

1 **0801 ms 2101**

2 Assessment of leech therapy for knee osteoarthritis

3 A randomized study

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8 **Supplementary Article Data**

9 **Details of the randomization process**

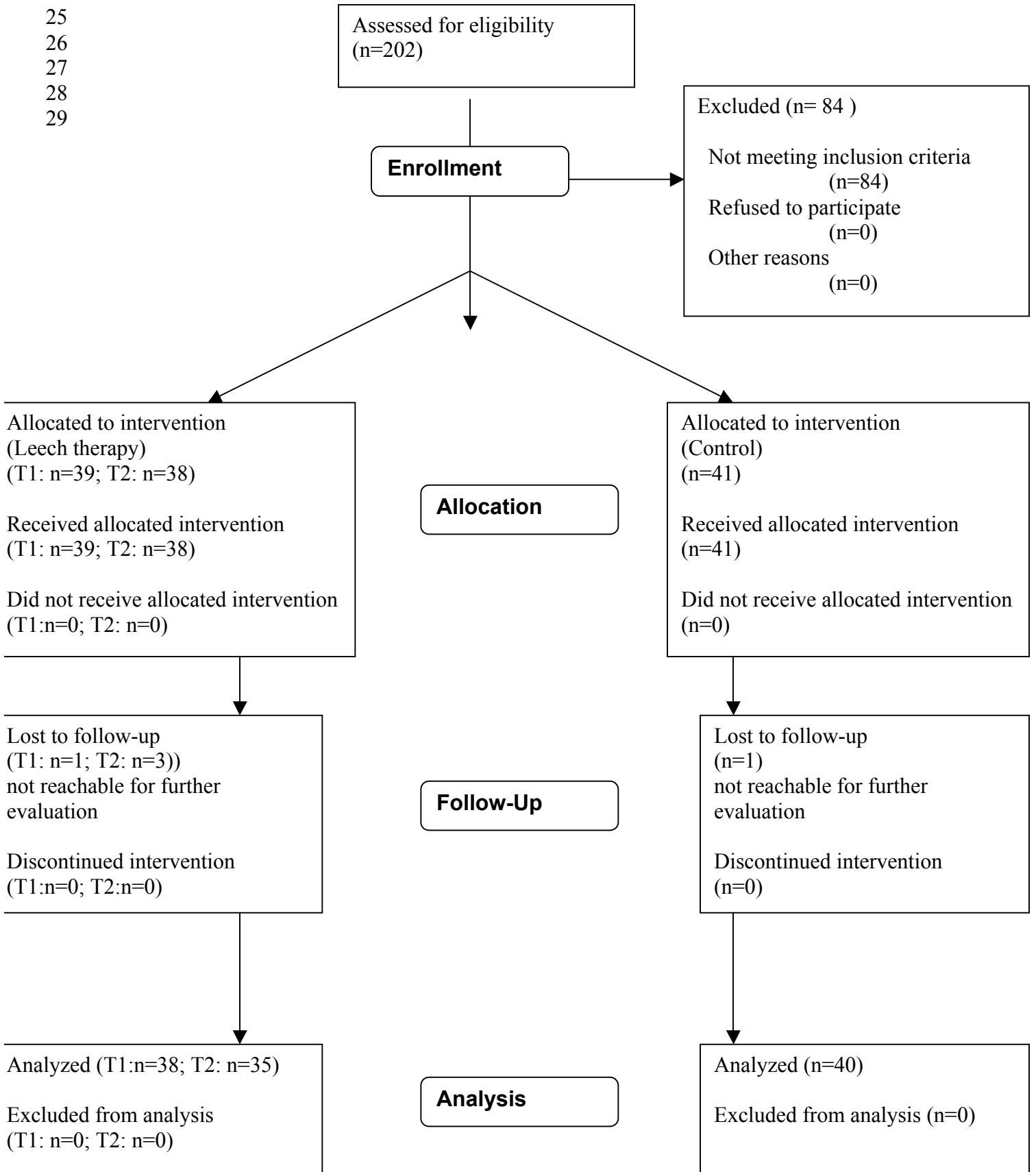
10 A specific computer program was used in order to create the randomization list defining
11 the treatment assignments of the patients. This list consisted of a random sequence of
12 balanced, randomly permuted treatment blocks of block lengths 6 [C,C,T,T,T,T] or 9
13 [C,C,C,T,T,T,T,T] (2:1 randomization). In generating this list, first the block lengths of
14 all treatment blocks (6 or 9) were chosen randomly with probability 0.5. Afterwards, for
15 each of these blocks one of the possible permutations of the treatments entailed in this
16 block was drawn randomly.

17 In accordance with this randomization list, a randomization box was built containing
18 sequentially ordered sealed envelopes. Each of these envelopes contained a card, on
19 which the type of therapy to be applied to the corresponding patient was printed.
20 Drawing and opening of the envelopes was done not before it was checked that a
21 specific patient fulfilled all inclusion and exclusion criteria and thus could be included into
22 the study.

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The Consort E-Flowchart

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29 Evaluation data and the changes over time of various parameters expressed as
 30 descriptive data and p-values determined with the paired Wilcoxon-test for the individual
 31 populations
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| Score | T1 | p-value | T2 | p-value | C | p-value |
|------------------|-----------------|------------------|-----------------|------------------|-----------------|------------------|
| | m(Q25;Q75) | | m(Q25;Q75) | | m(Q25;Q75) | |
| Cumulative KOOS | | | | | | |
| 0 | 44(35.5;58.5) | | 34(24.3;41.8) | | 45(33;54) | |
| 1 week | 50(39;63.1) | <0.001 | 45(36;54) | <0.001 | 45(37.8;58.5) | 0.02 |
| 4 weeks | 54.5(38.8;64.5) | <0.001 | 51(35.5;55) | <0.001 | 50(39;60) | 0.003 |
| 6 weeks | 54.5(39.8;66) | 0.003 | 51(36.8;60) | <0.001 | 50(34;60.5) | <0.001 |
| 3 months | 55(41;62) | <0.001 | 49(41;60.3) | <0.001 | 48(36;62) | 0.002 |
| 6 months | 54.5(40.3;66.5) | 0.015 | 51.5(35.6;60) | <0.001 | 48(35;70) | 0.048 |
| Cumulative WOMAC | | | | | | |
| 0 | 50(35.5;60) | | 58(50;70) | | 48(39;60) | |
| 1 week | 41.5(24.8;54) | <0.001 | 51(39.3;56.8) | <0.001 | 45.5(34.3;55.3) | 0.13 |
| 4 weeks | 38.5(28.8;50.3) | <0.001 | 43.5(33.8;55.8) | <0.001 | 44.5(29.5;52) | 0.03 |
| 6 weeks | 38(27.5;51.5) | 0.001 | 41(31.3;56) | <0.001 | 44(28.5;56.5) | 0.01 |
| 3 months | 38(29.5;51.5) | <0.001 | 43(34;52) | <0.001 | 45.5(27;56) | 0.049 |
| 6 months | 37.5(24.3;50.5) | 0.003 | 40(29.5;54) | <0.001 | 45(24;56) | 0.12 |
| VAS | | | | | | |
| 0 | 6.5(5;8) | | 7.5(7;8) | | 7(6;7.5) | |
| 1 week | 5(2.8;7) | <0.001 | 6(5;7) | <0.001 | 6.5(4.9;7.5) | 0.02 |
| 4 weeks | 5(3.8;6) | <0.001 | 5(4;6.5) | <0.001 | 6(5;7) | <0.001 |
| 6 weeks | 4.5(3.9;6) | 0.002 | 4(3;5) | <0.001 | 6.5(5;7) | <0.001 |
| 3 months | 4.5(3;6.3) | 0.002 | 4.3(3.5;5) | <0.001 | 6.5(4;7.5) | 0.004 |
| 6 months | 5(2.8;7.3) | 0.006 | 4(3;6.6) | <0.001 | 6.5(3;7.5) | 0.01 |
| Pain (WOMAC) | | | | | | |
| 0 | 11(9;13) | | 12(11;14) | | 10(7;12) | |
| 1 week | 9(4;11) | <0.001 | 10(6.1;11) | <0.001 | 9(5.8;12) | 0.13 |
| 4 weeks | 7(4.8;9.3) | <0.001 | 8.5(7;11) | <0.001 | 9(5;11) | 0.008 |
| 6 weeks | 7(4.5;10) | <0.001 | 7(5;10) | <0.001 | 10(5;12) | 0.01 |
| 3 months | 7(4.5;9) | <0.001 | 9(5;10) | <0.001 | 10(5;12) | 0.01 |
| 6 months | 7(5.5;10) | <0.001 | 8.5(4.2;11) | <0.001 | 9(6;12) | 0.21 |

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| Score | T1 | p-value | T2 | p-value | C | p-value |
|--------------------------------|---------------|--------------|-----------------|--------------|-----------------|--------------|
| | m(Q25;Q75) | | m(Q25;Q75) | | m(Q25;Q75) | |
| Stiffness (WOMAC) | | | | | | |
| 0 | 4.5(2.8;6) | | 6(4;7) | | 4(3;5) | |
| 1 week | 4(2;6) | 0.12 | 5(4;6) | <0.001 | 4(3.8;5.3) | 0.95 |
| 4 weeks | 4(2;5) | 0.01 | 4(3;6) | <0.001 | 4(2;6) | 0.63 |
| 6 weeks | 4(2;6) | 0.054 | 4(3;6) | <0.001 | 4(3;6) | 0.64 |
| 3 months | 4(2;4.5) | 0.02 | 4(2.3;5) | <0.001 | 4(2;6) | 0.86 |
| 6 months | 4(2;5) | 0.03 | 4(2.3;5) | <0.001 | 4(3;6) | 0.98 |
| Function (WOMAC) | | | | | | |
| 0 | 32(22.5;42.3) | | 41(35;50) | | 34(28;43) | |
| 1 week | 32(17.8;38.3) | <0.001 | 36(27.3;40.8) | <0.001 | 32.5(24.6;39) | 0.11 |
| 4 weeks | 27(18.8;37) | <0.001 | 30(24.3;41) | <0.001 | 32(20.8;38.3) | 0.009 |
| 6 weeks | 25(18.8;35.5) | 0.005 | 29(23;38) | <0.001 | 30(19.5;39) | 0.003 |
| 3 months | 27(20.5;37.5) | 0.004 | 31.5(23.3;38) | <0.001 | 32(20.8;39.3) | 0.03 |
| 6 months | 27.5(17;38) | 0.02 | 28(23.3;39) | <0.001 | 32(17;38) | 0.03 |
| Pain (KOOS) | | | | | | |
| 0 | 44(33;57) | | 36(28;42) | | 44(36;58) | |
| 1 week | 53(39;72) | <0.001 | 48.5(37.9;63.3) | <0.001 | 48.5(38.3;64.8) | 0.03 |
| 4 weeks | 58(46.3;69.5) | <0.001 | 50(39;62.1) | <0.001 | 50(39;64) | 0.02 |
| 6 weeks | 63(48.5;73.5) | <0.001 | 58(47;66.3) | <0.001 | 47(35;70.5) | 0.002 |
| 3 months | 61(47;70.5) | <0.001 | 50(42;64) | <0.001 | 50(39;69) | 0.009 |
| 6 months | 56(42;72) | <0.001 | 54.5(39;68.5) | <0.001 | 50(39;69) | 0.16 |
| ADL (KOOS) | | | | | | |
| 0 | 53(37.8;66) | | 40(26;49) | | 50(37;59) | |
| 1 week | 53(43.8;74.3) | <0.001 | 47(40.3;59.8) | <0.001 | 52.5(42.8;63.9) | 0.11 |
| 4 weeks | 60.5(46;72.5) | <0.001 | 55.5(40;64.5) | <0.001 | 53(42.8;69.3) | 0.008 |
| 6 weeks | 63(46;72.3) | 0.005 | 56(43.3;66) | <0.001 | 56(43;71) | 0.003 |
| 3 months | 60(48;71) | 0.001 | 53.5(44;65.8) | <0.001 | 53(42.5;69.5) | 0.03 |
| 6 months | 59.5(44;77) | 0.02 | 58.5(43;65.8) | <0.001 | 53(44;75) | 0.02 |
| Requirement of pain medication | | | | | | |
| 0 | 100(100;100) | | 100(100;100) | | 100(100;100) | |
| 1 week | 70(0;100) | 0.008 | 50(0;100) | <0.001 | 100(100;100) | 1.00 |
| 4 weeks | 28.5(0;92.5) | 0.002 | 43(0;100) | <0.001 | 100(100;100) | 1.00 |
| 6 weeks | 32(0;100) | 0.002 | 48(0;100) | <0.001 | 100(100;100) | 1.00 |
| 3 months | 12(0;100) | 0.001 | 45.5(0;100) | 0.003 | 100(100;100) | 1.00 |
| 6 months | 37.5(0;100) | 0.001 | 50(21.8;73) | 0.04 | 100(100;100) | 1.00 |

37 Evaluation of the differences obtained for various parameters over time expressed as
 38 descriptive data and p-values determined with the unpaired Wilcoxon-test for the
 39 individual populations
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| Score | T1 | T2 | C | p-value | p-value | p-value |
|------------------|------------------|-----------------|--------------|--------------|------------------|--------------|
| | m(Q25;Q75) | m(Q25;Q75) | m(Q25;Q75) | C-T1 | C-T2 | T1-T2 |
| Cumulative KOOS | | | | | | |
| 1 week vs. BI | 5(-0.3;12) | 9.5(3;18) | 3(-1;8) | 0.21 | 0.002 | 0.047 |
| 4 weeks vs. BI | 10.5(2;16.3) | 15(2.8;20.8) | 4(-2;10) | 0.16 | 0.009 | 0.15 |
| 6 weeks vs. BI | 11(-2.3;17.3) | 21(4.5;24.8) | 4(-1.5;9) | 0.23 | <0.001 | 0.003 |
| 3 months vs. BI | 7(-2;15) | 13.8(5.3;24) | 4(-2;11) | 0.54 | 0.007 | 0.02 |
| 6 months vs. BI | 6(-2.1;14.8) | 18(3;24.8) | 3(-5;12) | 0.65 | 0.02 | 0.04 |
| Cumulative WOMAC | | | | | | |
| 1 week vs. BI | -8(-13.5;-1.8) | -10.5(-15.5;-4) | -2.5(-9;3.5) | 0.04 | 0.005 | 0.34 |
| 4 weeks vs. BI | -11.5(-19.3;-5) | -13.5(-19;-4.3) | -4(-10;3) | 0.02 | 0.01 | 0.77 |
| 6 weeks vs. BI | -14.5(-22.3;0.3) | -17.5(-25;-2) | -2(-7.5;4) | 0.03 | 0.002 | 0.35 |
| 3 months vs. BI | -8.5(-19;0) | -14(-29.8;-4) | -4(-11;4) | 0.18 | 0.005 | 0.053 |
| 6 months vs. BI | -8(-22;0) | -16.5(-28.8;0) | -1(-11;5) | 0.20 | 0.02 | 0.21 |
| VAS | | | | | | |
| 1 week vs. BI | -1(-2;0) | -1.5(-2.4;0) | 0(-1;0) | 0.06 | <0.001 | 0.37 |
| 4 weeks vs. BI | -1.3(-2;0) | -2(-3.9;-0.5) | 0(-1.5;0) | 0.07 | <0.001 | 0.053 |
| 6 weeks vs. BI | -1.8(-3.5;0) | -3(-4;-2) | 0(-1;0) | 0.01 | <0.001 | 0.005 |
| 3 months vs. BI | -1(-3.5;0) | -2.8(-3.5;-1.6) | 0(-1.5;0) | 0.07 | <0.001 | 0.03 |
| 6 months vs. BI | -1(-3;0) | -3(-4;-0.3) | 0(-2.4;0) | 0.35 | 0.015 | 0.07 |
| Pain (WOMAC) | | | | | | |
| 1 week vs. BI | -2(-4.3;-0.8) | -2(-4.8;0) | -1(-3;1) | 0.02 | 0.03 | 0.94 |
| 4 weeks vs. BI | -4(-5.1;-2) | -3(-5;-1.3) | -1(-3;0) | 0.002 | 0.008 | 0.46 |
| 6 weeks vs. BI | -3.5(-5.1;-1.8) | -4.5(-5.8;-2.3) | -1(-3;1) | 0.002 | <0.001 | 0.31 |
| 3 months vs. BI | -3(-5;-0.5) | -3(-6;-2) | -1(-3;1) | 0.02 | 0.002 | 0.42 |
| 6 months vs. BI | -3(-5;0) | -3.5(-6;-1) | 0(-3;1) | 0.007 | 0.001 | 0.22 |

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| Score | T1 | T2 | C | p-value | p-value | p-value |
|--------------------------------|-------------------|------------------|------------|--------------|------------------|--------------|
| | m(Q25;Q75) | m(Q25;Q75) | m(Q25;Q75) | C-T1 | C-T2 | T1-T2 |
| Stiffness (WOMAC) | | | | | | |
| 1 week vs. BI | 0(-1;0) | -1(-2;0) | 0(-1;1) | 0.30 | 0.002 | 0.01 |
| 4 weeks vs. BI | 0(-2;1) | -1.5(-2;-1) | 0(-1;1) | 0.31 | <0.001 | 0.06 |
| 6 weeks vs. BI | -0.5(-2;0.3) | -2(-2;-1) | 0(-1;1) | 0.28 | <0.001 | 0.008 |
| 3 months vs. BI | -1(-2;0.5) | -2(-2;-0.3) | 0(-1;1) | 0.14 | <0.001 | 0.03 |
| 6 months vs. BI | 0(-2;0) | -2(-3;-0.3) | 0(-1;1) | 0.10 | <0.001 | 0.02 |
| Function (WOMAC) | | | | | | |
| 1 week vs. BI | -5(-9;-0.8) | -6(-11.5;-0.3) | -2(-7;3) | 0.12 | 0.02 | 0.35 |
| 4 weeks vs. BI | -7.5(-13;-2.8) | -9.5(-12.8;-2) | -3(-9;2) | 0.10 | 0.04 | 0.56 |
| 6 weeks vs. BI | -8.5(-13.3;2.3) | -11(-17.8;-1) | -3(-7;2) | 0.24 | 0.008 | 0.07 |
| 3 months vs. BI | -4.5(-11;1.5) | -9.5(-19.5;-1.3) | -3(-8;2) | 0.50 | 0.02 | 0.051 |
| 6 months vs. BI | -4(-13.5;0.5) | -12.5(-19.8;1) | -2(-8;2) | 0.55 | 0.04 | 0.20 |
| Pain (KOOS) | | | | | | |
| 1 week vs. BI | 11(1.5;19) | 12(0.5;25) | 4(0;9) | 0.05 | 0.02 | 0.44 |
| 4 weeks vs. BI | 17(4.3;23.5) | 17(4.3;25) | 4(-3;13) | 0.005 | 0.003 | 0.68 |
| 6 weeks vs. BI | 14.8(4.3;25) | 21(11;29.5) | 3(-3;11) | 0.006 | <0.001 | 0.13 |
| 3 months vs. BI | 14.8(2.8;23) | 17(11;28) | 3(-3;11) | 0.03 | <0.001 | 0.18 |
| 6 months vs. BI | 11.8(0;25) | 18(5.3;30.3) | 0(-6;14) | 0.048 | 0.01 | 0.13 |
| ADL (KOOS) | | | | | | |
| 1 week vs. BI | 7(0.8;13) | 12(1;17) | 2(-4;10) | 0.15 | 0.02 | 0.23 |
| 4 weeks vs. BI | 11(4.3;19) | 14(3;20) | 4(-3;13) | 0.11 | 0.04 | 0.56 |
| 6 weeks vs. BI | 13(-4.3;19.3) | 16(2;26) | 4(-3;11) | 0.29 | 0.008 | 0.08 |
| 3 months vs. BI | 6.5(-4.5;21.3) | 16(2;29) | 5(-3;11) | 0.40 | 0.007 | 0.053 |
| 6 months vs. BI | 5.5(-0.8;15.8) | 19(-1;29) | 3(-3;11) | 0.67 | 0.04 | 0.07 |
| Requirement of pain medication | | | | | | |
| 1 week vs. BI | -30(-89.5;0) | -37.5(-100;0) | 0(0;0) | 0.01 | 0.006 | 0.94 |
| 4 weeks vs. BI | -57(-100;0) | -53.5(-100;0) | 0(0;0) | 0.005 | 0.007 | 0.58 |
| 6 weeks vs. BI | -50(-100;0) | -51(-100;0) | 0(0;0) | 0.006 | <0.001 | 0.77 |
| 3 months vs. BI | -43(-100;0) | -52(-100;0) | 0(0;0) | 0.005 | 0.001 | 0.84 |
| 6 months vs. BI | -72.5(-100;-33.3) | -50(-74.5;-12.5) | 0(0;0) | 0.001 | 0.001 | 0.24 |

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