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Melatonin (sleep disorders in children and adolescents with autism spectrum disorders and / or Smith-Magenis syndrome) –

Addendum to Commission A19-04[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CGAS	Children's Global Assessment Scale
CSDI	Composite Sleep Disturbance Index
ESS	Epworth Sleepiness Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PSQI	Pittsburgh Sleep Quality Index
PT	preferred term
RCT	randomized controlled trial
SAE	serious adverse event
SDQ	Strength and Difficulties Questionnaire
SGB	Sozialgesetzbuch (Social Code Book)
WHO-5	World Health Organization Well-Being Index

1 Background

On 27 May 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-04 (Melatonin – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier, the pharmaceutical company (hereinafter referred to as "the company") presented the NEU_CH_7911 study [2]. This randomized controlled trial (RCT) compared melatonin with placebo in children and adolescents aged 2 to 17.5 with autism spectrum disorder and/or certain neurogenetic diseases, who have insomnia. This study was not included in the assessment of the added benefit, because treatment in the comparator group did not comply with the appropriate comparator therapy (ACT) "best supportive care" (BSC) specified by the G-BA [1].

Following the oral hearing on dossier assessment A19-04, the G-BA commissioned IQWiG with the assessment of the study NEU_CH_7911.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

As explained in detail in dossier assessment A19-04, the NEU_CH_7911 study on the comparison of melatonin with placebo presented by the company was not included in the benefit assessment, because treatment in the comparator group did not comply with the ACT specified by the G-BA (BSC) [1]. The assessments in the comments submitted to the G-BA were contradictory regarding the implementation of the ACT. In some instances, the parties submitting the comments regarded the ACT as implemented, in others they confirmed the estimation of the benefit assessment A19-04 [3-5].

The following Sections 2.1 to 2.5 describe and assess the NEU_CH_7911 study in accordance with the commission by the G-BA. The references for the NEU_CH_7911 study are found in Section 2.6

2.1 Study description

Characteristics of the study included by the company – RCT/Non-RCT, direct comparison: melatonin vs. placebo Table 1 and Table 2 describe the NEU_CH_7911 study.

Table 1: Characteristics of the study included by the company – RCT/Non-RCT, direct comparison: melatonin vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
NEU_CH_7911	RCT, double-blind, parallel	Children and adolescents (aged 2 to 17.5 years) with autism spectrum disorder or neurogenetic diseases[b], who have insomnia[c]	Melatonin (N = 60) Placebo (N = 65)	Screening: 4 weeks before randomization[d] Run-in phase[e]: 2 weeks Randomized treatment phase: 13 weeks Extension phase[f]: 91 weeks Run-out phase[g]: 2 weeks	10 study centres in Europe (Great Britain, France, the Netherlands and Finland) and 14 study centres in the USA 01/2014–02/2018	Primary: TST Secondary: morbidity, AEs, including deaths

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively contain data on relevant available outcomes from the information provided by the company in Module 4 of the dossier.
b: The following diseases are included according to the study protocol: Smith-Magenis syndrome, Angelman syndrome and Bourneville syndrome (tuberous sclerosis).
c: Insomnia with ≤ 6 hours of continuous sleep and/or ≥ 0.5 hours of sleep latency after the lights have been turned off in 3 of 5 nights for at least 3 months of sleep disorders; assessment on the basis of reports provided by parents and on the medical history.
d: Children and adolescents who had not yet received documented behavioural therapy (sleep hygiene measures) underwent 4-week basic therapy with sleep hygiene training and behavioural therapy.
e: In this period, all children and adolescents received placebo (single-blind).
f: In the open-label extension phase, all children and adolescents received melatonin. This phase was irrelevant for the analysis of the study and was thus not considered in the subsequent tables.
g: In this period, all children and adolescents received placebo.
AE: adverse event; N: number of randomized patients; RCT: randomized controlled trial; TST: Total Sleep Time; vs.: versus

Table 2: Characteristics of the intervention – RCT, direct comparison: melatonin vs. placebo

Study	Intervention	Comparison	Prior and concomitant treatment
NEU_CH_7911[a]	▪ Melatonin 2 mg, once daily for the first 3 weeks ▪ Thereafter, dose adjustment to 5 mg daily was possible[b] ▪ Dose reduction from 5 mg to 2 mg daily was permitted	▪ Placebo once daily ▪ Corresponding adjustment of placebo dose was possible[b]	**Pretreatment** ▪ Washout phase and (for patients who had not yet received sleep hygiene measures or behavioural intervention) performance of sleep hygiene training and behavioural therapy **Concomitant treatment** ▪ The sleep hygiene measures did not have to be continued during the study

a: Data on the intervention exclusively refer to the randomized treatment phase.
b: The criteria of inadequate response were defined in the study protocol for the decision on the dose adjustment.
RCT: randomized controlled trial; vs.: versus

The NEU_CH_7911 study is a double-blind RCT which investigated the drug melatonin in comparison with placebo. The study included children and adolescents aged 2 to 17.5 years with autism spectrum disorder or neurogenetic diseases, e.g. Smith-Magenis syndrome, who have insomnia.

The study comprised several study phases: screening phase, run-in phase, randomized treatment phase, extension phase and run-out phase.

The screening phase started 4 weeks prior to randomization. Before the start of the study, children and adolescents who had not yet received documented behavioural therapy (sleep hygiene measures) underwent 4-week basic therapy with sleep hygiene training and behavioural therapy. At the same time, any hypnotic drugs were washed out during this period. All children and adolescents who still had insomnia after completion of the basic therapy, subsequently received placebo for 2 weeks (run-in-phase, single-blind). Children and adolescents who had received sleep hygiene measures in the past were directly included in the run-in phase.

After the run-in phase, a total of 125 participants were randomly assigned to the two study arms (melatonin: 60, placebo: 65) and received melatonin or placebo over the next 13 weeks. If necessary, the dose of the study drug could be escalated from 2 mg to 5 mg per day (see Table 2). The sleep hygiene measures did not have to be continued during the study.

The randomized treatment phase was followed by an extension phase in which all children and adolescents received melatonin. The extension phase was followed by a 2-week run-out phase in which the patients received placebo.

The present assessment is based on the randomized treatment phase.

Total Sleep Time (TST) at night was the primary outcome of the study. Relevant outcomes of the study include outcomes on morbidity and adverse events (AEs), including deaths.

2.2 Patient characteristics

Table 3 shows the characteristics of the patients in the NEU_CH_7911 study.

Table 3: Characteristics of the study population – RCT, direct comparison: melatonin vs. placebo

Study Characteristics Category	**Melatonin**	**Placebo**
NEU_CH_7911	N[a] = 60	N[a] = 65
Age [years], mean (SD)	9 (4)	8 (4)
2 to 6, n (%)	19 (32)	25 (39)
7 to 12, n (%)	28 (47)	29 (45)
13 to 17, n (%)	13 (22)	11 (17)
Sex [F/M], %	25/75	28/72
Ethnicity, n (%)		
White	57 (95)	55 (85)
Black/African American	1 (2)	8 (12)
Asian	0 (0)	2 (3)
Other	3 (5)	3 (5)
Neurodevelopmental disorders, n (%)		
Autism spectrum disorders	58 (96.7)	63 (96.9)
Smith-Magenis syndrome	2 (3.3)	2 (3.1)
Prior sleep hygiene measures, n (%)		
Yes	51 (85.0)	53 (81.5)
No	9 (15.0)	12 (18.5)
Attention deficit/hyperactivity disorder		
Yes	16 (26.7)	20 (30.8)
No	44 (73.3)	45 (69.2)
Treatment discontinuation, n (%)	9 (15.0)	21 (32.3)
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The essential demographic and disease-specific characteristics of the patients included in the study are largely balanced.

2.3 Results

2.3.1 Outcomes included

The following patient-relevant outcomes were considered in the assessment:

- Mortality
  - All-cause mortality

- Morbidity
  - Sleep quality of the children: no relevant usable data were available, see comments in Appendix B.
  - "Emotional functioning" and "behavioural functioning" measured with the Instruments Children's Global Assessment Scale (CGAS)
  - Behavioural strengths and difficulties measured with the Strength and Difficulties Questionnaire (SDQ) instrument
- Health-related quality of life
  - No data were recorded for this outcome
- Side effects
  - Serious adverse events (SAEs)
  - Discontinuation due to AEs
  - Specific AE "somnolence" (preferred term [PT] of the Medical Dictionary for Regulatory Activities [MedDRA]). This outcome was chosen on the basis of frequencies and under consideration of the patient relevance.

Moreover, outcomes on parents or caregivers (sleep quality, measured using the Pittsburgh Sleep Quality Index [PSQI] as well as "mental well-being", measured using the World Health Organization Well-Being Index [WHO-5]), are presented for the present therapeutic indication.

Explanatory comments on the outcomes can be found in Appendix B.

2.3.2 Risk of bias

Table 4 describes the risk of bias for the results of the considered outcomes.

Table 4: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: melatonin vs. placebo

Study	Study level	Patient-relevant outcomes							Outcomes on parents or caregivers	
		All-cause mortality	Sleep quality	Emotional and behavioural functioning (CGAS)	Behavioural strengths and difficulties (SDQ)	SAEs	Discontinuation due to AEs	Somnolence (PT, AE)	Sleep quality (PSQI)	Mental well-being (WHO-5)
NEU_CH_7911	L	L	–[a]	H[b]	H[b]	L	L	L	H[b]	H[b]

a: Relevant data are not available; see Appendix B.

b: Decreasing response to questionnaire over the course of the study, which, moreover, clearly differs between the treatment arms.

AE: adverse event; CGAS: Children's Global Assessment Scale; H: high; L: low; PSQI: Pittsburgh Sleep Quality Index; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SDQ: Strength and Difficulties Questionnaire; vs.: versus

The risk of bias across outcomes was rated as low.

The risk of bias of the results on the outcomes "all-cause mortality", "SAEs", "discontinuation due to AEs" and "somnolence" was also rated as low. The risk of bias for the results of the outcomes on morbidity, in contrast, is rated as high. The reason for this is that the response to the questionnaires used for measuring "morbidity" decreased in the course of the study, and the return of the questionnaires clearly differed between the treatment arms. The same applies to the outcomes on parents or caregivers.

2.3.3 Results

Patient-relevant outcomes

Table 5 and Table 6 summarize the results on the comparison of melatonin with placebo in children and adolescents aged 2 to 17.5 with autism spectrum disorder or neurogenetic diseases who have insomnia. Results on common AEs are presented in Appendix A of the full dossier assessment. Explanatory comments on the outcomes as well as a supplementary presentation on the sleep-related outcomes can be found in Appendix B.

Table 5: Results (mortality, side effects) – RCT, direct comparison: melatonin + vs. placebo

Study Outcome category Outcome	Melatonin		Placebo		Melatonin vs. placebo
	L	Patients with event n (%)	L	Patients with event n (%)	RR [95% CI]; p-value[a]
NEU_CH_7911					
Mortality					
All-cause mortality	60	0 (0)	65	0 (0)	-
Side effects					
AEs (additional information)[b]	60	51 (85.0)	65	50 (76.9)	-
SAEs	60	0 (0)	65	1 (1.5)	0.36 [0.01 8.69]; 0.515
Discontinuation due to AEs[b]	60	1 (1.7)	65	1 (1.5)	1.08 [0.07; 16.94]; > 0.999
Somnolence (PT, AE)[b]	60	17 (28.3)	65	8 (12.3)	2.30 [1.07 4.94]; 0.027

a: Institute‘s calculation of RR, 95% CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [6]). In case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of RR and CI.

b: Discrepancy between information in Module 4 A and Module 5 of the dossier. The presented data are from Module 5.

AE: adverse event; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 6: Results (morbidity, continuous) – RCT, direct comparison: melatonin + vs. placebo

Study Outcome category Outcome	Melatonin N[a]	Values at start of study mean[b] (SD)	Change at week 15 mean[c] (SE)	Placebo N[a]	Values at start of study mean[b] (SD)	Change at week 15 mean (SE)	Melatonin vs. placebo MD [95% CI]; p-value[c]
NEU_CH_7911							
Morbidity							
Sleep quality	No relevant data; see Appendix B						
Emotional functioning and behavioural functioning (CGAS)[d]	ND	45.5 (19.42)	1.96 (1.33)	ND	47.5 (18.43)	1.84 (1.36)	0.13 [-3.64; 3.89]; 0.948
Behavioural strengths and difficulties (SDQ)							
SDQ total problem value[e]	ND	20.2 (5.28)	-0.84 (0.39)	ND	21.1 (5.86)	0.17 (0.41)	-1.01 [-2.12; 0.11]; 0.077
Behavioural problems	ND	3.0 (2.00)	-0.24 (0.14)	ND	3.5 (1.98)	0.05 (0.14)	-0.29 [-0.69; 0.11]
Emotional problems	ND	4.3 (2.69)	-0.11 (0.23)	ND	4.3 (2.98)	-0.02 (0.24)	-0.10 [-0.75; 0.55]
Hyperactivity disorder/attention deficit	ND	8.0 (2.00)	-0.47 (0.20)	ND	8.0 (2.27)	0.07 (0.21)	-0.54 [-1.12; 0.03]
Problems in dealing with peers	ND	4.9 (2.15)	-0.02 (0.15)	ND	5.4 (2.11)	0.03 (0.16)	-0.05 [-0.49; 0.39]
SDQ prosocial behaviour[f]	ND	4.9 (2.94)	0.21 (0.24)	ND	4.4 (2.89)	0.34 (0.25)	-0.13 [-0.81; 0.55]; 0.702
SDQ impact score[e]	ND	5.3 (2.84)	-0.57 (0.28)	ND	5.3 (2.69)	0.16 (0.30)	-0.74 [-1.55; 0.08]; 0.076

a: Unclear number of patients considered in the analysis; but based on the response it is certain that it is sufficiently high.
b: Corresponds to the time point of randomization: week 2 of the study.
c: Mean and SE (change at week 15 per treatment group) as well as MD, 95% CI and p-value (group comparison): MMRM.
d: Higher values indicate better functioning; a positive group difference corresponds to an advantage of melatonin.
e: Higher values indicate more problems or stronger impairment; a negative group difference corresponds to an advantage of melatonin.
f: Higher values indicate better prosocial behaviour; a positive group difference corresponds to an advantage of melatonin.

CI: confidence interval; CGAS: Children's Global Assessment Scale; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SDQ: Strength and Difficulties Questionnaire; vs.: versus

Mortality

No child or adolescent died in the NEU-CH_7911 study.

Morbidity

Sleep quality

No relevant data on the sleep quality were available. Results on other sleep-related outcomes are presented in Appendix B as additional information.

Emotional and behavioural functioning (CGAS)

There is no statistically significant difference between the treatment arms for the outcome "emotional and behavioural functioning" (measured using CGAS).

Behavioural strengths and difficulties (SDQ)

A statistically significant difference between the study arms is neither shown for the factors of the SDQ instrument nor for the impact score.

Side effects

SAEs and discontinuation due to adverse events

There was no statistically significant difference between the study arms for the outcomes "SAEs" and "discontinuation due to AEs".

Somnolence

A statistically significant difference to the disadvantage of melatonin was shown for the specific AE "somnolence".

Outcomes on parents or caregivers

Table 7 presents the results of the outcomes on parents or caregivers.

Table 7: Results (outcomes on parents or caregivers) – RCT, direct comparison: melatonin vs. placebo

Study Outcome	Melatonin			Placebo			Melatonin vs. placebo
	N[a]	Values at baseline[b] mean (SD)	Change at week 15 mean[c] (SE)	N[a]	Values at baseline[b] mean (SD)	Change at week 15 mean[c] (SE)	MD [95% CI]; p-value[c] Hedges' g [95% CI][d]
NEU_CH_7911							
Sleep quality of the parents or the caregivers (PSQI)[e]	ND	8.7 (3.43)	-1.11 (0.40)	ND	9.2 (4.05)	-0.29 (0.43)	-0.81 [-1.97; 0.34]; 0.166
Mental well-being of the parents or the caregivers (WHO-5)[f]	ND	12.0 (4.65)	1.43 (0.57)	ND	11.3 (4.96)	-0.75 (0.61)	2.17 [0.53; 3.82]; 0.010 0.48 [0.11; 0.85]

a: Unclear number of patients considered in the analysis; but based on the response it is certain that it is sufficiently high.
b: Corresponds to the time point of randomization: week 2 of the study.
c: Mean and SE (change at week 15 per treatment group) as well as MD, 95% CI and p-value (group comparison): MMRM.
d: Institute's calculation based on MD and CI estimation of the MMRM under the assumption that all patients with baseline values (58 [melatonin] vs. 57 [placebo]) were considered in the analysis.
e: Higher values reflect a worse state; a negative group difference corresponds to an advantage of melatonin.
f: Higher values reflect a better state; a positive group difference corresponds to an advantage of melatonin.
CI: confidence interval; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; PSQI: Pittsburgh Sleep Quality Index; RCT: randomized controlled trial; SE: standard error; SD: standard deviation; vs.: versus; WHO: World Health Organization

Sleep quality (PSQI)

There was no statistically significant difference between the study arms for the outcome "sleep quality of the parents or the caregivers".

Mental well-being (WHO-5)

There is a statistically significant difference in favour of melatonin for the outcome "mental well-being of the parents or the caregivers". However, the CI for Hedges' g was not fully outside the irrelevance range [−0.2; 0.2]. Relevance of the effect could thus not be derived [7].

2.4 Subgroups and other effect modifiers

The following subgroups were relevant for the present assessment:

- Age (2 to ≤ 6 years versus 7 to ≤ 12 years versus > 12 years)
- Sex (male versus female)
- Geographical region (USA vs. Europe)

- Autism type (autism spectrum disorders versus Smith-Magenis syndrome)

Subgroup analyses were only used if each subgroup comprised at least 10 persons and, for binary data, if at least 10 events had occurred in one of the subgroups. Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. Moreover, subgroups are only presented if there is a statistically significant and relevant effect in at least one subgroup.

According to the named methodology, no relevant effect modifications were observed.

2.5 Summary

Relevant data on the sleep quality of the children and adolescents are not available. The sleep-related outcomes presented as supplementary information demonstrate that sleep duration is prolonged and sleep latency is shortened under melatonin in comparison with placebo, however, this does not verifiably influence external assessment of the sleep disorders of the children or adolescents in comparison with placebo (measured with the unvalidated CSDI instrument).

No advantage or disadvantage of melatonin is shown for each of the outcomes “emotional and behavioural functioning” and “behavioural strengths and difficulties” of the children and adolescents.

For the AE “somnolence”, there is a disadvantage of melatonin versus placebo, which is in consistence with the influence on the sleep duration.

No advantage or disadvantage of melatonin is shown for the outcomes on parents or caregivers. The result for “sleep quality” is not statistically significant; there is a statistically significant result in favour of melatonin on “mental well-being”, however, the group difference is irrelevant.

Overall, the data of the NEU_CH_7911 study resulted in no advantage or disadvantage of melatonin versus placebo.

The G-BA decides on the added benefit.

2.6 List of sources for the NEU_CH_7911 study

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Appendix A – Results on side effects

The following Tables present the SOCs and PTs in accordance with MedDRA for the overall rates AEs on the basis of the following criteria:

- Overall rate AEs (irrespective of the severity grade): events that occurred in at least 10% of the patients in one study arm
- in addition for all events irrespective of the severity grade: events that occurred in at least 10 patients and in at least 1% of the patients in one study arm

Due to the low number of events (see Table 5), the common AEs were not presented for the overall rates SAEs.

All events (SOCs/PTs) that resulted in discontinuation were completely presented for the outcome “discontinuation due to adverse events”.

Table 8: Common AEs – RCT, direct comparison: melatonin vs. placebo

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Melatonin** **N = 60**	**Placebo** **N = 65**
NEU_CH_7911		
Overall rate AEs	51 (85.0)	50 (76.9)
Psychiatric disorders	23 (38.3)	20 (30.8)
Mood swings	10 (16.7)	11 (16.9)
Agitation	11 (18.3)	7 (10.8)
Infections and infestations	23 (38.3)	18 (27.7)
Upper respiratory tract infection	9 (15.0)	7 (10.8)
Nervous system disorders	25 (41.7)	15 (23.1)
Somnolence	17 (28.3)	8 (12.3)
Headache	8 (13.3)	4 (6.2)
General disorders and administration site conditions	21 (35.0)	18 (27.7)
Fatigue	15 (25.0)	12 (18.5)
Gastrointestinal disorders	18 (30.0)	15 (23.1)
Vomiting	8 (13.3)	10 (15.4)
Respiratory, thoracic and mediastinal disorders	16 (26.7)	14 (21.5)
Cough	7 (11.7)	5 (7.7)
Dyspnoea	6 (10.0)	4 (6.2)
Skin and subcutaneous tissue disorders	7 (11.7)	8 (12.3)

a: MedDRA version 18.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 9: Discontinuation due to AEs – RCT, direct comparison: melatonin vs. placebo

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Melatonin** **N = 60**	**Placebo** **N = 65**
NEU_CH_7911		
Overall rate of discontinuations due to AEs	1 (1.7)	1 (1.5)
General disorders and administration site conditions	1 (1.7)	0 (0)
Fatigue	1 (1.7)	0 (0)
Infections and infestations	0 (0)	1 (1.5)
Pneumonia	0 (0)	1 (1.5)
Virus infection of the respiratory tract	0 (0)	1 (1.5)
Psychiatric disorders	1 (1.7)	0 (0)
Agitation	1 (1.7)	0 (0)
Stereotypy	1 (1.7)	0 (0)
Respiratory, thoracic and mediastinal disorders	0 (0)	1 (1.5)
Tachypnoea	0 (0)	1 (1.5)

a: MedDRA version 18.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Appendix B – Comments on the outcomes and supplementary presentation of the results on sleep-related outcomes

The company included a series of outcomes and instruments on morbidity or health-related quality of life in its assessment and rated them as being patient-relevant or validated. They are hereinafter commented in summary.

Emotional and behavioural functioning, measured with CGAS

The CGAS scale is an instrument that helps the investigator to fully assess the affected child on a scale from 1 to 100 supported by the parents or a caregiver [8]. Higher values on the scale indicate better functioning. According to the developers of this instrument, the CGAS scale records the general functioning of the children over the period 1 month prior to the time point of measurement. The company provides a series of publications on the validation of this instrument [9,10].

The CGAS instrument is considered to be validated in the present therapeutic indication and is used to illustrate the morbidity. In the NEU_CH_7911 study, however, the company used a modified and - in this form - unvalidated version of the instrument, in which emotional and behavioural functioning was queried instead of general functioning. Moreover, the query was made for the period “3 months” (and not “1 month”).

For the outcome “emotional and behavioural functioning”, the company presents the analysis on both the mean change in comparison with the start of the study and the portion of children and adolescents who had exceeded a scale threshold value of ≥ 71 points at the end of the randomized treatment phase. This threshold value is indicated in the publication [10]. However, this threshold value was not used, because the company had modified the original version to which the publication [10] refers. Moreover, this analysis was not prespecified. Therefore, the present assessment only used the prespecified analysis on the mean change versus the start of the study.

Behavioural strengths and difficulties, measured using SDQ instrument

The DSQ instrument is a questionnaire which measures the behavioural strengths and difficulties [11-16]. This questionnaire comprises 25 items with the response categories “not true”, “somewhat true” and “absolutely true”. These are coded with 0, 1 or 2. 5 items each are allocated to one so-called factor for which the item values are added up. This results in a value form 0 to 10 for each factor.

The 5 factors queried by the DSQ are: emotional problems, behavioural disorders, attention deficit/hyperactivity disorder, problems in dealing with peers as well as prosocial behaviour. A total score reaching from 0 to 40 (SDQ total problem score) can be calculated for the first 4 factors. Higher values indicate stronger impairment. The factor “prosocial behaviour” was considered separately; higher values in this factor indicate better prosocial behaviour.

Moreover, there was a supplement for the recording of the impact score which records problems at home, at school, with friends and during leisure activities; moreover, it provides information on how much the child suffers from the difficulties. Values ranged from 0 to 10; higher values indicate more problems.

The SDQ instrument was used. Considered were analyses on the mean change in the SDQ total problem score, the factor "prosocial behaviour" and the impact score since the start of the study.

The externalising score (sum of the subscales "behavioural disorders, attention deficit/ hyperactivity disorder") considered by the company cannot be derived from the source cited by it [13]. Moreover, there is the internalising score comprising the results of the subscales "emotional problems", "problems in dealing with peers" and "prosocial behaviour". These analyses were not used, because the data on the externalising and internalising score were presented via the other analyses and the company only presented the externalising score.

Sleep-related outcomes

Table 10 shows the results on the sleep-related outcomes "sleep disorders" (measured using the Composite Sleep Disturbance Index [CSDI] instrument) as well as "TST and sleep latency" as supplementary information.

Table 10: Supplementary results (TST and sleep latency – RCT, direct comparison: melatonin + vs. placebo

Study Outcome	Melatonin			Placebo			Melatonin vs. placebo
	N[a]	Values at baseline[b] mean (SD)	Change at week 15 mean[c] (SE)	N[a]	Values at baseline[b] mean (SD)	Change at week 15 mean[c] (SE)	MD [95% CI]; p-value[c]
NEU_CH_7911							
Sleep disorders (CSDI)[d]	ND	7.71 (2.39)	-2.44 (0.35)	ND	8.23 (2.55)	-1.52 (0.37)	-0.92 [-1.93; 0.09]; 0.074
TST (minutes)	ND	457.21 (101.28)	51.03 (10.46)	ND	459.85 (109.22)	18.71 (10.82)	32.32 [2.38; 62.26]; 0.035
Sleep latency (minutes)	ND ND	95.16 (59.25)	-37.77 (6.82)	ND ND	98.76 (73.90)	-12.57 (7.01)	-25.20 [-44.61/-5.80]; 0.011
	L	**Patients with event n (%)**		**N**	**Patients with event n (%)**		**RR [95% CI]; p-value[e]**
TST (increase by ≥ 45 minutes)	58	22 (37.9)[f]		61	10 (16.4)[f]		2.31 [1.20; 4.46]; 0.009
Sleep latency (reduction by ≥ 15 minutes)	58	37 (63.8)[f]		61	20 (32.8)[f]		1.95 [1.29 2.93]; 0.001

a: Unclear number of patients considered in the analysis for continuous outcomes; but based on the response it is certain that it is sufficiently high.
b: Corresponds to the time point of randomization: week 2 of the study.
c: Mean and SE (change at week 15 per treatment group) as well as MD, 95% CI and p-value (group comparison): MMRM.
e: Higher values indicate more sleep disorders; a negative group difference corresponds to an advantage of melatonin.
e: Institute‘s calculation, unconditional exact test (CSZ method according to [6]).
f: Missing values were imputed as non-response (melatonin: 6 [10.3%]; placebo: 13 [21.3%])
CI: confidence interval; CSDI: Composite Disturbance Index; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; vs.: versus

Sleep disorders measured with the Composite Sleep Disturbance Index (CSDI) instrument

The CSDI is a measurement instrument which records the frequency and duration of sleep disorders and, according to the company, is thus supposed to record the sleep quality of the child. Making reference to the publications [17-19], the company describes this instrument as being validated.

In contrast to the company’s assessment, the sources cited by it are unsuitable to demonstrate the validity of the CSDI. The sources are publications on studies with melatonin which also used the CSDI. However, use of this instrument in previous studies on melatonin alone does not result in its validation. Other instruments specifically developed for the present therapeutic indication [20] were not used in the study conducted by the company.

TST and sleep latency

The company describes the outcomes "TST" and "sleep latency" as immediately patient-relevant, because they reflect insufficient sleep and thus the health status of the patients.

However, TST and sleep latency only address one aspect of sleep [20,21]. No conclusions on the sleep quality can be drawn from these values.

Outcomes on the impact on the parents or the caregivers

The company presented a series of outcomes for the assessment of the impact the children's sleep disorders exert on parents or caregivers. These outcomes included "somnolence measured using the Epworth Sleepiness Scale (ESS)" as well as "sleep quality measured using the Pittsburgh Sleep Quality Index (PSQI) and the WHO-5 Well-being Index" instrument for the measurement of mental well-being.

The ESS instrument solely measures the probability of the affected person to fall asleep or drowse in different situation over the day. The sleep quality is not measured by this instrument.

The PSQI instrument is suitable to measure the sleep quality [21].

The World Health Organization Well-Being Index (WHO-5) instrument is suitable for the measurement of mental well-being [22].