that patients with hip/knee OA experience (i.e. intermittent and constant pain), independent of the effect of OA on physical function. Using baseline scores for the measures assessed, we confirmed the very high correlation between WOMAC pain and function scores both for individuals with knee and hip OA (approximately 0.90 for both). In comparison, the correlations between ICOAP scores and either measure of knee function (WOMAC or KOOS) were substantially lower (0.75 – 0.81 and 0.51 – 0.62, respectively), indicating that the two new measures are evaluating different constructs.

The original qualitative study from which the ICOAP was developed also identified the predictability of the intermittent pain, when present, as important to patients with hip and knee OA. Participants reported that intense unpredictable intermittent pain was most distressing, and most likely to impact their ability to participate in valued activities. Unfortunately, intermittent pain predictability was not assessed in this trial. Since initiation of this trial, two predictability items have been developed and are being administered alongside the two pain subscales in individuals who report ‘pain that comes and goes’; these may be found on the OARSI website ([www.oarsi.org](http://www.oarsi.org)). These items ask about the frequency with which their intermittent pain comes on ‘without warning’ and ‘after a trigger’ (from never to always). Ongoing research in multiple longitudinal OA cohorts is evaluating the determinants and outcomes associated with different OA pain patterns, including the impact on treatment response, participation, demand for joint replacement, and health care utilization. Coupled with ongoing research

to elucidate the role of peripheral and central sensitization in painful OA, this research will be important in elucidating pain phenotypes within OA, the ultimate goal of which is to improve the targeting of pain interventions, and thus efficacy with respect to pain relief.

The HOOS-PS and KOOS-PS are shorter versions of the original HOOS and KOOS measures<sup>18,19</sup>, which were designed to evaluate a broader spectrum of physical function impairments in people with hip and knee OA than has been previously demonstrated using the WOMAC. In particular, the inclusion of items assessing sports-related activity limitations aim at over-coming the previously documented floor effects seen with the WOMAC function scale<sup>18</sup>. The current study was not designed to address this aspect of the new measures, and did not include the spectrum of individuals by age or arthritis severity that would be required to do so. The current study has, however, documented the responsiveness of the KOOS-PS in knee OA to pharmacologic intervention. As the KOOS-PS has fewer items (7 items)<sup>16</sup> than either the original WOMAC physical function scale (17 items)<sup>7</sup> or the validated WOMAC function short form (11 items)<sup>8,9</sup>, it may be less burdensome for patients to complete<sup>20</sup>. Further research is needed to compare these measures for use in higher functioning individuals, such as those with sports-related knee injury, with respect to ceiling and floor effects.

As noted, no treatment response was observed overall, or by treatment arm, for any measure, among hip OA trial participants. Although inadequate power due to a small number of patients may have limited our ability to detect meaningful changes following treatment, non-response to therapeutic intervention<sup>26</sup> and in the placebo arms<sup>27</sup> of controlled clinical trials of hip OA has also been reported by others. This finding supports the evaluation of the effect of pharmacologic interventions separately in individuals with hip versus knee OA, as well as the need for research to better understand why these differences in therapeutic response might occur<sup>28,29</sup>.

Some study limitations should be noted in addition to those above. First, the absence of significant improvement in hip OA pain and physical function precluded assessment of the responsiveness of the new measures in hip OA. Second, this is the first study to examine the responsiveness of the new OARSI-OMERACT measures in the context of OA pharmacologic therapeutic intervention; additional studies are warranted to confirm our findings, and to tease out whether or not difference in response may occur for individuals with different ICOAP pain patterns, incorporating the concept of intermittent pain predictability.

In conclusion, ICOAP and KOOS-PS have been shown to be responsive to changes in pain and function following pharmacologic intervention in OA. Additional research is warranted to confirm and elucidate explanations for differential therapeutic response in patients with hip versus knee OA, and to confirm the responsiveness of the ICOAP, HOOS-PS and KOOS-PS in larger samples of OA patients receiving myriad therapies, and across the spectrum of OA symptom severity. Assuming these studies confirm the responsiveness of these new measures, studies are needed to establish the degree of change associated with each measure that patients consider meaningful (i.e., the minimal clinically important difference). ICOAP is a multi-dimensional OA-specific measure designed to evaluate the pain experience in people with hip or knee OA, including pain intensity, frequency and impact on mood, sleep and quality of life, independent of the effect of pain on physical function. Thus, ICOAP is intended to be used together with a measure of physical function and should be seen as providing information that is complementary to that provided by the WOMAC pain scale, which largely evaluates pain on activity. For assessment of physical function in OA, ongoing research will test the hypothesis that, in high functioning individuals, such as those with sports related knee injury, use of the KOOS-PS and HOOS-PS is associated with reduced floor and ceiling affects relative to the WOMAC function subscale. If so, this would suggest these new measures be used preferentially in this clinical setting.

## **Author Contributions**

Conception and design: Hawker, Davis, Lohmander

Analysis and interpretation of the data: Bond, Hawker, Davis, Lohmander

Drafting of the article: Bond, Hawker

Critical revision of the article for important intellectual content: Hawker, Davis, Lohmander

Final approval of the article: Bond, Hawker, Davis, Lohmander

Provision of study materials or patients: Hawker, Lohmander, Davis

Statistical expertise: Hawker, Davis, Lohmander

Obtaining of funding: Hawker

Administrative, technical, or logistic support: Hawker

Collection and assembly of data: Hawker

## **Competing Interest Statement**

None of the authors have any competing interests related to this work.

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**Table 1 – Study Sample Characteristics**

<b>Demographic Characteristics</b>	<b>Knee N = 156</b>	<b>Hip N = 48</b>
Age – Mean (SD)	61.2 (9.2)	60.3 (9.4)
Female – n (%)	107 (68.6%)	33 (68.8%)
Caucasian – n (%)	129 (82.7%)	40 (83.3%)
OA symptom duration (years) – median (inter-quartile range)	7.4 (3.2-12.9)	6.4 (2.5-10.4)
Most painful joint – n (%)		
Right	102 (65.4%)	27 (56.25%)
Left	54 (34.6%)	21 (43.75%)
Treatment arm – n (%)		
1	33 (21.15%)	8 (16.7%)
2	36 (23.1%)	10 (20.8%)
3	28 (17.95%)	12 (25.0%)
4	33 (21.15%)	8 (16.7%)
5	26 (16.7%)	10 (20.8%)



**Table 2 – Pearson Correlation Coefficients between Pre-Treatment Scores\***

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; ICOAP = Intermittent and Constant Osteoarthritis Pain measure;

KOOS-PS = Knee Disability and Osteoarthritis Outcome Score Physical Function Short Form; HOOS-PS = Hip Disability and Osteoarthritis Outcome

Score Physical Function Short Form

	<b>WOMAC Pain</b>	<b>ICOAP Intermittent Pain</b>	<b>ICOAP Constant Pain</b>	<b>ICOAP Total</b>	<b>WOMAC Function</b>	<b>KOOS-PS/ HOOS-PS</b>
<b>Knee Osteoarthritis (n=156)</b>						
WOMAC Pain	1.00	0.79	0.75	0.81	0.91	0.55
ICOAP Intermittent Pain	0.79	1.00	0.81	0.95	0.78	0.61
ICOAP Constant Pain	0.75	0.81	1.00	0.95	0.76	0.57
ICOAP Total	0.81	0.95	0.95	1.00	0.81	0.62

WOMAC Function	0.91	0.78	0.76	0.81	1.00	0.57
KOOS-PS	0.55	0.61	0.57	0.62	0.57	1.00

**Hip Osteoarthritis (n=48)**

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WOMAC Pain	1.00	0.78	0.77	0.81	0.89	0.68
ICOAP Intermittent Pain	0.78	1.00	0.80	0.95	0.75	0.62
ICOAP Constant Pain	0.76	0.80	1.00	0.95	0.75	0.51
ICOAP Total	0.81	0.95	0.95	1.00	0.79	0.59
WOMAC Function	0.89	0.75	0.75	0.79	1.00	0.71
HOOS-PS	0.68	0.62	0.51	0.59	0.71	1.00

\* P values < 0.0001



**Table 3 – Baseline and Mean Change in Scores, Effect Sizes and Standardized Response Means for Pain and Function Measures**

ICOAP = Intermittent and Constant Osteoarthritis Pain measure; HOOS-PS = Hip Disability and Osteoarthritis Outcome Score Physical Function

Short Form; KOOS-PS = Knee Disability and Osteoarthritis Outcome Score Physical Function Short Form; WOMAC = Western Ontario and

McMaster Universities Osteoarthritis Index

Measure	Baseline Mean Scores (SD) (min-max)	Mean Change (SD)	Effect Size (95% CI)	Standardized Response Mean (95% CI)	
<b>Knee Osteoarthritis (n=156)(n per treatment group: 1 n=33; 2 n=36, 3 n=28, 4 n=33, 5 n=26) - PAIN</b>					
<b>ICOAP</b>	<b>Constant (5 arms combined)</b>	40.7 (22.5)	-10.3 (21.1)*	-0.46 (-0.61 - -0.32)	-0.49 (-0.65 - -0.34)
	<b>Trial Arm 1<sup>§</sup></b>	42.4 (20.9)	-9.4 (21.5)***	-0.45 (-0.95, -0.12)	-0.44 (-0.84, -0.12)
	<b>Trial Arm 2</b>	44.6 (22.9)	-11.4 (21.1)**	-0.50 (-0.86, -0.18)	-0.54 (-0.95, -0.23)
	<b>Trial Arm 3</b>	36.6 (21.1)	-8.0 (23.1)	-0.38 (-0.80, 0.03)	-0.35 (-0.76, 0.02)
	<b>Trial Arm 4</b>	41.5 (26.4)	-16.2 (21.7)**	-0.61 (-0.91, -0.39)	-0.75 (-1.05, -0.52)
	<b>Trial Arm 5</b>	36.35 (20.0)	-4.8 (16.8)	-0.24 (-0.58, 0.09)	-0.29 (-0.76, 0.10)
<b>Intermittent (5 arms combined)</b>		48.3 (20.1)	-10.9 (19.9)*	-0.54 (-0.72 - -0.38)	-0.55 (-0.75 - -0.38)
	<b>Trial Arm 1</b>	50.1 (18.5)	-12.0 (25.2)**	-0.65 (-1.27, -0.19)	-0.48 (-0.96, -0.14)
	<b>Trial Arm 2</b>	49.0 (21.35)	-9.0 (16.95)**	-0.42 (-0.83, -0.16)	-0.53 (-1.06, -0.20)
	<b>Trial Arm 3</b>	46.4 (20.4)	-9.2 (20.0)***	-0.45 (-0.97, -0.09)	-0.46 (-0.94, -0.09)
	<b>Trial Arm 4</b>	53.0 (19.9)	-19.1 (16.5)*	-0.96 (-1.41, -0.65)	-1.15 (-1.54, -0.89)

	<b>Trial Arm 5</b>	41.0 (19.6)	-3.7 (17.3)	-0.19 (-0.58, 0.17)	-0.21 (-0.64, 0.18)
	<b>Total (5 arms combined)</b>	44.8 (20.2)	-10.6 (18.8)*	-0.53 (-0.68 - -0.39)	-0.56 (-0.74 - -0.41)
	<b>Trial Arm 1</b>	46.6 (18.0)	-10.8 (22.1)**	-0.60 (-1.11, -0.17)	-0.49 (-0.97, -0.14)
	<b>Trial Arm 2</b>	47.0 (21.4)	-10.1 (16.9)**	-0.47 (-0.80, -0.20)	-0.60 (-1.09, -0.24)
	<b>Trial Arm 3</b>	42.0 (19.4)	-8.7 (19.7)***	-0.45 (-0.86, -0.09)	-0.44 (-0.89, -0.08)
	<b>Trial Arm 4</b>	47.8 (21.9)	-17.7 (16.9)*	-0.81 (-1.12, -0.61)	-1.05 (-1.42, -0.88)
	<b>Trial Arm 5</b>	38.9 (19.35)	-4.2 (16.6)	-0.22 (-0.56, 0.10)	-0.25 (-0.70, 0.10)
<b>WOMAC Pain</b>	<b>5 arms combined</b>	45.0 (21.6)	-11.8 (20.5)*	-0.55 (-0.72 - -0.40)	-0.58 (-0.75 - 0.43)
	<b>Trial Arm 1</b>	49.4 (20.2)	-15.9 (21.3)**	-0.79 (-1.27, -0.46)	-0.75 (-1.09, -0.47)
	<b>Trial Arm 2</b>	45.6 (22.0)	-8.6 (20.3)***	-0.39 (-0.76, -0.10)	-0.42 (-0.77, -0.12)
	<b>Trial Arm 3</b>	42.7 (20.2)	-10.2 (21.8)***	-0.50 (-0.96, -0.12)	-0.47 (-0.92, -0.11)
	<b>Trial Arm 4</b>	46.0 (22.4)	-17.2 (18.1)*	-0.77 (-1.15, -0.48)	-0.94 (-1.37, -0.64)
	<b>Trial Arm 5</b>	39.5 (23.3)	-6.0 (19.9)	-0.26 (-0.62, 0.095)	-0.30 (-0.73, 0.10)
<b>Knee Osteoarthritis (n=156)(n per treatment group: 1 n=33; 2 n=36, 3 n=28, 4 n=33, 5 n=26) - FUNCTION</b>					
<b>WOMAC Function</b>	<b>5 arms combined</b>	47.7 (22.7)	-11.8 (20.4)*	-0.52 (-0.68 - -0.37)	-0.58 (-0.74 - -0.42)
	<b>Trial Arm 1</b>	52.3 (21.0)	-15.85 (22.9)**	-0.76 (-1.27, -0.39)	-0.69 (-1.01, -0.41)
	<b>Trial Arm 2</b>	46.0 (23.3)	-6.1 (16.7)***	-0.26 (-0.55, -0.03)	-0.37 (-0.73, -0.04)
	<b>Trial Arm 3</b>	45.6 (23.2)	-9.3 (21.3)***	-0.40 (-0.75, -0.08)	-0.44 (-0.90, -0.08)
	<b>Trial Arm 4</b>	51.5 (22.0)	-20.8 (20.3)*	-0.94 (-1.47, -0.61)	-1.02 (-1.47, -0.73)
	<b>Trial Arm 5</b>	41.9 (23.8)	-5.0 (16.3)	-0.21 (-0.50, 0.07)	-0.31 (-0.80, 0.08)

<b>KOOS-PS</b>	<b>5 arms combined</b>	42.3 (13.0)	- 6.8 (13.1)*	-0.53 (-0.72 - -0.36)	-0.52 (-0.68 - -0.36)
	<b>Trial Arm 1</b>	48.0 (15.9)	-11.2 (16.0)**	-0.71 (-1.17, -0.36)	-0.70 (-1.08, -0.39)
	<b>Trial Arm 2</b>	39.8 (13.0)	-4.4 (13.3)	-0.34 (-0.75, 0.03)	-0.33 (-0.75, 0.03)
	<b>Trial Arm 3</b>	38.7 (12.1)	-4.9 (8.8)**	-0.40 (-0.97, -0.12)	-0.56 (-1.13, -0.15)
	<b>Trial Arm 4</b>	44.3 (11.0)	-10.6 (12.3)*	-0.96 (-1.55, -0.65)	-0.86 (-1.17, -0.61)
	<b>Trial Arm 5</b>	39.7 (9.95)	-1.7 (11.3)	-0.18 (-0.74, 0.27)	-0.16 (-0.65, 0.25)
<b>Hip Osteoarthritis (n=48) (n per treatment group: 1 n=8; 2 n=12, 3 n=12, 4 n=8, 5 n=10)- PAIN</b>					
<b>ICOAP</b>	<b>Constant (5 arms combined)</b>	35.4 (22.7)	- 4.2 (23.95)	-0.18 (-0.50 - 0.12)	-0.17 (-0.50 - 0.11)
	<b>Trial Arm 1</b>	38.75 (16.4)	-9.4 (10.5)***	-0.57 (-5.08, -0.14)	-0.89 (-2.02, -0.50)
	<b>Trial Arm 2</b>	46.0 (20.4)	-7.0 (32.9)	-0.34 (-2.03, 0.81)	-0.21 (-1.23, 0.49)
	<b>Trial Arm 3</b>	22.9 (21.4)	-2.9 (25.7)	-0.14 (-0.88, 0.57)	-0.11 (-0.87, 0.38)
	<b>Trial Arm 4</b>	35.0 (30.5)	6.25 (24.5)	0.21 (-0.35, 1.17)	0.26 (-0.77, 1.13)
	<b>Trial Arm 5</b>	37.5 (21.0)	-7.0 (20.3)	-0.33 (-1.10, 0.29)	-0.35 (-1.01, 0.35)
	<b>Intermittent (5 arms combined)</b>	42.9 (17.9)	- 2.5 (20.3)	-0.14 (-0.52 - 0.16)	-0.12 (-0.46 - 0.14)
	<b>Trial Arm 1</b>	43.2 (12.4)	-1.04 (14.4)	-0.08 (-1.27, 0.82)	-0.07 (-1.44, 0.74)
	<b>Trial Arm 2</b>	51.25 (22.05)	-6.25 (20.0)	-0.28 (-1.61, 0.24)	-0.31 (-1.13, 0.42)
	<b>Trial Arm 3</b>	34.4 (19.0)	1.04 (25.75)	0.06 (-0.94, 0.73)	0.04 (-1.04, 0.55)
	<b>Trial Arm 4</b>	38.5 (17.5)	4.69 (14.7)	0.27 (-0.36, 1.25)	0.32 (-0.60, 1.41)
	<b>Trial Arm 5</b>	47.9 (12.8)	-10.0 (21.8)	-0.78 (-2.42, 0.36)	-0.46 (-1.35, 0.27)
	<b>Total (5 arms combined)</b>	39.5 (19.1)	- 3.3 (20.0)	-0.17 (-0.49 - 0.14)	-0.17 (-0.49 - 0.12)

	<b>Trial Arm 1</b>	41.2 (13.2)	-4.8 (10.5)	-0.36 (-1.96, 0.14)	-0.46 (-1.73, 0.27)
	<b>Trial Arm 2</b>	48.9 (20.5)	-6.6 (24.8)	-0.32 (-1.72, 0.49)	-0.26 (-1.06, 0.45)
	<b>Trial Arm 3</b>	29.2 (19.4)	-0.8 (23.4)	-0.04 (-0.74, 0.67)	-0.03 (-1.01, 0.44)
	<b>Trial Arm 4</b>	36.9 (22.3)	5.4 (17.6)	0.25 (-0.26, 1.34)	0.31 (-0.58, 1.36)
	<b>Trial Arm 5</b>	43.2 (15.2)	-8.6 (19.0)	-0.57 (-1.41, 0.27)	-0.45 (-1.56, 0.19)
<b>WOMAC Pain</b>	<b>5 arms combined</b>	42.0 (21.9)	- 2.8 (20.8)	-0.13 (-0.42, 0.14)	-0.13 (-0.44 – 0.15)
	<b>Trial Arm 1</b>	44.2 (11.8)	-4.7 (6.6)	-0.40 (-1.60, -0.08)	-0.72 (-1.74, -0.17)
	<b>Trial Arm 2</b>	55.4 (26.0)	-11.0 (23.8)	-0.42 (-1.33, 0.10)	-0.46 (-1.12, 0.31)
	<b>Trial Arm 3</b>	30.75 (20.1)	+3.8 (20.45)	0.19 (-0.44, 0.81)	0.18 (-0.66, 0.70)
	<b>Trial Arm 4</b>	41.45 (20.15)	+6.9 (22.2)	0.34 (-0.51, 1.42)	0.30 (-0.52, 1.81)
	<b>Trial Arm 5</b>	40.8 (23.0)	-8.7 (22.7)	-0.38 (-1.18, 0.25)	-0.38 (-1.00, 0.36)
<b>Hip Osteoarthritis (n=48)(n per treatment group: 1 n=8; 2 n=12, 3 n=12, 4 n=8, 5 n=10)- - FUNCTION</b>					
<b>WOMAC Function</b>	<b>5 arms combined</b>	42.3 (23.5)	- 3.9 (20.9)	-0.17 (-0.43 – 0.06)	-0.19 (-0.46 – 0.07)
	<b>Trial Arm 1</b>	47.9 (20.5)	-4.5 (6.9)	-0.22 (-1.54, 0.03)	-0.65 (-2.05, 0.09)
	<b>Trial Arm 2</b>	46.0 (26.8)	-11.3 (24.5)	-0.42 (-1.12, 0.03)	-0.46 (-0.94, 0.12)
	<b>Trial Arm 3</b>	35.2 (25.0)	+1.7 (19.3)	0.07 (-0.37, 0.56)	0.08 (-0.69, 0.64)
	<b>Trial Arm 4</b>	39.5 (24.9)	+6.6 (19.2)	0.26 (-0.26, 1.42)	0.34 (-0.47, 1.22)
	<b>Trial Arm 5</b>	44.0 (20.6)	-9.55 (25.0)	-0.46 (-1.95, 0.29)	-0.38 (-1.17, 0.27)
<b>HOOS-PS</b>	<b>5 arms combined</b>	30.3 (17.8)	- 3.0 (16.6)	-0.17 (-0.4 – 0.1)	-0.18 (-0.45 – 0.1)
	<b>Trial Arm 1</b>	39.6 (14.75)	-10.3 (15.3)	-0.70 (-1.92, -0.03)	-0.67 (-1.77, -0.04)
	<b>Trial Arm 2</b>	33.7 (22.5)	-11.2 (19.25)	-0.50 (-1.00, -0.12)	-0.58 (-1.30, -0.13)

<b>Trial Arm 3</b>	22.6 (11.95)	+2.0 (12.96)	0.17 (-0.49, 0.84)	0.16 (-0.56, 0.79)
<b>Trial Arm 4</b>	27.4 (22.5)	+7.7 (16.43)	0.34 (-0.16, 1.09)	0.47 (-0.26, 1.93)
<b>Trial Arm 5</b>	30.4 (13.8)	-2.0 (13.2)	-0.14 (-0.89, 0.54)	-0.15 (-0.85, 0.83)

\* Indicates statistically significant improvement from baseline values at  $p < 0.0001$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.05$

§ Trial treatment arms were: naproxinod 750mg, naproxinod 375mg, naproxen 500mg, naproxen 250mg, and ibuprofen 600mg.