

## **EMA SUMMARY OF RESULTS FOR THE TRIAL: Melatonin for Fatigue and Other Symptoms in Patients with Advanced Cancer**

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## **Data has been published:**

[Lund Rasmussen C, Klee Olsen M, Thit Johnsen A, Petersen MA, Lindholm H, Andersen L, Villadsen B, Groenvold M, Pedersen L. Effects of melatonin on physical fatigue and other symptoms in patients with advanced cancer receiving palliative care: A double-blind placebo-controlled crossover trial. Cancer. 2015 Oct 15;121\(20\):3727-36. doi: 10.1002/cncr.29563. Epub 2015 Jul 15.](#)

## **Aim of the trial**

The aim of the trial was to determine whether oral administered melatonin at night would reduce fatigue in patients with advanced cancer who were being treated in a palliative care facility.

## **Methods**

### **Design**

The study was a double-blind, randomised, placebo-controlled crossover trial.

### **Inclusion criteria**

Patients who were aged 18 years, had a histologically confirmed stage IV cancer (TNM Classification), and who reported feeling significantly tired according to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) were recruited from the palliative care unit at the study institution.

### **Intervention and control**

Patients received one week of melatonin at a dose of 20 mg orally each night followed by one week of placebo or the other way around (first one week of placebo, then one week of melatonin). Between the two periods, a washout period of two days was implemented.

### **Assessments**

Outcomes were measured using the Multidimensional Fatigue Inventory (MFI-20) and The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. Physical fatigue from the MFI-20 was the primary outcome.

### **Analysis**

Outcomes were calculated as the difference in mean change between the week with melatonin and the week with placebo.

The primary analysis was a complete complier analysis (i.e. it included only those patients who had consumed at least five tablets of placebo and five tablets of melatonin and who had answered the MFI-20 on days 1, 7, 10, and 17). Sensitivity analysis using multiple imputations including all randomized patients and all patients completing the intervention were conducted.

## **Summary of Results**

### Patients

In total, 72 patients were randomised (see Figure 1). However, 22 patients dropped out of the trial in the trial period. Thus, 50 patients completed the trial period. Of these, 44 were 'complete compliers', meaning that they participated fully in the intervention and responded to the outcome measures.

Characteristics of the patients can be seen in Table 1.

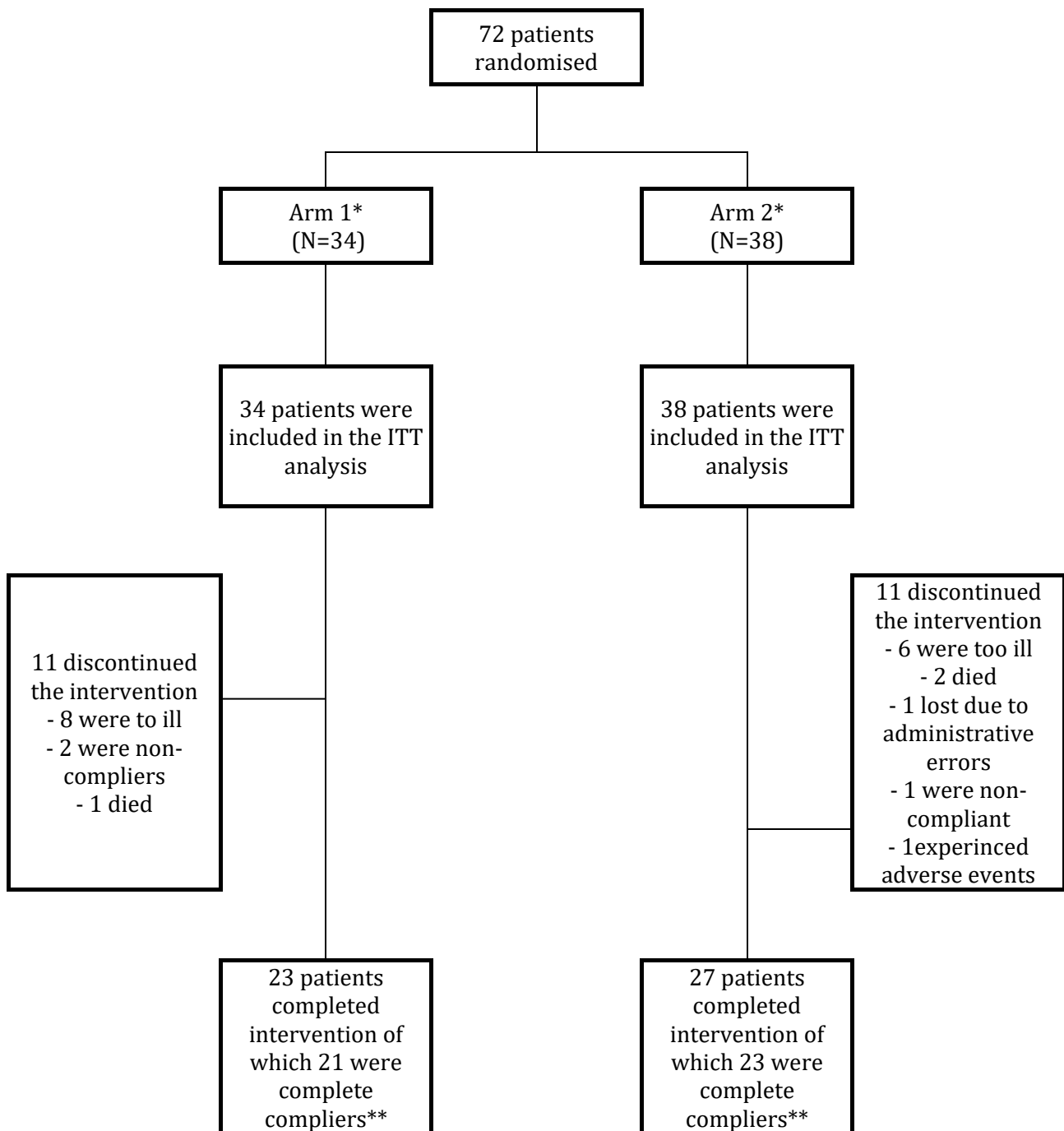
### Primary and secondary outcomes measure

No significant difference between groups were found (Table 2). This was both the case when including 'complete compliers' and in a sensitivity analysis including all randomized patients.

## **Summary of Results**

This trial found no effect of melatonin on fatigue in patients with advanced cancer.

**Figure 1.** Flowchart for part I.



\* Arm 1: melatonin followed by placebo. Arm 2: placebo followed by melatonin.

\*\*Complete compliers being patients who had consumed a minimum 5 capsules each week and answered the MFI-20 at day 1, 7, 10 and 17

**Table 1.** Baseline characteristics of participants.

| Characteristics  | Arm 1  |              | Arm 2  |                 |
|--|--|--------------|--|-----------------|
|  | No. of Patients (%)<br>Complete<br>compliers | ITT analysis | No. of Patients (%)<br>Complete<br>compliers | ITT<br>analysis |
| Sex  |  |              |  |                 |
| Male   | 8 (38)                                       | 10 (29)      | 7 (30)                                       | 13 (66)         |
| Female   | 13 (62)                                      | 24 (71)      | 16 (70)                                      | 25 (34)         |
| Age  |  |              |  |                 |
| Mean [range]   | 64 [35-84]                                   | 65 [35-84]   | 60 [33-86]                                   | 62 [33-89]      |
| WHO performance  |  |              |  |                 |
| 1  | 4 (19)                                       | 7 (21)       | 6 (26)                                       | 7 (19)          |
| 2  | 17 (81)                                      | 25 (74)      | 16 (70)                                      | 25 (68)         |
| 3  | 0 (0)  | 2 (6)        | 1 (4)  | 5 (14)          |
| Cancer diagnosis   |  |              |  |                 |
| Breast   | 5 (24)                                       | 9 (38)       | 10 (43)                                      | 14 (37)         |
| Lung   | 1 (5)  | 2 (6)        | 1 (4)  | 4 (11)          |
| Gastro-intestinal (liver, extrahepatic<br>bile duct, pancreas, ventricle, colon,<br>rectal)            | 5 (24)                                       | 10 (29)      | 8 (35)                                       | 8 (21)          |
| Gynaecological (ovarian, cervical<br>uterine)  | 6 (29)                                       | 10 (29)      | 2 (9)  | 4 (11)          |
| Other (brain, leukemia, laryngeal,<br>esophageal,<br>prostate, kidney, malignant melanoma,<br>unknown) | 4 (19)                                       | 5 (15)       | 2 (9)  | 8 (21)          |

**Table 2.** Complete compliers analysis of MFI-20 and EORTC QLQ-C15-PAL scores at baseline and changes in scores following treatment with melatonin and placebo. Complete compliers were patients who consumed a minimum 5 capsules each week and answered the MFI-20 physical fatigue subscale at days 1, 7, 10 and 17.

|                                     | Baseline<br>score, mean<br>[SD]* | Change in<br>score after<br>MLT, mean<br>[SD] | Change in<br>score after<br>placebo,<br>mean [SD] | Difference in<br>change between<br>week with MLT and<br>placebo, mean [SD]<br>(N) | P-<br>value |
|-------------------------------------|----------------------------------|---|---|---|-------------|
| <b>Primary outcome</b>              |                                  |   |   |   |             |
| Physical fatigue**                  | 72.02 [21.21]                    | -1.14 [15.96]                                 | -3.98 [18.14]                                     | 2.84 [25.59] (N=44)   | 0.47        |
| <b>Secondary outcomes</b>           |                                  |   |   |   |             |
| Fatigue***                          | 60.98 [15.59]                    | -3.17 [18.57]                                 | -2.07 [24.76]                                     | -1.36 [34.08] (N=41)  | 0.80        |
| Insomnia***                         | 32.58 [33.32]                    | -9.85 [23.38]                                 | -4.55 [30.99]                                     | -5.30 [38.00] (N=44)  | 0.36        |
| Appetite loss***                    | 33.33 [30.49]                    | -0.76 [25.40]                                 | -3.23 [21.57]                                     | -0.76 [33.32] (N=44)  | 0.88        |
| Pain***                             | 34.85 [27.33]                    | 0.76 [19.34]                                  | 1.89 [22.22]                                      | -1.14 [32.63] (N=44)  | 0.82        |
| Emotional function***               | 76.55 [23.79]                    | -0.58 [23.46]                                 | 3.29 [18.47]                                      | -4.37 [30.87] (N=42)  | 0.36        |
| Overall quality of<br>life (QOL)*** | 56.59 [18.59]                    | -0.78 [13.59]                                 | -3.17 [19.21]                                     | 2.85 [21.69] (N=41)   | 0.41        |
| <b>Explorative outcomes</b>         |                                  |   |   |   |             |
| General fatigue**                   | 65.54 [16.64]                    | -5.97 [19.29]                                 | 2.69 [21.46]                                      | -8.66 [32.85] (N=44)  | 0.09        |
| Reduced activity**                  | 67.14 [26.35]                    | -4.21 [20.75]                                 | -0.43 [14.91]                                     | -3.79 [22.99] (N=44)  | 0.28        |
| Reduced motivation**                | 33.52 [20.62]                    | -1.56 [16.73]                                 | 2.98 [13.31]                                      | -4.55 [19.13] (N=44)  | 0.12        |
| Mental fatigue**                    | 34.94 [24.24]                    | -0.85 [19.23]                                 | -2.89 [16.99]                                     | 2.03 [28.19] (N=44)   | 0.63        |
| Dyspnea***                          | 25.00 [27.96]                    | 3.03 [22.53]                                  | 4.55 [23.39]                                      | -1.52 [35.91] (N=44)  | 0.78        |
| Constipation***                     | 18.25 [25.72]                    | -0.79 [20.15]                                 | 1.59 [25.45]                                      | -3.25 [35.59] (N=41)  | 0.56        |
| Physical function***                | 47.59 [19.44]                    | 3.57 [11.39]                                  | -1.39 [13.46]                                     | 5.08 [18.79] (N=43)   | 0.09        |
| Nausea/vomiting***                  | 8.71 [13.68]                     | 2.27 [19.22]                                  | -2.33 [12.38]                                     | 5.08 [18.79] (N=43)   | 0.11        |

MLT = melatonin, SD = Standard Deviation. All scores range from 0-100. In all scores except emotional function, physical function and overall quality of life, a higher score indicates more symptoms/problems.

\*Baseline is scores from day 1.

\*\* Item from MFI-20.

\*\*\*Item from EORTC-QLQ-C15-PAL.

