



## Clinical trial results:

### Diabetic retinopathy: Effects of melatonin treatment on visual functions and circadian rhythm.

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-003955-23 |
| Trial protocol           | DK             |
| Global end of trial date | 07 July 2021   |

#### Results information

|                                   |                                                                                       |
|-----------------------------------|---------------------------------------------------------------------------------------|
| Result version number             | v1 (current)                                                                          |
| This version publication date     | 20 March 2023                                                                         |
| First version publication date    | 20 March 2023                                                                         |
| Summary attachment (see zip file) | Trial summary_Eudract no 2015-003955-23 (Trial summary_Eudract no 2015-003955-23.pdf) |

#### Trial information

##### Trial identification

|                       |     |
|-----------------------|-----|
| Sponsor protocol code | DR2 |
|-----------------------|-----|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03478306 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                                               |
|------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Rigshospitalet                                                                                                                |
| Sponsor organisation address | Valdemar Hansens vej 1-13, Glostrup, Denmark, 2600                                                                            |
| Public contact               | Research laboratory section 37, Dept. of Ophthalmology, Rigshospitalet – Glostrup, +45 31614923, shakoor.ba-ali.04@regionh.dk |
| Scientific contact           | Research laboratory section 37, Dept. of Ophthalmology, Rigshospitalet – Glostrup, +45 31614923, shakoor.ba-ali.04@regionh.dk |

Notes:

#### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 26 January 2023 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 07 July 2021    |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 07 July 2021    |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the effects of melatonin treatment on visual functions and circadian rhythm in diabetic patients with or without diabetic retinopathy.

Protection of trial subjects:

The physical and mental health of each subject was assessed during each visit, i.e. at baseline and after treatments. In addition each subject were consulted through phone calls 3 days after the first treatment date to assess their physical and mental health. Moreover, blood pressure and puls were measured during each visit. Also, blood tests were taken at baseline and at the end of each trial arms to assess red/white blood count, liver and kidney function.

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 28 March 2018 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Denmark: 31 |
| Worldwide total number of subjects   | 31          |
| EEA total number of subjects         | 31          |

Notes:

### Subjects enrolled per age group

|                                           |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 22 |
| From 65 to 84 years                       | 9  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Diabetic subjects with and without non-proliferative diabetic retinopathy were recruited from march 27th 2018 to april 1st 2021 from Steno Diabetes Center Copenhagen or Department of Ophthalmology Rigshospitalet-Glostrup encompassing the capital region in Denmark

### Pre-assignment

Screening details:

Inclusion Criteria:

- Diabetic patients
- Age range 40-75 years
- Participant should be legally competent

Exclusion Criteria:

- Other known eye disease.
- Eye disease manifestation during ocular examination.
- Competing neurologic and systemic conditions affecting retina.
- Use of any drugs influencing

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 31 |
| Number of subjects completed | 31 |

### Period 1

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Period 1 title               | Baseline 1                                                    |
| Is this the baseline period? | Yes                                                           |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind                                                  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

The subjects were randomized by a central third party, Glostrup pharmacy.

### Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes                      |
| <b>Arm title</b>             | Baseline 1 for melatonin |

Arm description:

Baseline for melatonin group 1st period

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Melatonin    |
| Investigational medicinal product code | SUB11496MIG  |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Baseline for melatonin group

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Baseline 1 for placebo |
|------------------|------------------------|

Arm description:

Baseline for placebo group 1st period

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |
| Dosage and administration details:     |          |
| Baseline for placebo group             |          |

| Number of subjects in period 1 | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------|--------------------------|------------------------|
| Started                        | 16                       | 15                     |
| Completed                      | 15                       | 14                     |
| Not completed                  | 1                        | 1                      |
| Consent withdrawn by subject   | 1                        | 1                      |

## Period 2

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Period 2 title               | Treatment 1                                                   |
| Is this the baseline period? | No                                                            |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind                                                  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

### Blinding implementation details:

The participants were randomized into two treatment arms by an independent party, Glostrup pharmacy A/S, and the lists of the randomization were kept in a closed envelope, which was locked in a box. The melatonin- and placebo tablets were manufactured by the Glostrup Pharmacy A/S and was identical in form, taste and color. The subjects received a bottle with tablets for each treatment arm. Neither the investigator nor the subjects were aware of the active ingredients of the tablets.

## Arms

|                              |             |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes         |
| <b>Arm title</b>             | Melatonin 1 |

### Arm description:

Subjects received 1 tablet melatonin 4 mg every evening 2 hours before bedtime in 3 weeks.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Melatonin    |
| Investigational medicinal product code | SUB11496MIG  |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

### Dosage and administration details:

1 tablet melatonin 4 mg every evening 2 hours before bedtime in 3 weeks.

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Placebo 1 |
|------------------|-----------|

### Arm description:

Subjects received 1 tablet placebo every evening 2 hours before bedtime in 3 weeks.

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|                                        |          |
|----------------------------------------|----------|
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Subjects recieved 1 tablet placebo every evening 2 hours before bedtime in 3 weeks.

| <b>Number of subjects in period 2</b> | Melatonin 1 | Placebo 1 |
|---------------------------------------|-------------|-----------|
| Started                               | 15          | 14        |
| Completed                             | 15          | 14        |

### Period 3

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Period 3 title               | Baseline 2                                                    |
| Is this the baseline period? | No                                                            |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind                                                  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

see previous periods

### Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes                      |
| <b>Arm title</b>             | Baseline 2 for melatonin |

Arm description: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Arm type                                                  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Baseline 2 for placebo |
|------------------|------------------------|

Arm description: -

|                                        |          |
|----------------------------------------|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

1 tablet placebo 2 hours before bedtime

| Number of subjects in period 3 | Baseline 2 for melatonin | Baseline 2 for placebo |
|--------------------------------|--------------------------|------------------------|
| Started                        | 14                       | 15                     |
| Completed                      | 14                       | 15                     |

#### Period 4

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Period 4 title               | Treatment 2                                                   |
| Is this the baseline period? | No                                                            |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind                                                  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

#### Arms

|                              |           |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes       |
| <b>Arm title</b>             | Placebo 2 |

Arm description: -

|                                        |          |
|----------------------------------------|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

1 tablet placebo every evening 2 hours prior to bedtime for 3 weeks.

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Melatonin 2 |
|------------------|-------------|

Arm description: -

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Melatonin    |
| Investigational medicinal product code | SUB11496MIG  |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

1 tablet melatonin 4 mg every evening 2 hours prior to bedtime for 3 weeks.

| Number of subjects in period 4 | Placebo 2 | Melatonin 2 |
|--------------------------------|-----------|-------------|
| Started                        | 15        | 14          |
| Completed                      | 14        | 14          |
| Not completed                  | 1         | 0           |
| Consent withdrawn by subject   | 1         | -           |



## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Baseline 1 |
|-----------------------|------------|

Reporting group description: -

| Reporting group values                    | Baseline 1 | Total |  |
|-------------------------------------------|------------|-------|--|
| Number of subjects                        | 31         | 31    |  |
| Age categorical                           |            |       |  |
| Units: Subjects                           |            |       |  |
| Age continuous                            |            |       |  |
| age range 40-74                           |            |       |  |
| Units: years                              |            |       |  |
| arithmetic mean                           | 61         |       |  |
| standard deviation                        | ± 8        | -     |  |
| Gender categorical                        |            |       |  |
| Units: Subjects                           |            |       |  |
| Female                                    | 10         | 10    |  |
| Male                                      | 21         | 21    |  |
| BMI                                       |            |       |  |
| Units: kilogram(s)/square metre           |            |       |  |
| arithmetic mean                           | 29         |       |  |
| standard deviation                        | ± 5        | -     |  |
| blood pressure systolic                   |            |       |  |
| Units: mmHg                               |            |       |  |
| arithmetic mean                           | 138        |       |  |
| standard deviation                        | ± 20       | -     |  |
| Blood pressure - diastolic                |            |       |  |
| Units: mmHg                               |            |       |  |
| arithmetic mean                           | 77         |       |  |
| standard deviation                        | ± 10       | -     |  |
| Alcohol consumption                       |            |       |  |
| Units: unit/week                          |            |       |  |
| arithmetic mean                           | 7          |       |  |
| standard deviation                        | ± 6        | -     |  |
| HbA1c                                     |            |       |  |
| Units: mmol/mol                           |            |       |  |
| arithmetic mean                           | 60         |       |  |
| standard deviation                        | ± 15       | -     |  |
| Glucose                                   |            |       |  |
| Plasma glucose level at the visiting day. |            |       |  |
| Units: mmol/L                             |            |       |  |
| arithmetic mean                           | 10         |       |  |
| standard deviation                        | ± 4        | -     |  |
| Hemoglobin                                |            |       |  |
| plasma hemoglobin level during the visit  |            |       |  |
| Units: mol/L                              |            |       |  |
| arithmetic mean                           | 11         |       |  |

|                                                                            |       |   |  |
|----------------------------------------------------------------------------|-------|---|--|
| standard deviation                                                         | ± 11  | - |  |
| Albumin                                                                    |       |   |  |
| Plasma albumin level prior to treatment start.                             |       |   |  |
| Units: g/dL                                                                |       |   |  |
| arithmetic mean                                                            | 44    |   |  |
| standard deviation                                                         | ± 3   | - |  |
| Bilirubin                                                                  |       |   |  |
| Plasma bilirubin level prior to treatment start.                           |       |   |  |
| Units: µmol/l                                                              |       |   |  |
| arithmetic mean                                                            | 8     |   |  |
| standard deviation                                                         | ± 3   | - |  |
| ALAT                                                                       |       |   |  |
| Plasma alanintransaminase                                                  |       |   |  |
| Units: U/L                                                                 |       |   |  |
| arithmetic mean                                                            | 31    |   |  |
| standard deviation                                                         | ± 11  | - |  |
| Creatinine                                                                 |       |   |  |
| Units: µmol/L                                                              |       |   |  |
| arithmetic mean                                                            | 82    |   |  |
| standard deviation                                                         | ± 27  | - |  |
| Cholesterol, total                                                         |       |   |  |
| Units: mmol/L                                                              |       |   |  |
| arithmetic mean                                                            | 4     |   |  |
| standard deviation                                                         | ± 1   | - |  |
| HDL                                                                        |       |   |  |
| High Density Lipoprotein Cholesterol level prior to treatment start.       |       |   |  |
| Units: mmol/L                                                              |       |   |  |
| arithmetic mean                                                            | 1.5   |   |  |
| standard deviation                                                         | ± 0.6 | - |  |
| LDL                                                                        |       |   |  |
| Low Density Lipoprotein cholesterol measured prior to treatment start      |       |   |  |
| Units: mmol/L                                                              |       |   |  |
| arithmetic mean                                                            | 1.8   |   |  |
| standard deviation                                                         | ± 1.0 | - |  |
| VLDL                                                                       |       |   |  |
| Very Low Density Lipoprotein cholesterol measured prior to treatment start |       |   |  |
| Units: mmol/                                                               |       |   |  |
| arithmetic mean                                                            | 0.9   |   |  |
| standard deviation                                                         | ± 0.4 | - |  |
| Triglycerides                                                              |       |   |  |
| Plasma triglycerides measured prior to treatment start                     |       |   |  |
| Units: mmol/L                                                              |       |   |  |
| arithmetic mean                                                            | 2.4   |   |  |
| standard deviation                                                         | ± 1.5 | - |  |
| Diabetes duration                                                          |       |   |  |
| Units: year                                                                |       |   |  |
| arithmetic mean                                                            | 31    |   |  |
| standard deviation                                                         | ± 10  | - |  |
| Visual acuity                                                              |       |   |  |
| Units: ETDRS                                                               |       |   |  |
| arithmetic mean                                                            | 85.1  |   |  |
| standard deviation                                                         | ± 6.8 | - |  |

|                            |       |   |  |
|----------------------------|-------|---|--|
| Intraocular pressure (IOP) |       |   |  |
| Units: mmHg                |       |   |  |
| arithmetic mean            | 14.1  |   |  |
| standard deviation         | ± 3.0 | - |  |

## End points

### End points reporting groups

|                                                                                                                            |                          |
|----------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Reporting group title                                                                                                      | Baseline 1 for melatonin |
| Reporting group description:<br>Baseline for melatonin group 1st period                                                    |                          |
| Reporting group title                                                                                                      | Baseline 1 for placebo   |
| Reporting group description:<br>Baseline for placebo group 1st period                                                      |                          |
| Reporting group title                                                                                                      | Melatonin 1              |
| Reporting group description:<br>Subjects recieved 1 tablet melatonin 4 mg every evening 2 hours before bedtime in 3 weeks. |                          |
| Reporting group title                                                                                                      | Placebo 1                |
| Reporting group description:<br>Subjects recieved 1 tablet placebo every evening 2 hours before bedtime in 3 weeks.        |                          |
| Reporting group title                                                                                                      | Baseline 2 for melatonin |
| Reporting group description: -                                                                                             |                          |
| Reporting group title                                                                                                      | Baseline 2 for placebo   |
| Reporting group description: -                                                                                             |                          |
| Reporting group title                                                                                                      | Placebo 2                |
| Reporting group description: -                                                                                             |                          |
| Reporting group title                                                                                                      | Melatonin 2              |
| Reporting group description: -                                                                                             |                          |

### Primary: OP1

|                                                   |         |
|---------------------------------------------------|---------|
| End point title                                   | OP1     |
| End point description:<br>Oscillatory potential 1 |         |
| End point type                                    | Primary |
| End point timeframe:<br>Before treatment          |         |

| End point values                     | Melatonin 1     | Placebo 1       | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|-----------------|-----------------|--------------------------|------------------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15              | 14              | 16                       | 15                     |
| Units: $\mu V$                       |                 |                 |                          |                        |
| arithmetic mean (standard deviation) | 19 ( $\pm$ 14)  | 12 ( $\pm$ 5)   | 19 ( $\pm$ 10)           | 11 ( $\pm$ 7)          |

| End point values            | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2       | Melatonin 2     |
|-----------------------------|--------------------------|------------------------|-----------------|-----------------|
| Subject group type          | Reporting group          | Reporting group        | Reporting group | Reporting group |
| Number of subjects analysed | 14                       | 15                     | 14              | 14              |

|                                      |               |                |               |               |
|--------------------------------------|---------------|----------------|---------------|---------------|
| Units: $\mu\text{V}$                 |               |                |               |               |
| arithmetic mean (standard deviation) | 16 ( $\pm$ 8) | 19 ( $\pm$ 13) | 19 ( $\pm$ 7) | 15 ( $\pm$ 4) |

## Statistical analyses

|                                         |                                                                                                                                                           |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Wilcoxon signed-rank test                                                                                                                                 |
| Comparison groups                       | Melatonin 1 v Placebo 1 v Baseline 1 for melatonin v Baseline 1 for placebo v Baseline 2 for melatonin v Baseline 2 for placebo v Placebo 2 v Melatonin 2 |
| Number of subjects included in analysis | 117                                                                                                                                                       |
| Analysis specification                  | Pre-specified                                                                                                                                             |
| Analysis type                           | non-inferiority                                                                                                                                           |
| P-value                                 | $\leq 0.05$                                                                                                                                               |
| Method                                  | Wilcoxon (Mann-Whitney)                                                                                                                                   |
| Parameter estimate                      | Mean difference (final values)                                                                                                                            |
| Variability estimate                    | Standard deviation                                                                                                                                        |

## Primary: OP2

|                        |                                                                       |
|------------------------|-----------------------------------------------------------------------|
| End point title        | OP2                                                                   |
| End point description: | Oscillatory potential amplitude as measure of the amacrine in retina. |
| End point type         | Primary                                                               |
| End point timeframe:   | OP1 measured before (baseline) and after treatment                    |

| <b>End point values</b>              | Melatonin 1     | Placebo 1       | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|-----------------|-----------------|--------------------------|------------------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15              | 14              | 16                       | 15                     |
| Units: $\mu\text{V}$                 |                 |                 |                          |                        |
| arithmetic mean (standard deviation) | 60 ( $\pm$ 17)  | 53 ( $\pm$ 26)  | 55 ( $\pm$ 28)           | 53 ( $\pm$ 26)         |

| <b>End point values</b>              | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2       | Melatonin 2     |
|--------------------------------------|--------------------------|------------------------|-----------------|-----------------|
| Subject group type                   | Reporting group          | Reporting group        | Reporting group | Reporting group |
| Number of subjects analysed          | 14                       | 15                     | 14              | 14              |
| Units: $\mu\text{V}$                 |                          |                        |                 |                 |
| arithmetic mean (standard deviation) | 50 ( $\pm$ 18)           | 71 ( $\pm$ 28)         | 59 ( $\pm$ 18)  | 51 ( $\pm$ 25)  |

## Statistical analyses

|                                         |                                                                                                                                                           |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Wilcoxon signed-rank test                                                                                                                                 |
| Comparison groups                       | Melatonin 1 v Placebo 1 v Baseline 1 for melatonin v Baseline 1 for placebo v Baseline 2 for melatonin v Baseline 2 for placebo v Placebo 2 v Melatonin 2 |
| Number of subjects included in analysis | 117                                                                                                                                                       |
| Analysis specification                  | Pre-specified                                                                                                                                             |
| Analysis type                           | equivalence                                                                                                                                               |
| P-value                                 | $\leq 0.05$                                                                                                                                               |
| Method                                  | Wilcoxon (Mann-Whitney)                                                                                                                                   |
| Parameter estimate                      | Mean difference (final values)                                                                                                                            |
| Variability estimate                    | Standard deviation                                                                                                                                        |

## Primary: OP3

|                        |                                                |
|------------------------|------------------------------------------------|
| End point title        | OP3                                            |
| End point description: | Oscillatory potential 2, measured with ff-ERG. |
| End point type         | Primary                                        |
| End point timeframe:   |                                                |
| Before treatment       |                                                |

|                                      |                 |                 |                          |                        |
|--------------------------------------|-----------------|-----------------|--------------------------|------------------------|
| <b>End point values</b>              | Melatonin 1     | Placebo 1       | Baseline 1 for melatonin | Baseline 1 for placebo |
| Subject group type                   | Reporting group | Reporting group | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15              | 14              | 16                       | 15                     |
| Units: $\mu\text{V}$                 |                 |                 |                          |                        |
| arithmetic mean (standard deviation) | 19 ( $\pm 13$ ) | 23 ( $\pm 11$ ) | 23 ( $\pm 16$ )          | 20 ( $\pm 14$ )        |

|                                      |                          |                        |                 |                 |
|--------------------------------------|--------------------------|------------------------|-----------------|-----------------|
| <b>End point values</b>              | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2       | Melatonin 2     |
| Subject group type                   | Reporting group          | Reporting group        | Reporting group | Reporting group |
| Number of subjects analysed          | 14                       | 15                     | 14              | 14              |
| Units: $\mu\text{V}$                 |                          |                        |                 |                 |
| arithmetic mean (standard deviation) | 23 ( $\pm 12$ )          | 24 ( $\pm 21$ )        | 20 ( $\pm 12$ ) | 24 ( $\pm 8$ )  |

## Statistical analyses

|                                   |                                                                                                                                                           |
|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b> | Wilcoxon signed-rank test                                                                                                                                 |
| Comparison groups                 | Melatonin 1 v Placebo 1 v Baseline 1 for melatonin v Baseline 1 for placebo v Baseline 2 for melatonin v Baseline 2 for placebo v Placebo 2 v Melatonin 2 |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 117                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | equivalence                    |
| P-value                                 | ≤ 0.05                         |
| Method                                  | Wilcoxon (Mann-Whitney)        |
| Parameter estimate                      | Mean difference (final values) |
| Variability estimate                    | Standard deviation             |

### Primary: It1

|                                              |         |
|----------------------------------------------|---------|
| End point title                              | It1     |
| End point description:                       |         |
| Implicit time of the 1st amplitude in ff-ERG |         |
| End point type                               | Primary |
| End point timeframe:                         |         |
| Before and after                             |         |

| End point values                     | Melatonin 1     | Placebo 1       | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|-----------------|-----------------|--------------------------|------------------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15              | 14              | 16                       | 15                     |
| Units: ms                            |                 |                 |                          |                        |
| arithmetic mean (standard deviation) | 20 (± 1)        | 19 (± 1)        | 22 (± 5)                 | 19 (± 1)               |

| End point values                     | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2       | Melatonin 2     |
|--------------------------------------|--------------------------|------------------------|-----------------|-----------------|
| Subject group type                   | Reporting group          | Reporting group        | Reporting group | Reporting group |
| Number of subjects analysed          | 14                       | 15                     | 14              | 14              |
| Units: ms                            |                          |                        |                 |                 |
| arithmetic mean (standard deviation) | 20 (± 4)                 | 20 (± 2)               | 20 (± 1)        | 20 (± 1)        |

### Statistical analyses

|                            |                                                                                                                                                           |
|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Statistical analysis title | Wilcoxon signed-rank test                                                                                                                                 |
| Comparison groups          | Melatonin 1 v Placebo 1 v Baseline 1 for melatonin v Baseline 1 for placebo v Baseline 2 for melatonin v Baseline 2 for placebo v Placebo 2 v Melatonin 2 |

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 117                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | equivalence             |
| P-value                                 | ≤ 0.05                  |
| Method                                  | Wilcoxon (Mann-Whitney) |
| Parameter estimate                      | Mean difference (net)   |
| Variability estimate                    | Standard deviation      |

### Primary: It2

|                                              |         |
|----------------------------------------------|---------|
| End point title                              | It2     |
| End point description:                       |         |
| Implicit time of the 1st amplitude in ff-ERG |         |
| End point type                               | Primary |
| End point timeframe:                         |         |
| Before and after                             |         |

| End point values                     | Melatonin 1     | Placebo 1       | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|-----------------|-----------------|--------------------------|------------------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15              | 14              | 16                       | 15                     |
| Units: ms                            |                 |                 |                          |                        |
| arithmetic mean (standard deviation) | 27 (± 1)        | 27 (± 1)        | 29 (± 4)                 | 27 (± 2)               |

| End point values                     | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2       | Melatonin 2     |
|--------------------------------------|--------------------------|------------------------|-----------------|-----------------|
| Subject group type                   | Reporting group          | Reporting group        | Reporting group | Reporting group |
| Number of subjects analysed          | 14                       | 15                     | 14              | 14              |
| Units: ms                            |                          |                        |                 |                 |
| arithmetic mean (standard deviation) | 27 (± 2)                 | 28 (± 1)               | 28 (± 1)        | 27 (± 1)        |

### Statistical analyses

|                            |                                                                                                                                                           |
|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Statistical analysis title | Wilcoxon signed-rank test                                                                                                                                 |
| Comparison groups          | Melatonin 1 v Placebo 1 v Baseline 1 for melatonin v Baseline 1 for placebo v Baseline 2 for melatonin v Baseline 2 for placebo v Placebo 2 v Melatonin 2 |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 117                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | equivalence                    |
| P-value                                 | $\leq 0.05$                    |
| Method                                  | Wilcoxon (Mann-Whitney)        |
| Parameter estimate                      | Mean difference (final values) |
| Variability estimate                    | Standard deviation             |

### Primary: It 3

|                                              |         |
|----------------------------------------------|---------|
| End point title                              | It 3    |
| End point description:                       |         |
| Implicit time of the 1st amplitude in ff-ERG |         |
| End point type                               | Primary |
| End point timeframe:                         |         |
| Before and after                             |         |

| End point values                     | Melatonin 1     | Placebo 1       | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|-----------------|-----------------|--------------------------|------------------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15              | 14              | 16                       | 15                     |
| Units: ms                            |                 |                 |                          |                        |
| arithmetic mean (standard deviation) | 34 ( $\pm 2$ )  | 33 ( $\pm 1$ )  | 35 ( $\pm 5$ )           | 34 ( $\pm 3$ )         |

| End point values                     | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2       | Melatonin 2     |
|--------------------------------------|--------------------------|------------------------|-----------------|-----------------|
| Subject group type                   | Reporting group          | Reporting group        | Reporting group | Reporting group |
| Number of subjects analysed          | 14                       | 15                     | 14              | 14              |
| Units: ms                            |                          |                        |                 |                 |
| arithmetic mean (standard deviation) | 34 ( $\pm 4$ )           | 34 ( $\pm 1$ )         | 34 ( $\pm 1$ )  | 33 ( $\pm 1$ )  |

### Statistical analyses

|                            |                                                                                                                                                           |
|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Statistical analysis title | Wilcoxon signed-rank test                                                                                                                                 |
| Comparison groups          | Melatonin 1 v Placebo 1 v Baseline 1 for melatonin v Baseline 1 for placebo v Baseline 2 for melatonin v Baseline 2 for placebo v Placebo 2 v Melatonin 2 |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 117                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | equivalence                    |
| P-value                                 | ≤ 0.05                         |
| Method                                  | Wilcoxon (Mann-Whitney)        |
| Parameter estimate                      | Mean difference (final values) |
| Variability estimate                    | Standard deviation             |

### Secondary: DA0.01 b-wave amplitude

|                        |                                                                      |
|------------------------|----------------------------------------------------------------------|
| End point title        | DA0.01 b-wave amplitude                                              |
| End point description: | Dark adapted b-wave amplitude (rod bipolar cells) measured with ERG. |
| End point type         | Secondary                                                            |
| End point timeframe:   | Measured before and after treatment                                  |

| End point values                     | Melatonin 1     | Placebo 1        | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|-----------------|------------------|--------------------------|------------------------|
| Subject group type                   | Reporting group | Reporting group  | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15              | 14               | 16                       | 15                     |
| Units: $\mu\text{V}$                 |                 |                  |                          |                        |
| arithmetic mean (standard deviation) | 138 ( $\pm$ 57) | 171 ( $\pm$ 118) | 159 ( $\pm$ 74)          | 192 ( $\pm$ 80)        |

| End point values                     | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2       | Melatonin 2     |
|--------------------------------------|--------------------------|------------------------|-----------------|-----------------|
| Subject group type                   | Reporting group          | Reporting group        | Reporting group | Reporting group |
| Number of subjects analysed          | 14                       | 15                     | 14              | 14              |
| Units: $\mu\text{V}$                 |                          |                        |                 |                 |
| arithmetic mean (standard deviation) | 139 ( $\pm$ 46)          | 184 ( $\pm$ 92)        | 163 ( $\pm$ 62) | 152 ( $\pm$ 52) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: DA0.01 b-wave implicit time

|                        |                                                                                                   |
|------------------------|---------------------------------------------------------------------------------------------------|
| End point title        | DA0.01 b-wave implicit time                                                                       |
| End point description: | Dark adapted b-wave amplitude (rod bipolar cells) measured with ERG (DA0.01 b-wave implicit time) |
| End point type         | Secondary                                                                                         |
| End point timeframe:   | Measured before and after treatment                                                               |

| End point values                     | Melatonin 1     | Placebo 1       | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|-----------------|-----------------|--------------------------|------------------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15              | 14              | 16                       | 15                     |
| Units: ms                            |                 |                 |                          |                        |
| arithmetic mean (standard deviation) | 138 (± 57)      | 94 (± 21)       | 93 (± 12)                | 97 (± 8)               |

| End point values                     | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2       | Melatonin 2     |
|--------------------------------------|--------------------------|------------------------|-----------------|-----------------|
| Subject group type                   | Reporting group          | Reporting group        | Reporting group | Reporting group |
| Number of subjects analysed          | 14                       | 15                     | 14              | 14              |
| Units: ms                            |                          |                        |                 |                 |
| arithmetic mean (standard deviation) | 99 (± 8)                 | 95 (± 13)              | 94 (± 10)       | 93 (± 11)       |

## Statistical analyses

No statistical analyses for this end point

## Secondary: LA3.0 a-wave amplitude

|                           |                                                                                                |
|---------------------------|------------------------------------------------------------------------------------------------|
| End point title           | LA3.0 a-wave amplitude                                                                         |
| End point description:    | Light adapted a-wave amplitude (cone bipolar cells) measured with ERG (LA3.0 a-wave amplitude) |
| End point type            | Secondary                                                                                      |
| End point timeframe:      |                                                                                                |
| Measured before and after |                                                                                                |

| End point values                     | Melatonin 1     | Placebo 1       | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|-----------------|-----------------|--------------------------|------------------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15              | 14              | 16                       | 15                     |
| Units: µV                            |                 |                 |                          |                        |
| arithmetic mean (standard deviation) | 24 (± 12)       | 20 (± 8)        | 28 (± 16)                | 22 (± 8)               |

| End point values                     | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2       | Melatonin 2     |
|--------------------------------------|--------------------------|------------------------|-----------------|-----------------|
| Subject group type                   | Reporting group          | Reporting group        | Reporting group | Reporting group |
| Number of subjects analysed          | 14                       | 15                     | 14              | 14              |
| Units: µV                            |                          |                        |                 |                 |
| arithmetic mean (standard deviation) | 20 (± 6)                 | 24 (± 9)               | 25 (± 8)        | 20 (± 8)        |

## Statistical analyses

No statistical analyses for this end point

### Secondary: LA3.0 a-wave implicit time

|                 |                            |
|-----------------|----------------------------|
| End point title | LA3.0 a-wave implicit time |
|-----------------|----------------------------|

End point description:

Light adapted a-wave implicit time measured with ERG.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Measured before and after

| End point values                     | Melatonin 1     | Placebo 1       | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|-----------------|-----------------|--------------------------|------------------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15              | 14              | 16                       | 15                     |
| Units: ms                            |                 |                 |                          |                        |
| arithmetic mean (standard deviation) | 15 ( $\pm$ 1)   | 15 ( $\pm$ 1)   | 16 ( $\pm$ 1)            | 15 ( $\pm$ 1)          |

| End point values                     | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2       | Melatonin 2     |
|--------------------------------------|--------------------------|------------------------|-----------------|-----------------|
| Subject group type                   | Reporting group          | Reporting group        | Reporting group | Reporting group |
| Number of subjects analysed          | 14                       | 15                     | 14              | 14              |
| Units: ms                            |                          |                        |                 |                 |
| arithmetic mean (standard deviation) | 14 ( $\pm$ 2)            | 15 ( $\pm$ 1)          | 15 ( $\pm$ 2)   | 15 ( $\pm$ 1)   |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pupil size

|                 |            |
|-----------------|------------|
| End point title | Pupil size |
|-----------------|------------|

End point description:

Pupillary size (mm) prior to light stimulation, measured with pupillometry.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

measured before and after

| End point values                     | Melatonin 1      | Placebo 1        | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|------------------|------------------|--------------------------|------------------------|
| Subject group type                   | Reporting group  | Reporting group  | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15               | 14               | 16                       | 15                     |
| Units: mm                            |                  |                  |                          |                        |
| arithmetic mean (standard deviation) | 5.7 ( $\pm$ 0.8) | 5.6 ( $\pm$ 1.0) | 5.8 ( $\pm$ 0.9)         | 5.6 ( $\pm$ 0.9)       |

| End point values                     | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2        | Melatonin 2      |
|--------------------------------------|--------------------------|------------------------|------------------|------------------|
| Subject group type                   | Reporting group          | Reporting group        | Reporting group  | Reporting group  |
| Number of subjects analysed          | 14                       | 15                     | 14               | 14               |
| Units: mm                            |                          |                        |                  |                  |
| arithmetic mean (standard deviation) | 6.0 ( $\pm$ 1.0)         | 5.7 ( $\pm$ 0.8)       | 5.7 ( $\pm$ 0.9) | 5.8 ( $\pm$ 1.2) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximal pupillary contraction

|                                                                                                                                                               |                               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| End point title                                                                                                                                               | Maximal pupillary contraction |
| End point description:<br>Maximal pupillary contraction in relation to baseline pupillary light size during light stimulation.<br>Measured with pupillometer. |                               |
| End point type                                                                                                                                                | Secondary                     |
| End point timeframe:<br>Measured before and after                                                                                                             |                               |

| End point values                     | Melatonin 1      | Placebo 1        | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|------------------|------------------|--------------------------|------------------------|
| Subject group type                   | Reporting group  | Reporting group  | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15               | 14               | 16                       | 15                     |
| Units: ratio                         |                  |                  |                          |                        |
| arithmetic mean (standard deviation) | 0.6 ( $\pm$ 0.1) | 0.6 ( $\pm$ 0.0) | 0.6 ( $\pm$ 0.0)         | 0.6 ( $\pm$ 0.1)       |

| End point values            | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2       | Melatonin 2     |
|-----------------------------|--------------------------|------------------------|-----------------|-----------------|
| Subject group type          | Reporting group          | Reporting group        | Reporting group | Reporting group |
| Number of subjects analysed | 14                       | 15                     | 14              | 14              |
| Units: ratio                |                          |                        |                 |                 |

|                                      |                  |                  |                  |                  |
|--------------------------------------|------------------|------------------|------------------|------------------|
| arithmetic mean (standard deviation) | 0.6 ( $\pm$ 0.1) | 0.6 ( $\pm$ 0.0) | 0.6 ( $\pm$ 0.0) | 0.6 ( $\pm$ 0.1) |
|--------------------------------------|------------------|------------------|------------------|------------------|

## Statistical analyses

No statistical analyses for this end point

### Secondary: PIPR\_early

|                                                                                                                                                             |            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| End point title                                                                                                                                             | PIPR_early |
| End point description:<br>Pupillary contraction measured 0-10 seconds after termination of blue light stimuli in 20 seconds.<br>Measured with pupillometer. |            |
| End point type                                                                                                                                              | Secondary  |
| End point timeframe:<br>Measured before and after                                                                                                           |            |

| End point values                     | Melatonin 1      | Placebo 1        | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|------------------|------------------|--------------------------|------------------------|
| Subject group type                   | Reporting group  | Reporting group  | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15               | 14               | 16                       | 15                     |
| Units: ratio                         |                  |                  |                          |                        |
| arithmetic mean (standard deviation) | 0.5 ( $\pm$ 0.1) | 0.4 ( $\pm$ 0.1) | 0.5 ( $\pm$ 0.1)         | 0.4 ( $\pm$ 0.1)       |

| End point values                     | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2        | Melatonin 2      |
|--------------------------------------|--------------------------|------------------------|------------------|------------------|
| Subject group type                   | Reporting group          | Reporting group        | Reporting group  | Reporting group  |
| Number of subjects analysed          | 14                       | 15                     | 14               | 14               |
| Units: ratio                         |                          |                        |                  |                  |
| arithmetic mean (standard deviation) | 0.4 ( $\pm$ 0.1)         | 0.5 ( $\pm$ 0.1)       | 0.4 ( $\pm$ 0.1) | 0.4 ( $\pm$ 0.1) |

## Statistical analyses

No statistical analyses for this end point

### Secondary: PIPR\_late

|                                                                                                                                                              |           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| End point title                                                                                                                                              | PIPR_late |
| End point description:<br>Pupillary contraction measured 10-20 seconds after termination of blue light stimuli in 20 seconds.<br>Measured with pupillometer. |           |
| End point type                                                                                                                                               | Secondary |

End point timeframe:  
Measured before and after treatment

| End point values                     | Melatonin 1     | Placebo 1       | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|-----------------|-----------------|--------------------------|------------------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15              | 14              | 16                       | 15                     |
| Units: ratio                         |                 |                 |                          |                        |
| arithmetic mean (standard deviation) | 0.4 (± 0.1)     | 0.4 (± 0.1)     | 0.4 (± 0.1)              | 0.1 (± 0.1)            |

| End point values                     | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2       | Melatonin 2     |
|--------------------------------------|--------------------------|------------------------|-----------------|-----------------|
| Subject group type                   | Reporting group          | Reporting group        | Reporting group | Reporting group |
| Number of subjects analysed          | 14                       | 15                     | 14              | 14              |
| Units: ratio                         |                          |                        |                 |                 |
| arithmetic mean (standard deviation) | 0.1 (± 0.1)              | 0.4 (± 0.1)            | 0.4 (± 0.1)     | 0.3 (± 0.1)     |

### Statistical analyses

No statistical analyses for this end point

### Secondary: PSQI global score

End point title PSQI global score

End point description:

End point type Secondary

End point timeframe:

Before and after treatment

| End point values                     | Melatonin 1     | Placebo 1       | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|-----------------|-----------------|--------------------------|------------------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15              | 14              | 16                       | 15                     |
| Units: Global score                  |                 |                 |                          |                        |
| arithmetic mean (standard deviation) | 5.2 (± 3.2)     | 4.1 (± 3.5)     | 6.4 (± 3.0)              | 5.1 (± 3.5)            |

| End point values            | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2       | Melatonin 2     |
|-----------------------------|--------------------------|------------------------|-----------------|-----------------|
| Subject group type          | Reporting group          | Reporting group        | Reporting group | Reporting group |
| Number of subjects analysed | 14                       | 15                     | 14              | 14              |

|                                      |                  |                  |                  |                  |
|--------------------------------------|------------------|------------------|------------------|------------------|
| Units: Global score                  |                  |                  |                  |                  |
| arithmetic mean (standard deviation) | 3.8 ( $\pm$ 2.6) | 6.0 ( $\pm$ 3.6) | 4.8 ( $\pm$ 3.1) | 4.3 ( $\pm$ 3.4) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Melatonin at 04:00 AM

|                                                 |                       |
|-------------------------------------------------|-----------------------|
| End point title                                 | Melatonin at 04:00 AM |
| End point description:                          |                       |
| Salivary melatonin level measured at 04:00 AM   |                       |
| End point type                                  | Secondary             |
| End point timeframe:                            |                       |
| Measured at 04:00 AM befor and after treatment. |                       |

| End point values                     | Melatonin 1        | Placebo 1          | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|--------------------|--------------------|--------------------------|------------------------|
| Subject group type                   | Reporting group    | Reporting group    | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15                 | 14                 | 16                       | 15                     |
| Units: Pg/mL                         |                    |                    |                          |                        |
| arithmetic mean (standard deviation) | 35.5 ( $\pm$ 43.5) | 10.6 ( $\pm$ 14.7) | 7.0 ( $\pm$ 12.8)        | 4.4 ( $\pm$ 4.2)       |

| End point values                     | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2         | Melatonin 2        |
|--------------------------------------|--------------------------|------------------------|-------------------|--------------------|
| Subject group type                   | Reporting group          | Reporting group        | Reporting group   | Reporting group    |
| Number of subjects analysed          | 14                       | 15                     | 14                | 14                 |
| Units: Pg/mL                         |                          |                        |                   |                    |
| arithmetic mean (standard deviation) | 5.2 ( $\pm$ 7.4)         | 11.3 ( $\pm$ 14.7)     | 7.0 ( $\pm$ 12.7) | 26.7 ( $\pm$ 18.6) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: p-Glucose at 04:00 AM

|                                              |                       |
|----------------------------------------------|-----------------------|
| End point title                              | p-Glucose at 04:00 AM |
| End point description:                       |                       |
| End point type                               | Secondary             |
| End point timeframe:                         |                       |
| Capillary glucose level measured at 04:00 AM |                       |

| <b>End point values</b>              | Melatonin 1     | Placebo 1       | Baseline 1 for melatonin | Baseline 1 for placebo |
|--------------------------------------|-----------------|-----------------|--------------------------|------------------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group          | Reporting group        |
| Number of subjects analysed          | 15              | 14              | 16                       | 15                     |
| Units: mmol/L                        |                 |                 |                          |                        |
| arithmetic mean (standard deviation) | 7.2 (± 1.9)     | 8.2 (± 3.7)     | 7.6 (± 2.5)              | 8.2 (± 2.2)            |

| <b>End point values</b>              | Baseline 2 for melatonin | Baseline 2 for placebo | Placebo 2       | Melatonin 2     |
|--------------------------------------|--------------------------|------------------------|-----------------|-----------------|
| Subject group type                   | Reporting group          | Reporting group        | Reporting group | Reporting group |
| Number of subjects analysed          | 14                       | 15                     | 14              | 14              |
| Units: mmol/L                        |                          |                        |                 |                 |
| arithmetic mean (standard deviation) | 9.0 (± 3.9)              | 7.0 (± 2.4)            | 7.4 (± 1.5)     | 9.0 (± 3.2)     |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

---

### Adverse events information<sup>[1]</sup>

---

Timeframe for reporting adverse events:

No serious adverse events (SAE) or Serious Adverse (Drug) Reaction (SAR) were observed

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

---

### Dictionary used

---

|                 |               |
|-----------------|---------------|
| Dictionary name | Annual report |
|-----------------|---------------|

---

|                    |   |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

---

Frequency threshold for reporting non-serious adverse events: 1 %

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Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: There were no non-serious adverse events recorded for these results.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

---

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date             | Interruption                                                                                                                                                                                                                                                                                                                               | Restart date  |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| 14 November 2019 | The recruitment process was interrupted by Danish Medicines Agency due to suspicious laboratory analysis in the process of melatonin production by our external lab-analyse provider. After further investigation the Danish Medicines Agency found that the lab-analysis was conducted properly, and the research was allowed to restart. | 09 March 2020 |

Notes:

### Limitations and caveats

None reported