**Supplemental file - Amoxicillin did not reduce Modic change oedema in patients with chronic low back pain – subgroup analyses of a randomised trial (the AIM study)**

**Table A1 - Inclusion and exclusion criteria for the AIM (Antibiotics In Modic changes) study**

|  |  |
| --- | --- |
| **Inclusion criteria** | **Exclusion criteria** |
| * Age between 18 and 65 years
* Low back pain (LBP) of more than 6 months duration in the area below the 12th rib and above the gluteal folds with a Numerical Rating Scale (NRS) pain intensity score of ≥5 (mean of three 0–10 NRSs: current LBP, the worst LBP within the last 2 weeks, and the usual/ mean LBP within the last 2 weeks)
* MRI-confirmed lumbar disc herniation within the preceding 2 years
* Type 1 and/or type 2 MC in the vertebral body marrow at the same level as the previously herniated disc. For patients with previous surgery for disc herniation, the MC has to be located at an operated level
* Written informed consent
 | * Allergy to penicillin or cephalosporins
* Allergy/hypersensitivity to any of the excipients of the study drug
* Current pregnancy or lactation
* Kidney (creatinine) or hepatic (ALAT/ASAT) laboratory values above the normal range
* Phenylketonuria (Følling’s disease)
* Mononucleosis or leukaemia
* Any specific diagnosis that may explain the patient’s low back symptoms (e.g., tumour, fracture, spondyloarthritis, infection, spinal stenosis)
* Previous low back surgery (L1–S1) for reasons other than disc herniation (e.g., fusion, decompression, disc prosthesis)
* Surgery for disc herniation within the last 12 months
* Previous surgery for disc herniation, but MC located at level(s) that has/have not been operated on only
* Reservation about the intake of gelatine (the capsules used to encapsulate the study medicine contains gelatine, which, among other things, is produced using ingredients derived from pigs)
* Regular use of glucocorticoids
* Regular use of opioids with the exception of codeine and tramadol
* Not understanding Norwegian language
* Unlikely to adhere to treatment and/or complete follow-up (e.g., serious ongoing psychiatric disease, drug abuse, plans to move)
* Antibiotic treatment within the preceding one month before treatment start
* Contraindications to MRI (e.g., cardiac pacemaker electrodes, metal implant in the eye or brain, claustrophobia)
* Unwilling to participate
 |

**Description of the per protocol population (155 of 180 randomized patients)**

The per protocol population consisted of all patients who completed the trial without major protocol deviations, defined as:

(a) intake of <80% of the pills (amoxicillin or placebo),

(b) pause of the study medication for ≥2 weeks (in the antibiotic group: without other ‘relevant’ antibiotic treatment in that period, i.e. treatment likely to affect *a Cutibacterium acnes* discitis),

(c) ‘relevant’ antibiotic treatment in the placebo group for ≥4 continuous weeks between baseline and one-year follow-up, and

(d) back surgery during the one-year follow-up.

Further events registered as major protocol deviations were incorrect enrolment (2 patients treated with antibiotics last month prior to inclusion), both amoxicillin and placebo given to patient by mistake (1 patient), and spondyloarthritis diagnosed during follow-up (1 patient).

See summary in the table below.

|  |  |
| --- | --- |
| **Amoxicillin group**  | **Placebo group**  |
| **89** Randomized (intention to treat population) | **91** Randomized (intention to treat population) |
| **77** Completed trial without major protocol deviations (**per protocol population**) | **78** Completed trial without major protocol deviations (**per protocol population**) |
|  |  |
|  **3** End of study before 3 months  |  **2** End of study before 3 months  |
|  **7** Treatment non-completion |  **8** Treatment non-completion |
|  **1** Operation for disc herniation |  **1** Diagnosed as having spondyloarthritis |
|  **1** Incorrect enrolment |  **1** Given both amoxicillin and placebo |
|  |  **1** Incorrect enrolment |

|  |
| --- |
| **Table A2 - Variables included in the multiple imputation model\*** |
|  | **Variable type used in model** | **Missing %** | **Application in model** |
| Treatment group (amoxicillin or placebo) | Nominal | 0 | Use as predictor only |
| Prior surgery for disc herniation (yes/no) | Nominal | 0 | Use as predictor only |
| **MC type group** (1 or 2) | Nominal | 0 | Use as predictor only |
| **STIR volume** (0-4)  | Scale | 0 | Use as predictor only |
| **STIR height** (continuous) | Scale | 0 | Use as predictor only |
| **STIR intensity** (<25%, 25-40%, >40%) | Ordinal | 0 | Use as predictor only |
| **MC volume** (1-4) | Scale | 0 | Use as predictor only |
| **MC height** (continuous) | Scale | 0 | Use as predictor only |
| Age (continuous) | Scale | 0 | Use as predictor only |
| Comorbidity (score 1, 2 or >2) | Ordinal  | 0 | Use as predictor only |
| EQ5D-5L baseline | Scale  | 0 | Use as predictor only |
| Leg pain baseline (0-10) | Scale  | 0.56 | Impute and use as predictor  |
| FABQ physical activity (0-24) | Scale  | 0.56 | Impute and use as predictor |
| Emotional distress (HSCL-25) | Scale  | 0.56 | Impute and use as predictor |
| Body mass index (continuous) | Scale  | 0.56 | Impute and use as predictor |
| Smoking (yes/no) | Nominal  | 1.11 | Impute and use as predictor |
| RMDQ baseline (0-24) | Scale  | 1.11 | Impute and use as predictor |
| Back pain intensity baseline (0-10) | Scale  | 1.11 | Impute and use as predictor |
| ODI baseline (0-100) | Scale  | 1.67 | Impute and use as predictor |
| FABQ work (0-42) | Scale  | 2.22 | Impute and use as predictor |
| **1ySTIR change** (decreased or not) | Nominal  | 4.44 | Impute and use as predictor |
| **1yMC1vol change** (smaller or not) | Nominal  | 4.44 | Impute and use as predictor |
| RMDQ 3 months | Scale  | 4.44 | Impute and use as predictor |
| ODI 3 months | Scale  | 5.00 | Impute and use as predictor |
| Back pain intensity 3 months | Scale  | 5.56 | Impute and use as predictor |
| RMDQ one-year | Scale  | 6.11 | Impute and use as predictor |
| ODI one-year | Scale  | 6.11 | Impute and use as predictor |
| Back pain intensity one-year | Scale  | 6.11 | Impute and use as predictor |
| EQ5D-5L 3 months | Scale  | 6.67 | Impute and use as predictor |
| EQ5D-5L 12 months | Scale  | 7.22 | Impute and use as predictor |
| RMDQ 6 months | Scale  | 10.56 | Impute and use as predictor |
| Back pain intensity 6 months | Scale  | 11.11 | Impute and use as predictor |
| RMDQ 9 months | Scale  | 13.33 | Impute and use as predictor |
| Back pain intensity 9 months | Scale  | 13.89 | Impute and use as predictor |
| Physical workload (1-4) | Scale  | 16.11 | Impute and use as predictor |
| **STIR3** (yes/no) | Nominal | 0 | Imputation stratified on STIR3 |
| **STIR3** (yes/no)**\*1ySTIR change** (decreased or not) | Interaction |  | Added after imputation |
| **STIR3** (yes/no)**\*treatment group** | Interaction |  | Added after imputation |
| MC, Modic Change. STIR, Short Tau Inversion Recovery. EQ5D-5L, EuroQol 5L Questionnaire. FABQ, Fear-Avoidance Beliefs Questionnaire. RMDQ, Roland-Morris Disability Questionnaire. ODI, Oswestry Disability Index.\*The multiple imputation model (n=180) was performed with SPSS 26, using the fully conditional specification, 100 imputations, predictive mean matching for scale variables, variables ordered by less to more missingness, and Mersenne Twister as random number generator with a fixed starting point (2 000 000). We stratified the imputation on STIR3 (yes/no) and used the imputed data set to derive the interactions with STIR3. The planned 50 imputations (but not 100 imputations) provided a slightly high λ-value (0.23) in one analysis.  |

**Table A3 – Baseline characteristics by treatment group**

|  |  |  |
| --- | --- | --- |
|  | Amoxicillin groupN = 89 | Placebo groupN = 91 |
|  | n | % | n | % |
| **Age**, mean (SD) | 44.7 (9.0) | 45.2 (9.0) |
| **Sex**, women | 53 | 60 | 52 | 57 |
| **RMDQ** score, mean (SD) | 12.7 (4.7), n=88 | 12.8 (3.7), n=90 |
| **LBP Intensity** score, mean (SD) | 6.4 (1.2), n=88 | 6.3 (1.5), n=89 |
| **LBP Duration,** years, median (IQR) | 3.0 (1.5-5.6), n=89 | 3.4 (1.7-7), n=90 |
| **Prior disc herniation surgery**, yes | 18 | 20 | 20 | 22 |
| **MC type group**,type 1 | 58 | 65 | 60 | 66 |
| **Body mass index**, mean (SD) | 26.1 (4.1), n=89 | 25.9 (4.0), n=90 |
| **Smoking**, yes | 25 | 28 | 21 (of 89) | 24 |
| **Physical workload** |
|  Mostly sitting | 37 (of 77)  | 48 | 26 (of 74)  | 35 |
|  Job requires a lot of walking | 20 (of 77)  | 26 | 20 (of 74)  | 27 |
|  Job requires a lot of walking and lifting | 17 (of 77)  | 22 | 24 (of 74) | 32 |
|  Job requires physically heavy work |  3 (of 77)  |  4 |  4 (of 74)  |  5 |
| **Index level(s)**  |
|  L2/L3 |  2 |  2.2 |  2 |  2.2 |
|  L3/L4 |  7 |  7.9 |  5 |  5.5 |
|  L4/L5 | 48 | 53.9 | 29 | 31.9 |
|  L5/S1 | 58 | 65.2 | 74 | 81.3 |
| **STIR composite group** |
|  STIR 1 | 23 | 25.8 | 25 | 27.5 |
|  STIR 2 | 42 | 47.2 | 45 | 49.5 |
|  STIR 3 | 24 | 27.0 | 21 | 23.1 |
| **STIR volume\*** |
|  0 (0%) | 11 | 12.4 |  5 |  5.5 |
|  1 (<10%) | 21 | 23.6 | 27 | 29.7 |
|  2 (<25%) | 31 | 34.8 | 36 | 39.6 |
|  3 (25-50%) | 21 | 23.6 | 18 | 19.8 |
|  4 (>50%) |  5 |  5.6 |  5 |  5.5 |
| **MC volume\*** |
|  1 (<10%) | 17 | 19.1 | 15 | 16.5 |
|  2 (<25%) | 33 | 37.1 | 35 | 38.5 |
|  3 (25-50%) | 30 | 33.7 | 29 | 31.9 |
|  4 (>50%) |  9 | 10.1 | 12 | 13.2 |
| SD, standard deviation. RMDQ, Roland-Morris disability questionnaire. LBP, low back pain. IQR, interquartile range. MC, Modic change. STIR, short tau inversion recovery.\* Highest score at an index-level endplate (% of vertebral body marrow volume; visually estimated) |

**Table A4 – Inter-rater agreement for MRI change variables**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | A vs. B |  | A vs. C |  | B vs. C |  | All observes |
|   |   | N | Kappa (95%CI) |   | N | Kappa (95%CI) |   |  N | Kappa (95%CI) |   | **Mean** |
| **1ySTIR change** (decreased, unchanged, increased) |  |  |  |  |  |  |  | **0.71** |
|  | L4/L5 sup to disc | 172 | 0.83(0.73,0.93) |  | 172 | 0.68(0.56,0.80) |  | 172 | 0.62(0.49,0.75) |  |  |
|  | L4/L5 inf to disc | 172 | 0.80(0.69,0.92) |  | 172 | 0.66(0.53,0.79) |  | 172 | 0.64(0.51,0.77) |  |  |
|  | L5/S1 sup to disc | 172 | 0.82(0.74,0.89) |  | 172 | 0.67(0.58,0.77) |  | 172 | 0.64(0.54,0.74) |  |  |
|  | L5/S1 inf to disc | 172 | 0.84(0.76,0.92) |  | 172 | 0.66(0.56,0.75) |  | 172 | 0.64(0.54,0.74) |  |  |
| **1ySTIRvol change** (smaller, unchanged, larger) |  |  |  |  |  |  |  | **0.72** |
|  | L4/L5 sup to disc | 172 | 0.74(0.61,0.86) |  | 172 | 0.72(0.60,0.84) |  | 172 | 0.57(0.43,0.72) |  |  |
|  | L4/L5 inf to disc | 172 | 0.77(0.64,0.89) |  | 172 | 0.75(0.62,0.87) |  | 172 | 0.70(0.56,0.83) |  |  |
|  | L5/S1 sup to disc | 172 | 0.82(0.74,0.90) |  | 172 | 0.67(0.57,0.77) |  | 172 | 0.67(0.57,0.77) |  |  |
|  | L5/S1 inf to disc | 172 | 0.85(0.78,0.93) |  | 172 | 0.69(0.59,0.79) |  | 172 | 0.71(0.61,0.80) |  |  |
| **1yMC1vol change on T1/T2** (smaller, unchanged, larger) |  |  |  |  |  |  | **0.74** |
|  | L4/L5 sup to disc  | 66 | 0.73(0.59,0.87) |  | 71 | 0.83(0.72,0.95) |  | 65 | 0.79(0.66,0.91) |  |  |
|  | L4/L5 inf to disc | 67 | 0.59(0.42,0.76) |  | 73 | 0.70(0.55,0.84) |  | 67 | 0.75(0.60,0.89) |  |  |
|  | L5/S1 sup to disc | 126 | 0.70(0.58,0.82) |  | 131 | 0.74(0.63,0.84) |  | 127 | 0.72(0.61,0.83) |  |  |
|  | L5/S1 inf to disc | 119 | 0.82(0.72,0.91) |  | 127 | 0.74(0.63,0.85) |  | 122 | 0.76(0.66,0.87) |  |  |
| **1yMCvol change on T1/T2** (smaller, unchanged, larger) |  |  |  |  |  |  |  | **0.68** |
|  | L4/L5 sup to disc | 66 | 0.73(0.53,0.93) |  | 71 | 0.74(0.52,0.95) |  | 65 | 0.62(0.37,0.88) |  |  |
|  | L4/L5 inf to disc | 67 | 0.77(0.58,0.96) |  | 73 | 0.66(0.43,0.89) |  | 67 | 0.69(0.48,0.90) |  |  |
|  | L5/S1 sup to disc | 126 | 0.78(0.64,0.92) |  | 131 | 0.53(0.34,0.72) |  | 127 | 0.63(0.46,0.81) |  |  |
|  | L5/S1 inf to disc | 119 | 0.73(0.56,0.89) |  | 127 | 0.71(0.56,0.87) |  | 122 | 0.58(0.40,0.75) |  |  |
| MRI=magnetic resonance imaging. STIR=short tau inversion recovery, N=number of patients with data from both observers, 95%CI=95% confidence interval, MC=Modic change, sup=superior, inf=inferior. T1/T2=T1- and T2-weighted fast spin-echo images.Variables are change in MC oedema on STIR based on volume and intensity of high signal (**1ySTIR change**) and based on volume of high signal alone (**1ySTIRvol change**) and change in volume of the type 1 part of MCs (**MC1vol change**) and in total MC volume (any type) (**MCvol change**) on T1/T2-weighted series from baseline to one-year follow-up. Tabled are linearly weighted Cohen’s kappa values with 95%CIs for observer pairs AB, AC and BC and mean kappa for all observer pairs.  |