# ANNEX

## PATIENT REPORTED OUTCOMES (PRO'S)

*Short-Form-36 Health Survey (SF-36)*

The SF-36 is a generic, health-related quality of life instrument (1,2). It consists of 35 items, which are used to assess eight health domains; 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. One additional item assesses change of health over the past year and is not scored. Individual items are scored on Likert scales and item responses summed to produce the eight scale scores, which are then transformed linearly into a 0–100 scale, with 100 representing the best possible state of health. Two summary scores, the physical component summary (PCS) and the mental component summary (MCS), are provided and are standardised to reflect a general population mean of 50 and a SD of 10 (3). The SF-36 has been widely used in normal and diseased populations, including subjects with fibromyalgia (4).

*Fibromyalgia Impact Questionnaire (FIQ)*

The FIQ is a disease specific, self-report instrument developed and validated in 1991 to measure health status in patients with fibromyalgia (5). Modifications were made in 1997, 2002, and 2009, each with different scoring systems. Subscales in the original 1991 version, which was applied in this study, include physical function (10 sub-items), feel good (1 item), missed work (1 item), do job (1 item), pain (1 item), fatigue (1 item), rested (1 item), stiffness (1 item), anxiety (1 item), and depression (1 item). The physical function items use a 4-point Likert scale response set ranging from "always to never". The feel good item response set is the number of days of the past week. The work missed item response is the number of workdays in the past week. The other symptom-based items use 100-mm anchored visual analogue scales. The score for each item, all standardised to range from 0–10, can be reported individually or summed to report a FIQ total score ranging from 0–100, with higher scores indicating more disease impact. The FIQ is one of the most widely used assessment instruments in fibromyalgia populations, having been cited in over 300 papers and recommended as a primary efficacy endpoint in fibromyalgia clinical trials (6). Adequate test-retest stability (7) and concurrent validity of the FIQ subscales, including depression and anxiety subscales, are reported (5).

*Generalised Anxiety Disorder (GAD-10)*

GAD-10 is a self-report instrument developed from the Hamilton 6-item anxiety scale (HAM-A6) to assess the severity of generalised anxiety, but is not a diagnostic tool. It contains 10 items, each of which are scored on a 6-point Likert scale according to how much of the time the individual symptom has been present during the past 14 days; 0 representing 'the symptom has not been present at all' and 5 representing 'the symptom has been present all of the time'. Scores are summed up with a theoretical score range from 0–50. Scores between 15–19 are suggested to represent mild anxiety disorder, between 20–29 moderate anxiety disorder, and between 30–50 severe anxiety disorder (8).

*Major Depression Inventory (MDI)*

The MDI is developed to cover both the ICD-10 and DMS-IV symptoms of depression (9). It contains 10 items, each of which are scored on a 6-point Likert scale according to how much of the time the individual symptom has been present during the past 14 days; 0 representing 'the symptom has not been present at all' and 5 representing 'the symptom has been present all of the time'. Item 8 and 10 are divided into two sub-items, a and b, but only the highest score on each item is included in the overall scoring of the instrument. As a diagnostic instrument, the MDI items are dichotomised to indicate the presence or absence of each of the symptoms. In both DSM-IV and ICD-10 the items of depressed mood and lack of interest in daily activities (item 1 and 2) are considered core symptoms of depression. In ICD-10, the lack of energy (item 3) is also considered a core symptom. Consequently, for diagnostic purposes, item 1, 2and 3 are considered significantly present at scores 4 and 5 (i.e. most of the time, all of the time). For the remaining items (item 4–10) the symptom is considered significantly present at scores 3 to 5 (i.e. more than half of the time, most of the time, and all of the time). The algorithm for DSM-IV is: items 4 and 5 are combined and only the highest score is considered. Thus, the number of items is 9. Major depression is defined as the presence of at least five of the nine items. However, either item 1 or item 2 should be among the five items. The algorithm for ICD-10 moderate to severe (major) depression is the presence of at least two of the three core symptoms (items 1–3) and at least four of the other seven items (9). As a measuring instrument, the 10 items are summed up with a theoretical score range from 0–50. A cutoff at 20 representing clinical depression (mild, moderate, severe) and 26 representing major (moderate, severe) depression have been proposed (10,11). The MDI has been validated in mental health (10,12) as well as population-based samples (11) and used in prevalence studies of major depression in the Danish background population (13).

*The Coping Strategy Questionnaire (CSQ)*

The CSQ is a self-report instrument used to evaluate one behavioural and six cognitive coping strategies (14). Scoring of items on each coping strategy subscale are based on the frequency with which they are used (0= never, 6 = always) with

a total score ranging from 0 to 36. In addition, there are two self-efficacy items reflecting "perceived control over pain" and "ability to reduce pain" with a score ranging from 0 to 6. Pain studies have found significant relations between both the factor scores and subscales of the CSQ and various measures of adjustment to chronic pain (15,16). For this study, only the subscale for Pain Catastrophizing and self-efficacy items were included in the analysis.

*The Mobility-Tiredness (Mob-T) scale*

The Mob-T scale is one of four subscales of the "Measure of functional ability" developed for the elderly population (17). The Mob-T scale is used to evaluate tiredness related to performance of six mobility items. For each item, the respondents are asked to report if they get tired (0 = yes, 1 = no) when performing the mobility task. A simple sum score is calculated, the total score ranging from 0 to 6, with low scores indicating more tiredness related to mobility. Tiredness in mobility has been found to be an early indicator of later disability and use of social and health services among elderly (17,18).

*The Pain Self-Efficacy Questionnaire (PSEQ)*

The PSEQ is a self-report instrument developed to assess self-efficacy beliefs individuals with chronic pain. It contains 10 items where patients are asked to reflect their ability to perform activities despite their pain. Items reflect a variety of tasks and activities, frequently reported as problematic for patients living with chronic pain. The patients are asked to rate their confidence in own ability to perform the different activities despite their pain, by selecting a number on a 7-point numeric scale, where 0 equals not at all sure, and 6 equals completely sure, yielding a sum score ranging from 0–60, with higher scores indicating greater pain self-efficacy. Psychometric testing of the source version, found the instrument to be reliable: Internal consistency evaluated by Cronbach's α coefficient, was 0.92. Test-retest analysis with Pearson's correlation was 0.73. Validity was evaluated by a principal factor analysis showing that the correlations ranged from 0.64 to 0.84 (19).

*The painDetect Questionnaire (PDQ)*

The PDQ is a patient-administered screening questionnaire developed and validated to predict the likelihood of a neuropathic pain component being present in individual patients (20). It comprises questions regarding pain intensity (VAS intensity values for current, average, and worst pain), course of pain (selection between 4 pain course patterns), subjective experience of a radiating quality of the pain (yes/no), and the presence and perceived severity of seven somatosensory symptoms of neuropathic pain scored on a 6-category Likert scale (never, hardly noticed, slightly, moderately, strongly, and very strongly). For diagnostic purposes, a validated algorithm is used to calculate a total score ranging from 0 to 38 based on the patient's answers. A total score above 18 indicates that a predominantly neuropathic pain component is likely, whereas a total score below 12 indicates that this is unlikely. The PDQ has been applied in studies of specific sensory profiles in established neuropathic pain conditions (21) as well as in studies of clinical manifestations of central sensitization in generalized (22,23)and regional musculoskeletal pain conditions e.g. osteoarthritis (24).

## CLINICIAN REPORTED AND OBSERVATION-BASED OUTCOMES

*Assessment of pressure pain threshold and tolerance*

Pressure pain sensitivity was determined on the lower leg using computerized cuff pressure algometry (CPA). The setup consisted of a pneumatic tourniquet cuff, a computerized compressor and an electronic 10 cm Visual Analogue Scale (VAS). Double-Chambered Textile Tourniquet Cuffs (VBM Medizintechnik GmbH, Sulz, Germany) were used for pressure application (25). Measurements were carried out with the patient in supine position, and on the patient's dominant side. At all measurements a compression rate of 1.0 kPa/sec were used. To minimize bias due to summation of pain, all measurements were carried out with a time interval of 5 minutes.

Following parameters were determined: *Pain Threshold* defined as the pressure of the cuff at the subject's first sensation of pain when applying a constantly raising pressure (Unit kPa). *Pain Tolerance* defined as the pressure of the cuff when the pressure is switched off by the patient due to worst tolerable pain caused by pressure stimulation (Unit kPa). Reduced pressure-pain thresholds assessed by CPA has been demonstrated in patients with fibromyalgia, and CPA is reported to be less influenced by psychological distress, indicating that this method is a more objective tool for the assessment of deep tissue pain hypersensitivity in this condition (26).

*Manual tender point examination and tender point count (TPC)*

Standardised, manual tender point examination was performed on all patients by two experienced and calibrated raters. The 18 predefined tender points were assessed according to the 1990-ACR guidelines (27) by applying a digital pressure of approximately 4 kg at each site and the pain response to palpation, scored as 0 = no tenderness, 1 = affirmative response to questioning, 2 = spontaneous expression of tenderness, 3 = withdrawal reaction, registered at each tender point site. Tender points with a score of 1 or more were included in the overall TPC in individual patients. Studies support high inter- and intra-rater agreement of manual TP examination among calibrated raters (28).

*Maximal isokinetic knee muscle strength*

An isokinetic dynamometer (Lido Multi Joint II, USA) was used to measure maximal voluntary muscle strength of the dominant knee extensors and flexors. Concentric contractions were performed in all patients at an angular velocity of 60°/s and the highest value of 7 repetitions recorded as the maximal

muscle strength measured in Nm (29–31). Published norms are available for the Danish background population (32).

*The Grippit® dynamometer*

Grippit® was used to measure maximal grip strength (N), as well as sustained grip strength averaged over a 10 sec period (N) (33). Grippit® has demonstrated good intra- and inter-rater reliability in healthy adults (34) as well as ability to detect changes in grip strength in patients with fibromyalgia (35).

*Six-Minute Walk Test (6-MW)*

The 6-MW test was standardised and performed in a hospital corridor with a length of 100 meters. Patients were given standard instructions to walk for 6 minutes at a pace that was efficient, but comfortable escorted by a physiotherapist. The distance walked in 6 minutes was recorded in meters. 6-MW testing has been applied in fibromyalgia training studies and found to be reliable in this specific population (36, 37).

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