25 July 2024
EMA/426789/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Slenyto

International non-proprietary name: Melatonin

Procedure No. EMEA/H/C/004425/II/0025

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADHD	Attention deficit hyperactivity disorder
ADR	Adverse drug reaction
AE	Adverse event
AS	Angelman syndrome
ASD	Autism Spectrum Disorder
AUC	Area under the concentration-time curve
$AUC_{0\text{-}8hr}$	Area under the concentration-time curve from time zero to 8 hours
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve from time zero extrapolated to infinity
$AUC_{0\text{-}last}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration
BL	Baseline
CI	Confidence interval
C_{max}	Maximum concentration
CPC	Compassionate Prescribing Framework
CSDI	Composite Sleep Disturbance Index
DSM	Diagnostic and Statistical Manual
EMA	European Medicines Agency
EU	European Union
FAS	Full analysis set
IR	Immediate release
LSE	Longest sleep episode
MAH	Marketing Authorization Holder
Max	maximum
Min	minimum
MMRM	Mixed-effects model for repeated measures
NNT	Number needed to treat
PAM	Post-Authorization Measure
PDD	Pervasive developmental disorder
PK	Pharmacokinetic
Po	Oral administration
PPP	Per protocol population
PR	Prolonged release
PUMA	Pediatric Use Marketing Authorization
REM	Rapid eye movement
RTU	Temporary Recommendation for Use
SAE	Serious adverse event
SD	Standard deviation
SDQ	Strength and Difficulties Questionnaire

SE	Standard error
SEM	Standard error of the mean
SL	Sleep latency
SmPC	Summary of Product Characteristics
SMS	Smith-Magenis syndrome
SND	Sleep and nap diary
SOC	System Organ Class
TD	Typically developing
TEAE	Treatment-emergent adverse event
TSC	Tuberous sclerosis complex
TST	Total sleep time
UK	United Kingdom
WHO-5	World Health Organization Well-Being Index

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, RAD Neurim Pharmaceuticals EEC SARL submitted to the European Medicines Agency on 29 November 2023 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of neurogenetic disorders (e.g., Angelman syndrome, Rett syndrome, Tuberous sclerosis complex and Williams syndrome) for SLENYTO, based on Phase III study NEU_CH_7911, post-marketing data and literature; As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Tomas Radimersky

Timetable	Actual dates
Submission date	29 November 2023
Start of procedure:	23 December 2023
CHMP Rapporteur Assessment Report	14 February 2024
PRAC Rapporteur Assessment Report	23 February 2024
CHMP Co-Rapporteur Assessment	28 February 2024
Updated PRAC Rapporteur Assessment Report	29 February 2024
PRAC Outcome	7 March 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 March 2024
Request for supplementary information (RSI)	21 March 2024
CHMP Rapporteur Assessment Report	19 June 2024
PRAC members comments	n/a
CHMP members comments	15 July 2024
Opinion	25 July 2024

2. Scientific discussion

The European Union (EU) marketing authorization for Slenyto, a paediatric prolonged release melatonin formulation, was granted on 20 September 2018. Slenyto is indicated for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient. The Marketing Authorization Holder (MAH), RAD Neurim Pharmaceuticals EEC SARL (hereafter referred to as Neurim) is now seeking to expand the approved indications to include the treatment of insomnia in children and adolescents aged 2-18 years with neurodevelopmental disorders associated with neurogenetic disorders (Angelman syndrome, Rett syndrome, Tuberous sclerosis complex and Williams syndrome), where sleep hygiene measures have been insufficient. Melatonin deficiency or misalignment has been shown to be a key pathophysiological mechanism for insomnia in these neurogenetic disorders.

Slenyto was initially developed for the treatment of insomnia characterized by maintenance problems and sleep onset difficulties in children with pervasive developmental disorders (PDD) and neurogenetic disease (refer to EMEA-000440-PIP02-11-M05). The term PDD was used based on the Diagnostic and Statistical Manual (DSM) IV classification – this included autism disorder, Rett's disorder, child disintegrative disorder, Asperger's disorder and PDD not otherwise specified. The term PDD was changed to ASD, as individuals with a well-established DSM-IV diagnosis of autism disorder, Asperger's disorder, or PDD were given the diagnosis of ASD by DSM-V. In addition, the indication was narrowed from neurogenetic disease to SMS during the assessment of the initial marketing authorisation as the pivotal Phase III study included mainly children with ASD and SMS. No children with other neurogenetic disorders, like Rett's syndrome, AS, or TSC were enrolled because of their orphan prevalence, although it was planned to enrol these populations.

Based on new data that have accumulated since the initial license grant, it is proposed to extend the indication of Slenyto to treat insomnia in children and adolescents aged 2-18 with neurodevelopmental disorders associated with neurogenetic disorders including Angelman syndrome, Rett syndrome, Tuberous sclerosis complex and Williams syndrome, where sleep hygiene measures have been insufficient.

2.1. Non-clinical aspects

The environmental risk assessment concerns the active substance melatonin in the medicinal product Slenyto 1 mg and 5 mg prolonged-release tablets. The active ingredient is identical to endogenous melatonin. The recommended dose is 2 mg once daily, potentially rising to 5 mg once daily if an inadequate response has been observed, with a maximal dose of 10 mg.

The environmental risk assessment has been prepared to support the Type II variation to extend the indication to include the following additional neurogenetic disorders: Angelman syndrome (AS), Rett syndrome, Tuberous sclerosis complex (TSC) and Williams syndrome. The ERA contains a Phase I assessment and PBT screening of the active substance.

Phase I exposure assessment was calculated by using the maximum daily dose (10 mg) and the refined market penetration factor of 0.0016. The refinement was based on the prevalence data of the diseases targeted by the medicinal product (i.e., ASD and/or the neurogenetic disorders SMS, AS, Rett syndrome, TSC and Williams syndrome) in pediatric patients. The resulting PEC_{SW} amounted to 0.008 µg/L. The log K_{OW} of the active substance is below the threshold of 4.5, and therefore, further PBT screening was not required.

Since the potential target patient population using Slenyto 1 mg and 5 mg prolonged-release tablets is relatively small, and the dose of melatonin administered is low (compared to the normal levels in young subjects), while the active substance is naturally occurring, the use of Slenyto is unlikely to have a significant effect on environmental levels.

2.1.1. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of melatonin.

2.2. Clinical aspects

2.2.1. Pharmacokinetics

Two different medicinal products containing melatonin were used in the clinical development programme to support new indications. The marketed formulation of Circadin (prolonged-release melatonin 2 mg) tablets was used in the RTU programme. The marketed formulation of Slenyto (prolonged-release melatonin 1 mg and 5 mg) mini-tablets was used in the NEU_CH_7911 Phase III study and the CPC compassionate use programme.

Bioavailability of both medicinal products under fed conditions was compared in the PK Study CHDR1742. For the comparison of AUC0-∞ between 5 mg Slenyto and 2 mg Circadin, 90% confidence interval (CI) lay between the acceptance ranges 0.8-1.25. For the comparison of AUC0-∞ between 1 mg Slenyto and 2 mg Circadin, the lower limit was also within the predefined acceptance limit, but the upper 90% CI exceeded the acceptance limit of 1.25. For Cmax, the lower limit was within range for

both 1 mg and 5 mg Slenyto, but the upper 90% CI exceeded the wider acceptance limit. Despite that strict bioequivalence was not demonstrated, the point estimates of the slopes were close to 1 for 1 mg Slenyto and the 90% CI for the slope estimates contained 1 for Cmax and AUC0-∞.

Furthermore, the PK profiles of 1 mg Slenyto, 2 mg Circadin and 5 mg Slenyto under fed conditions were similar in shape and the dose adjusted PK parameters considered to be comparable and dose proportional.

Conclusions

The PK profiles of 1 mg Slenyto, 2 mg Circadin and 5 mg Slenyto are similar in shape and the dose adjusted PK parameters are considered comparable and dose proportional allowing extrapolation of data from studies with Circadin to Slenyto from the PK point of view.

2.2.2. Pharmacodynamics and literature data

The MAH has presented a short literature overview over the circadian rhythm and melatonin release disturbances and clinical study data reported in the literature for children with Angelman syndrome, Rett syndrome, Tuberous sclerosis complex, and Williams syndrome, the neurogenetic disorders proposed by the MAH to be included in the revised Indication text. The CHMP has added more details from some of the clinical studies.

Angelman Syndrome

Angelman syndrome (AS) is a rare genetic and neurological disorder characterized by severe developmental delay and learning disabilities; absence or near absence of speech; inability to coordinate voluntary movements (ataxia); tremulousness with jerky movements of the arms and legs and a distinct behavioral pattern characterized by a happy disposition and unprovoked episodes of laughter and smiling. Seizures are present in 85% of people with AS (Fiumara et al., 2010). Although those with the syndrome may be unable to speak, many gradually learn to communicate through other means such as gesturing. In addition, children may have enough receptive language ability to understand simple forms of language communication. Additional symptoms may occur including sleep disorders and feeding difficulties. The prevalence of AS is estimated to be approximately 1 in 12,000-20,000 people in the general population (NORD).

AS is caused by deletion or abnormal expression of the UBE3A gene. Angelman syndrome has a high comorbidity with autism and shares a common genetic basis with some forms of autism. The current view states that AS is considered a 'syndromic' form of autism spectrum disorder (Peters et al., 2012). Different deletion classes (class I versus class II) in AS have further been shown to range in the severity score for autism spectrum disorders (Peters et al., 2004). This may be attributed to additional genes that are deleted in AS individuals with a class I deletion.

Sleep disturbances, abnormal sleep-wake cycles and a diminished need for sleep are included in the consensus guidelines for the diagnostic criteria of AS and are highly common in patients, especially in early childhood between 2-6 years of age; methods for assessing sleep quality and timing in AS patients have been well described (Trickett, et al., 2019). The prevalence of sleep disorders in AS is high and is reported to be between 20-80% (Williams et al., 1995; Williams et al., 2006; Shelton and Malow, 2021).

Melatonin secretion profile is impaired in AS patients (Paprocka et al., 2017; Buonfiglio et al., 2020) and a variety of sleep problems are observed, including difficulty initiating and maintaining sleep, multiple nocturnal awakenings, difficulties falling asleep, reduced total sleep time, sleep-wake rhythm disorders, nocturnal movement disorders, enuresis, bruxism, sleep terrors, sleep walking, sleep

paralysis, excessive daytime sleepiness, and sleep related breathing difficulties (Williams et al., 2006; Dosier et al., 2017; Spruyt et al., 2018).

Poor sleep in children and adolescents with AS increases parental stress, decreasing their parenting abilities (Goldman et al., 2012; Allen et al., 2013; Trickett et al., 2017). Thus, diagnosing and treating sleep disruption in this population is important. There is a relationship between disruptive behavior and sleep onset. Targeted treatment to improve sleep environment, sleep hygiene, and parent-child interactions during sleep times reduces disruptive behaviours in a sustainable way (Allen et al., 2013). Treatment may include a trial of melatonin for help in initially falling asleep.

The effects of low dose melatonin therapy on sleep behaviour and serum melatonin levels were studied in N=13 Angelman syndrome (AS) children aged 2-10 years suffering from insomnia. 24-hour motor activity was monitored in their home environments for 7 days prior to melatonin treatment and for 5 days during which a 0.3 mg dose of melatonin was administered daily 0.5-1 hour before the patient's habitual bedtime. Blood samples were with-drawn at hourly intervals over two 21-hour periods in order to measure individual endogenous serum melatonin levels and the levels induced by melatonin treatment. Actigraphic recording of motor activity, confirmed by parents' reports, showed a significant improvement in the patients' nocturnal sleep pattern as a result of melatonin treatment. Analysis of the group data revealed a significant decrease in motor activity during the total sleep period following melatonin treatment, and an increase in the duration of the total sleep period. Parents of these children reported improved sleep consolidation and quality. Endogenous peak nocturnal melatonin values ranged from 19 to 177 pg/ml. The administration of melatonin elevated peak serum hormone levels to 128-2800 pg/ml in children of different ages and body mass. This treatment also resulted in a 2 to 3-hour phase advance in the onset of melatonin secretion in children that otherwise exhibited a significant phase delay in nighttime melatonin secretion. (Zhdanova et al., 1999).

Braam et al. (2008) conducted a randomized, double-blind, placebo-controlled study on N=7 children (aged 4-13) and 1 adult (aged 20) with Angelman Syndrome and chronic idiopathic insomnia. Criteria for participation were sleep latency more than 30 minutes, or 2 or more wakes, lasting more than 15 minutes a night, at least 5 nights a week, during more than 1 year preceding inclusion. Exclusion criteria were prior use of melatonin, liver disease, renal failure, chronic pain, and age less than 24 months. See Table 1 for baseline characteristics. The trial consisted of 2 consecutive periods: a 1-week qualification period and 4 weeks of treatment during which participants were randomly allocated to melatonin or placebo therapy. Saliva specimens for measuring melatonin concentrations were collected in the qualification period (baseline) to examine whether there was a delayed sleep phase syndrome or another disturbance in melatonin circadian rhythm and at the end of the last week of the treatment period to examine whether 4 weeks of treatment had changed endogenous melatonin circadian rhythm. After the 4-week placebo-controlled phase of the study, all patients received 4 weeks open treatment with melatonin. Primary outcome measures were the between-group differences of sleep latency, sleep onset, wake up time, and number and length of wakes. Secondary outcome measures were the between group differences of salivary melatonin concentrations, number of epileptic seizures, as well as adverse reactions of melatonin. Sleep variables were assessed by parents and recorded in a sleep diary. Seven patients showed sleep onset as well as sleep maintenance problems, and 1 patient suffered from sleep onset problems only. Treatment with melatonin significantly advanced sleep onset by 28 minutes, decreased sleep latency by 32 minutes, increased total sleep time by 56 minutes and reduced the number of nights with wakes from 3.1 to 1.6 nights a week. These changes significantly differed from those during placebo treatment (Table 2). Parents indicated that their children were less sleepy and more attentive during the day, with easier to manage behaviour. (Braam et al., 2008).

Table 1: Participant Characteristics and Medication Use During the Study

	Patient							
	1	2	3	4	5	6	7	8
Type of Angelman syndrome	Deletion	Deletion	Disomy	Deletion	Deletion	Disomy	Deletion	Deletion
Age, y:mo	4:10	12:10	6:7	5:7	8:10	9:2	20:11	13:4
Gender	Male	Female	Female	Male	Female	Female	Male	Female
Weight, kg	20	48	26	22.5	31	37	56	40
Sleep onset problem	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nighttime awakening	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Antiepileptic drug use	cbz,clb,vpa	–	vpa	–	esm	–	vpa	clb,vpa
Present sleep medication	mid	pip	–	–	–	–	–	–

NOTE: cbz = carbamazepin; clb = clobazam; esm = ethosuximide; vpa = valproate; mid = midazolam; pip = pipamperon.

Table 2: Different in Sleep Parameters From Baseline to Week 4

	Baseline					Intervention (4 weeks)				
	Melatonin Mean (SD)	Placebo Mean (SD)	*t*	*df*	*P*	Melatonin Mean (SD)	Placebo Mean (SD)	*t*	*df*	*P*
Lights out time[a]	20:10 (0:55)	20:09 (1:12)	.011	6	.99	20:14 (0:52)	20:14 (1:12)	0	6	1
Sleep onset time[a]	21:00 (1:10)	21:05 (1:30)	–.096	6	.93	20:32 (0:56)	21:10 (1:31)	–.715	6	.02[c]
Sleep latency[b]	50.00 (17.49)	56.50 (21:17)	–.473	6	.65	17.5 (5.74)	55.75 (20.64)	–3.570	6	.01[c]
Sleep offset time[a]	07:49 (0:36)	07:02 (0:33)	1.715	5	.15	07:42 (0:38)	07:02 (0:02)	1.768	5	.14
No. of nights/week with wakes	3.1 (2.95)	5.9 (1.41)	–1.724	6	.14	1.6 (2.01)	5.6 (1.24)	–3.357	6	.01[d]
No. of wakes/night	1.5 (1.41)	1.7 (0.69)	–.127	6	.9	0.9 (0.61)	1.8 (0.79)	–1.926	6	.1
Duration of wakes[b]	39.50 (35.25)	55.00 (37.53)	–.602	6	.57	11.75 (9.87)	60.75 (45.02)	–2.126	6	.08
Total sleep time[a]	10:08 (1:22)	9:40 (0:37)	.545	5	.61	11:04 (0:46)	9:31 (0:28)	2.996	5	.03[c]

a. Hours:minutes.
b. Minutes.
c. $P < .05$.
d. $P < .01$.

Takaesu et al. (2012) studied the sleep-wake patterns of AS patients and its relationship to the serum melatonin levels. The serum melatonin levels of 15 AS patients were measured every 4h for one day and the values were compared with those of age-matched controls. A total of eight of the 15 AS patients had CRSD (irregular sleep-wake type, n=4; free-running type n=2; delayed sleep phase type, n=2). The nighttime serum melatonin levels of the AS patients were significantly lower than those of the controls at the measured time points during the night. The nocturnal melatonin levels were comparably low both in AS patients with and without CRSD except for the cases with delayed sleep phase type, which showed normal but delayed peak melatonin level. Six out of eight CRSD cases were given a daily dose of 1mg of melatonin between 18:00 and 19:00 regularly for three months. After

receiving the treatment, the sleep patterns improved in four cases

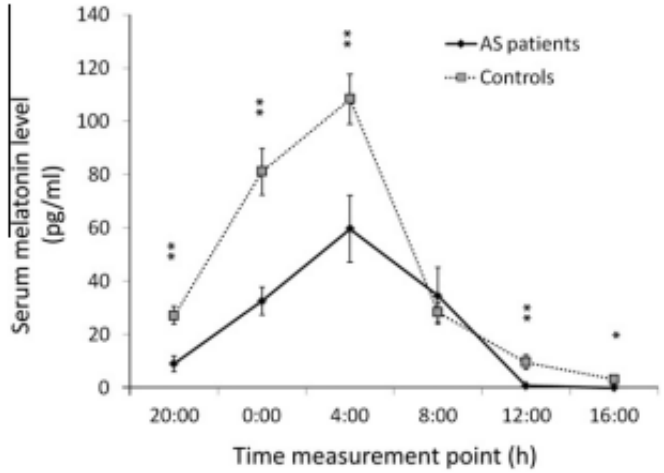


Fig. 1. Comparison of diurnal changes in serum melatonin level between the AS patients and the controls. AS: Angelman syndrome. $^{**}p < 0.01$, $^{*}p < 0.05$. Two-way repeated ANOVA and the Bonferroni–Dunn test were used to compare the serum melatonin levels between the AS patients and the controls. The vertical error bars represent standard error (SE) of the mean.

Figure 1

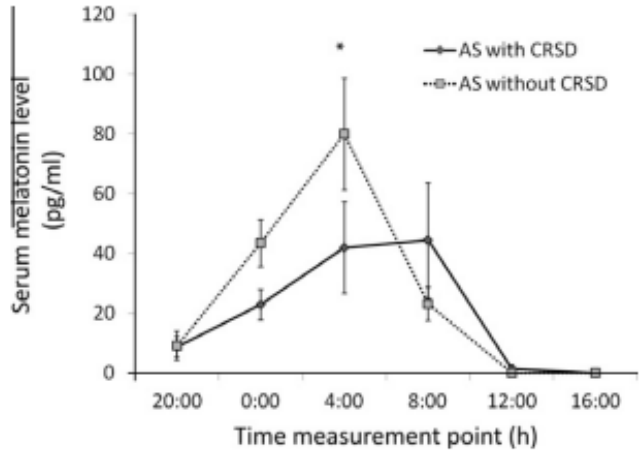


Fig. 2. Comparison of diurnal changes in serum melatonin level between the AS patients with and without CRSD. AS: Angelman syndrome. CRSD: Circadian rhythm sleep disorder. $^{**}p < 0.01$, $^{*}p < 0.05$. Two-way repeated ANOVA and the Bonferroni–Dunn test were used to compare the serum melatonin levels between the AS patients and the controls. The vertical error bars represent the SE of the mean.

Figure 2

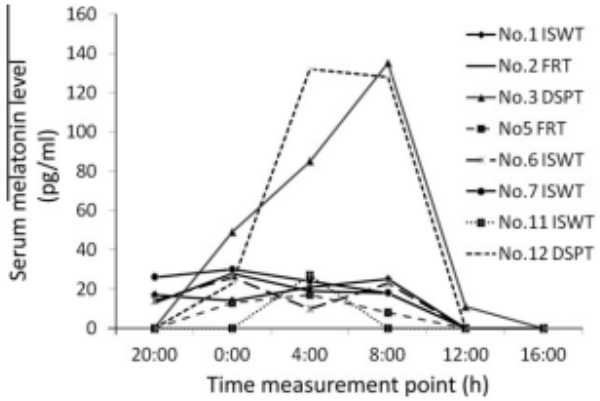


Fig. 3. Individual melatonin profiles of the AS subjects with CRSD. ISWT: irregular sleep–wake type FRT: free-running type DSPT: delayed sleep phase type.

Figure 3

Rett Syndrome

Rett syndrome is a progressive neurodevelopmental disorder that almost exclusively affects females. Only in rare cases are males affected. Infants with Rett syndrome generally develop normally for about 7 to 18 months after birth. At this point, they lose previously acquired skills (developmental regression) such as purposeful hand movements and the ability to communicate. Additional abnormalities occur including impaired control of voluntary movements (ataxia) and the development of distinctive, uncontrolled hand movements such as hand clapping or rubbing. Some children also have slowing of head growth (acquired microcephaly). Affected children often develop autistic-like behaviors, breathing irregularities, feeding and swallowing difficulties, growth retardation, and seizures. The global prevalence of Rett syndrome is estimated to be 1.7 per 100,000 females (Petriti, et al., 2023).

Most Rett syndrome cases are caused by identifiable mutations of the MECP2 gene on the X chromosome and can present with a wide range of disability ranging from mild to severe. The course and severity of Rett syndrome is determined by the location, type and severity of the MECP2 mutation and the process of random X-inactivation. Some girls with a diagnosis of autism have also been shown to have mutations in the MECP2 gene.

Over 80% of individuals with Rett syndrome are affected by sleep disorders, which vary with age and mutation type (Young et al., 2007; Tascini et al., 2022). Tascine et al. (2022) summarise that sleep disorders reported for patients with Rett syndrome include dysregulation of the sleep/wake cycle, difficulty falling asleep or staying asleep, night laughter or screaming and frequent awakenings. Impaired sleep pattern is included in the supportive criteria for Rett syndrome (Neul et al., 2010; Shelton and Malow, 2021). Children with Rett syndrome have also been found to have impaired secretion of melatonin, leading to severe sleep problems (Miyamoto et al., 1999).

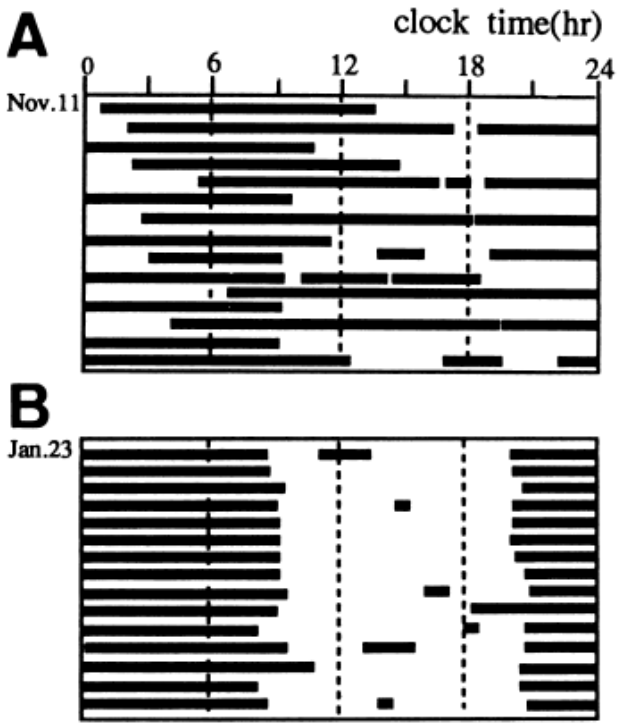


Fig. 1. Sleep-wake periods as observed and recorded by the mother of patient 1 before melatonin treatment (A) and during treatment with oral melatonin, 5 mg/day (B).

Figure 4

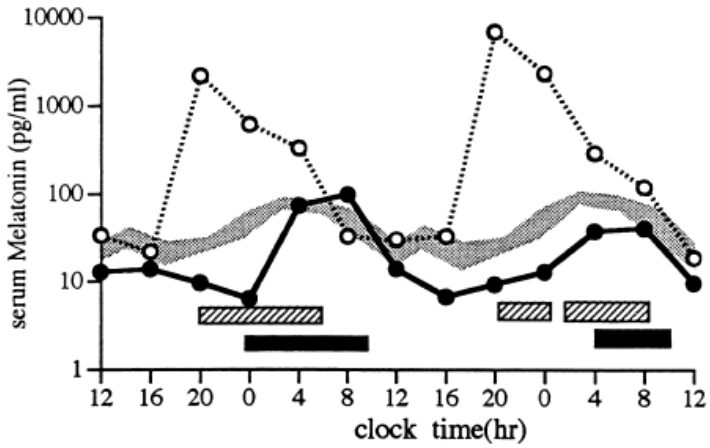


Fig. 2. Serum melatonin pattern before (closed circle) and during (open circle) melatonin treatment in patient 1. Oral melatonin, 5 mg administration at 1930 h. Sleep time before (closed box) and during (stippled box) melatonin treatment. Serum melatonin levels in normal prepubertal children reported by Ehrenkranz et al. [11] (shaded box).

Figure 5

Figures from Miyamoto et al. (1999)

Melatonin is the most commonly used medication to treat sleep disturbances in Rett syndrome followed by antiepileptic medications and variants of benzodiazepines (Wong et al., 2015; Shelton and Malow, 2021).

In a double-blind, placebo-controlled crossover study, the effects of exogenous melatonin treatment on sleep dysfunction were examined in children with Rett syndrome (McArthur and Budden, 1998). Nine girls with Rett syndrome (mean age: 10.1 years) underwent a 4-week treatment period (melatonin or placebo) with a 1-week washout between treatments. Melatonin doses ranged from 2.5 to 7.5 mg, based upon individual body weight. Sleep-wake patterns were monitored 24 hours a day over the 10-week study period (including a 1-week baseline period) using wrist actigraphy. Patients' baseline sleep quality was poor compared with healthy children. At baseline the group demonstrated a low sleep efficiency (mean [+/- SE], 68.0+/-3.9%), long sleep-onset latency (42.1+/-12.0 minutes), and a short and fragmented total sleep time (7.5+/-0.3 hours; 15+/-2 awakenings per night). Melatonin significantly decreased sleep-onset latency to 19.1+/-5.3 minutes ($P<0.05$) during the first 3 weeks of treatment. While the variability of individual responsiveness was high, melatonin appeared to improve total sleep time and sleep efficiency in the patients with the worst baseline sleep quality. No adverse effects were observed over the 4-week melatonin treatment period.

Other clinical trials have shown that exogenous melatonin treatment in Rett syndrome children improves sleep-wake cycle and sleep onset for more than 2 years without any adverse effects (Miyamoto et al., 1999; Tascini et al., 2022).

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a rare genetic multisystem disorder that is typically apparent shortly after birth. The disorder can cause a wide range of potential signs and symptoms and is associated with the formation of benign (non-cancerous) tumours in various organ systems of the body. The skin, brain, eyes, heart, kidneys and lungs are frequently affected. These tumours are often referred to as hamartomas; they are not malignant, can grow larger and can damage the affected organ system. The number, size, and specific location of these abnormal growths in individuals with TSC can vary widely and consequently the severity of the disorder can vary widely as well. The prevalence of TSC in Europe is estimated to be approximately 1 in 25,000 to 1 in 11,300 (NORD). As many as 2 million people worldwide are believed to have the disorder.

TSC results from alterations (mutations) in a gene or genes that may occur spontaneously (sporadically) for unknown reasons or be inherited as an autosomal dominant trait. Most cases represent new (sporadic or de novo) gene mutations, with no family history of the disease. Mutations within at least two different genes are known to cause TSC, the TSC1 gene or the TSC2 gene.

Affected individuals may have normal development and cognitive function but a majority experience delays in reaching developmental milestones (developmental delays) and have some degree of intellectual disability. Individuals can potentially develop a range of neuropsychiatric disorders including autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), sleep disturbances or disorders, learning and cognitive impairments, or behavioural issues including disruptive and emotional behaviours or problems. Sleep problems are common in TSC patients (Bruni et al., 1995).

Hancock et al. (2005) compered the melatonin excretion patterns in patients with tuberous sclerosis complex and compared these with healthy children without sleep disorder. They measured6-sulfatoxymelatonin excretion in 21 healthy children and in 7 patients with tuberous sclerosis complex and sleep disorder responsive to melatonin (a 5 mg oral dose increasing total sleep time). Total excretion, percentage of perfect consinor melatonin diurnal excretion curve, and time of maximal excretion during 24-h were measured. In tuberous sclerosis, normal patterns of melatonin excretion compared to healthy controls were seen in the melatonin responders.

O'Callaghan et al. (1999) examined the effect of melatonin in children with Tuberous sclerosis complex and severe sleep problems. In this double-blind, placebo-controlled crossover study, 7 patients underwent a 2-week treatment period (5 mg melatonin or placebo) with a 1-week washout period

between treatments. The patient's response during the 5-week study period was monitored by a sleep diary completed by the main caregiver. Outcome measures were total sleep time, sleep-onset time and number of awakenings during the night. Patients treated with melatonin had a small but clinically significant improvement in total sleep time (mean improvement 0.55 hours, P<0.05). They also tended to have an improvement in sleep-onset time, but this did not reach statistical significance. Melatonin, in this trial, had no discernible effect on sleep fragmentation.

Williams Syndrome

Williams syndrome, also known as Williams-Beuren syndrome, is a rare genetic disorder characterized by growth delays before and after birth (prenatal and postnatal growth retardation), short stature, a varying degree of mental deficiency, and distinctive facial features that typically become more pronounced with age. Williams syndrome may also be associated with cardiac defects, infantile hypercalcemia, musculoskeletal defects, and/or other abnormalities. In addition, most affected individuals have mild to moderate mental retardation; poor visual-motor integration skills; a friendly, outgoing, talkative manner of speech; a short attention span; and are easily distracted. The prevalence of this disorder is approximately 1 in 7,500-18,000 people (Medline Plus).

In most individuals with Williams syndrome, the disorder appears to occur spontaneously for unknown reasons, however, familial cases have also been reported. Sporadic and familial cases are thought to result from deletion of genetic material from adjacent genes (contiguous genes) within a specific region of chromosome 7 (7q11.23).

In Williams syndrome, a high rate of sleep disturbances has been reported as early as 18 months old (Gwilliam et al., 2020; Shelton and Malow, 2021). As sleep disturbance is so common in Williams syndrome, some have argued that it should be part of the defining characteristic (Annaz et al., 2011; Shelton and Malow, 2021). Sleep problems in Williams syndrome have recently been added to the Williams syndrome clinical management guidelines (William Syndrome Guidelines Development Group, 2017).

Sniecinska-Cooper et al. (2015) examined levels of melatonin and cortisol in 25 children with WS and 27 typically developing age- and gender-matched comparison children. Saliva was collected from each child at three time points: 4-6 pm, before natural bedtime, and after awakening. The levels of salivary melatonin and cortisol were analysed by specific enzyme-linked immunoassays. Sleep patterns were examined using actigraphy and the Children's Sleep Habit Questionnaire. A median increase in the level of melatonin in the TD group was 1.83-fold between afternoon and bedtime samples, whereas for the WS group no such increase was observed. A lack of a marked rise in melatonin concentrations before bedtime may play an underlying and/or contributory role in reported problems with settling down and falling asleep.

Table 3: Comparison of actigraphic scores in Williams syndrome (WS) and typically developing (TD) children using ANOVA. The table includes mean and standard deviation (SD) corresponding to categories of actigraphic scores on the left-hand column; the *F* value and *P* value for determination of significance at 95% confidence interval (*P* <0.05) are also shown.

Category of actigraphic scores	**TD (*n* = 22) Mean (SD)**	**WS (*n* = 21) Mean (SD)**	***F***	***P***
Time in bed (hh:mm)	10:24 (00:31)	10:27 (00:50)	0.24	0.62
Sleep latency (hh:mm)	00:34 (00:25)	00:53 (00:29)	5.02	0.03
Actual wake time (%)	10.65 (3.07)	13.10 (4.37)	4.28	0.04
Night waking	29.02 (6.51)	28.52 (8.73)	0.04	0.84

Category of actigraphic scores	TD ($n = 22$) Mean (SD)	WS ($n = 21$) Mean (SD)	*F*	*P*
Sleep efficiency (%)	82.55 (5.60)	78.92 (6.40)	3.63	0.06
Moving time (%)	13.59 (2.98)	17.45 (5.71)	6.92	0.01
Sleep fragmentation index	30.05 (6.71)	39.75 (13.59)	7.97	0.01

Table 4: Comparison of Child's Sleep Habit Questionnaire (CSHQ) scores in Williams syndrome (WS, $n = 25$) and typically developing children (TD, $n = 27$) using ANOVA. Table includes mean, standard deviation (SD) as well as *F* and *P* value for the determination of significance at 95% confidence interval ($P < 0.05$).

Subscale (possible score range)	TD ($n = 22$) Mean (SD)	WS ($n = 21$) Mean (SD)	*F*	*P*
Bedtime resistance (6–18)	6.41 (1.04)	8.02 (2.67)	8.67	0.01
Sleep onset delay (1–3)	1.56 (.80)	2.04 (.84)	4.53	0.04
Sleep duration (3–9)	3.31 (0.61)	5.23 (1.76)	25.62	<0.001
Sleep anxiety (4–12)	4.70 (1.24)	5.96 (1.90)	8.09	0.01
Night wakings (3–9)	3.89 (.85)	4.80 (1.55)	7.03	0.01
Parasomnias (7–21)	8.37 (1.60)	9.92 (1.91)	10.11	0.003
Sleep disordered breathing (3–9)	3.30 (.67)	3.44 (0.71)	0.56	0.46
Daytime sleepiness (8–24)	11.00 (2.50)	11.24 (2.65)	0.11	0.74
Total score (33–99)	40.44 (4.73)	48.08 (7.51)	19.74	<0.001

A survey of one hundred and thirty Williams syndrome patients identified melatonin as the most commonly taken sleep medication and 91% of the patients taking melatonin reported it as either helpful or somewhat helpful with very few, if any, side effects (Martens et al., 2017).

Melatonin (IR) is recommended as a first line medication for sleep disturbances in children for whom sleep hygiene measures have been insufficient (Sleep disturbances in children and adolescents - Treatment guideline (Medical Products Agency, Sweden, 2014, updated 2022)). Melatonin IR is approved for insomnia in children with ADHD, but commonly used as a first-line sleep medication also for otherwise healthy children.

However, since melatonin is available both in immediate release (IR) and prolonged release (Circadin, Slenyto) formulations, IR melatonin is primarily effective for the treatment of prolonged sleep latency, i.e. problems with falling asleep in the evening. For this effect, the sedative effects of melatonin may be the most relevant. However, the IR melatonin has an insufficiently long half-life to have an effect on night awakenings later during the night. The prolonged-release formulations on the other hand are released too slowly to have an impact on sleep latency at bedtime but may prevent the child from nightly awakenings, disturbing both the sleep of the child and its parents / caregivers. Nightly awakenings are believed to be more related to insufficient levels of melatonin during the dark hours, which could be either due to an aberrant circadian rhythm of the melatonin release or insufficient amounts of melatonin being secreted.

All the neurogenetic disorders discussed in this dossier are rare (i.e. affecting less than 5 in 10,000) and Rett Syndrome is even ultra-rare (affecting less than 1 in 50,000), thus making the standard controlled clinical trials with a sufficient number of enrolled patients not feasible to perform.

For Angelman syndrome (1 in 12,000-20,000), there appears to be a relation to sleep disturbances including abnormal sleep-wake cycles and reduced levels of melatonin. Even though rare, a handful of clinical studies on the effects of IR melatonin, each study including only a low number of patients, indicate a beneficial effect from IR melatonin on sleep, proving the mechanism of action of melatonin in this disorder.

For Rett syndrome (1 in 100,000 females), impaired sleep pattern is included in the diagnostic criteria and although the scientific evidence appears weaker. A randomized controlled cross-over study in 9 girls with Rett syndrome using wrist actigraphy showed that IR melatonin decreased sleep-onset latency from 42.1+/-12.0 minutes at baseline to 19.1+/-5.3 minutes, which was significant vs placebo ($P<0.05$) and appears clinically relevant. This study indicates that IR melatonin improves sleep in Rett syndrome, proving the MoA.

For Tuberous Sclerosis Complex (1 in 11,000-25,000), sleep problems are reported as common. However, Hancock et al. (2005) reports that they did not find any important alterations in the diurnal melatonin excretion curve in patients with TSC compared to normal. Thus, it is considered that aberrant melatonin secretion has not been shown for TSC. Still, O'Callaghan et al. (1999) reported that melatonin (IR) had positive effects on sleep in TSC, probably due to its sedative effects. However, it may be doubted that prolonged-release melatonin is the appropriate formulation for these children, since an aberrant diurnal melatonin excretion curve has not been shown.

For Williams syndrome (1 in 7,500-18,000), a vast majority of the affected individuals are reported to suffer from sleep disturbances. Lower rise in melatonin levels before sleep have been reported compared to healthy controls. Interestingly, actigraph measurements only showed a prolonged sleep latency without signs of nightly awakenings, whereas the Child's sleep habit questionnaire showed a significantly higher score for nightly awakenings (Sniecinska-Cooper et al., 2015). Since the whole 24-h melatonin secretion curve was not measured in this report, it is uncertain whether indeed prolonged-release melatonin is needed or if treatment with IR melatonin may be the appropriate for these children. The MAH presented data in support of the specific need of the prolonged -release formulation of melatonin for treatment of the sleep disturbances of children with Williams syndrome.

Due to the rarity of each of these neurogenetic syndromes, being rare (Angelman syndrome, Tuberous sclerosis complex and Williams syndrome) or even ultra-rare (Rett syndrome), it is understandable that it will not be feasible to recruit patients to sufficiently sized randomised controlled studies to enable the demonstration of beneficial effects of prolonged -release melatonin in each of these syndromes. However, it is considered that a combination of demonstration of aberrant diurnal melatonin secretion pattern and positive effects of melatonin on sleep measures, especially nightly awakenings, will be sufficient.

Many children with neurodevelopmental disorders such as neurogenetic diseases have problems falling asleep in the evening and maintaining sleep during the night which has a negative impact on the quality of life of themselves and their caregivers/parents. Melatonin has positive effects on sleep in children through its sedative effects and/or through effects on the circadian rhythm, which help these children and their parents to a better quality of life.

The results from the open-label single armed French RTU with low retention rates for the small number of treated patients with Angelman syndrome, Rett syndrome, Tuberous sclerosis complex does not allow conclusions on the benefit of the prolonged -release formulation of melatonin to treat the sleep problems in these patients. The MAH has briefly summarised the field of knowledge on disturbances of

diurnal melatonin excretion patterns for these neurogenetic disorders and published clinical data on the effects of IR melatonin.

2.3. Clinical efficacy

The new data in this submission includes data from an RTU in France using Circadin tablets instead of Slenyto for treatment of sleep disorders in children aged 6-18 with ASD or neurogenetic disorders.

2.4. Clinical efficacy

2.4.1. Main study - French RTU

Methods

Open-label observational study

Study participants

A total of 926 children aged 6 -18 years with poor to very poor sleep quality, including 839 with ASD, 35 with SMS, 29 with Angelman syndrome, 15 with Rett syndrome, and 8 with Tuberous sclerosis complex.

Treatments

Circadin 2 mg prolonged release tablets.

The recommended dose of Circadin under this RTU was 4 to 6 mg per day, taken one hour before bedtime and after a meal. To reach the recommended dose, a progressive titration was advised (2 mg/day for one week, then 4 mg/day for one week, then 6 mg/day).

Objectives

Outcomes/endpoints

The efficacy of Circadin treatment was evaluated at each visit (P1-P9) based on the child's quality of sleep (very good, good, fair, poor, very poor) and the child's state upon waking (fully alert, alert, fair, tired, very tired). Changes compared to baseline in the quality of sleep and the child's state upon waking were assessed at each visit (improvement, unchanged, deterioration).

The efficacy of Circadin treatment were analyzed at six-month intervals following the baseline visit. Study periods consisted of: P1 (0-7 months), P2 (7-13 months), P3 (13-19 months), P4 (19-25 months), P5 (25-31 months), P6 (31-37 months), P7 (37-43 months), P8 (43-49 months) and P9 (49-55 months).

Results

Recruitment

A total of 1,100 patients were enrolled in this study. Of those patients, 1,038 were treated with Circadin, 926 of whom made up the eligible population. The eligible population consisted of patients who were treated with Circadin and who satisfied the criteria for RTU initiation (patients from 6 to 18 years old, with a condition consistent with the indication in the RTU). The modified eligible population consisted of patients for whom one follow-up form was completed for study periods P1 to P9 and for whom Circadin treatment was ongoing.

Conduct of the study

Baseline data

Table 5: Baseline demographic characteristics by patient condition - Circadin RTU Programme (eligible population)

	Autism spectrum disorder N = 839	**Rett syndrome N = 15**	**Smith-Magenis syndrome N = 35**	**Angelman syndrome N = 29**	**Tuberous sclerosis N = 8**	**Total N = 926**
Gender, n (%)						
N	837	15	35	29	8	924
Male	632 (75.5)	0	13 (37.1)	14 (48.3)	7 (87.5)	666 (72.1)
Female	205 (24.5)	15 (100.0)	22 (62.9)	15 (51.7)	1 (12.5)	258 (27.9)
Patient's age at baseline (years)						
N	839	15	35	29	8	926
Mean (SD)	10.1 (3.2)	8.7 (3.2)	10.1 (3.6)	9.6 (3.4)	8.1 (2.2)	10.0 (3.3)
Median	10	8	9	9	8	10
Min - Max	6 - 18	6 - 17	6 - 18	6 - 17	6 - 13	6 - 18
Age at baseline, n (%)						
N	839	15	35	29	8	926
6-12 years	564 (67.2)	13 (86.7)	22 (62.9)	21 (72.4)	7 (87.5)	627 (67.7)
12-18 years	275 (32.8)	2 (13.3)	13 (37.1)	8 (27.6)	1 (12.5)	299 (32.3)
Height (cm)						
N	817	14	34	26	8	899
Mean (SD)	139.38 (19.20)	123.43 (15.88)	135.82 (22.50)	134.58 (16.17)	128.25 (11.18)	138.76 (19.27)
Median	137.00	120.50	135.50	132.50	128.50	136.00
Min - Max	94.00 - 189.00	100.00 - 160.00	100.00 - 178.00	110.00 - 170.00	111.00 - 143.00	94.00 - 189.00
Weight (kg)						
N	827	15	34	29	8	913

	Autism spectrum disorder N = 839	Rett syndrome N = 15	Smith-Magenis syndrome N = 35	Angelman syndrome N = 29	Tuberous sclerosis N = 8	Total N = 926
Mean (SD)	37.52 (16.57)	25.95 (8.41)	42.68 (26.29)	35.64 (12.85)	29.11 (9.84)	37.39 (16.86)
Median	33.00	27.00	37.70	32.00	26.70	33.00
Min - Max	10.60 - 110.00	14.00 - 38.00	15.00 - 140.00	19.00 - 74.00	18.50 - 52.00	10.60 - 140.00
Body Mass Index (kg/m²)						
N	816	14	34	26	8	898
Mean (SD)	18.47 (4.30)	16.30 (2.83)	21.05 (6.14)	19.56 (2.96)	17.53 (4.22)	18.56 (4.36)
Median	17.48	15.17	19.33	19.73	16.42	17.58
Min - Max	9.34 - 39.21	11.89 - 20.35	14.24 - 44.19	13.42 - 25.61	12.76 - 25.43	9.34 - 44.19

Max = maximum; Min = minimum; SD = standard deviation

At baseline, most patients (94.1%, n = 871) had been experiencing sleep disorders for more than three months. The insomnia was considered to be severe for 57.8% of patients (n = 535) and moderate for 40.9% of patients (n = 379). The sleep quality was considered poor for 567 patients (61.2%) and very poor for 173 patients (18.7%). The child's state upon waking was described as "tired" for 475 patients (51.4%), "fair" for 213 patients (23.1%), "very tired" for 94 patients (10.2%), "alert" for 95 patients (10.3%), and "fully alert" for 47 patients (5.1%).

The insomnia history by patient condition showed that:

Autism spectrum disorder: 94.0% (n = 789) of patients had been experiencing insomnia for more than three months. Their insomnia was mainly severe (57.1%; n = 479) or moderate (41.6%; n = 349). Their quality of sleep was mainly considered poor (62.5%; n = 524) or very poor (18.2%; n = 153). Upon waking, the children were usually in a tired (51.7%; n = 433), fair (22.2%; n = 186), or very tired state (10.9%; n = 91).

Rett syndrome: 86.7% (n = 13) of patients had been experiencing insomnia for more than three months. Their insomnia was either severe (60.0%; n = 9) or moderate (40.0%; n = 6). The children's quality of sleep was mainly poor (66.7%; n = 10), very poor (13.3%; n = 2), or fair (20.0%; n = 3). Upon waking, the children were usually in a tired (60.0%; n = 9) or fair state (33.3%; n = 5).

Smith-Magenis syndrome: 97.1% of patients (n = 34) had been experiencing insomnia for more than three months. Their insomnia was either severe (48.6%; n = 17) or moderate (51.4%; n = 18). Their quality of sleep was mainly poor (37.1%; n = 13), very poor (25.7%; n = 9), fair (22.9%; n = 8), or good (14.3%; n = 5). The children's state upon waking was usually tired (40.0%; n = 14), fair (34.3%; n = 12), alert (14.3%; n = 5), or fully alert (11.4%; n = 4).

Angelman syndrome: 96.6% of patients (n = 28) had been experiencing insomnia for more than three months. It was severe for 89.7% of them (n = 26), and the quality of sleep of the patients was either poor (55.2%; n = 16), very poor (27.6%; n = 8), or fair (10.3%; n = 3), and it was good for two patients. Upon waking, the majority of children were tired (57.1%; n = 16).

Tuberous sclerosis: 87.5% of patients (n = 7) had been experiencing insomnia for more than three months. It was either severe (50.0%; n = 4) or moderate (50.0%; n = 4). Sleep quality was either poor (50.0%; n = 4) or fair (37.5%; n = 3) and very poor for one patient. The children's state upon waking was either fair (62.5%; n = 5) or tired (37.5%; n = 3).

Before enrolment in the RTU, 647 patients (71.4%), regardless of the condition, had already received at least one treatment for a sleep disorder. In most cases, it was a single treatment (90.3%; n = 584). The most common treatment was melatonin IR (immediate release) for 528 patients (81.6%). The other most frequently reported treatments were psycholeptics (15.5%) and antihistamines (5.7%).

Numbers analysed

Outcomes and estimation

Sleep quality

Table 6: Sleep quality by study period – Circadin RTU Programme (modified eligible population)

	Study Period								
	P1 (N=301)	**P2 (N=127)**	**P3 (N=83)**	**P4 (N=54)**	**P5 (N=29)**	**P6 (N=16)**	**P7 (N=7)**	**P8 (N=7)**	**P9 (N=2)**
Sleep Quality, n (%)									
N	300	127	83	54	29	15	7	7	2
Very Good	51 (17.0)	23 (18.1)	10 (12.0)	8 (14.8)	4 (13.8)	1 (6.7)	1 (14.3)	1 (14.3)	0
Good	107 (35.7)	58 (45.7)	37 (44.6)	22 (40.7)	13 (44.8)	10 (66.7)	2 (28.6)	2 (28.6)	1 (50.0)
Fair	93 (31.0)	36 (28.3)	30 (36.1)	17 (31.5)	7 (24.1)	4 (26.7)	3 (42.9)	4 (57.1)	1 (50.0)
Poor	46 (15.3)	10 (7.9)	5 (6.0)	7 (13.0)	5 (17.2)	0	1 (14.3)	0	
Very Poor	3 (1.0)	0	1 (1.2)	0	0	0	0	0	0
Change from Baseline in Sleep Quality, n (%)									
N	300	127	83	54	29	15	7	7	2
Improvement	235 (78.3)	106 (83.5)	74 (89.2)	42 (77.8)	23 (79.3)	12 (80.0)	5 (71.4)	6 (85.7)	2 (100.0)
Unchanged	54 (18.0)	17 (13.4)	7 (8.4)	6 (11.1)	2 (6.9)	3 (20.0)	2 (28.6)	1 (14.3)	0
Deterioration	11 (3.7)	4 (3.1)	2 (2.4)	6 (11.1)	4 (13.8)	0	0	0	0

Source: Circadin RTU Annual Report No. 6, Section 6.4.6

During the 55-month treatment period, quality of sleep improved for more than 71.4% of patients.

Child's State upon Waking

Table 7: Child's state upon waking by study period – Circadin RTU Programme (modified eligible population)

	Study Period								
	P1 (N=301)	**P2 (N=127)**	**P3 (N=83)**	**P4 (N=54)**	**P5 (N=29)**	**P6 (N=16)**	**P7 (N=7)**	**P8 (N=7)**	**P9 (N=2)**
Child's State upon Waking, n (%)									
N	298	127	83	54	29	15	7	7	2
Fully Alert	58 (19.5)	29 (22.8)	18 (21.7)	9 (16.7)	8 (27.6)	5 (33.3)	1 (14.3)	1 (14.3)	0
Alert	89 (29.9)	41 (32.3)	32 (38.6)	27 (50.0)	13 (44.8)	5 (33.3)	1 (14.3)	4 (57.1)	1 (50.0)

Fair	99 (33.2)	46 (36.2)	28 (33.7)	14 (25.9)	7 (24.1)	5 (33.3)	4 (57.1)	2 (28.6)	1 (50.0)
Tired	49 (16.4)	11 (8.7)	4 (4.8)	3 (5.6)	1 (3.4)	0	1 (14.3)	0	0
Very Tired	3 (1.0)	0	1 (1.2)	1 (1.9)	0	0	0	0	0
Change from Baseline in Child's State upon Waking, n (%)									
N	298	127	83	54	29	15	7	7	2
Improvement	191 (64.1)	82 (64.6)	56 (67.5)	34 (63.0)	20 (69.0)	13 (86.7)	3 (42.9)	4 (57.1)	1 (50.0)
Unchanged	78 (26.2)	30 (23.6)	21 (25.3)	11 (20.4)	6 (20.7)	2 (13.3)	3 (42.9)	2 (28.6)	1 (50.0)
Deterioration	29 (9.7)	15 (11.8)	6 (7.2)	9 (16.7)	3 (10.3)	0	1 (14.3)	1 (14.3)	0

Source: Circadin RTU Annual Report No. 6, Section 6.4.6

Ancillary analyses

Subgroup analyses for Angelman syndrome (N=7), Rett syndrome (N=6), Tuberous sclerosis complex (N=1)

Table 8: Sleep quality and child's state upon waking by study period in patients with Angelman syndrome – Circadin RTU Programme (modified eligible population by condition)

	Study Period								
	P1 (N=7)	**P2 (N=4)**	**P3 (N=6)**	**P4 (N=2)**	**P5 (N=1)**	**P6 (N=2)**	**P7 (N=1)**	**P8 (N=1)**	**P9 (N=0)**
Sleep Quality, n (%)									
N	7	4	6	2	1	2	1	1	0
Very good	2 (28.6)	2 (50.0)	1 (16.7)	0	1 (100.0)	0	0	0	-
Good	1 (14.3)	1 (25.0)	3 (50.0)	0	0	1 (50.0)	0	1 (100.0)	-
Fair	4 (57.1)	1 (25.0)	2 (33.3)	2 (100.0)	0	1 (50.0)	1 (100.0)	0	-
Poor	0	0	0	0	0	0	0	0	-
Very poor	0	0	0	0	0	0	0	0	-
Change from Baseline in Sleep Quality, n (%)									
N	7	4	6	2	1	2	1	1	0
Improvement	6 (85.7)	4 (100.0)	6 (100.0)	2 (100.0)	1 (100.0)	1 (50.0)	1 (100.0)	1 (100.0)	-
Unchanged	1 (14.3)	0	0	0	0	1 (50.0)	0	0	-
Deterioration	0	0	0	0	0	0	0	0	-
Child's State upon Waking, n (%)									
N	7	4	6	2	1	2	1	1	0
Fully alert	3 (42.9)	3 (75.0)	1 (16.7)	0	1 (100.0)	1 (50.0)	0	0	-
Alert	2 (28.6)	0	2 (33.3)	2 (100.0)	0	1 (50.0)	0	1 (100.0)	-
Fair	2 (28.6)	1 (25.0)	3 (50.0)	0	0	0	0	0	-
Tired	0	0	0	0	0	0	1 (100.0)	0	-
Very tired	0	0	0	0	0	0	0	0	-

Change from Baseline in Child's State upon Waking, n (%)									
N	7	4	6	2	1	2	1	1	0
Improvement	5 (71.4)	4 (100.0)	6 (100.0)	2 (100.0)	1 (100.0)	2 (100.0)	0	1 (100.0)	-
Unchanged	0	0	0	0	0	0	1 (100.0)	0	-
Deterioration	2 (28.6)	0	0	0	0	0	0	0	-

Source: Circadin RTU Annual Report No. 6, Section 6.4.6

Table 9: Sleep quality and child's state upon waking by study period in patients with Rett syndrome – Circadin RTU Programme (modified eligible population by condition)

	Study Period								
	P1 (N=6)	**P2 (N=3)**	**P3 (N=2)**	**P4 (N=2)**	**P5 (N=1)**	**P6 (N=1)**	**P7 (N=1)**	**P8 (N=0)**	**P9 (N=0)**
Sleep Quality, n (%)									
N	6	3	2	2	1	1	1	0	0
Very good	0	0	0	1 (50.0)	0	0	1 (100.0)	-	-
Good	2 (33.3)	1 (33.3)	1 (50.0)	0	0	1 (100.0)	0	-	-
Fair	3 (50.0)	1 (33.3)	1 (50.0)	1 (50.0)	1 (100.0)	0	0	-	-
Poor	1 (16.7)	1 (33.3)	0	0	0	0	0	-	-
Very poor	0	0	0	0	0	0	0	-	-
Change from Baseline in Sleep Quality, n (%)									
N	6	3	2	2	1	1	1	0	0
Improvement	6 (100.0)	2 (66.7)	2 (100.0)	2 (100.0)	0	1 (100.0)	1 (100.0)	-	-
Unchanged	0	1 (33.3)	0	0	1 (100.0)	0	0	-	-
Deterioration	0	0	0	0	0	0	0	-	-
Child's State upon Waking, n (%)									
N	6	3	2	2	1	1	1	0	0
Fully alert	1 (16.7)	0	1 (50.0)	0	0	0	0	-	-
Alert	3 (50.0)	2 (66.7)	1 (50.0)	2 (100.0)	0	0	0	-	-
Fair	1 (16.7)	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	-	-
Tired	1 (16.7)	1 (33.3)	0	0	0	0	0	-	-
Very tired	0	0	0	0	0	0	0	-	-
Change from Baseline in Child's State upon Waking, n (%)									
N	6	3	2	2	1	1	1	0	0
Improvement	5 (83.3)	2 (66.7)	2 (100.0)	2 (100.0)	0	0	0	-	-
Unchanged	0	1 (33.3)	0	0	1 (100.0)	1 (100.0)	1 (100.0)	-	-
Deterioration	1 (16.7)	0	0	0	0	0	0	-	-

Source: Circadin RTU Annual Report No. 6, Section 6.4.6

Table 10: Sleep quality and child's state upon waking by study period in patients with Tuberous Sclerosis Complex – Circadin RTU Programme (modified eligible population by condition)

	Study Period								
	P1 (N=1)	**P2 (N=1)**	**P3 (N=0)**	**P4 (N=0)**	**P5 (N=0)**	**P6 (N=0)**	**P7 (N=0)**	**P8 (N=0)**	**P9 (N=0)**
Sleep Quality, n (%)									
N	1	1	0	0	0	0	0	0	0
Very good	0	0	-	-	-	-	-	-	-
Good	0	1 (100.0)	-	-	-	-	-	-	-
Fair	1 (100.0)	0	-	-	-	-	-	-	-
Poor	0	0	-	-	-	-	-	-	-
Very poor	0	0	-	-	-	-	-	-	-
Change from Baseline in Sleep Quality, n (%)									
N	1	1	0	0	0	0	0	0	0
Improvement	0	1 (100.0)	-	-	-	-	-	-	-
Unchanged	1 (100.0)	0	-	-	-	-	-	-	-
Deterioration	0	0	-	-	-	-	-	-	-
Child's State upon Waking, n (%)									
N	1	1	0	0	0	0	0	0	0
Fully alert	0	1 (100.0)	-	-	-	-	-	-	-
Alert	0	0	-	-	-	-	-	-	-
Fair	1 (100.0)	0	-	-	-	-	-	-	-
Tired	0	0	-	-	-	-	-	-	-
Very tired	0	0	-	-	-	-	-	-	-
Change from Baseline in Child's State upon Waking, n (%)									
N	1	1	0	0	0	0	0	0	0
Improvement	0	1 (100.0)	-	-	-	-	-	-	-
Unchanged	1 (100.0)	0	-	-	-	-	-	-	-
Deterioration	0	0	-	-	-	-	-	-	-

Source: Circadin RTU Annual Report No. 6, Section 6.4.6

Background

The main study (RTU programme) (held from 2015 to 2021) was conducted using Circadin as it was initiated 3 years before Slenyto approval. Due to the size of the Circadin tablet, the RTU study was limited to children over 6 years of age; younger children were not permitted to enter the study.

Although this study was limited to children over 6 years of age, it is considered that the efficacy observed in 6+ year-olds would be applicable to 2 to 6-year-olds based on the results of sub-group analysis conducted for the Phase III study NEU_CH_791. In this analysis, results for the primary efficacy endpoint (total sleep time) and the key secondary efficacy endpoint (sleep latency) were compared for children aged 2-6 years and 7-17 years for the double-blind period (Table 11).

Table 11: Change from baseline at 13 weeks (double-blind) including age as a factor

SND parameter	Age (years)	Slenyto Change from BL min (SE)	Placebo Change from BL min (SE)	P-value (t-test)	Effect size
Total Sleep Time (TST)	2-6 (N=31)	79.22 (35.4) (N=15)	28.76 (23.76) (N=16)	0.24	0.42
	7-17 (N=69)	48.5 (15.31) (N=37)	-0.68 (12.62) (N=32)	0.018	0.58
Sleep Latency (SL)	2-6 (N=31)	-46.32 (15.8) (N=15)	-9.13 (8.57) (N=16)	0.04	-0.74
	7-17 (N=69)	-36.67 (9.9) (N=37)	-14.21 (9.82) (N=32)	0.11	-0.38

BL = baseline; SE = standard error; SND = sleep and nap diary

In addition, a responders' analysis on the primary endpoint, the sleep and nap diary (SND) total sleep time, and the key secondary endpoint, sleep latency, for ages 2-6 and 7-17 years for the double-blind 13-week period was performed (Table 12).

Table 12: Responder analysis at 13 weeks (double-blind) including age as a factor

SND parameter	Age (years)	% Responders			
		Slenyto	Placebo	P-value (Chi-square)	Number Needed to Treat (NNT)
Total Sleep Time (TST)[a]	2-6 (N=31)	40% (6/15)	25% (4/16)	0.37	6.6
	7-17 (N=69)	43.2% (16/37)	18.75% (6/32)	0.02	4.12
Sleep Latency (SL)[b]	2-6 (N=31)	73.3% (11/15)	37.5% (6/16)	0.04	2.81
	7-17 (N=69)	70.27% (26/37)	43.75% (14/32)	0.02	3.8

[a] ≥ 45 minutes; [b] ≥ 15 minutes

SND = sleep and nap diary

These analyses show that the Slenyto treatment effect is not significantly different among age groups; hence there is no age dependency in response.

While data from the RTU study are based on Circadin tablets rather than Slenyto mini-tablets, a comparative bioavailability study has demonstrated that Circadin tablets have a similar pharmacokinetic profile compared to Slentyo mini-tablets (refer to the Pharmacokinetics section). Based on this, the results from the Circadin RTU Programme are considered applicable to Slenyto. It should be noted that at least 25% of the children in the Circadin RTU Programme did not take the tablets whole as Circadin is not an age-appropriate formulation. Moreover, the mean daily dose in the RTU study (3.3 mg/day) was lower than the mean daily dose reported for Slenyto (6.06 mg/day) in the clinical study NEU CH 7911 (Malow et al., 2021), most probably due to the difficulty in intake of more than one uncoated, Circadin 2 mg 8 mm tablet a day. Consequently, these children might not have fully benefited from the optimal dose and the prolonged release formulation. It is therefore reasonable to stipulate that the results presented for Circadin are less significant than expected with the correct dose and form that Slenyto would provide.

Supportive data

Slenyto Compassionate Prescribing Framework

A Compassionate Prescribing Framework (CPF or CPC in French) was established for Slenyto in the treatment of sleep-wake rhythm disorders related to Rett syndrome, Angelman syndrome or tuberous sclerosis of Bourneville, in children (2-18 years old). During the period of the first annual summary report (29 March 2022 to 01 March 2023), only one physician registered on the Slenyto CPF portal (www.cpcslenyto.fr). This physician included a single 11-year-old female patient with Rett syndrome associated with sleep-wake rhythm disturbances present for more than 3 months and whose insomnia

was considered moderate and sleep quality was considered poor. On awakening, the child was considered "tired".

Additional analyses presented in response to questions

Data from sponsor-conducted studies, expanded access programmes and published literature indicate that children with neurogenetic syndromes (Angelman syndrome, Rett syndrome, Tuberous sclerosis complex and Williams syndrome) suffer from disturbances in sleep initiation, sleep maintenance and sleep duration that are related to disturbances of diurnal melatonin excretion patterns. Treatment with prolonged release (PR) melatonin improves sleep maintenance and total sleep time in addition to sleep initiation in children with neurogenetic syndromes. Sponsor-Conducted Studies In the Phase III, placebo-controlled, clinical trial (NEU_CH_7911), Slenyto treatment (2 or 5 mg daily) was evaluated in 119 children with sleep problems associated with neurodevelopmental disorders (autism spectrum disorder [ASD] or Smith-Magenis syndrome [SMS]). After 13 weeks of double-blind treatment, Slenyto treatment resulted in statistically significant improvements in total sleep time, sleep maintenance and sleep latency. The study met the primary endpoint, demonstrating statistically significant effects of Slenyto 2/5 mg versus placebo on change from baseline in mean Sleep and Nap Diary (SND)-assessed Total Sleep Time (TST) after 13 weeks of double-blind treatment. At baseline, mean TST was 457.2 minutes in the Slenyto and 459.9 minutes in the placebo group.

After 13 weeks of double-blind treatment, participants slept on average 57.5 minutes longer at night with Slenyto compared to 9.1 minutes with placebo (adjusted mean treatment difference Slenyto–placebo: 33.1 minutes in the All Randomized Set; multiple imputation (MI) (p=0 .026)). At baseline, mean Sleep Latency (SL) was 95.2 minutes in the Slenyto and 98.8 minutes in the placebo group. By the end of the 13-week treatment period, children fell asleep on average 39.6 minutes faster with Slenyto and 12.5 minutes faster with placebo (adjusted mean treatment difference Slenyto–placebo: -25.3 minutes in the All Randomized Set; MI (p=0.012)), without causing earlier wakeup time. The rate of participants attaining clinically meaningful responses in TST (increase of 45 minutes from baseline) and/or SL (decrease of 15 minutes from baseline) was significantly higher with Slenyto than with placebo (68.9% versus 39.3% respectively; p=0 .001). Besides shortening of SL, increase in the longest sleep episode (LSE) (= uninterrupted sleep duration) compared to placebo was observed. By the end of the 13-week double-blind period, the mean LSE increased on average by 77.9 minutes in the Slenyto-treated group, compared to 25.5 minutes in the placebo-treated group. The adjusted estimated treatment differences were 43.2 minutes in the All Randomized Set (MI, p=0.039). Wake up time was unaffected; after 13 weeks, patient wake up time was delayed insignificantly by 0.09 hour (0.215) (5.4 minutes) with Slenyto compared to placebo treatment.

Slenyto treatment (13 weeks) resulted in statistically significant improvements in mean Strength and Difficulties Questionnaire (SDQ)-assessed externalizing behaviours (hyperactivity/inattention and conduct difficulties) compared to placebo. By the end of the 13 weeks, the adjusted mean (SE) difference from placebo in externalizing behaviours score between Slenyto-treated and placebo-treated subjects was -0.83 (0.355) (p=0.021). This improvement was correlated to the improvement in total sleep time (TST) and longest sleep episode (LSE). Caregivers benefitted from their children’s treatment with Slenyto in improved quality of life in a statistically significant (p=0.01) manner compared to treatment with placebo. This improvement was correlated to the improvement in total SDQ score.

Since the mechanism of action of PR melatonin is independent of the background disorder, the beneficial effects of Slenyto on sleep maintenance and total sleep time observed in ASD and SMS patients in the Phase III study are considered applicable to patients with Angelman syndrome, Rett syndrome, Tuberous sclerosis complex (TSC) and Williams syndrome as these patients also experience sleep disturbances associated with aberrant diurnal melatonin secretion patterns as detailed below under Published Literature.

Expanded Access Programmes Slenyto Compassionate Prescribing Framework (CPC).

As of 01 March 2024, two eligible patients (one with Rett syndrome and one with Angelman syndrome) have been treated in the Slenyto CPC. Improvements in sleep quality, waking state and maximum uninterrupted sleep duration were observed during follow-up for the patient with Rett syndrome. The second patient with Angelman syndrome stopped treatment with Slenyto 5.1 months after initiation.

Prior to Slenyto approval, an observational study was conducted with Circadin under the RTU programme in France. In the RTU programme, Circadin was prescribed to treat welle stablished sleep disorders in children aged 6-18 years whose quality of sleep was deemed poor (61.2%) or very poor (18.7%). The study enrolled a total of 926 eligible children, including 839 with ASD, 35 with SMS, 29 with Angelman syndrome, 15 with Rett syndrome, and 8 with TSC. Despite the fact that the population was over the age of 6 years old, as Circadin tablets are not age appropriate (8 mm diameter uncoated tablets), some patients had difficulty swallowing the formulation intact and required the tablets to be divided or crushed. Breaking the intact tablet would be expected to result in loss of the prolonged-release properties and alteration of its clinical effect. Prolonged-release (PR) melatonin mimics the endogenous release profile in healthy subjects, and consequently improves sleep maintenance and total sleep time (TST), as well as sleep-onset latency. In contrast, immediate-release (IR) melatonin is primarily effective for the treatment of extended sleep latency as it delivers an immediate, transient, high dose of melatonin that subsides rapidly. IR melatonin has an insufficient half-life to affect nightly awakenings.

Chua et al. (2016) examined the release profile of melatonin from Circadin tablets when divided or crushed, compared with release from intact tablets. Dissolution tests were performed using the pharmacopoeial paddle apparatus, with melatonin release analysed by high performance liquid chromatography. When divided into halves, Circadin retained most of the prolonged-release characteristics (f2=58), whereas a more immediate-release profile was observed when the tablet was quartered (f2=45) or crushed (f2=23). Therefore, the efficacy of prolonged-release melatonin is best demonstrated in patients who received either whole or halved tablets in the Circadin RTU programme. Approximately 75% of patients in the Circadin RTU programme took the tablets whole, while the remaining patients divided or crushed the tablets. Most patients with Angelman syndrome (23/29; 79.3%) and TSC (7/8; 87.5%) took the Circadin tablets whole, while approximately half of the patients with Rett syndrome (7/15; 46.7%) took the tablets whole. None of these patients received halved tablets.

Changes compared to baseline in the child's quality of sleep and the child's state upon waking were recorded at each visit (improvement, unchanged, deterioration). The MAH has re-analysed the raw data from the RTU programme to focus on the efficacy achieved for patients receiving a whole tablet, see below discussion per condition.

Angelman Syndrome

Thirty seven patients with AS were screened for inclusion in the RTU program and 8 patients were excluded for non-eligibility (6 being less than 6 years old). Therefore, 29 patients with AS were considered as part of the eligible population. Of these 29 AS patients, 7 patients had follow-up data available and are considered part of the per protocol population (PPP) according to the RTU report. The MAH's re-analysis of the raw data determined 12 patients with efficacy data (i.e., with at least 1 follow-up assessment). Note that 7 of these patients are also considered part of the per protocol 1

The original RTU study report and raw data was prepared in French and translated into English. In the RTU study report, the child's quality of sleep (assessed at each follow-up visit in relation to the baseline quality of sleep) is translated as "very good/good/fair/poor/very poor" and the child's state upon waking (assessed at each follow-up visit in relation to the child's state upon waking at baseline)

is translated as "fully alert/alert/fair/tired/very tired". In the raw data source, the child's quality of sleep is translated as "very good, good, correct, bad, very bad" and the child's state upon waking is translated as "completely alert, alert, correct, tired, very tired". The MAH considered that 6 patients should also be considered in the efficacy population since these patients are between 6 – 18 years of age with a reported Circadin dosage, apart from another patient for which no dosage is reported. This population of 12 AS patients with efficacy data was considered the full analysis set (FAS) by the MAH.

Efficacy was evaluated in 10 patients with Angelman syndrome) who received Circadin (2 mg, 4 mg or 6 mg) administered as a whole tablet (Table 13). For 9 patients, baseline nighttime behaviour was reported as bad (n=6) or very bad (n=3). In all of these cases, administration of Circadin resulted in an improvement in nighttime behaviour (correct, good or very good); improvement was observed at the first follow-up visit and was maintained at all subsequent visits. For 6 patients, baseline daytime behaviour was reported as tired (n=4) or very tired (n=2). In 5 of these cases, administration of Circadin resulted in improvement in daytime behaviour (correct, alert, or completely alert), with improvements observed at the first follow-up visit for 4 of them and maintained throughout the following visits. The remaining patient showed improvement in daytime behaviour (tired to correct) from the second follow-up visit. In one patient, the form of administration was not reported. This patient showed improvement in both nighttime and daytime behaviour. One more patient was administered with crushed tablets and improvement was reported for both nighttime and daytime behaviour.

Table 13: Form of Administration and Efficacy in Patients with Angelman Syndrome – Circadin RTU Program

Patient # (Age*)	Dose (mg)	Visit	Assessment of Nighttime Behaviour	Assessment of Daytime Behaviour	Evaluation of Efficacy
Whole Tablet					
0029 (6.1 years)	2	0	Bad	Correct	↑ Improvement in nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 4 years
		1	Very good	Completely alert	
		2	Good	Completely alert	
		3	Good	Alert	
		4	Correct	Alert	
		5	Correct	Alert	
		6	Good	Alert	
0563 (6.5 years)	2	0	Good	Alert	↔ Maintenance of good nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 2 years, 7 months
		1	Good	Completely alert	
		2	Very good	Alert	
		3	Very good	Completely alert	
		4	Very good	Completely alert	
		5	Good	Completely alert	
0117 (7.0 years)	2	0	Very bad	Very tired	↑ Improvement in nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 1 year, 6 months
		1	Very good	Tired	
		2	Very good	Completely alert	
		3	Very good	Completely alert	
		4	Correct	Correct	
0159 (10.2 years)	2	0	Bad	Tired	↑ Improvement in nighttime behaviour. Variable daytime behaviour. Treatment Duration: 3 years, 2 months
		1	Good	Correct	
		2	Correct	Tired	
5474 (13.5 years)	2	0	Bad	Alert	↑ Improvement in nighttime behaviour. ↔ Maintenance of alert daytime behaviour. Treatment Duration: 6 months
		1	Correct	Alert	
		2	Correct	Correct	
5332 (17.9 years)	2	0	Bad	Tired	↑ Improvement in nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 1 year, 1 month
		1	Correct	Correct	
0541 (17.2 years)	2	0	Correct	Correct	--

Patient # (Age*)	Dose (mg)	Visit	Assessment of Nighttime Behaviour	Assessment of Daytime Behaviour	Evaluation of Efficacy
0755 (9.8 years)	2	0	Correct	Tired	--
0820 (7.6 years)	2	0	Bad	Alert	--
5482 (9.4 years)	2	0	Bad	Tired	--
0402 (8.7 years)	4	0	Very bad	Very tired	↑ Improvement in nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 2 years, 5 months
		1	Very good	Completely alert	
		--	Correct	Alert	7 days post-treatment: ↓ Decline in nighttime and daytime behaviour.
5002 (15.5 years)	4	0	Bad	Tired	↑ Improvement in nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 1 year, 1 month
		1	Good	Alert	
5081 (9.0 years)	4	0	Very bad	Completely alert	↑ Improvement in nighttime behaviour. ↔ Maintenance of alert daytime behaviour. Treatment Duration: 6 months
		1	Correct	Alert	
0827 (6.5 years)	4	0	Good	Correct	--
5351 (9.4 years)	4	0	Very bad	Correct	--
0379 (9.0 years)	4	0	Bad	Tired	--
0390 (10.9 years)	4	0	Very bad	Tired	--
0472 (9.9 years)	4	0	Bad	Tired	--
0533 (12.6 years)	4	0	Correct	NA	--
5075 (5.8 years)	6	0	Bad	Tired	↑ Improvement in nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 12 months
		1	Correct	Tired	
		2	Correct	Correct	

Patient # (Age*)	Dose (mg)	Visit	Assessment of Nighttime Behaviour	Assessment of Daytime Behaviour	Evaluation of Efficacy
5238 (6.0 years)	6	0	Very bad	Tired	--
5434 (10.2 years)	6	0	Bad	Tired	--
0516 (12.6 years)	6	0	Bad	Tired	--
Crushed Tablet					
5288 (6.4 years)	2	0	Very bad	Tired	↑ Improvement in nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 1 year, 9 months
		1	Correct	Alert	
		2	Correct	Correct	
		3	Correct	Alert	
0040 (10.7 years)	2	0	Very bad	Alert	--
0393 (7.4 years)	4	0	Bad	Correct	--
5344 (6.0 years)	4	0	Bad	Tired	--
5480 (16.4 years)	6	0	Bad	Tired	--
Not Reported					
5087 (6.0 years)	NA	0	Bad	Tired	↑ Improvement in nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 7 months
		1	Correct	Correct	

NA = not available.

* At study enrolment.

Importantly, Angelman syndrome patients who received whole tablets were more likely to continue Circadin treatment than those who received crushed tablets. Of the 29 eligible patients with Angelman syndrome, 10/23 (43.5%) patients who received whole tablets continued Circadin treatment past the initial study visit (visit 0) compared with 1/5 (20%) patients who received crushed tablets (Table 14). Treatment duration tended to be longer in the 10 patients who received whole tablets and continued with treatment past initial visit (mean duration of treatment: 21.4 months, maximum: 4 years) compared with the patient who received crushed tablets and continued with treatment past initial visit (1 year, 9 months). These results underscore the superior efficacy of prolonged release melatonin (whole Circadin tablets) over immediate release melatonin (crushed Circadin tablets) on nighttime and daytime behaviour in patients with Angelman syndrome, particularly as daytime behaviour is associated with total sleep time and sleep maintenance.

Table 14: Treatment duration by form of administration in patients with Angelman Syndrome (modified eligible population)

	Patients with Angelman Syndrome (N=29)		
	Whole Tablets (n=23)	Crushed Tablets (n=5)	Other[a] (n=1)
Last visit			
0	13	4	0
1	4	0	1
2	3	0	0
3	0	1	0
4	1	0	0
5	1	0	0
6	1	0	0
Mean number of visits	1.09	0.60	1.00
Treatment duration for patients with follow-up visits			
n	10	1	1
Minimum	6 months	--	--
Maximum	4 years	1 year, 9 months	7 months

[a] Not reported.

Rett Syndrome

Eighteen patients with Rett syndrome were screened for inclusion in the RTU program and 3 patients were excluded for non-eligibility (less than 6 years old). Therefore, 15 patients with Rett syndrome were considered as part of the eligible population. Of these 15 Rett syndrome patients, 6 patients had follow-up data available and are considered part of the per protocol population according to the RTU report. The MAH's re-analysis of the raw data determined 8 patients with efficacy data (i.e., with at least 1 follow-up assessment). Note that 6 of these patients are also considered part of the per protocol population according to the RTU report. The MAH considered that 2 patients should also be considered in the efficacy population since one patient is 8.9 years of age and one patient is 13.9 years of age, both with a documented Circadin dosage. This population of 8 Rett syndrome patients with efficacy data was considered the full analysis set by the MAH. Efficacy was evaluated in 4 patients with Rett syndrome who received Circadin (2 mg or 6 mg) administered as a whole tablet (Table 15).

For 3 patients, baseline nighttime behaviour was reported as bad (n=2) or very bad (n=1). In two of these cases (nighttime behaviour assessed as very bad, administered 2 mg Circadin; nighttime behaviour assessed as bad, administered 6 mg Circadin), improvement in nighttime behaviour (good or correct) was observed following treatment. Improvement was reported at the first follow-up visit and was maintained throughout the following visits. In addition, improvement in nighttime behaviour (from correct to very good) was observed in 1 patient treated with 2 mg Circadin. For 2 patients (Circadin 2 mg and 6 mg), baseline daytime behaviour was reported as tired. Improvement in daytime behaviour (completely alert) was observed for one patient at the first follow-up visit and was maintained at the subsequent visit. Maintenance of correct daytime behaviour was observed in 2 patients (Circadin 2 mg).

Table 15: Form of Administration and Efficacy in Patients with Rett Syndrome – Circadin RTU Program

Patient # (Age*)	Dose (mg)	Visit	Assessment of Nighttime Behaviour	Assessment of Daytime Behaviour	Evaluation of Efficacy
Whole Tablet					
0042 (9.5 years)	2	0	Very bad	Correct	↑ Improvement in nighttime behaviour. ↔ Maintenance of correct daytime behaviour. Treatment Duration: 2 years, 8 months
		1	Bad	Tired	
		2	Correct	Alert	
		3	Correct	Alert	
		4	Correct	Correct	
		5	Correct	Alert	
		6	Good	Correct	
5127 (7.0 years)	2	0	Correct	Correct	↑ Improvement in nighttime behaviour. ↔ Maintenance of correct daytime behaviour. Treatment Duration: 3 years, 1 month
		1	Good	Correct	
		2	Good	Alert	
		3	Very good	Alert	
		4	Correct	Correct	
		5	Very good	Correct	
0451 (13.9 years)	2	0	Bad	Tired	↔ No effect on poor nighttime behaviour. ↔ No effect on poor daytime behaviour. Treatment Duration: 1 year
		1	Bad	Tired	
0122 (8.2 years)	2	0	Bad	Tired	--
0608 (11.7 years)	2	0	Correct	Tired	--
5244 (17.6 years)	4	0	Very bad	Tired	--
0349 (6.1 years)	6	0	Bad	Tired	↑ Improvement in nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 2 years, 2 months
		1	Good	Completely alert	
		2	Good	Completely alert	

Patient # (Age*)	Dose (mg)	Visit	Assessment of Nighttime Behaviour	Assessment of Daytime Behaviour	Evaluation of Efficacy
Crushed Tablet					
0034 (6.6 years)	2	0	Bad	Correct	↑ Improvement in nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 6 months
		1	Correct	Alert	
5343 (8.9 years)	2	0	Bad	Tired	↑ Improvement in nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 2 months
		1	Correct	Correct	
0069 (7.2 years)	2	0	Bad	Tired	--
5294 (6.1 years)	2	0	Bad	Tired	--
0476 (6.7 years)	4	0	Bad	Correct	↑ Improvement in nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 1 year, 9 months
		1	Correct	Alert	
0219 (11.9 years)	4	0	Bad	Tired	--
5622 (10.4 years)	4	0	Correct	Correct	--
Quartered Tablet					
0409 (6.3 years)	4	0	Bad	Tired	↑ Improvement in nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 2 months
		1	Good	Alert	

NA = not available.

* At study enrolment.

Rett syndrome patients who received whole tablets were more likely to continue Circadin treatment than those who received crushed tablets. Of the 15 eligible patients with Rett syndrome, 3/7 (42.9%) patients who received whole tablets continued Circadin treatment past the first follow-up visit (visit 1) compared with 0/7 (0%) patients who received crushed tablets (Table 16). Maximum treatment duration was longer for the patients who received whole tablets (3 years, 1 month) compared with the patients who received crushed tablets (1 year, 9 months). These results underscore the superior efficacy of prolonged release melatonin (whole Circadin tablets) over immediate release melatonin (crushed Circadin tablets) on nighttime and daytime behaviour in patients with Rett syndrome, particularly as daytime behaviour is associated with total sleep time and sleep maintenance.

Table 16: Treatment duration by form of administration in patients with Rett Syndrome (modified eligible population)

	Patients with Rett Syndrome (N=15)		
	Whole Tablets (n=7)	Crushed Tablets (n=7)	Quartered (n=1)
Last visit			
0	3	3	0
1	1	4	1
2	1	0	0
3	0	0	0
4	0	0	0
5	1	0	0
6	1	0	0
Mean number of visits	2.00	0.57	1.00
Treatment duration for patients with follow-up visits			
n	4	4	1
Minimum	1 year	2 months	--
Maximum	3 years, 1 month	1 year, 9 months	2 months

Tuberous Sclerosis Complex

8 patients with TSC were screened for inclusion in the RTU program; all of these patients were considered as part of the eligible population. Of these 8 TSC patients, 1 patient had follow-up data available and is considered part of the per protocol population according to the RTU report. The MAH's re-analysis of the raw data determined 2 patients with efficacy data (i.e., with at least 1 follow-up assessment). Note that 1 of these patients is also considered part of the per protocol population according to the RTU report (5488). The MAH considered that one patient should also be considered in the efficacy population since there is a reported age of 8.9 years and documented Circadin dosage. This population of 2 TSC patients with efficacy data is considered the full analysis set by the MAH. Efficacy was evaluated in 2 patients with TSC who received Circadin (2 mg or 4 mg) administered as a whole tablet (Table 17). For 1 patient, baseline nighttime behaviour was reported as bad. This patient showed an improvement in nighttime behaviour (good) at the first follow-up visit after 7 months of treatment. The other patient showed maintenance of correct nighttime and daytime behaviour at the first follow-up visit after 4 months of treatment.

Table 17: Form of Administration and Efficacy in Patients with Tuberous Sclerosis – Circadin RTU Program

Patient # (Age*)	Dose (mg)	Visit	Assessment of Nighttime Behaviour	Assessment of Daytime Behaviour	Evaluation of Efficacy
Whole Tablet					
5488 (13.1 years)	2	0	Bad	Correct	↑ Improvement in nighttime behaviour. ↑ Improvement in daytime behaviour. Treatment Duration: 7 months
		1	Good	Completely alert	
0189 (7.6 years)	2	0	Bad	Correct	--
0582 (6.9 years)	2	0	Bad	Tired	--
0727 (8.9 years)	2	0	Correct	Correct	--
0830 (8.2 years)	2	0	Correct	Correct	--
0304 (8.9 years)	4	0	Correct	Correct	↔ Maintenance of correct nighttime behaviour. ↔ Maintenance of correct daytime behaviour. Treatment Duration: 4 months
		1	Correct	Correct	
		--	Bad	Tired	1.5 years post-treatment: ↓ Decline in nighttime and daytime behaviour.
0317 (6.1 years)	6	0	Very bad	Tired	--
Crushed Tablet					
5252 (9.7 years)	6	0	Bad	Tired	--

* At study enrolment.

TSC patients who received whole tablets were more likely to continue Circadin treatment than those who received crushed tablets. Of the 8 eligible patients with TSC, 2/7 (28.6%) patients who received whole tablets continued Circadin treatment past the initial study visit (visit 0) compared with 0/1 (0%) patient who received crushed tablets (Table 18). These results are consistent with the beneficial effects expected for prolonged release melatonin in patients receiving whole tablets.

Table 18: Treatment duration by form of administration in patients with Tuberous Sclerosis Complex (modified eligible population)

	Patients with Tuberous Sclerosis Complex (N=8)	
	Whole Tablets (n=7)	Crushed Tablets (n=1)
Last visit		
0	5	1
1	2	0
Mean number of visits	0.29	0
Treatment duration for patients with follow-up visits		
n	2	0
Minimum	4 months	--
Maximum	7 months	--

Conclusions

Overall, administration of PR melatonin (as whole Circadin tablets) demonstrated a positive effect on parent-reported assessments of nighttime and daytime behaviour in patients with Angelman syndrome, Rett syndrome and TSC in the Circadin RTU programme. Moreover, since the mean daily dose for these patients (~3 mg/day) was lower than the mean daily dose reported for Slenyto in the Phase III clinical study NEU_CH_7911 (6.06 mg/day) – because of the challenge taking 4-5 tablets of Circadin, these children might not have fully benefited from the optimal dose of prolonged release melatonin. It is therefore reasonable to speculate that the correct dose of Slenyto would provide more pronounced beneficial effects than those observed in the Circadin RTU programme.

It was noted that the Circadin RTU programme lacks a comparator. However, given that Angelman syndrome and TSC are rare disorders (affecting 1 in 12,000-20,000 and 1 in 11,000-25,000 individuals, respectively) and Rett Syndrome is an ultra-rare disorder (affecting 1 in 100,000 females), it is not feasible to perform a standard controlled clinical trial in these indications. The Circadin RTU programme has a low retention rate. However, it should be noted that the Circadin RTU programme was a registry study rather than a standard controlled clinical study. Patients in this programme were not required to return for a study visit on a certain date. Consequently, some of the patients may have continued treatment but failed to return for a visit, and other patients on treatment may have returned for a visit but failed to complete the study forms. Data from these patients would not be captured. Nonetheless, the number of evaluable patients in the Circadin RTU programme and the length of treatment is on par with the numbers quoted in previous trials that have to date dictated clinical practice in these conditions and is therefore considered to be acceptable.

Please see Table 19 for the number of patients for each condition per analysis group. Despite the limited number of patients in this programme, efficacy data for a total of 32.59 patient-years were collected.

Table 19: Number of Patients per Condition in the Circadin RTU Programme

Analysis Group/ Condition	Rett Syndrome	Angelman Syndrome	Tuberous Sclerosis Complex	Total
Screened	18	37	8	63
Screened Eligible	15	29	8	52
Full Analysis Set	8	12	2	22
Per Protocol Population	6	7	1	14
Length of treatment, months (minimum-maximum)	2-37	6-48	4-7	2-48
Patient-years (Full Analysis Set)	11.50	20.17	0.92	32.59

The beneficial effect of PR melatonin (Slenyto) on sleep maintenance and latency has been established in children and adolescents experiencing disturbed diurnal melatonin secretion patterns across various neurogenetic disorders specifically ASD and SMS. Since the mechanism of action of PR melatonin is independent of the background disorder, and as patients with Angelman syndrome, Rett syndrome, TSC and Williams syndrome experience sleep disturbances associated with aberrant diurnal melatonin secretion patterns (as discussed below), and positive effects of Circadin were demonstrated in this population in the RTU program, it is reasonable to expect that Slenyto will have a similar or even better beneficial effect on the sleep quality of children with these disorders.

Published Literature

As reported in a recent publication (Kotagal, 2024), the International Paediatric Sleep Association (IPSA) established a task force to provide practical guidance to clinicians on the use of melatonin for managing insomnia in children with autism and other neurogenic disorders (Smith-Magenis syndrome, Angelman syndrome, Rett syndrome, and Tuberous sclerosis complex). Recommendations on the use of melatonin were based on data from 8 clinical trials published between 2012 and 2022, with a total of 1027 subjects (2 to 17.5 years of age). Of the 8 studies examined, 5 studies used PR or CR melatonin, including 4 studies with pediatric prolonged-release melatonin (Slenyto). This panel of pediatric sleep specialists determined that melatonin, when administered in a hypnotic dose (2-10 mg) prior to bedtime, helped subjects fall asleep more quickly and prolonged their nocturnal sleep. The expert panel recommended that clinicians consider prescribing melatonin to children with autism and neurogenetic syndromes (Smith-Magenis syndrome, Angelman syndrome, Rett syndrome, and Tuberous sclerosis complex) with comorbid chronic insomnia if behavioural strategies alone have not been effective or only partially effective and coexisting medical conditions and concomitant medications such as anti-epileptic drugs (e.g., felbamate) that might worsen sleep have been addressed. Notably, the recommendations of the IPSA task force did not differentiate between autism and other neurogenic disorders (Smith-Magenis syndrome, Angelman syndrome, Rett syndrome, and Tuberous sclerosis complex).

Neurodevelopmental Disabilities

Controlled-release (CR) melatonin has been shown to improve total night-time sleep, sleep latency, sleep efficiency and longest sleep episode in children with neurodevelopmental disabilities. Wasdell et al. (2008) conducted a randomized, placebo-controlled study to determine the efficacy of CR melatonin in the treatment of delayed sleep phase syndrome and impaired sleep maintenance of children with neurodevelopmental disabilities. This crossover study of CR melatonin (5 mg) was followed by a 3-month open-label study in which the melatonin dose was gradually increased until the therapy showed optimal beneficial effects. The primary outcome measure of efficacy was total night-time sleep as recorded on caregiver-completed somnologs, which provided a running record of the time when the child was asleep or awake during the relevant measurement period. Secondary outcome measures of

sleep characteristics derived from the somnolog were sleep onset latency, sleep efficiency, longest sleep episode and number of night-time wakings. In addition, actigraph wrist watches were worn nightly by patients on the non-dominant wrist. Actigraph measures were summarized for total night-time sleep, sleep onset latency, sleep efficiency, longest sleep episode and number of night-time wakings. Clinician rating of severity of the sleep disorder and improvement from baseline, along with caregiver ratings of global functioning and family stress were also obtained. Patients were eligible to participate if they were between the ages of 2-18 years old, had multiple neurodevelopmental disabilities (NDD) and chronic delayed sleep phase syndrome (DSPS) or impaired sleep maintenance (ISM) (longer than 1.5 years). Children were not eligible when their sleep difficulties were mild and not associated with daytime symptoms of insomnia (such as excessive drowsiness, inability to stay awake, lethargy, increased irritability and decreased functioning) and had progressive degenerative neurologic disorders, or life-threatening illnesses. Fifty-one children who did not respond to sleep hygiene intervention were enrolled. Fifty patients completed the crossover trial and 47 completed the open-label phase. All children had more than one concurrent neurodevelopmental diagnosis such as severe intellectual loss (32), cerebral palsy (26), epilepsy (23), visual impairment (20), lack of mobility (18), and autism spectrum disorder (16). Medical chart review of neuroimaging (42) and electroencephalogram reports (46) identified diffuse brain damage in 18 patients, cerebral atrophy in 11 patients, malformation in 7 patients, and focal brain damage in 7 patients. Structural brain damage was not noted or suspected in 25 children. Delayed sleep phase syndrome was noted in 32 cases and ISM in 34 cases. DSPS alone was seen in 16 patients and 8 patients had sleep maintenance difficulties alone. For the primary outcome measure of total night-time sleep by somnolog recording, improvement of approximately 31 min on CR-melatonin compared with placebo was observed, and the test for treatment effect was significant ($p<0.01$) with an effect size of 0.4 (Table 20). Analysis of secondary outcome measures of sleep characteristics derived from somnologs (Table 20) showed significantly shorter sleep latency with CR-melatonin ($p< 0.01$) The effect size of the difference between CR-melatonin and placebo on sleep latency was 0.9. A similar pattern of results was observed in the analysis for treatment differences of the actigraph recordings where CR-melatonin treatment was associated with significantly longer total nighttime sleep ($p<0.01$) and shorter sleep latency ($p<0.01$). Actigraph data were not obtained from seven patients who were not compliant with wearing the device. No other treatment differences were observed and there were no significant carry-over or period effects evident in any of the analyses.

Table 20: Efficacy measures: baseline, crossover trial and period differences by treatment sequence

Outcome measure	Baseline	Crossover trial		Period differences by treatment sequence		*P* (analysis of period differences)
	No treatment	Placebo	Melatonin	Melatonin –placebo	Placebo–melatonin	
Somnolog						
Night-time sleep (min)	496.37 (71.06)	503.63 (87.72)	534.80 (86.22)	−37.00 (85.32)	24.54 (62.76)	<0.01
Sleep latency (min)	72.87 (38.99)	65.18 (41.79)	32.48 (28.67)	24.83 (38.95)	−41.94 (43.99)	<0.01
Longest sleep episode (min)	415.41 (106.23)	434.26 (109.09)	453.30 (118.41)	−27.33 (87.40)	9.30 (76.27)	0.12
Sleep efficiency (%)	93.84 (6.21)	94.72 (6.01)	94.95 (5.84)	0.49 (3.49)	1.08 (4.81)	0.62
Number of waking episodes	2.19 (1.34)	1.92 (0.95)	1.88 (1.23)	−0.05 (0.50)	−0.16 (0.70)	0.53
Actigraph						
Night-time sleep (min)	449.27 (92.29)	443.12 (79.98)	466.84 (91.08)	−26.40 (48.34)	20.35 (61.70)	<0.01
Sleep latency (min)	76.59 (52.10)	66.79 (37.26)	42.53 (31.80)	15.99 (28.46)	−34.68 (45.86)	<0.01
Longest sleep episode (min)	185.17 (102.63)	189.25 (99.98)	199.37 (100.46)	−27.33 (78.84)	−11.61 (92.96)	0.55
Sleep efficiency (%)	86.04 (9.59)	84.77 (10.63)	85.16 (8.96)	0.26 (7.00)	1.21 (7.60)	0.67
Number of waking episodes	12.08 (4.86)	11.38 (4.82)	11.83 (5.41)	−6.10 (3.04)	0.20 (4.35)	0.48
Clinical Global Impression						
Severity	4.52 (0.79)	4.42 (0.90)	3.16 (1.40)	1.04 (1.45)	−1.52 (1.38)	<0.01
Improvement	4.10 (0.42)	4.30 (1.01)	2.36 (1.17)	2.11 (1.80)	−1.74 (1.74)	<0.01
Parents' Global Assessment Scale	29.54 (7.96)	29.94 (8.14)	26.40 (8.45)	2.85 (5.63)	−4.35 (5.46)	<0.01
Family stress	2.06 (0.61)	2.04 (0.35)	1.86 (0.45)	0.15 (0.60)	−0.22 (0.60)	<0.05

Values are represented as mean (S.D.).

During the open-label phase, the doses were 5 mg for 21 patients, 10 mg for 25 patients, and 15 mg for 4 patients. Somnology measures were obtained after 3 months of open-label drug therapy for 46 patients. Significant improvement was observed in longest sleep episode ($p<0.05$) and sleep efficiency ($p<0.01$) in the open-label phase when compared with melatonin treatment in the crossover trial (Table 21). No additional improvement at the last melatonin visit during the crossover study was seen in sleep latency, total night-time sleep and number of waking episodes. Valid actigraph data were obtained for only 32 patients from both the randomized melatonin and open-label periods. There was no further improvement in sleep latency or total night-time sleep in this subset of the original sample.

Table 21: Efficacy measures: randomized trial melatonin versus open-label melatonin

Outcome measure	Randomized trial (melatonin)	Open label (melatonin)	*P*-value
Somnolog (n = 46)			
Night-time sleep (min)	539.91 (83.38)	540.78 (86.72)	0.90
Sleep latency (min)	33.48 (29.45)	27.77 (24.97)	0.81
Longest sleep episode (min)	456.20 (120.86)	488.12 (122.69)	0.02
Sleep efficiency (%)	95.34 (5.18)	97.11 (4.52)	<0.01
Number of waking episodes	1.83 (1.22)	1.50 (1.46)	0.10
Actigraph (n = 32)			
Night-time sleep (min)	461.76 (86.36)	434.69 (96.02)	0.08
Sleep latency (min)	44.07 (30.14)	46.49 (48.43)	0.80
Longest sleep episode (min)	174.15 (75.70)	174.29 (78.99)	0.99
Sleep efficiency (%)	84.45 (8.81)	86.74 (9.33)	0.10
Number of waking episodes	12.61 (5.63)	12.20 (5.37)	0.60
Clinical Global Impression (n = 46)			
Severity	3.04 (1.38)	2.24 (1.29)	<0.01
Improvement	2.28 (1.17)	1.74 (1.06)	<0.01
Parents' Global Assessment Scale	26.17 (8.64)	21.70 (11.85)	<0.01
Family stress	1.89 (0.43)	1.65 (0.60)	0.01

Values are represented as mean (S.D.).

Carr et al. (2007) conducted a prospective follow-up of the study by Wasdell et al. of 44 children aged 2-15 years with neurodevelopmental disabilities and treatment-resistant circadian rhythm sleep disorders (CRSD) who had participated in the placebo controlled, double blind cross-over trial of CR-melatonin (5 mg). The follow-up study involved a structured telephone interview of caregivers every 3 months for up to 3.8 years. All (41/41) of the caregivers reported a benefit to their child and to their families from melatonin therapy on specific parameters. Caregivers rated melatonin as having the greatest impact on sleep difficulties but also rated melatonin as having positive effects on overall health, behaviour, education, learning, and development. Adverse reaction to melatonin therapy and development of tolerance were not evident. Of note, at the beginning of the effectiveness study, the melatonin doses were 5 mg for 19 patients, 10 mg for 21 patients, and 15 mg for 4 patients. Controlled release melatonin (5 mg) was used until the middle of the effectiveness study when it was replaced with fast release (5 mg) tablets as the CR was not marketed at that time. The authors report that due to its short half-life, the fast-release formulation was not as effective for impaired sleep maintenance, therefore the caregivers compensated by using larger doses (5 mg for 13 children, 10 mg for 21 children, and 15 mg for 10 children). At the end of the study, in the survey, 80.5% (33/41) of respondents stated that they would like to have a commercially available controlled-release melatonin product, which would promote sleep for 8-10 hr rather than 5-6 hr.

Angelman Syndrome (AS)

Sleep disturbances (maintenance of sleep/nightly awakenings) Sleep concerns are common in children with Angelman syndrome, with 20-80% of individuals having a decreased sleep need and/or abnormal sleep-wake cycles. Didden et al. (2002) report that frequent night awakenings and problems with sleep maintenance are severe and more prevalent than settling problems in children with Angelman syndrome.

As reported by Zhdanova et al. (1999), symptoms of insomnia, in particular difficulty initiating or maintaining sleep, are primary concerns for patients with Angelman syndrome. Sleep problems are usually detectable at several months of age and persist for many years. Long latencies to sleep and prolonged awakenings at night lead to fatigue and sleepiness upon morning awakening and cause a chronic sleep debt which may potentiate other behavioural and neurologic problems.

Spruyt et al. (2018) performed an integrative research review and a meta-analysis of studies with sleep as the primary aim of investigation in Angelman syndrome patients. The results show that arousal during sleep, somnolence and possibly sleep duration are the primary sleep problems in individuals with Angelman syndrome.

In a study by Goldman et al. (2012), the sleep behaviours of 15 children/adolescents with Angelman syndrome were characterized using standardised questionnaires, wrist actigraphy and polysomnography (PSG). When compared to the normative sample, children/adolescents with Angelman syndrome scored higher on all sub-scales of the Children's Sleep Habits Questionnaire (CSHQ) (Table 22).

Table 22: Children's Sleep Habits Questionnaire sub-scale scores in children/adolescents with Angelman syndrome compared to normative sample

CSHQ sub-scale	Angelman syndrome (n = 15)	Normative sample* (n = 469)
Bedtime resistance	8.2 (2.9)	7.1 (1.9)
Sleep onset latency	1.5 (0.8)	1.3 (0.5)
Sleep anxiety	6.0 (1.4)	4.9 (1.5)
Sleep duration	5.6 (1.6)	3.2 (0.9)
Night wakings	5.8 (1.6)	3.5 (0.9)
Parasomnias	10.4 (1.4)	8.1 (1.3)
Sleep-disordered breathing	4.4 (1.4)	3.2 (0.6)
Daytime sleepiness	11.4 (3.2)	9.6 (2.8)
Sleep total	49.0 (7.3)	41

PSG and actigraphy results of the Angelman syndrome patients are presented in Table 23.

Table 23: Objective sleep measurements [mean (standard deviation)] of children and adolescents with Angelman syndrome

Sleep measurement/measure	Sleep onset latency (min)	Sleep duration (min)	Night wakings WASO (min)	Fragmentation (index)	Time in bed (min)
Child – polysomnography	37.6 (50.3)	373.9 (132.8)	57.2 (91.5)	10.8 (14.4)	504.4 (107.0)
Child – actigraphy on polysomnography night	32.9 (33.1)	381.9 (100.5)	123.0 (85.0)	52.5 (21.2)	499.9 (149.5)
Child – in-home actigraphy	40.8 (23.3)	405.5 (54.8)	114.0 (32.5)	49.7 (6.1)	519.6 (63.5)

Night wakings were noted both subjectively by parental report and objectively with actigraphy and PSG. Wake after sleep onset measured by PSG averaged almost 1 h over all children and, when measured with actigraphy, both in the laboratory and at home, averaged almost 2 h. These findings, along with the high fragmentation index in both the sleep lab and at home, highlight the disturbed sleep in these individuals.

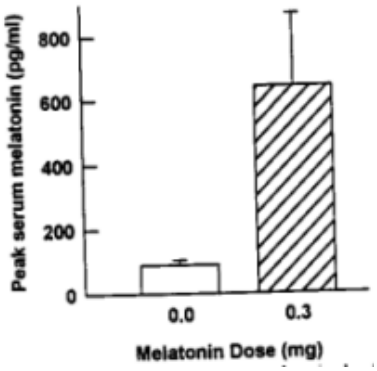
Disturbances of diurnal melatonin secretion

Although few studies have examined the melatonin secretion profile of Angelman syndrome (AS) patients, the available data (summarized below) indicate that it varies broadly between individuals with a tendency towards reduced levels and/or altered timing of nighttime melatonin secretion.

Nighttime melatonin secretion patterns in AS children compared to published reports of healthy children:

Zhdanova et al. (1999) examined the endogenous serum melatonin profiles of 13 AS children aged 2-10 years suffering from insomnia. Blood samples were drawn hourly from 15:00 to 10:00 the next morning. Peak nocturnal values ranged from 81.9 pmol/L (19 pg/mL) to 762.9 pmol/L (177 pg/mL); the group mean value (± SE) was 387.9±63.4 pmol/L (90±14.72 pg/ mL) (Figure 6). Melatonin AUC values ranged from 607.7 pmol/L (141 pg/mL/h) to 4775 pmol/L (1108 pg/mL/h) in different subjects; the group mean (SEM) was 2745±429.3 pmol/L (637±99.61 pg/mL/h).

Figure 6: Mean (± SEM) peak serum melatonin levels in thirteen AS children: endogenous levels and following administration of a 0.3 mg dose of melatonin



The study showed that both the average hourly rate of production across the 24-hour period and peak nighttime levels of melatonin production were highly variable between individuals. In the majority of these children, peak nighttime melatonin levels were noticeably lower compared to a published report of unaffected children of a similar age where the mean melatonin peak was 153.6±72.6 pg/mL (Cavallo, 1992). In addition, the nighttime surge in melatonin secretion was significantly delayed in 3 AS children (relative to habitual bedtime and sleep onset). Two of these children exhibited prolonged morning sleepiness that was correlated with low sleep quality and quantity.

Braam et al. (2008) also measured endogenous melatonin levels in a study of 8 AS patients with idiopathic insomnia (4-9 years, n=5; 12-20 years, n=3). Seven of these patients showed sleep onset as well as sleep maintenance problems, and 1 patient suffered from sleep onset problems only. Endogenous melatonin levels were measured via salivary samples collected hourly during 5 consecutive hours. Sampling was initiated at 5 pm in children 2-4 years of age, at 6 pm in children 5 and 6 years of age, and at 7 pm in older children. The authors reported low levels of endogenous melatonin (Table 24). However, as the sampling times were restricted to 5-11 pm in this study, it is impossible to distinguish between low melatonin vs. a delayed onset in nighttime melatonin secretion.

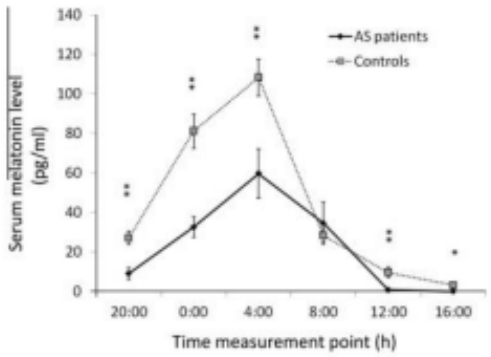
Table 24: Endogenous melatonin (pg/mL) in saliva at baseline

		Patient							
Melatonin or placebo[b]	Time (PM)	1 P	2 M	3 P	4 M	5 M	6 P	7 P	8 M
Baseline week	5				<0.5	<0.5			
	6	4.9		3.7	<0.5	1.4	<0.5		
	7	4.0	0.6	3.1	0.6	#	#	1.4	#
	8	4.7	0.7	4.2	#	3.3	#	<0.5	<0.5
	9	#	1.6	#	#	#	#	<0.5	#
	10	#	#	#			#	#	9.1
	11		#					#	

#: Not enough saliva was collected.

Melatonin secretion profiles of AS patients compared to unaffected age-matched controls: Takaesu et al. (2012) compared the diurnal changes in serum melatonin levels of 15 AS patients (including children, adolescents, and young adults) with and without circadian rhythm sleep disorder (CRSD) to those of age-matched controls. A total of 8 AS patients (53%) had CRSD (irregular sleep-wake type [ISWT], n=4; delayed sleep phase type [DSPT], n=2; free-running type [FRT], n=2). Blood samples were collected intravenously every 4 h for 24 h. The diurnal changes in serum melatonin levels of the AS patients were compared with those of the controls using the blood samples. AS patients vs. controls – Overall, individuals with AS exhibited significantly lower nighttime melatonin levels than that of the controls. The peak serum melatonin level of the AS patients was significantly lower than that of the control subjects (AS: 59.8±46.1 pg/mL; control: 108.4±35.0 pg/mL; p<0.01) Figure 7. The serum melatonin levels of the AS patients were significantly lower than those of the controls at 20:00, 0:00, 04:00 (p<0.01 for all), and slightly but significantly higher at 12:00 and 16:00 (p<0.0.1 and p<0.03, respectively). On the other hand, there was no significant difference in the serum melatonin levels between the AS patients and the controls at 08:00.

Figure 7: Comparison of diurnal changes in serum melatonin levels between AS patients and controls

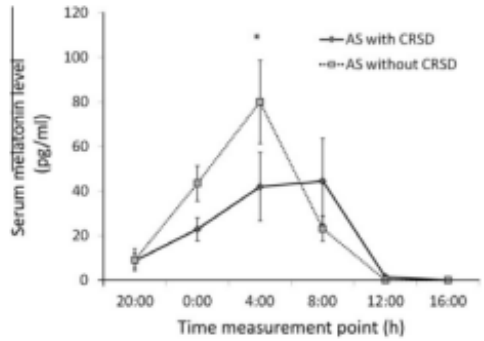


AS = Angelman syndrome.

**p0.01, *p <0.05. Two-way repeated ANOVA and the Bonferroni–Dunn test were used to compare the serum melatonin levels between the AS patients and the controls. The vertical error bars represent standard error (SE) of the mean.

AS patients with and without CRSD – AS patients with CRSD also exhibited a significantly smaller nighttime peak in melatonin secretion compared to AS patients without CRSD (Figure 8). At 04:00, the serum melatonin levels of the AS patients with CRSD were significantly lower than those of the AS patients without CRSD (p=0.043); there were no significant differences in the serum melatonin levels between the AS patients with and without CRSD at any other time measurement points.

Figure 8: Comparison of diurnal changes in serum melatonin level between AS patients with and without CRSD

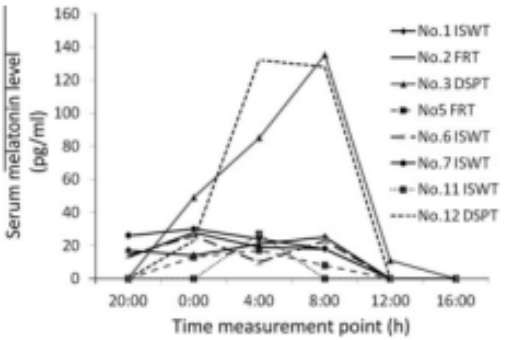


AS = Angelman syndrome. CRSD = Circadian rhythm sleep disorder.

**p<0.01, *p<0.05. Two-way repeated ANOVA and the Bonferroni– Dunn test were used to compare the serum melatonin levels between the AS patients and the controls. The vertical error bars represent the SE of the mean.

AS patients with CRSD – AS patients with free-running type and irregular sleep-wake type CRSDs exhibited low serum levels of melatonin throughout the 24-hour day with virtually no nighttime surge in melatonin (Figure 9). Peak melatonin levels in AS patients with delayed sleep phase type CRSD were similar to controls, but the peak was significantly delayed.

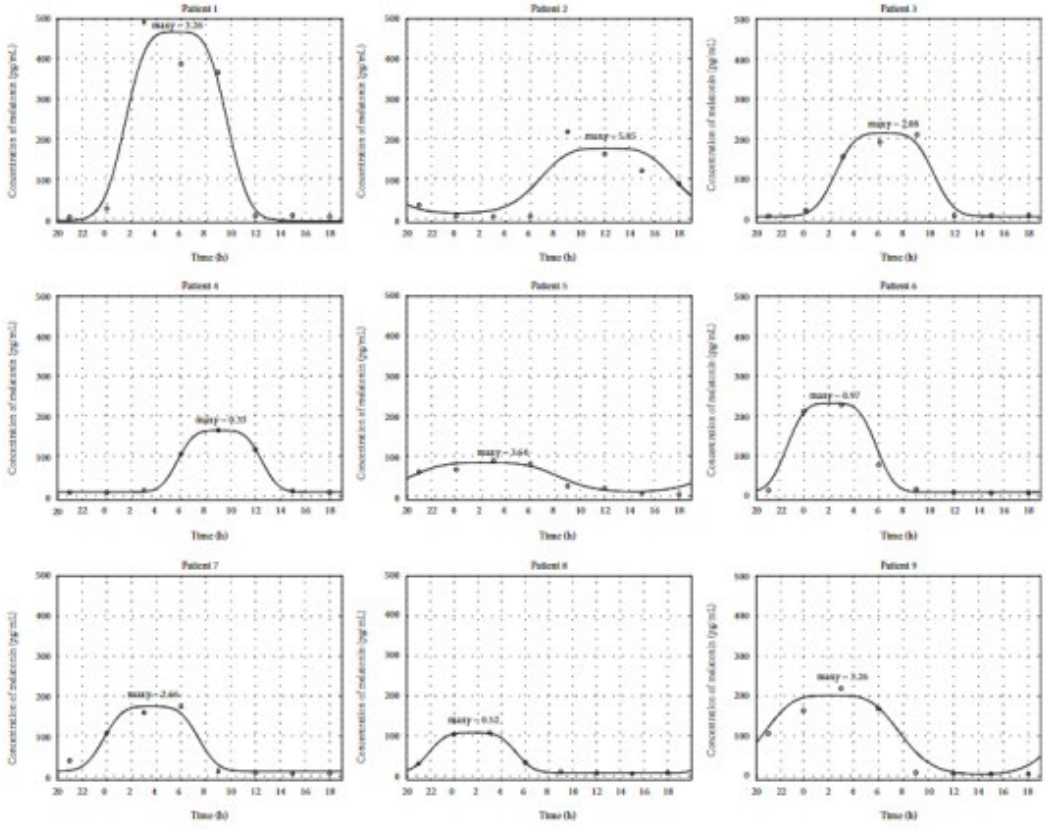
Figure 9: Individual melatonin profiles of AS subjects with CRSD



ISWT = irregular sleep-wake type; FRT = free-running type; DSPT = delayed sleep phase type

Another study (Paprocka, 2017) examined the melatonin rhythms in AS children (n=9) compared with non-AS/epilepsy (n=80) and non-AS/non-epilepsy (n=40) age-matched controls. All of the AS patients included in the study were diagnosed with a CRSD (irregular sleep-wake type, n=3; free-running type, n=2; delayed sleep phase type, n=4). The characteristics of diurnal hormone secretion, such as minimum melatonin concentration, release amplitude, phase shift of melatonin release and sleep duration as well as the dim light melatonin onset (DLMO) of melatonin secretion (being an important circadian marker), were estimated using a mathematical model of melatonin circadian secretion. The results of this study showed differences in the pattern, but not levels, of melatonin secretion in AS patients. Although these AS children had melatonin levels similar to levels reported in the literature for both age-matched control groups and healthy children (Cavallo, 1992), their individual melatonin secretion curves were highly variable (Figure 10). For 67% patients of the AS group (patients 1, 2, 3, 5, 7, and 9), max γ (shown in Figure 10 above the modelled function) is higher than 2, which means that melatonin secretion is severely disturbed in the AS group.

Figure 10: Melatonin secretion in 9 AS patients



Solid line = estimated model; circles = measured values.
The obtained maximum gamma values are given above the models.

A comparison of the AS group and the control group (Table 25) showed that sleep duration is elongated ($p<0.05$; Figure 11), and both the phase shift ($p<0.005$; Figure 12) and the offset of nighttime melatonin secretion ($p<0.005$; DLMOoff50: Figure 13, DLMOoff25: Figure 14) are significantly delayed in AS children. Rather than the typical bell-shaped curve, these children exhibited a 'triangular" melatonin secretion profile that may explain the sleep onset insomnia and sleep maintenance problems so common to AS.

Table 25: Comparison of melatonin diurnal secretion in Angelman patients and controls

Model parameters	Median of the CG group	Median of the AG group	*p* value
b_1, minimum melatonin concentration (pg/mL)	6.16	7.83	0.6065
b_2, melatonin release amplitude (pg/mL)	142.51	167.46	0.372
b_3, phase shift of melatonin release (h)*	1.38	3.59	**0.0039**
b_4, estimated sleep duration (h)*	7.07	8.05	**0.0427**
Maximum melatonin concentration (pg/mL)	152.14	175.69	0.372
$DLMOon_{50}$ (h)*	22.1	23.74	0.1592
$DLMOoff_{50}$ (h)*	5.2	8.72	**0.0005**
$DLMOon_{25}$ (h)*	21.33	22.69	0.2039
$DLMOoff_{25}$ (h)*	6.06	10.47	**0.0004**
Max gamma	1.81	2.65	0.3906

*Time in decimal scale.

AG = Angelman syndrome group; CG = control group; DLMO = dim light melatonin onset.

Figure 11: Boxplot of the estimated sleep duration (represented by the b_4 parameters) for the Angelman syndrome and control groups

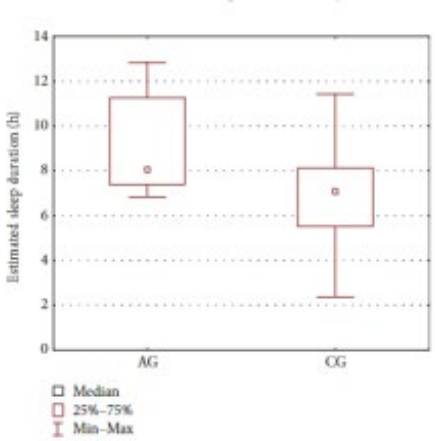


Figure 12: Boxplot of the phase shift of melatonin release (represented by the b_3 parameters) for the Angelman syndrome and control groups

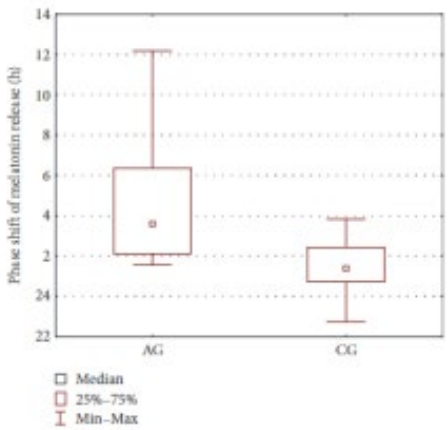


Figure 13: Boxplot of the $DMLOoff_{50}$ parameter for the Angelman syndrome and control groups

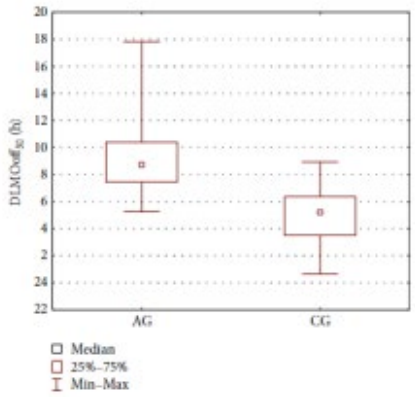
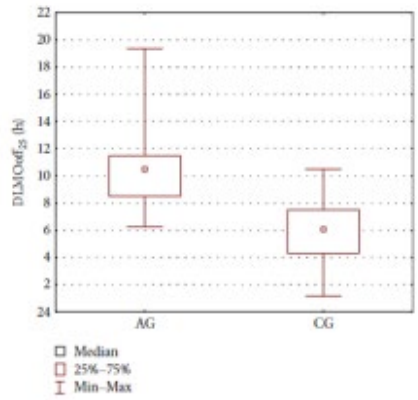


Figure 14: Boxplot of the $DLMOoff_{25}$ parameter for the Angelman syndrome and control groups



Effects of exogenous melatonin on sleep

Melatonin is commonly used by caregivers and routinely recommended by physicians as a treatment for sleep disruption in AS patients (Schwichtenberg, 2015; Braam 2008). Despite the limited number and inconsistent methodologies of investigations into the effectiveness of melatonin in AS children, the available data consistently indicate that melatonin administration improves sleep latency, efficiency, duration, and nighttime awakenings (Buonfiglio, 2020). Zhdanova et al. (1999) conducted an open-label study to examine the effects of low dose melatonin therapy on sleep behaviour and serum melatonin levels in AS children suffering from insomnia. Thirteen children (aged 2-10 years) were monitored for 24-hour motor activity in their home environments for 7 days prior to melatonin treatment and for 5 days during which a 0.3 mg dose of melatonin was administered daily 0.5-1 hour before the patient's habitual bedtime. Blood samples were withdrawn at hourly intervals over two 21-hour periods in order to measure individual endogenous serum melatonin levels and the levels induced by melatonin treatment.

Actigraphic recording of motor activity, confirmed by parents' reports, showed a significant improvement in the patients' nocturnal sleep pattern as a result of melatonin treatment (Figure 15, Figure 16, Figure 17). Analysis of the group data revealed a significant decrease in motor activity during the total sleep period following melatonin treatment, and an increase in the duration of the total sleep period. Parents of these children reported improved sleep consolidation and quality. Endogenous peak nocturnal melatonin values ranged from 19 to 177 pg/mL. The administration of melatonin elevated peak serum hormone levels to 128- 2800 pg/mL in children of different ages and body mass.

This treatment also resulted in a 2 to 3-hour phase advance in the onset of melatonin secretion in children that otherwise exhibited a significant phase delay in nighttime melatonin secretion (see Figure 6). Therefore, a physiological dose of melatonin (0.3 mg) just before bedtime decreased sleep latency, reduced motor activity during sleep, and increased sleep duration in children with AS.

Figure 15: Mean (±SEM) number of body movements per hour of the sleep period in thirteen AS children before and during melatonin treatment

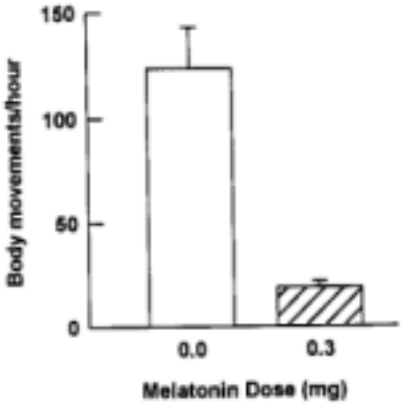
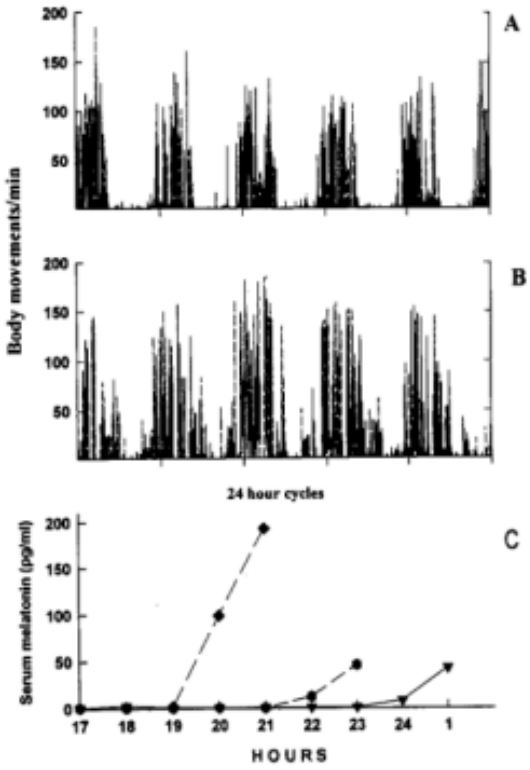
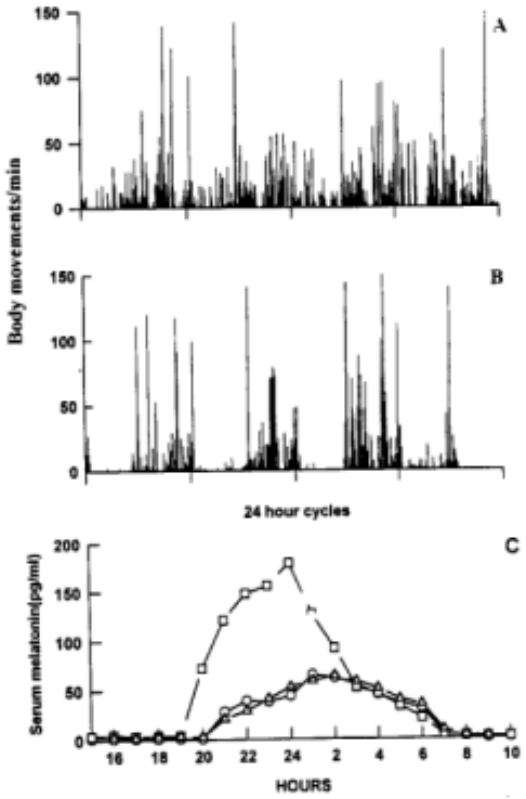


Figure 16: Sleep onset (judged from motor activity) in Patient #1



Sleep onset in patient #1 (A) during melatonin treatment, and (B) during melatonin withdrawal after 4 weeks of treatment; (C) timing of the onset of elevated serum melatonin prior to treatment (▲), during treatment (♦), and after 4 weeks of melatonin treatment (●).

Figure 17: Motor activity of Patient #5



Motor activity of patient #5 during (A) four days of no treatment, and (B) during four days of melatonin treatment; and (C) the profiles of serum melatonin concentrations prior to treatment (Δ), during treatment (□), and after 4 weeks of melatonin treatment (○).

Braam et al. (2008) conducted a randomized, double-blind, placebo-controlled study in children (4-13 years; n=7) and an adult (20 years; n=1) with AS and chronic idiopathic insomnia. Criteria for participation were sleep latency more than 30 minutes, or 2 or more wakes, lasting more than 15 minutes a night, at least 5 nights a week, during more than 1-year preceding inclusion. Exclusion criteria were prior use of melatonin, liver disease, renal failure, chronic pain, and age less than 24 months. Baseline characteristics are presented in Table 26. Seven patients had sleep onset as well as sleep maintenance problems, and 1 patient suffered from sleep onset problems only.

Table 26: Participant characteristics and medication

	Patient							
	1	2	3	4	5	6	7	8
Type of Angelman syndrome	Deletion	Deletion	Disomy	Deletion	Deletion	Disomy	Deletion	Deletion
Age, y:mo	4:10	12:10	6:7	5:7	8:10	9:2	20:11	13:4
Gender	Male	Female	Female	Male	Female	Female	Male	Female
Weight, kg	20	48	26	22.5	31	37	56	40
Sleep onset problem	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nighttime awakening	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Antiepileptic drug use	cbz,clb,vpa	–	vpa	–	esm	–	vpa	clb,vpa
Present sleep medication	mid	pip	–	–	–	–	–	–

NOTE: cbz = carbamazepin; clb = clobazam; esm = ethosuximide; vpa = valproate; mid = midazolam; pip = pipamperon.

The trial consisted of 2 consecutive periods: a 1-week qualification period and 4 weeks of treatment during which participants were randomly allocated to melatonin or placebo therapy. Saliva specimens

for measuring melatonin concentrations were collected in the qualification period (baseline) to examine whether there was a delayed sleep phase syndrome or another disturbance in melatonin circadian rhythm and at the end of the last week of the treatment period to examine whether 4 weeks of treatment had changed endogenous melatonin circadian rhythm. After the 4-week placebo-controlled phase of the study, all patients received 4 weeks open treatment with melatonin. During the 4 treatment weeks, patients 6 years of age and older received a daily oral dose of 5 mg of melatonin at 7 pm, patients under 6 years of age received a daily oral dose of 2.5 mg of melatonin at 6 pm. Primary outcome measures were the betweengroup differences of sleep latency, sleep onset, wake up time, and number and length of wakes. Secondary outcome measures were the between group differences of salivary melatonin concentrations, number of epileptic seizures, as well as adverse reactions of melatonin. Sleep variables were assessed by parents and recorded in a sleep diary.

Treatment with melatonin significantly advanced sleep onset by 28 minutes, decreased sleep latency by 32 minutes, increased total sleep time by 56 minutes and reduced the number of nights with wakes from 3.1 to 1.6 nights a week (Table 27). These changes significantly differed from those during placebo treatment. Parents indicated that their children were less sleepy and more attentive during the day, with easier to manage behaviour.

Table 27: Differences in sleep parameters from Baseline to Week 4

	Baseline					Intervention (4 weeks)				
	Melatonin Mean (SD)	Placebo Mean (SD)	*t*	*df*	*P*	Melatonin Mean (SD)	Placebo Mean (SD)	*t*	*df*	*P*
Lights out time[a]	20:10 (0:55)	20:09 (1:12)	.011	6	.99	20:14 (0:52)	20:14 (1:12)	0	6	1
Sleep onset time[a]	21:00 (1:10)	21:05 (1:30)	–.096	6	.93	20:32 (0:56)	21:10 (1:31)	–.715	6	.02[c]
Sleep latency[b]	50.00 (17.49)	56.50 (21:17)	–.473	6	.65	17.5 (5.74)	55.75 (20.64)	–3.570	6	.01[c]
Sleep offset time[a]	07:49 (0:36)	07:02 (0:33)	1.715	5	.15	07:42 (0:38)	07:02 (0:02)	1.768	5	.14
No. of nights/week with wakes	3.1 (2.95)	5.9 (1.41)	–1.724	6	.14	1.6 (2.01)	5.6 (1.24)	–3.357	6	.01[d]
No. of wakes/night	1.5 (1.41)	1.7 (0.69)	–.127	6	.9	0.9 (0.61)	1.8 (0.79)	–1.926	6	.1
Duration of wakes[b]	39.50 (35.25)	55.00 (37.53)	–.602	6	.57	11.75 (9.87)	60.75 (45.02)	–2.126	6	.08
Total sleep time[a]	10:08 (1:22)	9:40 (0:37)	.545	5	.61	11:04 (0:46)	9:31 (0:28)	2.996	5	.03[c]

a. Hours:minutes.
b. Minutes.
c. $P < .05$.
d. $P < .01$.

The results of this study show that evening melatonin treatment advances sleep onset, decreases sleep latency, reduces nighttime awakening, increases total sleep time, and improves daytime behaviour in children with AS.

Takaesu et al. (2012) examined the effectiveness of melatonin in 6 AS patients with CRSD (ISWT, n=4; FRT, n=2; DSPT, n=2). Patients received a daily dose of 1 mg of melatonin between 6-7 pm for three months. The changes in sleep-wake patterns were evaluated approximately three months after starting the treatment using sleep logs.

Melatonin treatment increased the percentage of nocturnal sleep in four of six AS patients with CRSD (mostly children) (Table 28). In particular, the FRT-CRSD of two AS patients (Cases 2 and 5) was completely suppressed after starting the melatonin treatment, and two out of the three ISWT patients (Cases 1 and 11) showed a decrease in the frequency of daytime sleep episodes and an increase in nocturnal sleep time. The mean percentages of nocturnal sleep of these four AS patients (Cases 1, 2, 5 and 11), as measured on their sleep logs recorded for one month before the clinical evaluation, improved to more than 80% (Figure 18). One out of two DSPT patients (Case 12) received the melatonin treatment but did not show any increase in nocturnal sleep time with the treatment.

Table 28: Patient characteristics and outcome of melatonin treatment

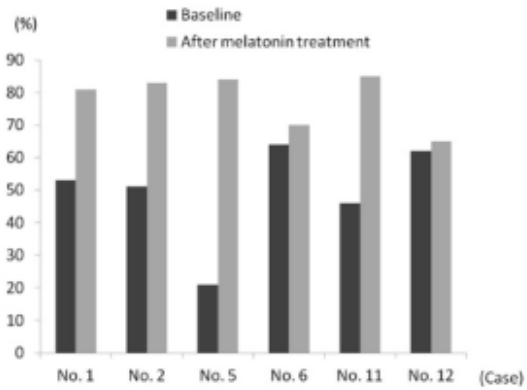
Patient No.	Diagnosis of CRSD	Onset age of CRSD (years)[a]	Total sleep time (h/day)	Percentage of nocturnal sleep (%)	Peak serum melatonin levels (pg/mL)	Treatment outcome[b]
1	ISWT	3	6.3	53	25	Effective
2	FRT	5	9	51	28	Effective
5	FRT	5	9.5	21	17	Effective
6	ISWT	5	7.3	64	26	Non-effective
11	ISWT	3	9.7	46	27	Effective
12	DSPT	7	9.3	62	132	Non-effective

ISWT: irregular sleep-wake type, FRT: free-running type, DSPT: delayed sleep phase type, VPA: sodium valproate, CBZ: carbamazepine, ZNS: zonisamide, PHT: phenytoin.

[a] The onset age of CRSD was estimated on the basis of information obtained from the family members of the AS patients.

[b] The outcome was defined as effective if the percentage of nocturnal sleep to total sleep time exceeded 80% after treatment.

Figure 18: Changes in the percentage of nocturnal sleep time with melatonin treatment



Jain et al. (2014) published a case study of a 9-year-old boy with AS that exhibited prolonged mid-night awakenings. Treatment with sustained-release melatonin (3 mg) 30 minutes before bedtime improved sleep efficiency, decreased nighttime arousals, and increased total sleep time.

Rett Syndrome

Sleep disturbances (maintenance of sleep/nightly awakenings)

Over 80% of individuals with Rett syndrome are affected by sleep disorders.

Tascini et al. (2022) summarise that sleep disorders reported for patients with Rett syndrome include dysregulation of the sleep/wake cycle, difficulty falling asleep or staying asleep, night laughter or screaming and frequent awakenings.

Young et al. (2007) conducted a large-scale analysis to characterize the prevalence and predictors of sleep problems in Rett syndrome based on data from the Australian Rett Syndrome Database. The authors report that awakenings at night appeared to be moderate to severe among the younger children (with 54% reporting frequent night awakenings for the 0 to 7-year-old age group). Awakenings at night were less common in the older cases but still reported frequently in 40% of the over 18-year-old age group.

The prevalence and elements of sleep disorders were further detailed by Boban et al. (2016) in 364/461 Rett syndrome and MECP2 mutation patients registered in the international Rett syndrome phenotype database (InterRett). Among the specific sleep problems (difficulty falling asleep, night laughing, night screaming, seizures at night, teeth grinding, night waking, daytime napping, and difficulty waking), the highest prevalence was found for nocturnal awakenings; 48.3% of the enrolled individuals woke up more frequently at night.

Disturbances of diurnal melatonin secretion

Children with Rett syndrome have been found to have impaired secretion of melatonin, leading to severe sleep problems.

Miyamoto et al. (1999) studied the circadian rhythm of serum melatonin levels in two patients with classical Rett syndrome having severe sleep disorders. Serum melatonin levels were measured before and during melatonin treatment using radioimmunoassay. Blood samples were drawn every 4 h for 48 h in Patient 1, and every 2 h for 24 h in Patient 2.

Patient 1 had a free-running rhythm of sleep-wake cycle from 3 years of age. At the age of 4 years, two peaks in serum melatonin were observed during her sleep periods. The time of each peak was delayed 6 h compared to normal control. The values of the two peaks were 98 and 41 pg/mL, which were at the lower limit (73.5-516 pg/mL, 90% confidence intervals for ages 3-5 years).

Patient 2 had a fragmented sleep pattern accompanied by night screaming from 1 year and 6 months of age. At the age of 10 years, the peak time of melatonin was 2 am, which corresponds to that of normal prepubertal children. The peak value of melatonin was 18 pg/mL, which was at the lower limit for normal children (14.5-282 pg/mL, 90% confidence intervals for ages 9- 11 years).

Effects of exogenous melatonin on sleep

Melatonin is the most commonly used medication to treat sleep disturbances in Rett syndrome followed by antiepileptic medications and variants of benzodiazepines (Wong, 2015; Shelton and Malow, 2021).

In a double-blind, placebo-controlled crossover study, the effects of exogenous melatonin treatment on sleep dysfunction were examined in children with Rett syndrome (McArthur and Budden, 1998). Nine girls with Rett syndrome (mean age: 10.1 years) underwent a 4-week treatment period (melatonin or placebo) with a 1-week washout between treatments. Melatonin doses ranged from 2.5 to 7.5 mg, based upon individual body weight. Sleep-wake patterns were monitored 24 hours a day over the 10-week study period (including a 1-week baseline period) using wrist actigraphy. Patients' baseline sleep quality was poor compared with healthy children, with a low sleep efficiency (mean [±SE], 68.0±3.9%), long sleep-onset latency (42.1±12.0 minutes), and a short and fragmented total sleep time (7.5±0.3 hours; 15±2 awakenings per night).

Sleep-onset latency was significantly reduced by melatonin treatment during the first 3 weeks of the trial (Figure 19). The mean (±SE) sleep-onset latency dropped from 32±8.6 minutes during the placebo treatment to 19.1±5.3 minutes ($p<0.05$) with melatonin treatment. Furthermore, the decrease in sleep-onset latency was apparent during the first nights of treatment (Figure 20).

Figure 19: Group mean sleep-onset latency by week of treatment

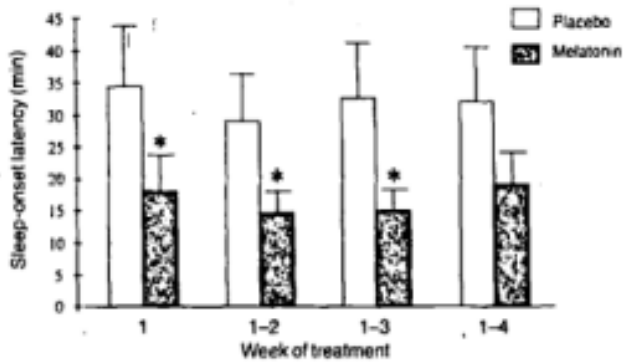
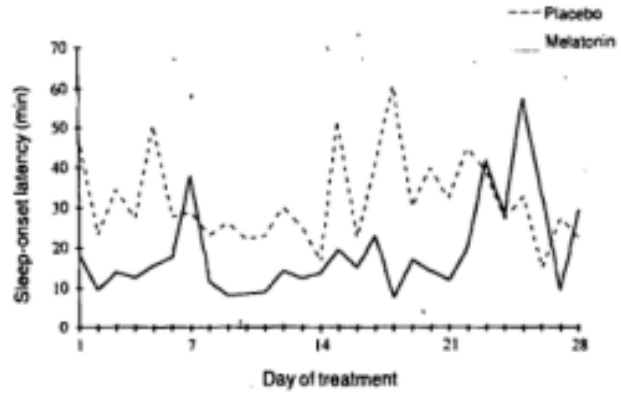


Figure 20: Group mean sleep-onset latency by day of treatment



Melatonin treatment improved total sleep time in the three patients with the lowest baseline sleep efficiency (Figure 21). Although it was not statistically significant, the group mean revealed a clinical improvement of 29 minutes in total sleep time. The melatonin effect also appeared to be immediate, with amelioration during the first nights of treatment (Figure 22). However, the increase in total sleep time cannot be attributed to a decrease in nighttime awakenings. Melatonin treatment did not alter the frequency of nighttime awakenings in this group.

Figure 21: Individual mean 4-week total sleep time plotted against the patient's baseline sleep efficiency

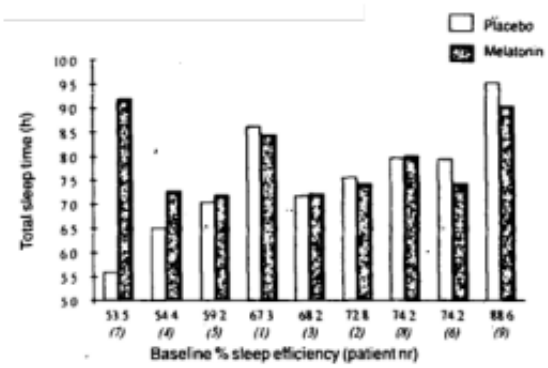
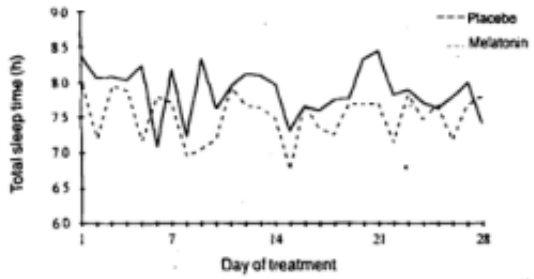


Figure 22: Group mean total sleep time by day of treatment



Sleep efficiency also increased in the patients with the lowest baseline sleep (Figure 23). However, the mean improvement in this measure was slight (4.27%). Daily group means of sleep efficiency are presented in Figure 24. While the daily mean sleep efficiency during melatonin treatment was consistently higher than the placebo, the mean difference was not significant.

Figure 23: Individual mean 4-week sleep efficiency plotted against the patient's baseline sleep efficiency

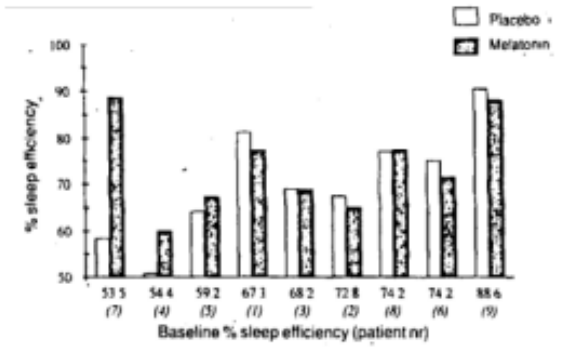
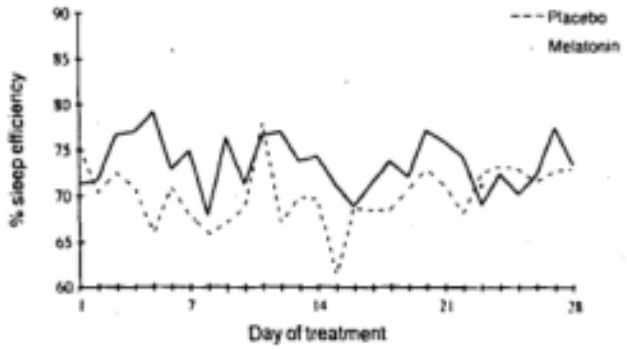


Figure 24: Group mean sleep efficiency by day of treatment



Overall, the results of this study showed a significant decrease in sleep-onset latency during melatonin treatment in patients with Rett syndrome. Melatonin treatment also improved total sleep time and sleep efficiency, although individual responsiveness was variable and dependent upon the severity of the sleep disorder.

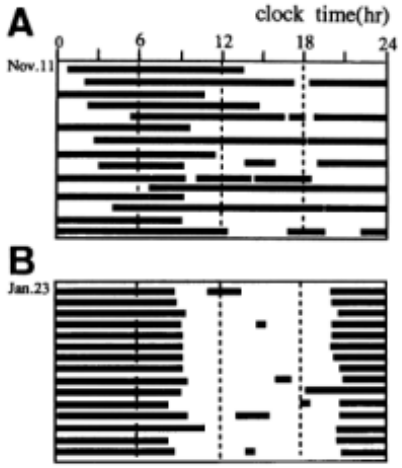
Miyamoto et al. (1999) have shown that exogenous melatonin treatment in Rett syndrome children improves sleep-wake cycle and sleep onset for more than 2 years without any adverse effects. In this study, two patients with classical Rett syndrome having severe sleep disorders were given 5 mg melatonin orally prior to bedtime. The patients showed different types of sleep disorders; Patient 1 had a free-running sleep-wake cycle, and Patient 2 had a fragmented sleep pattern accompanied by screaming during the night. Both patients got to sleep within 30 min of oral administration of 5 mg melatonin. Exogenous melatonin dramatically improved the sleep-wake cycle in Patient 1. In Patient 2, exogenous melatonin showed a hypnotic effect, but early morning awakenings occurred occasionally. When melatonin treatment was stopped, the sleep disorders recurred, and re-administration of 3 mg melatonin was effective in both patients. The effect was maintained over 2 years without any adverse effects. These findings suggests that sleep disorders in patients with Rett syndrome may relate to an impaired secretion of melatonin.

Detailed information for each patient is presented below.

Patient 1 developed a free-running rhythm of the sleep-wake cycle (Figure 25-A). Neither chloral hydrate nor vitamin B12 were effective. At 4 years and 3 months of age, the circadian rhythm of serum melatonin was examined every 4 h for 48 h, and two peaks were observed during her sleep periods (Figure 26). The time of each peak was delayed 6 h compared to normal control. The values of the two peaks were 98 and 41 pg/mL, which were at the lower limit (73.5-516 pg/mL, 90% confidence

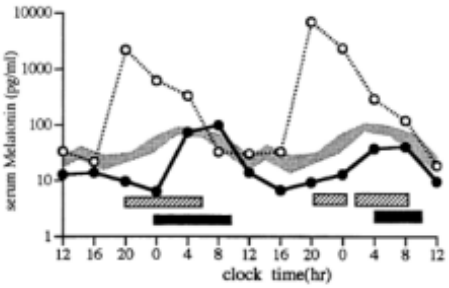
intervals for ages 3-5 years). The patient was given 5 mg melatonin orally at 19:30 h, and she got to sleep within 30 min. From the first day her sleep-wake cycle improved dramatically, and the effect continued for 2 years (Figure 25-B). Two months after melatonin treatment, the serum levels of melatonin at 30 min after the oral administration on 2 consecutive days were 2200 and 6800 pg/mL. When the melatonin treatment was stopped, delayed sleep onset occurred occasionally and 1 year after the free-running rhythm of the sleep-wake cycle recurred and the oral administration of 3 mg melatonin was effective in resetting the sleep-wake cycle. There were no remarkable adverse effects during the treatment.

Figure 25: Sleep-wake periods of Patient 1



Sleep-wake periods as observed and recorded by the mother of Patient 1 before melatonin treatment (A) and during treatment with oral melatonin, 5 mg/day (B).

Figure 26: Serum melatonin patterns in Patient 1

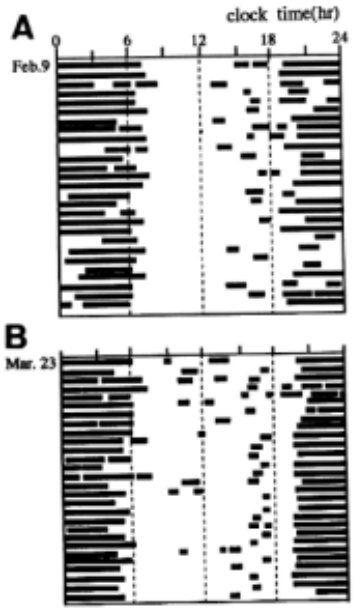


Serum melatonin pattern before (closed circle) and during (open circle) melatonin treatment in Patient 1. Oral melatonin, 5 mg administration at 19:30 h. Sleep time before (closed box) and during (stippled box) melatonin treatment. Serum melatonin levels in normal prepubertal children (shaded box).

Patient 2: Stereotyped hand movements and a fragmented sleep pattern accompanied by screaming during the night developed from 18 months of age (Figure 27-A). The patient was given 5 mg diazepam, 70 mg carbamazepine, and 0.5 mg bromocriptine, which were not effective in treating her sleep disorders. At 10 years of age, the patient's serum melatonin levels were examined every 2 h for 24 h (Figure 28). The peak time of melatonin was 02:00 h, which corresponds to that of normal prepubertal children. The peak value of melatonin was 18 pg/mL, which was at the lower limit for normal children (14.5-282 pg/mL, 90% confidence intervals for ages 9-11 years). After taking 5 mg melatonin at 20:00 h, serum melatonin levels elevated to 1400 pg/mL at 22:00 h, and 8 h later

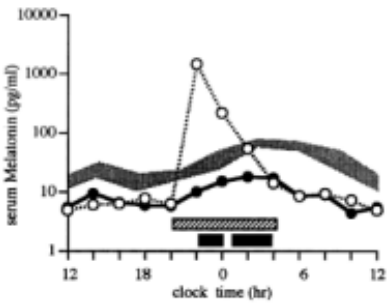
melatonin levels returned to the same levels (4-9 pg/mL) as before melatonin treatment (Figure 28). The patient slept within 30 min of melatonin administration, although she had sometimes had early morning awakenings (Figure 27-B). The dose of melatonin was increased from 5 to 10 mg, but this was not effective in treating the early morning awakenings. After the melatonin treatment was stopped, the fragmented sleep pattern recurred immediately, and 3 mg melatonin was then administered daily for 3 years without adverse effects.

Figure 27: Sleep-wake periods of Patient 2



Sleep-wake periods as observed and recorded by the mother of patient 2 before melatonin treatment (A) and durii treatment with oral melatonin, 5 mg/day (B).

Figure 28: Serum melatonin patterns in Patient 2



Serum melatonin pattern before (closed circle) and during (open circle) melatonin treatment in Patient 2. Oral melatonin, 5 mg administration at 20:00 h. Sleep time before (closed box) and during (stippled box) melatonin treatment. Serum melatonin levels in normal prepubertal children (shaded box).

Tuberous Sclerosis Complex

Sleep disturbances (maintenance of sleep/nightly awakenings)

Sleep problems are considered one of the most common behavioural manifestations in children with TSC.

Based on a survey of 300 patients with TSC, Hunt (1993) reports that the main sleep-related problems experienced by patients with TSC are settling (60%) and night waking (62%). Confidential Page 42 In a study by Bruni et al. (1995), overnight polysomnography was performed in 10 subjects with TSC and partial epilepsy in order to investigate the relationships between sleep organization, sleep disorders and epilepsy. Sleep architecture abnormalities were observed in 9 cases. Compared with 10 healthy age-matched controls, the TSC group showed a shorter total sleep time, reduced sleep efficiency, higher number of awakenings and stage transitions, increased wake after sleep onset and decreased REM sleep (Table 29). Children with seizures showed a more disrupted sleep architecture compared with seizure-free children.

Table 29: Comparison of polysomnographic variables of TSC children

	No. (age)									
	1 (10.7)	2 (16.6)	3 (13.7)	4 (14)	5 (14.5)	6 (2)	7 (15.3)	8 (3.1)	9 (17.1)	10 (3.7)
TIB (min)	491	553	378.5	379.5	462	531	688	569.5	483.5	519
TST (min)	433	342.5	334.5	356	378	319.0	537	405.5	306.5	395.5
SPT (min)	449.5	546.5	363.5	360.5	438	525.5	679.5	556.5	436.0	514
SEI (%)	88.2	61.9	88.4	93.8	81.8	60.1	79.2	71.2	63.4	76.2
SL (min)	18.5	8	15	14.5	12.5	5.5	5.5	3.5	22	5.0
# Awak	2	26	4	0	7	25	21	7	5	13
# St trans	33	64	37	58	96	57	127	36	109	63
MT (%)	1.7	12.5	2.6	1.2	2.7	7.5	3.7	1.7	0	8.9
WASO (%)	1.9	24.8	5.4	0	11	31.8	17.3	25.4	29.7	14.2
TS1 (%)	5.4	7.4	10.5	12.5	23.2	16.4	18.3	10.3	15.4	22.6
TS2 (%)	44.5	30.2	44.2	31.9	28.2	24.1	39.2	34.1	30	28.4
TSWS (%)	30	22.1	17.1	41.6	27.4	11.2	21.5	16.1	12.8	19
TREM (%)	16.5	3	20.2	12.8	7.5	9	0	12.4	12.1	7.0
REM Lat	156.5	386.5	70	72.5	129.5	134	176	47	77	179
No. of REM	5	2	5	4	2	3	0	4	4	3
PA density (%)	0	30	31	0	0	8	78	2	0	10

TIB, time in bed; TST, total sleep time; SPT, sleep period total; SEI, sleep efficiency index; SL, sleep latency; # Awak, number of awakenings; # St trans, number of stage transitions; MT, movement time; WASO, wake after sleep onset; TS1, time spent in stage 1; TS2, time spent in stage 2; TSWS, time spent in slow wave sleep; TREM, time spent in REM sleep; REM lat, Rem latency; PA, paroxysmal activity.

Disturbances of diurnal melatonin secretion

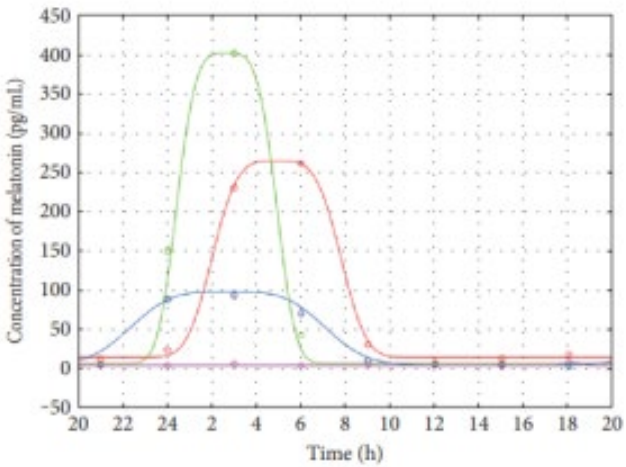
Significant differences have been reported between melatonin secretion profiles in children with TSC and controls.

Paprocka et al. (2017) examined melatonin secretion patterns in children with TSC compared with those in children with and without epilepsy. Melatonin secretion was measured every three hours using the radioimmunoassay method in children with recognized TSC. The circadian melatonin secretion rhythms in TSC children (n=4) were recorded and compared with those obtained for patients with epilepsy (n=76) and the children from the nonepileptic control group (n=36). To describe the diurnal melatonin secretion, a mathematical model was constructed and nonlinear least squares method with the Levenberg-Marquardt optimization algorithm was applied to approximate its parameters. The parameters describing the diurnal melatonin secretion, melatonin concentration, release amplitude, phase shift of melatonin release, and sleep duration in children with TSC were compared with data obtained for children with and without epilepsy. In addition, the mathematical model determined the dim light melatonin onset (DLMO) of melatonin secretion, as an important circadian marker.

The children in the TSC group were between 2 years 10 months to 6 years of age (mean age: 5 years 1.5 months). The average number of epileptic seizures a day ranged from 1-4. All TSC patients included in this study were treated for epilepsy (vigabatrin, valproic acid, and levetiracetam), and all suffered from delayed sleep onset or fragmented sleep, according to the parents' diaries.

Melatonin secretion curves were approximated for each patient separately. The melatonin profiles for the TSC patients are shown in Figure 29. The secretion patterns for the TSC patients differed markedly in release amplitudes and phase shifts of the releases.

Figure 29: Melatonin profiles for the TSC patients



Patient 1 (red line), patient 2 (green line), patient 3 (blue line), and patient 4 (magenta line). Measurement data are shown as coloured circles.

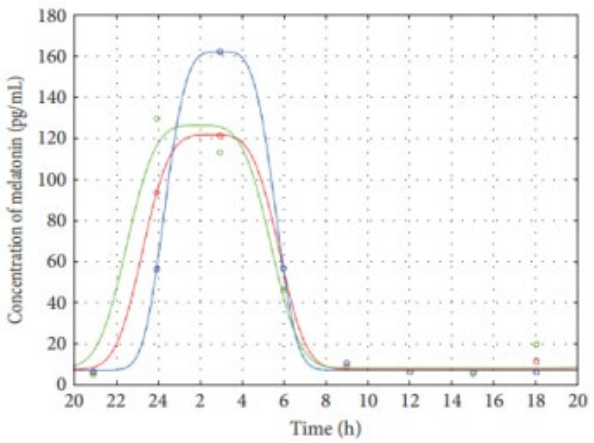
In order to compare the secretion model parameters, the median profiles were also computed for each group, consisting of the Tuberous sclerosis complex group (TSC-G), the epilepsy group (E-G), and the control group (C-G). The parameters' estimates obtained for the melatonin secretion models were subjected to statistical analysis to compare the TSC-G versus E-G group and TSC-G versus C-G group. As revealed from the Mann-Whitney-Wilcoxon tests, the secretion models' parameters for the TSC and epileptic groups did not differ statistically; however, there was a statistically significant difference between TSC-G and C-G in the following parameters: b3, DLMOon25, and DLMOon50 (Table 30). As shown in Figure 30, the melatonin synthesis was shifted in TSC-G patients.

Table 30: P-values for the Mann-Whitney-Wilcoxon tests obtained for the TSC-G and C-G comparison

Parameters	*p*
b_1—minimum melatonin concentration	0.730528
b_2—melatonin release amplitude	0.510837
b_3—phase shift of melatonin release	**0.041829**
b_4—sleep duration (FWHM)	0.551902
b_{max} given by a sum of b_1 and b_2	0.510837
$DLMOon_{25}$	**0.035919**
$DLMOoff_{25}$	0.331725
$DLMOon_{50}$	**0.022271**
$DLMOoff_{50}$	0.246655

Note: Statistically important values are in bold.

Figure 30: Average melatonin profiles for TSG-G, E-G, and C-G obtained from the medians of the parameters



TSC-G (blue line), E-G (red line), and C-G (green line)
Median data points of specific time intervals are shown as coloured circles.

The results of this study found statistically significant differences between the TSC melatonin secretion profiles and the nonepileptic control group, showing a shift in melatonin synthesis in the TSC patients.

Hancock et al. (2005) compared the melatonin excretion patterns in TSC patients with those in healthy children. 6-sulfatoxymelatonin excretion was measured in 21 healthy children without a sleep disorder and in 7 patients with TSC with sleep disorders responsive to exogenous melatonin (a 5 mg oral dose increasing total sleep time). Total excretion, cosinor percentage, and acrophase time of 6-sulfatoxymelatonin excretion were measured over a 24-hour period.

In normal children, total 6-sulfatoxymelatonin excretion ranged from 11.1 to 40.2 µg (mean 19.0 µg, SD 7.4 µg); cosinor percentage rhythm range was 52.9% to 100% (mean 87%, median 94%); and acrophase time ranged from 23 hours, 54 minutes to 10 hours, 42 minutes (mean 5 hours, 54 minutes; median 4 hours, 12 minutes). Fifth and 95th percentiles were 11.1 to 29.0 µg, 57.8% to 99.9%, and 2 hours, 1 minute to 10 hours, 4 minutes. In TSC, normal patterns of melatonin excretion were seen in responders. The authors suggest that exogenous melatonin may act by a simple sedative action, rather than correcting abnormal endogenous melatonin secretion.

Effects of exogenous melatonin on sleep

Melatonin treatment increases total sleep time and shows a trend toward decreased sleep latency in patients with TSC.

O'Callaghan et al. (1999) examined the effect of melatonin in patients with TSC and severe sleep problems. In this double-blind, placebo-controlled crossover study, 7 patients (2-28 years; median: 11 years) underwent a 2-week treatment period (5 mg melatonin or placebo) with a 1-week washout period between treatments. The patient's response during the 5-week study period was monitored by a sleep diary completed by the main caregiver. Outcome measures were total sleep time, sleep-onset time and number of awakenings during the night.

The presence of significant sleep difficulties was confirmed before recruitment by a sleep diary, completed by the patients' main caregiver over a 1-week period, which confirmed both delayed sleep onset and sleep fragmentation, and a Quine sleep-index score of greater than 6 out of 8. The sleep index focuses on four areas of difficulty: problems settling the child to sleep, nighttime waking, parental sleep loss, and frequency with which parents/carers have to attend to their child during the night. The sleep index sums the three-point scores (zero to two) for each of the four areas and gives a final score which can range from zero (no problems) to eight (severe problems in all four areas). Study treatment (melatonin or placebo) was given 20 minutes before each patient's usual bedtime.

Mean total sleep time improved in six patients while receiving melatonin (Figure 31). The mean improvement in total sleep time for the group was 0.55 hours (95% CI, 0.088 to 1.01) which, using a two-tailed t test, reached conventional levels of statistical significance (p=0.027). During melatonin treatment, mean sleep-onset time improved (i.e., decreased) in four patients, deteriorated in two, and stayed the same in one (

Figure 32). The mean improvement for the whole group was 0.39 hours (95% CI, -0.085 to 0.873); this did not quite reach conventional levels of statistical significance (p=0.079). There was no obvious trend in this group towards improvement in the mean number of awakenings per night while on immediate release melatonin: three patients showed improvement receiving melatonin, three deteriorated, and one patient was apparently unaffected (Figure 33).

Figure 31: Mean total sleep time

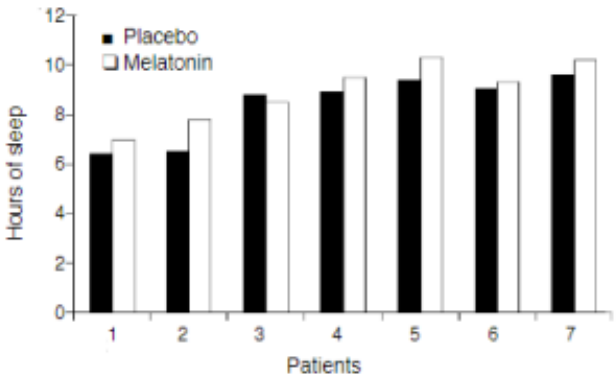


Figure 32: Mean sleep-onset time

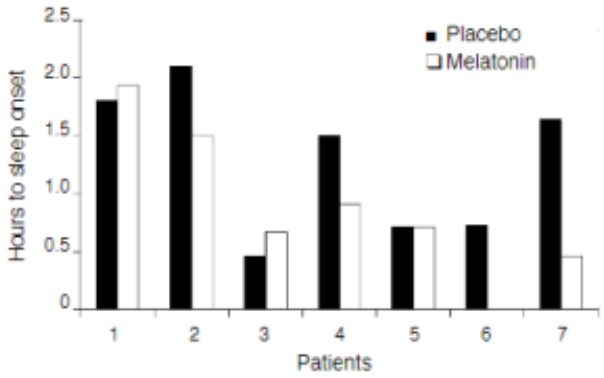
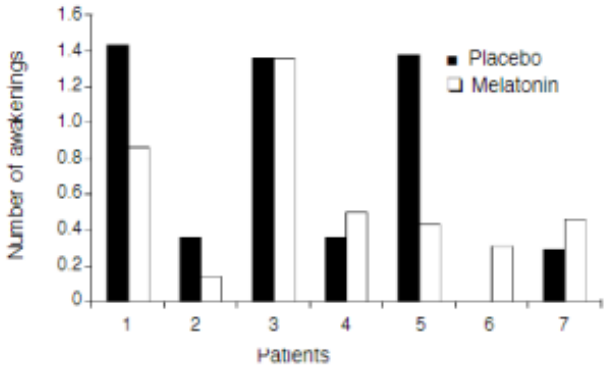


Figure 33: Mean number of awakenings



The authors conclude that melatonin has a beneficial effect in prolonging the total sleep time of patients with TSC and sleep disorder.

Williams Syndrome

Sleep disturbances (maintenance of sleep/nightly awakenings)

Sleep disorders are common in individuals with Williams syndrome (Santoro, 2014). Axelsson et al. (2013) assessed the sleep of children with Williams syndrome (n=18) compared with typically developing (TD) children (n=18) using the results of 6 questionnaires completed by parents of the children. Compared to TD children, those with Williams syndrome had shorter night sleep duration, more night wakings and more night wakefulness. Mason et al. (2011) analysed the sleep of children with Williams syndrome (n=35) compared with normal healthy controls (n=35) based on overnight polysomnography and a parental sleep questionnaire. Patients with Williams syndrome had significantly different sleep than controls, with decreased sleep efficiency, increased respiratory-related arousals, and increased slow wave sleep on overnight polysomnography. Parents rated William syndrome subjects as significantly more likely than controls to have difficulty falling asleep, restlessness and frequent and prolonged nighttime arousals.

Goldman et al. (2009) examined overnight sleep patterns in 23 adolescents and adults with Williams syndrome (age: 25.5 (8.0) years [mean (SD)]). Interviewer-administered sleep questionnaires and wrist actigraphy were used to evaluate nighttime sleep behaviours. Over 65% of participants reported awakening two or more times per night. Time in bed, documented with wrist actigraphy, averaged 9.0 (1.1) h and the average nighttime sleep duration was 7.6 (1.2) h. Williams syndrome subjects

experienced reduced sleep efficiency [74.4 (7.0)%] with prolonged sleep latency [37.7 (37.3) min], increased wake time after sleep onset [56.1 (17.6) min], and an elevated movement and fragmentation index [14.3 (4.6)]. Although individuals in the study averaged 9 h in bed at night, daytime sleepiness and measures of sleep disruption were common and comparable to those of other populations with neurodevelopmental disorders.

Sniecinska-Cooper et al. (2015) also examined sleep disturbances in children with Williams syndrome, as described below.

Disturbances of diurnal melatonin secretion

Children with Williams syndrome have a less pronounced increase in melatonin at bedtime compared to controls. Sniecinska-Cooper et al. (2015) examined the secretion of melatonin and cortisol in relation to sleep disturbances in children with Williams syndrome. The study included 25 children with Williams syndrome (WS) and 27 typically developing (TD) age- and gender-matched comparison children. Saliva was collected from each child at three time points: 4-6 pm, before natural bedtime, and after awakening. The levels of salivary melatonin and cortisol were analysed by specific enzyme-linked immunoassays. Sleep patterns were examined using actigraphy and the Children's Sleep Habit Questionnaire (CSHQ). High individual variability in the amount of melatonin secreted was observed in both groups. For the WS group, the melatonin level ranged from <0.3 to 17.40 pg/mL in the afternoon, from<0.3 to 26.47 pg/mL at bedtime, and from <0.3 to 14.71 pg/mL in the morning. In the TD group, these values were <0.3 –20.60, < 0.3–46.95 and <0.3 3–51.03 pg/mL, respectively. There was no significant difference between the groups in samples collected in the afternoon (p=0.127) and bedtime (p=0.797) (Table 31,

Figure 34). In order to investigate changes in the level of melatonin before bedtime, the ratio between bedtime and afternoon samples was calculated for each participant. There was a median-fold increase of 1.83 in the TD group; no such increase was observed in the WS (p=0.038) (Table 32 and

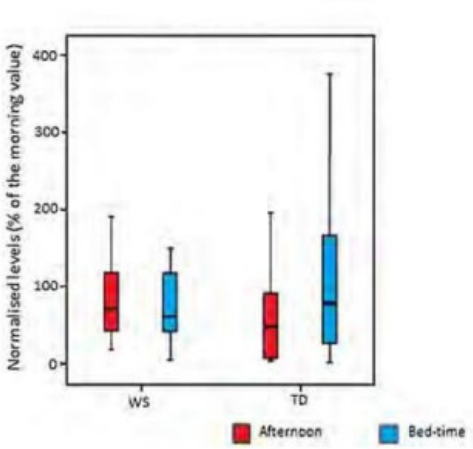
Figure 34).

Table 31: Comparison of normalized levels of melatonin in Williams syndrome (WS) and typically developing (TD) children using the Mann-Whitney test

	Groups	Median	*U* value	*P* value
Normalised melatonin afternoon (%)	TD ($n = 25$)	40.37	153.00	0.127
	WS ($n = 17$)	72.22		
Normalised melatonin bedtime (%)	TD ($n = 21$)	80.48	190.00	0.797
	WS ($n = 19$)	61.03		

Note: The U value and P value are also shown for determination of significance. The N value accounts for the differences from n=27, as some children failed to provide all three saliva samples.

Figure 34: Normalised levels of salivary melatonin in the afternoon and bedtime in children with Williams syndrome (WS) and typically developing (TD) control group



Note: Data are shown as a median and quartiles.

Table 32: Change in melatonin levels between afternoon and bedtime saliva samples collected from children with Williams syndrome (WS) and typically developing (TD)controls

	Groups	Minimum	Maximum	Median	*U* value	*P* value
Changes in melatonin levels from afternoon to bedtime	TD ($n = 20$)	0.36	10.73	1.83	102.00	0.038
	WS ($n = 17$)	0.19	2.72	0.96		

Note: The table includes minimum and maximum value, as well as median of the ratio of melatonin between afternoon and bedtime samples. The U value and P value are also shown for determination of significance. The N value accounts for the differences from n=27, as some children failed to provide all three saliva samples.

Actigraphy data were recorded from 47 (90%) of the 52 children involved in the study. In order to investigate if there were any differences between the WS and TD groups on each actigraphy, variable data were analysed using analysis of variance (ANOVA) tests. Children in the WS group showed significantly increased sleep latency, increased wake time, moving time, and sleep fragmentation in comparison with TD controls (Table 33). The outliers of over 3 standard deviations from the mean were excluded.

Table 33: Comparison of actigraphic scored in Williams syndrome (WS) and typically developing (TD) children using ANOVA

Category of actigraphic scores	TD ($n = 22$) Mean (SD)	WS ($n = 21$) Mean (SD)	*F*	*P*
Time in bed (hh:mm)	10:24 (00:31)	10:27 (00:50)	0.24	0.62
Sleep latency (hh:mm)	00:34 (00:25)	00:53 (00:29)	5.02	0.03
Actual wake time (%)	10.65 (3.07)	13.10 (4.37)	4.28	0.04
Night waking	29.02 (6.51)	28.52 (8.73)	0.04	0.84
Sleep efficiency (%)	82.55 (5.60)	78.92 (6.40)	3.63	0.06
Moving time (%)	13.59 (2.98)	17.45 (5.71)	6.92	0.01
Sleep fragmentation index	30.05 (6.71)	39.75 (13.59)	7.97	0.01

Note: The table includes mean and standard deviation (SD) corresponding to categories of actigraphic scores on the left-hand column; the F value and P value for determination of significance at 95% confidence interval ($p<0.05$) are also shown.

TD and WS group comparisons of scores on the CSHQ were made using one-way between group ANOVAs (Table 34). Based on parent responses, 15% of the children with WS had sleep problems in the past and 65% had current sleep issues, from which 23% demonstrate this problem occasionally. None of the parents of TD children responded that their child has/had sleep problems.

Table 34: Comparison of Child's Sleep Habit Questionnaire (CSHQ) scores in Williams syndrome (WS) and typically developing children (TD) using ANOVA

Subscale (possible score range)	TD ($n = 22$) Mean (SD)	WS ($n = 21$) Mean (SD)	*F*	*P*
Bedtime resistance (6–18)	6.41 (1.04)	8.02 (2.67)	8.67	0.01
Sleep onset delay (1–3)	1.56 (.80)	2.04 (.84)	4.53	0.04
Sleep duration (3–9)	3.31 (0.61)	5.23 (1.76)	25.62	<0.001
Sleep anxiety (4–12)	4.70 (1.24)	5.96 (1.90)	8.09	0.01
Night wakings (3–9)	3.89 (.85)	4.80 (1.55)	7.03	0.01
Parasomnias (7–21)	8.37 (1.60)	9.92 (1.91)	10.11	0.003
Sleep disordered breathing (3–9)	3.30 (.67)	3.44 (0.71)	0.56	0.46
Daytime sleepiness (8–24)	11.00 (2.50)	11.24 (2.65)	0.11	0.74
Total score (33–99)	40.44 (4.73)	48.08 (7.51)	19.74	<0.001

WS: n=25; TD: n=27

Note: Table includes mean, standard deviation (SD) as well as F and P value for the determination of significance at 95% confidence interval ($P < 0.05$).

It is worth noting that the subjective reporting of night awakenings by parents (Child's Sleep Habit Questionnaire) was higher for WS children compared to TD children (p=0.01). While actigraphy did not show a statistical difference in night awakenings between the two groups (p=0.84), this tool has limitations for the measurement of sleep. Actigraphy is unable to distinguish between quiet wakefulness versus sleep without movement, excessive movement in sleep versus wakefulness, and is dependent on the caretaker to mark "lights out" time and sleep offset time (Kotagal, 2024). For these reasons, the results of parent questionnaires are considered more reliable that actigraphy, and if anything, are more likely to underestimate the frequency of night awakenings.

The results of this study indicate that children with WS have a less pronounced increase in melatonin at bedtime compared to TD children. The median increase in the level of melatonin in the TD group

was 1.83-fold between afternoon and bedtime samples, whereas for the WS group no such increase was observed. The authors conclude that in children with WS a lack of a marked rise in melatonin concentrations before bedtime may play an underlying and/or contributory role in reported problems with settling down and falling asleep.

Effects of exogenous melatonin on sleep

Melatonin has been identified as the most commonly taken medication for sleep problems in WS. Studies have shown the positive benefit of melatonin for disrupted sleep in individuals with WS.

Martens et al. (2017) conducted a survey of the use and effectiveness of sleep medications in individuals with WS. The online survey asked for the age at initiation, degree of effectiveness (helpful, somewhat helpful, and not helpful), and side effects.

A total of 130/513 participants (25%) indicated that their family member with WS had taken medication to help with sleep. Melatonin was the most commonly reported medication taken for sleep, reported by 67% (n=87) of those who took any form of sleep medication. It was not noted if the melatonin was immediate or prolonged release. Melatonin had the highest helpfulness ratings, with 91% of parents reporting that it was "helpful" or "somewhat helpful" for their child with WS. In comparison, 66% of those who reported taking diphenhydramine (the second most commonly reported sleep medication) said that it was helpful or somewhat helpful. Side effects were reported by 6% (n=5) of patients taking melatonin.

Groswasser et al. (2009) reported on the circadian anomalies of two female patients (2.5 years old) with WS whose parents reported difficulty falling asleep and numerous awakenings during the night with daytime sleepiness. Based on 24 h melatonin measurements, it was determined that the patients had delayed phase melatonin secretion with the peak starting after 11 pm. Administration of melatonin, one hour before desired sleep time, improved the sleep-wake organization of these patients.

Conclusions

The beneficial clinical effects of PR melatonin on parent-reported assessments of nighttime and daytime behaviour have been demonstrated in patients with Angelman syndrome, Rett syndrome and TSC in the Circadin RTU programme. While the programme was not specifically designed to examine the effects of PR melatonin on sleep maintenance and nightly awakenings, subjective quality of sleep and child state upon awakening were assessed and improvements in both parameters were demonstrated in most patients. The data shows that patients who received whole tablets (with prolonged-release properties) were more likely to continue Circadin treatment than those who received crushed tablets (with immediate-release properties), thereby supporting the superior efficacy of PR melatonin over IR melatonin. Confidential Page 51 Overall, efficacy data for 22 patients was collected for treatment durations from 2 months to 48 months of treatment with 32.59 patient-years overall.

Published data confirm the high prevalence of sleep disorders including sleep initiation, sleep maintenance and duration, the parallel disturbance of diurnal melatonin excretion patterns in patients with Angelman syndrome, Rett syndrome, TSC and Williams syndrome, and demonstrate the positive effects of exogenous melatonin on sleep. Most of the published studies used IR melatonin mainly because of its higher availability during the time these studies were conducted – with the main consistent effect on sleep initiation and advance of the cycle. Two publications demonstrate the efficacy of CR melatonin in NDDs and the advantage of CR melatonin over IR melatonin. Moreover, the recent International Paediatric Sleep Association publication on melatonin use in managing insomnia in children with autism and other neurogenetic disorders (Smith-Magenis syndrome, Angelman

syndrome, Rett syndrome, Tuberous sclerosis complex) include recommendations that rely mainly on studies using PR melatonin (63%).

This submission also relies upon the general mechanism of action of PR melatonin. Since this mechanism is independent of the background disorder, the beneficial effects of Slenyto on sleep latency, sleep maintenance and total sleep time observed in ASD and SMS patients in the Phase III study are considered applicable to patients with Angelman syndrome, Rett syndrome, TSC and Williams syndrome as these patients also experience sleep disturbances associated with aberrant diurnal melatonin secretion patterns.

Taken together, these data support of the benefit of PR melatonin for the treatment of the sleep disturbances in children with neurogenetic syndromes, including Angelman syndrome, Rett syndrome, Tuberous sclerosis complex and Williams syndrome.

The MAH has re-analysed data from the French RTU, presenting results from patients treated with whole (=prolonged release effect) tablets separate from those with crushed (=immediate release effect) tablets. In the MAH's view, the patients with Angelman syndrome who received whole tablets (23) more often continued treatment past the first visit (10/23, 43.5%) than the patients who received crushed tablets (1/5, 20%) and had parents' reports of a better nighttime and daytime behaviour when on treatment. Treatment duration also tended to be longer when taking whole tablets. These limited data on the improved night- and daytime behaviour are considered of limited value but are somewhat supportive of a beneficial effect of prolonged release melatonin treatment in Angelman syndrome. For Rett syndrome, there were fewer patients (N=8 in total, of which 4 took whole tablets), but the tendency was the same. For Tuberous sclerosis complex, 2 patients had efficacy data and both these received whole tablets.

Published literature

Kotagal (2024): International Paediatric Sleep Association (IPSA) established a task force to provide practical guidance to clinicians on the use of melatonin for managing insomnia in children with autism and other neurogenic disorders.

The IPSA task force recommended that clinicians consider prescribing melatonin to children with autism and neurogenetic syndromes (Smith-Magenis syndrome, Angelman syndrome, Rett syndrome, and Tuberous sclerosis complex) with comorbid chronic insomnia if behavioural strategies alone have not been effective or only partially effective and coexisting medical conditions and concomitant medications such as antiepileptic drugs (e.g., felbamate) that might worsen sleep have been addressed.

Wasdell et al. (2008): An RCT on the effects of prolonged-release melatonin (5 mg) vs placebo on chronic insomnia in children with neurodevelopmental disabilities, as measured by caregivers' sleep diary and actigraph wrist watches. 51 patients aged 2-18 were enrolled with overlapping diagnoses of CP, EP, intellectual disability and ASD, and with delayed sleep phase and/or sleep maintenance difficulties. The primary endpoint total nighttime sleep (diary and actigraph recorded) was prolonged by 31 minutes ($p<0.01$) with significantly shorter bedtime sleep latency ($p<0.01$ but no effect was shown on number of nightly awakening episodes ($p=0.53$). Clinical Global Impression on improvement was significant ($p<0.01$).

Angelman syndrome

The MAH has presented a more thorough literature review of available data on melatonin secretion patterns and insomnia in children with Angelman syndrome.

Disturbances of diurnal melatonin secretion: available literature indicate that these children may suffer from either altered timing of melatonin secretion or reduced levels of melatonin with a broad variation between individuals. Importantly, in a study on 15 individuals with AS with (N=8) or without (N=7) circadian rhythm sleep disorder, the AS patients exhibited significantly lower nighttime melatonin levels than that of the controls (Takaesu et al., 2012).

Zhdanova et al. (1999) showed that a low dose 0.3 mg of IR melatonin 0.5-1 h before habitual bedtime decreased sleep latency and increased sleep duration in 13 children with AS, as measured by actigraph recordings.

Braam et al. (2008) conducted a placebo-controlled randomised study with 8 AS patients with chronic insomnia with a 4 week RCT period followed by 4 week open-label. Treatment with melatonin significantly advanced sleep onset by 28 minutes, decreased sleep latency by 32 minutes, increased total sleep time by 56 minutes and reduced the number of nights with wakes from 3.1 to 1.6 nights a week.

Takaesu et al. (2012) studied effect of 1 mg of IR melatonin in 6 AS patients with circadian rhythm sleep disorder, of which 4 had positive effects.

In summary, patients with Angelman syndrome appear to have either delayed phase melatonin release or decreased levels of melatonin. Various smaller studies report on a positive effects of IR or PR melatonin on nighttime sleep.

Rett syndrome

The MAH stated that over 80% of individuals with Rett syndrome are affected by sleep disorders.

Young et al. (2007) conducted questionnaire-based surveys in the years of 2000, 2002 and 2004, where carers or parents of 237 patients with Rett syndrome were asked about sleep problems. Of the 237 cases, 131 (55%) had questionnaires completed for all three years. The most commonly reported specific sleep problems in 2004 were laughing and teeth grinding (prevalences 58.9% and 55.0% respectively), followed by screaming and seizures (prevalences 35.6% and 26.2%, respectively). Frequent daytime napping was reported in over 77% of cases and long spells of night screaming in 36% of cases. Awakenings at night were reported for 54% of the younger children (0-7 years old).

Regarding disturbances of diurnal melatonin secretion, this has only been studied in two patients, showing a free-running rhythm in patient 1 and a fragmented sleep pattern accompanied by night screaming in patient 2 (Miyamoto et al., 1999). Both had positive effects of melatonin on sleep.

Regarding effects of exogenous melatonin on sleep, the study by McArthur and Budden (1998) has already been presented in the original submission, in which 9 girls with Rett syndrome showed reduced sleep latency from 32 min to 19 min with IR melatonin treatment at 2.5 to 7.5 mg.

In summary, patients with Rett syndrome are reported to have a broad range of sleep disturbances, of which night awakenings were reported by more than half. Scarce data indicate positive effects of melatonin treatment.

Tuberous sclerosis complex (TSC)

The MAH stated that sleep problems are common in patients with tuberous sclerosis complex.

Hunt (1993) reports from a survey of 300 patients with TSC that sleep latency (60%) and night waking (62%) are the most common.

Regarding disturbances of diurnal melatonin secretion, Paprocka et al. (2017) compared melatonin secretion patterns in 4 children with TSC to children with epilepsy and a healthy control group, showing

a delayed melatonin peak in children with TSC compared to the other groups. Hancock et al. (2005) compared the melatonin excretion patterns in 7 TSC patients with those in 21 healthy children. In tuberous sclerosis, normal patterns of melatonin excretion were seen.

Regarding effects of exogenous melatonin on sleep, O'Callaghan et al. (1999) examined the effect of melatonin in patients with TSC and severe sleep problems in a 5-week placebo-controlled crossover study. 7 TSC patients received IR melatonin at a 5 mg dose for 2 weeks, wash-out for 1 week, followed by 2 weeks of placebo. Melatonin increased total sleep time by 33 min (p=0.027), the effects on sleep latency were variable with a mean of 23.4 min (p=0.079). No effects on night awakenings.

In summary, inconclusive results are reported on melatonin secretion patterns in TSC. The beneficial effects of IR melatonin are suggested to be due to its sedative effects.

Williams syndrome

The MAH stated that sleep problems are common in individuals with Williams syndrome.

Xelsson et al. (2013) assessed the sleep of children with Williams syndrome (n=18) compared with healthy children (n=18) using questionnaires completed by the parents. Children with Williams syndrome had shorter night sleep duration, more night wakings and more night wakefulness.

Mason et al. (2011) analysed the sleep of children with Williams syndrome (n=35) compared with normal healthy controls (n=35) based on overnight polysomnography and a parental sleep questionnaire. Patients with Williams syndrome had decreased sleep efficiency, increased respiratory-related arousals, and increased slow wave sleep on overnight polysomnography.

Goldman et al. (2009) examined overnight sleep patterns in 23 adolescents and adults with Williams syndrome, using interviewer-administered sleep questionnaires and wrist actigraphy. Time in bed averaged 9.0 (1.1) h and the average nighttime sleep duration was 7.6 (1.2) h. Daytime sleepiness and measures of sleep disruption were common.

Sniecinska-Cooper et al. (2015) using actigraph data and a sleep habit questionnaire, found a prolonged sleep latency, more night wakings, parasomnias and a shorter sleep duration in 25 children with Williams syndrome compared to 27 healthy controls.

Regarding disturbances of diurnal melatonin secretion, Sniecinska-Cooper et al. (2015) examined the secretion of melatonin and cortisol in relation to sleep disturbances in 25 children with Williams syndrome and 27 healthy controls, using saliva collections. They found that children with Williams syndrome have a less pronounced increase in melatonin at bedtime compared to controls.

Regarding effects of exogenous melatonin on sleep, Martens et al. (2017) conducted a survey of the use and effectiveness of sleep medications in individuals with WS. 130 of 513 participants answered that their family member with WS had taken sleep medication, which in 67% of cases was melatonin. 91% of parents reported that melatonin was helpful.

Grosswasser et al. (2009) reported on 24 h melatonin measurements in 2 patients with WS showing a delayed phase melatonin secretion and alleviation of sleep problems with administration of melatonin 1 h before bedtime.

In summary, the results from a few studies are indicative of a less pronounced increase in melatonin at bedtime, possibly related to a delayed phase melatonin secretion, and sleep disturbances treatable by melatonin.

2.4.2. Discussion on clinical efficacy

This application concerns the extension of indication of Slenyto to treat insomnia in children and adolescents aged 2-18 with neurodevelopmental disorders associated with neurogenetic disorders including Angelman syndrome, Rett syndrome, Tuberous sclerosis complex and Williams syndrome, where sleep hygiene measures have been insufficient.

Slenyto is a paediatric prolonged release melatonin formulation, indicated for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.

Prolonged release formulation of the Slenyto proved advantage on maintenance of sleep and sleep latency based on the results of study NEU CH_7911, submitted during the initial marketing authorisation (paediatric use marketing authorisation; PUMA).

During the initial marketing authorisation, the originally planned population of patients with neurogenetic disease was narrowed to only patients with SMS as into the pivotal Phase III study no patients with Angelman syndrome, Rett syndrome, Tuberous sclerosis complex and Williams syndrome were included.

To support this present application, the MAH has discussed a literature on the disturbance of melatonin concentration in patients with Angelman syndrome, Rett syndrome, tuberous sclerosis complex and Williams syndrome, and data on clinical efficacy and safety after administration of melatonin (especially in the IR form), if available. Most of the publications were already submitted during initial marketing authorization, except of the publications of the authors Tascini G at all, Front Neurol. 2022; 13: 817195 and Takaesu Y at all, 2012.

The MAH presented data from a French RTU including children with ASD, Smith-Magenis syndrome, Angelman syndrome, Rett syndrome and Tuberous sclerosis syndrome. This Compassionate use programme was an open-label, single-armed study. The patients were not treatment naïve to melatonin. There was a large drop-out from the study during the follow-up period with few children in the Angelman syndrome, Rett syndrome and Tuberous sclerosis syndrome subgroups staying in the study for longer than 12 months. The sleep-related endpoint was based upon assessment at every study visit at 6 months' intervals, asking questions to the parent on the child's quality of sleep (very good, good, fair, poor, very poor) and the child's state upon waking (fully alert, alert, fair, tired, very tired). Changes compared to baseline in the quality of sleep and the child's state upon waking were assessed at each visit (improvement, unchanged, deterioration). This endpoint is considered weak in comparison to the endpoint used in the original pivotal study for Slenyto, using sleep diary to analyse sleep latency in the evening and longest sleep period during the night. The subgroup analyses for Angelman syndrome (N=7), Rett syndrome (N=6) and Tuberous sclerosis complex (N=1) include very few patients, of which even fewer were still in the RTU after the initial 6 months' study period (4, 3, 1, respectively) not enabling any conclusions of the effects of Circadin treatment on the children's sleep quality and state upon wakening.

The data from the RTU study are based on Circadin tablets and not the Slenyto mini-tablets, but a comparative bioavailability study has demonstrated that Circadin tablets have a similar pharmacokinetic profile compared to Slenyto mini-tablets.

It seems that an RTU program for Slenyto 1 and 5 mg is currently ongoing in France, according to information from ANSM webpage (Actualité - Décision du 26/03/2021 - Recommandation temporaire d'utilisation (RTU) du médicament Slenyto 1 mg / 5 mg, comprimé à libération prolongée - ANSM (sante.fr)). The MAH was invited to provide additional information regarding the RTU program Slenyto 1 and 5 mg since this program is relevant for this application. Data available after this program is

finished could be more appropriate as supportive data since the same formulation (i.e. Slenyto) is administered.

In addition, the MAH has presented literature data on sleep disturbances in patients with Williams syndrome and followingly proposes to include all these neurogenetic disorders in the indication text for Slenyto.

The literature summary of sleep disturbances in children with Angelman syndrome, Rett syndrome, Tuberous sclerosis syndrome and Williams syndrome together with the established effects of short-acting melatonin on sleep induction and prolonged -release melatonin on sleep maintenance in general are indicative of beneficial effects in children and adolescents with all kinds of neurogenetic disorders with insomnia, especially the type of insomnia with nightly awakenings, where sleep hygiene measures have been insufficient. Although the effects of prolonged -release melatonin are primarily understood to be beneficial in subjects with abnormal circadian rhythm related to aberrant diurnal melatonin secretion, this has not been sufficiently supported for the neurogenetic disorders applied for in the current variation.

The mechanism of action of prolonged -release melatonin such as Circadin or Slenyto is to increase sleep quality throughout the night in individuals with a low melatonin secretion during nighttime. The mechanism of prolonged-release melatonin is independent of background disorder. A disturbed diurnal melatonin secretion curve is common in various neurogenetic disorders. Sleep problems is one of the major concerns when caring for children with neurogenetic disorders and if these may be alleviated, the quality of life of the child and its caregivers may increase.

The results from the open-label single armed French RTU with low retention rates for the small number of treated patients with Angelman syndrome, Rett syndrome, Tuberous sclerosis complex does not allow conclusions on the benefit of the prolonged-release formulation of melatonin to treat the sleep problems in these patients. The MAH has briefly summarised the field of knowledge on disturbances of diurnal melatonin excretion patterns for these neurogenetic disorders and published clinical data on the effects of IR melatonin. The initially submitted data were considered insufficient to support the efficacy of Slenyto on insomnia in all these neurogenetic syndromes (Angelman syndrome, Rett syndrome, Tuberous sclerosis complex and Williams syndrome).

Taken together, the data is scarce, and most studies used IR melatonin instead of PR melatonin.

However, the positive effects of IR melatonin are already well characterised to primarily shorten bedtime sleep latency due to its sedative effects and lead to earlier sleep onset time due to its effects on diurnal rhythm. PR melatonin may normalise nighttime melatonin levels in children with insufficient nighttime endogenous melatonin secretion, which clinically leads to a reduced number of awakenings during the night and possible longer total sleep time and shorter bedtime sleep latency.

In the CHMP's opinion, the most important information provided is that the mechanism of action of prolonged release melatonin on sleep latency, sleep maintenance and total sleep time is independent of the background disorder. This implies that any patient with a neurodevelopmental or neurogenetic disorder with sleep disturbances associated with aberrant diurnal melatonin secretion patterns and/or insufficient nighttime melatonin secretion will benefit from PR melatonin. The CHMP recommended a broader indication with neurogenetic disorders with sleep disturbances associated with aberrant diurnal melatonin secretion patterns instead of listing specific neurogenetic disorders in the indication text. Melatonin has been extensively used over many years for children with sleep disturbances and is considered safe for this patient population. The benefit-risk balance of PR melatonin for the patient population in question is considered favourable in comparison to all other on label or off-label used insomnia medications commonly used in children.

2.4.3. Conclusions on the clinical efficacy

The MAH presented published data on sleep disturbances in the neurogenetic disorders Angelman syndrome, Rett syndrome, Tuberous sclerosis complex, and Williams syndrome. Although these data are scarce, related to the rareness of each disorder, the totality of data indicate that these children suffer from sleep disturbances and diurnal melatonin secretion is disturbed. It is accepted to broaden the indication to allow treatment with Slenyto for children with neurogenetic disorders with known diurnal disturbances of melatonin release (i.e. insufficient levels of nighttime melatonin release) clinically characterised by bedtime insomnia and nightly awakenings. However, in the CHMP's opinion, the indication should not list these specific neurogenetic disorders, since children with other neurogenetic disorders and insufficient levels of nighttime melatonin should not be excluded from the indication. Rather, it is preferred that the indication is broadened to include "neurogenetic disorders with aberrant diurnal melatonin release and /or nocturnal awakenings" or similar wording. This proposal was accepted by the MAH.

2.5. Clinical safety

The clinical safety data for this RTU study have already been submitted and assessed in procedure EMEA/H/C/004425/REC/002.2. This procedure was a post-authorisation measure (PAM) assessed by PRAC in 2022.

The MAH submitted the Annual report no. 6, version dated 29 March 2022, with data collected from 1st October 2015 to 1st October 2021, of the French Temporary Recommendation for Use (RTU) – *Follow-up protocol for children 6 to 18 years old treated with Circadin for a circadian rhythm sleep disorder associated with Rett syndrome, Smith-Magenis syndrome, Angelman syndrome, tuberous sclerosis, or autism spectrum disorders.*

During the period studied, ranging from 1st October 2015 to 1st October 2021, 1,100 patients were enrolled, 1,038 of whom were effectively treated with Circadin, and 926 of those patients made up the eligible population.

The conclusion on the review of the submitted report by the PRAC was that the AEs reported were overall consistent with the safety profile of Circadin, which is authorised for adults. Furthermore, it was concluded that safety concern "Delay of sexual maturation and development" could be removed from the RMP of Slenyto.

Summary of safety data from the French RTU

Exposure

Melatonin was administered to 35 patients (3.8%) with Smith- Magenis syndrome (SMS), 29 patients (3.1%) with Angelman syndrome (AS), 15 patients (1.6%) with Rett syndrome (RS), and 8 patients (0.9%) with tuberous sclerosis complex.

Table 35: Patients exposed to Circadin treatment by patient condition and study period – Circadin RTU Programme (modified eligible population)

	Patient Condition					
Study Period	**Autism spectrum disorder**	**Smith-Magenis syndrome**	**Angelman syndrome**	**Rett syndrome**	**Tuberous sclerosis**	**Total**
P1	274	13	7	6	1	301

P2	110	9	4	3	1	127
P3	72	3	6	2	0	83
P4	49	1	2	2	0	54
P5	25	2	1	1	0	29
P6	13	0	2	1	0	16
P7	5	0	1	1	0	7
P8	6	0	1	0	0	7
P9	2	1	0	0	0	3

Safety results

A total of 43 non-serious adverse events (AEs) were reported, belonging to the following System Organ Classes (SOC):

- Psychiatric disorders (17),
- Nervous system disorders (9),
- General disorders and administration site conditions (7),
- Gastrointestinal disorders (6),
- Skin and subcutaneous tissue disorders (2),
- Cardiac disorders (1),
- Nutrition and metabolism disorders (1).

These adverse events were reported in patients 6 to 17 years of age, including 26 who had autism spectrum disorders, 3 who had Smith-Magenis syndrome and 2 who had Angelman syndrome.

One SAE in a patient with Angelman syndrome and epilepsy, who experienced a status epilepticus, considered unrelated to treatment with Circadin.

Adverse events leading to discontinuation of Circadin treatment (n = 9) consisted of three cases of drowsiness, one case of drowsiness with fatigue, one of diarrhoea with abdominal pain, one case of nausea, and one case of agitation with hyperphagia, panic attacks, and nocturnal awakenings, one case of tachycardia, and one case of mood disturbance.

According to the Annual RTU report 6, adverse events were reported in patients 6 to 17 years of age (at the time the age was reported), including 3 who had Smith-Magenis syndrome (agitation, nocturnal awakenings, drug interaction, lack of efficacy; fatigue, nocturnal awakenings) and 2 who had Angelman syndrome (status epilepticus, fatigue)

One serious adverse event was reported in the follow-up for the Circadin RTU. It involved a 6-year-old patient with Angelman syndrome (most of the children who suffer this have recurrent epileptic seizures) treated with levetiracetam (anticonvulsant), and who experienced status epilepticus several months after the introduction of Circadin. Corrective treatment with clonazepam was administered to the patient and his Circadin treatment was discontinued between the summer and fall of that year. The treatment was then reintroduced and well tolerated; the patient was doing well at the next follow-up visit. The causality between the use of Circadin and the occurrence of the event was considered to be unrelated.

No adverse events were reported in patients with Rett syndrome or Tuberous sclerosis complex. No information on Williams syndrome was found.

According to CPC Annual report, Slenyto was prescribed to an 11-year-old female patient with RETT syndrome associated with sleep/wake rhythm disorders. Slenyto was prescribed for sleep disturbances present for more than 3 months. No adverse event was reported.

McArthur and Budden, 1998 - Nine girls with Rett syndrome (mean age: 10.1 years) underwent a 4-week treatment period (melatonin or placebo). Authors stated that no adverse side effects were detected, yet long-term effects of chronic melatonin use in paediatric patients were unknown at this time.

Post-marketing

Post-marketing data are available for Slenyto for the period of 2019 to 2023. The post-marketing data include 60 reports associated with alternative (off-label) indications. Cases include patients 1.5-49 years of age with sleep disorders associated with Angelman syndrome, communication disorder, developmental delay, intellectual disability, language disorder, neurodevelopment disorder, Rett syndrome, speech development disorder and tuberous sclerosis complex. Most patients did not report any adverse events.

Angelman syndrome

4 cases with an underlying history of Angelman syndrome have been received since the first authorization of Slenyto. 2 of these cases reported adverse events including 1 paediatric patient (nocturnal agitation, Slenyto was discontinued after 3 days, and the nocturnal agitation resolved the following day). Agitation is listed ADR for ASD and neurogenetic children.

Rett syndrome

8 cases with an underlying history of Rett syndrome have been received since the first authorization of the product. 2 of these cases reported adverse events, including 1 case in a paediatric patient (– difficulty swallowing - it is unclear whether the swallowing difficulty originated with the patient or with the tablet. The patient required a nasogastric tube for administration of some treatments in history.

Tuberous sclerosis complex

One case with an underlying history of Tuberous sclerosis complex has been received since the first authorization of the product. The case did not report any adverse events.

2.5.1. Discussion on clinical safety

The safety data from the French RTU has already been assessed in the PAM submitted in 2022. In the PAM, the safety profile of Slenyto/Circadin in children with children 6 to 18 years old with a circadian rhythm sleep disorder associated with Rett syndrome, Smith-Magenis syndrome, Angelman syndrome, tuberous sclerosis, or autism spectrum disorders was concluded to be consistent with the safety profile of Circadin in adults.

No new risks have been identified in the treatment of patients with Angelman syndrome, Rett syndrome or Tuberous sclerosis complex. No data associated with the treatment of patients with Williams syndrome was provided.

2.5.2. Conclusions on clinical safety

No new risks have been identified in the treatment of patients with Angelman syndrome, Rett syndrome or Tuberous sclerosis complex with Slenyto. The data on long-term safety of prolonged release melatonin (Slenyto/Circadin) collected in the French RTU in children with Rett syndrome, Angelman syndrome and Tuberous sclerosis complex is consistent with the safety profile of Circadin in adults.

PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version (version 2.0) with this application to reflect the new indication.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 is acceptable.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a result of this variation, sections 4.1 and 4.8 of the SmPC are being updated. In 4.1 to extend the indication to include children with neurogenetic disorders and 4.8 where the number of children exposed to Circadin is updated. The Package Leaflet (PL) is updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Paediatric insomnia in children and adolescents is a widespread problem. The prevalence of paediatric insomnia in children that goes beyond bedtime refusal and night awakenings ranges from 1% to 6% in the paediatric general population.

In children with neurodevelopmental or psychiatric comorbidities it is as high as 50–75%. This group of children is composed of many subpopulations with varying degrees of impairment and symptomatology, including pervasive developmental disorders (including ASD, Rett's disorder, childhood disintegrative disorder, Asperger's disorder, etc); ADHD; genetic disorders, such as Angelman syndrome; and chronic neurologic disorders, such as epilepsy and Tourette's disorder. Recent studies suggest that the prevalence of sleep disorders in children with developmental disabilities ranges from 25% to 86%, and that these sleep disorders are frequently chronic, characterised by difficulties initiating or staying asleep, and usually far more difficult to treat than their normally developing peers.

3.1.2. Available therapies and unmet medical need

The most commonly prescribed sleep medications to children are IR melatonin, Circadin, or Slenyto. In addition, antihistamines, alpha-adrenergic agonists, antidepressants, antipsychotics, benzodiazapines, and "Z-drugs" (zaleplon and zolpidem) may be used to treat insomnia. Most of these medications are being used for their sedative adverse effects rather than for primary effects on sleep/wake mechanisms or hyperarousal.

Circadin, approved for insomnia in adults, is primarily a prolonged -release formulation of melatonin appropriate for use in adults due to its size (round, with a diameter of 8 mm). Slenyto was approved for insomnia in children with ASD and Smith-Magenis syndrome in 2017, based on a 13-week placebo-controlled double-blind randomised study in children with ASD and neurogenetic disease using 1 mg mini-tablets of Melatonin-Neurim at the 2 mg and 5 mg doses. The patient population was children aged 2-17.5 years with ASD or neurogenetic disease (in total 4 patients with Smith-Magenis Syndrome) who suffered from sleep induction and/or sleep maintenance problems and whose sleep problems had not been sufficiently ameliorated by sleep hygiene measures. A significant increase in total sleep time (+32 min, p=0.034) and a shortened sleep latency (-25 min, p=0.011) as measured by sleep diary were seen compared to placebo. The secondary endpoints Number of awakenings per night (p= 0.474) and Wake time after sleep onset (p=0.981) were not significantly affected.

3.1.3. Main clinical studies

Efficacy and safety data have been collected in ASD and neurogenetic children treated with 2-6 mg of the adult melatonin prolonged-release formulation under a RTU program in France. The study enrolled a total of 926 eligible children aged between 6-18 years old, including 839 with ASD (90.6%), 35 with Smith-Magenis syndrome (3.8%), 29 with Angelman syndrome (3.1%), 15 with Rett syndrome (1.6%), and 8 with Tuberous sclerosis complex (0.9%).

Most of the children had already received at least one treatment for their sleep disorder (71.4%), mainly melatonin immediate release (IR) (81.6%). Due to the size of the Circadin tablet, the RTU study was limited to children over 6 years of age.

3.2. Favourable effects

The efficacy of Circadin treatment was evaluated at each 6-month interval clinic visit up to 55 months follow-up, based on the child's quality of sleep (very good, good, fair, poor, very poor) and the child's state upon waking (fully alert, alert, fair, tired, very tired). Changes compared to baseline in the quality of sleep and the child's state upon waking were assessed at each visit (improvement, unchanged, deterioration).

For the whole study population, follow-up data was available for 43.8% of patients. For these, the child's quality of sleep and state upon waking improved in the first 6 months of follow-up compared to baseline for 78.3% and 64.1% of patients, respectively. Follow-up data was available for very few of the patients in the subgroups of interest: Angelman syndrome (N=7), Rett syndrome (N=6), Tuberous sclerosis complex (N=1). It may be concluded that only improvement of unchaged status was reported and none reported deterioration of quality of sleep and state upon awakening.

In addition, the MAH provided a short summary of available literature data on the sleep disturbances and diurnal melatonin secretion profile of children with Angelman syndrome, Rett syndrome, Tuberous sclerosis complex, and Williams syndrome.

3.3. Uncertainties and limitations about favourable effects

The RTU was an open-label, single-armed study, the results from the RTU are only reported from a minority of the enrolled patients with Angelman syndrome, Rett syndrome and Tuberous sclerosis complex in the RTU and the retention in the study was poor. Due to the size of the Circadin tablet, the RTU study was limited to children over 6 years of age. Since some patients were unable to swallow tablets whole, patients took crushed or halved tablets, so the benefit of the prolonged-release formulation was negatively affected in these patients. The effects of Circadin on sleep were collected using parent-reported outcomes on sleep quality and state upon waking for 6-month intervals, which is considered of low quality. Other data submitted, literature references and Slenyto Compassionate Prescribing Framework, by themselves, are insufficient to demonstrate benefit of the Slenyto treatment in the newly proposed target population, and are considered supportive only.

3.4. Unfavourable effects

Safety data from the RTU study has already been assessed in a previous procedure and is not included in the present procedure.

3.5. Uncertainties and limitations about unfavourable effects

N/A

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

During the original approval procedure for Slenyto, the MAH applied for the indication "Treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Neurogenetic disorders, where sleep hygiene measures have been insufficient."

The benefit/risk balance was considered to be positive in children with ASD. With respect to neurogenetic disorders, a few patients with Smith-Magenis syndrome (and no patients with other neurogenetic syndromes) were included in the pivotal study. Considering that Smith-Magenis syndrome has a strong mechanistic rationale for prolonged-release melatonin treatment with their inverse melatonin diurnal profile of low levels during night and high during day, Smith-Magenis syndrome was included in the therapeutic indication while other neurogentic disorders were not.

The results from the open-label single armed French RTU with low retention rates for the small number of treated patients with Angelman syndrome, Rett syndrome, Tuberous sclerosis complex does not allow conclusions on the benefit of the prolonged-release formulation of melatonin to treat the sleep problems in these patients. However, The MAH has summarised the field of knowledge on disturbances of diurnal melatonin excretion patterns for these neurogenetic disorders and published clinical data on the effects on sleep of IR melatonin, and in some cases also prolonged-release melatonin, in subjects with these disorders. The mechanism of action of prolonged release melatonin on sleep latency, sleep maintenance and total sleep time is independent of the background disorder. This implies that any patient with a neurodevelopmental or neurogenetic disorder with sleep disturbances associated with aberrant diurnal melatonin secretion patterns and/or insufficient nighttime melatonin secretion may benefit from prolonged-release melatonin. Thus, based on the well-known general effects of melatonin on sleep and the diurnal sleep-wake cycle and the specific effects of prolonged release melatonin in mimicking release of endogenous melatonin during nighttime, it is reasonable to extrapolate the effects of prolonged-release melatonin from the approved indications ASD and Smith-Magenis syndrome to all neurogenetic disorders with a disturbance of the diurnal melatonin secretion and /or nocturnal awakenings.

3.6.2. Balance of benefits and risks

The benefits of Slenyto outweigh the risk in the discussed population.

3.7. Conclusions

The overall B/R of Slenyto for treatment of patients with neurogenetic disorders with a disturbance of the diurnal melatonin secretion and /or nocturnal awakenings is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of neurogenetic disorders (e.g., Angelman syndrome, Rett syndrome, Tuberous sclerosis complex and Williams syndrome) for SLENYTO, based on Phase III study NEU_CH_7911, post-marketing data and literature; As a consequence, sections 4.1 and 4.8 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Slenyto-H-C-Product Number-II-25'

Attachments

SmPC, Labelling and Package Leaflet (changes highlighted) Slenyto 1 mg prolonged release tablets as a relevant example with changes highlighted as adopted by the CHMP on 25 July 2024.

Appendix

1. CHMP AR on 1 year extension of market protection.