Evaluating the Effectiveness of a Digital Therapeutic (*somnovia*) for people with insomnia disorder - a randomized controlled trial

Clinical investigation report following ISO 14155:2020

Investigational device

somnovia

Study design

- pragmatic
- randomized (simple randomization)
- controlled (two arms)
- online

Study population

290 patients with insomnia disorder, aged 18 and above, who reported at least moderately impaired quality of sleep

Statement

This clinical investigation was performed in accordance with ISO 14155:2020 and the ethical principles in the Declaration of Helsinki.

Sponsor

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Study registration number

ClinicalTrials.gov ID: NCT05558865

Date

26.07.2024

Version

6.0

Summary of the revision history

Version	Date	Changes
2	09.01.2024	• Details on diagnoses relevant for inclusion were added (Chapter 4.7). • Figure 1 was updated. • Dropout reasons were differentiated by study

Version	Date	Changes
		group and time point (Chapters 5.4.2 and 5.4.3). ● Table 1 was updated (age in age groups and sick days added). ● Table 4 was updated (age in age groups and sick days added). ● Analyses of usage data were added (Chapters 5.4.4 and 5.7.2). ● Results for “Responder Rate of insomnia symptoms” and “Remission Rate of insomnia symptoms” were presented in tabular form (Table 12 and Table 13 Chapter 5.7.2). ● Data on user satisfaction (ZUF-8) were added (Chapter 5.7.2). ● Baseline-adjusted means derived from the ANCOVA model were added for analyses of the primary and secondary endpoints (Tables 17-20 in the Appendix).
3	27.02.2024	● Details on diagnoses relevant for inclusion were added (Chapter 4.7). ● Baseline data were described more comprehensively in text form (Chapter 5.5). ● Table 1 was updated (diagnostic categories added). ● Table 4 was updated (diagnostic categories added). ● Responder analyses were expanded to include the proportion of patients who demonstrated a deterioration in the investigated endpoints from baseline to T1 and the proportion of patients whose status did not change (Chapter 5.7). ● Results from the responder analysis of the primary endpoint were presented as a Sankey Diagram (Figure 3 in Chapter 5.7). ● Details on and results from the per protocol analyses were added (Chapters 4.11, 5.4.5 and Tables 7-10 in Chapter 5.7). ● Partial η^2 of the treatment effect from the ANCOVA was added for the primary and secondary endpoints (Tables 7-10 in Chapter 5.7). ● Results from the exploratory moderation analyses were added (Chapter 5.10). ● Results of an additional responder analysis (50% improvement from baseline) was added for the WSAS (Chapter 5.7.2).
4	15.03.2024	● A summary of the revision history was added. ● The information on the recruitment period was updated to only include dates for “First Patient

Version	Date	Changes
		First Visit" and "Last Patient Last Visit" (Chapters 1.5, 1.8, 1.9, 5.1 and 5.2). ● The sample size of the respective analysis populations were added (Tables 8-11 in Chapter 5.7 and Tables 14-17 in Chapter 5.9.1). ● A depiction of newly initiated pharmacotherapies and other therapies during the observation period was added (Table 7 in Chapter 5.5). ● Degrees of freedom and *F* values were added for the ANCOVA of the primary and secondary endpoints (Tables 8-11 in Chapter 5.7). ● The presentation of the Sankey Diagram was updated. Separate diagrams were added for the intervention and control group (Figures 2 and 3 in Chapter 5.7.2).
5	03.05.2024	● Details on the confirmation of the diagnosis chronic insomnia were added (Chapter 4.7). ● Details on the statistical design were added (Chapter 4.11). ● Responder analyses for the ITT population were added (Chapter 5.7 and Table 12). ● A discussion of the results within the context of the evidence of already listed DiGAs in the same indication was added (Chapter 6.3).
6	26.07.2024	● Results of subgroup analyses based on use of treatment during the course of the study, and their discussion, were added (Chapter 5.9.1 and Chapter 6.3).

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1. Summary

1.1 Title of the clinical investigation

Evaluating the Effectiveness of a Digital Therapeutic (*somnovia*) for people with insomnia disorder - a randomized controlled trial

1.2 Introduction

Sleep plays a crucial role in the regeneration of psychological and physiological processes and functions. Therefore, disruption of healthy sleep patterns can have enormous negative effects on mental and physical well-being [1], [2], [3], [4], [5]. Insomnia affects a large proportion of the population and is one of the most common medical complaints [6]. In Germany, one third of adults report sleep problems within 4 weeks [1]. Persistent poor sleep can develop into chronic insomnia affecting almost 6% of the German population [1]. Chronic insomnia is characterized by dissatisfaction with sleep duration or quality and difficulties in initiating or maintaining sleep, symptoms that are associated with significant distress and deficits in daytime functioning [6].

Chronic insomnia is associated with a variety of other mental and physical health disorders [2], [5]. People with sleep patterns that deviate from the “norm” have increased mortality, likely due to the association with overweight, obesity, and hypertension [1], [2], [3]. In addition, insomnia is a symptom and risk factor for depression, increasing the risk twofold [7]. Overall, the reduced quality of life and occupational performance caused by insomnia places a great burden on individuals and society [6].

Cognitive behavioral therapy for insomnia (CBT-I) is the therapy with the highest level of recommendation in the European guideline for the treatment of insomnia [8], and clinical trials comparing insomnia medications with CBT-I suggest that CBT-I leads to better sleep quality with fewer side effects in the long term [9], [10], [11]. However, access to CBT-I treatment is not readily available for all people affected by chronic insomnia. Only a minority of patients are referred to CBT-I therapists, and the availability of professionals is very limited [8], [12]. CBT-I, administered digitally as a low-threshold therapeutic approach, for example via digital health apps (DiGAs) to address this gap, has been shown to be acceptable and effective in previous studies [13], [14], [15], [16], [17]. DiGAs provide flexible, cost-effective access to mental health care and can evoke a sense of empowerment in patients [18], [19], [20].

The aim of the randomized controlled trial (RCT) presented here was to examine the effectiveness of the self-guided, Internet-based intervention program *somnovia* when used adjunctively to treatment-as-usual (TAU) compared to TAU only.

1.3 Purpose of the clinical investigation

The purpose of this clinical investigation was to assess the effectiveness of the self-guided digital health application *somnovia* in adult patients with insomnia disorder in terms of improving insomnia symptoms.

1.4 Description of the clinical investigation population

The study population consisted of adult patients with insomnia disorder who reported at least moderately impaired quality of sleep.

1.5 Clinical investigation method

Recruitment of patients was through an online campaign. Participants were then routed to a linked study website providing information about the trial and details about participation. First Patient First Visit was on 2022-11-08 and Last Patient Last Visit was on 2023-09-18.

1.6 Results of the clinical investigation

1.6.1 Primary endpoint

The intent-to-treat (ITT) analysis showed that after 3 months of using *somnovia*, patients in the TAU + *somnovia* intervention group had lower levels of insomnia symptoms than patients in the TAU-only control group: the estimated baseline-adjusted difference between the groups after 3 months was -3.3 points on the Insomnia Severity Index [ISI] total score (95% CI = [-4.5, -2.0], $p < 0.001$; Cohen's $d = 0.71$). This significant reduction in insomnia symptoms was confirmed in a conservative 'jump-to-reference' (J2R) sensitivity analysis, where missing values were imputed assuming that, following drop out, participants in the intervention group behave like those in the control group: here, the estimated baseline-adjusted group difference in insomnia symptoms at 3 months was -2.6 points on the ISI total score (95% CI = [-3.6, -1.6], $p < 0.001$; $d = 0.58$). A similar picture emerged in the complete case (CC) sensitivity analysis (baseline-adjusted group difference in the ISI total score = -3.2 points, 95% CI = [-4.5, -2.0], $p < 0.001$; $d = 0.71$).

1.6.2 Secondary endpoints

After 6 months, patients in the intervention reported significantly lower levels of insomnia symptoms than patients in the control group (ITT-analysis: baseline-adjusted group difference in the ISI total score = -2.8 points, 95% CI = [-4.2, -1.5], $p < 0.001$; $d = 0.59$). Similar patterns of results emerged in the J2R sensitivity analysis (baseline-adjusted group difference in the ISI total score = -2.3 points, 95% CI = [-3.3, -1.3], $p < 0.001$; $d = 0.50$) and the CC sensitivity analysis (baseline-adjusted group difference in the ISI total score = -2.7 points, 95% CI = [-4.1, -1.3], $p < 0.001$; $d = 0.60$).

After 3 months, the ITT analysis showed significant reductions in the intervention group compared to the control group for the secondary endpoint depression (estimated baseline-adjusted group difference on the PHQ-9 total score = -2.7 points, 95% CI = [-3.6, -1.8], $p < 0.001$; $d = 0.66$). Similarly, there were significant reductions in anxiety (estimated baseline-adjusted group difference on the GAD-7 total score = -2.2 points, 95% CI = [-3.0, -1.4], $p < 0.001$; $d = 0.56$) and significant improvements in social and work-related functioning (estimated baseline-adjusted group difference on the Work and Social

Adjustment Scale [WSAS] = -4.0 points, 95% CI = [-5.7, -2.2], $p < 0.001$; $d = 0.50$). All intervention effects on the secondary endpoints attained clinical relevance.

Also after 6 months, the ITT analysis showed significant intervention effects of *somnovia* on the secondary endpoint depression (estimated baseline-adjusted group difference on the PHQ-9 total score = -2.5 points, 95% CI = [-3.5, -1.4], $p < 0.001$; $d = 0.57$), anxiety (estimated baseline-adjusted group difference on the GAD-7 total score = -2.0 points, 95% CI = [-2.9, -1.2], $p < 0.001$; $d = 0.51$) as well as social and work-related functioning (estimated baseline-adjusted group difference on the WSAS total score = -3.9 points, 95% CI = [-5.7, -2.2], $p < 0.001$; $d = 0.50$).

Results of the responder analysis based on a minimally important clinical difference (MCID) of 6 points reduction in insomnia symptoms as assessed by the ISI total score [21] showed that more patients in the intervention group (51.6%) than in the control group (31.5%) achieved clinically relevant reductions in insomnia symptoms after 3 months ($\chi^2 = 10.41$, $p = 0.001$; Odds Ratio [OR] = 2.32, 95% CI = [1.39, 3.89]). This pattern of results corresponds to a Number Needed to Treat (NNT) of 5.

Results of the remission analysis based on an ISI total score of < 8 [22] showed that more patients in the intervention group (18.0%) than in the control group (7.9%) achieved remission of insomnia symptoms after 3 months ($\chi^2 = 5.73$, $p = 0.017$; OR = 2.57, 95% CI = [1.16, 5.69]).

1.7 Conclusion

Results of this clinical investigation show that the use of *somnovia* in addition to TAU leads to significant and clinically relevant reductions in insomnia symptoms compared to TAU alone after 3 months of use in patients with insomnia disorder. Regarding the primary endpoint, i.e., reduction of insomnia symptoms, *somnovia* has an NNT of 5.0. Effects on insomnia symptoms were stable after 6 months. Moreover, *somnovia* shows significant intervention effects on depression, anxiety, as well as social and work-related functioning after 3 months. These effects were also stable at the 6 month follow-up.

No adverse events or device effects were observed.

1.8 Date of the clinical investigation initiation

- First Patient First Visit: 2022-11-08

1.9 Completion date of the clinical investigation

- Last Patient Last Visit: 2023-09-18

2. Introduction

Sleep plays a crucial role in the regeneration of psychological and physiological processes and functions. Therefore, disruption of healthy sleep patterns can have enormous negative effects on mental and physical well-being [1], [2], [3], [4], [5]. Insomnia affects a large proportion of the population and is one of the most common medical complaints [6]. In Germany, one third of adults report sleep problems within 4 weeks [1]. Persistent poor sleep can develop into chronic insomnia affecting almost 6% of the German population [1]. Chronic insomnia is characterized by dissatisfaction with sleep duration or quality and difficulties in initiating or maintaining sleep, symptoms that are associated with significant distress and deficits in daytime functioning [6].

Chronic insomnia is associated with a variety of other mental and physical health disorders [2], [5]. People with sleep patterns that deviate from the “norm” have increased mortality, likely due to the association with overweight, obesity, and hypertension [1], [2], [3]. In addition, insomnia is a symptom and risk factor for depression, increasing the risk twofold [7]. Overall, the reduced quality of life and occupational performance caused by insomnia places a great burden on individuals and society [6].

Cognitive behavioral therapy for insomnia (CBT-I) is the therapy with the highest level of recommendation in the European guideline for the treatment of insomnia [8], and clinical trials comparing insomnia medications with CBT-I suggest that CBT-I leads to better sleep quality with fewer side effects in the long term [9]. However, access to CBT-I treatment is not readily available for all people affected by chronic insomnia. Only a minority of patients are referred to CBT-I therapists, and the availability of professionals is very limited [8], [12]. CBT-I, administered digitally as a low-threshold therapeutic approach, for example via digital health apps (DiGAs) to address this gap, has been shown to be acceptable and effective in previous studies [13], [14], [15], [16], [17]. DiGAs provide flexible, cost-effective access to mental health care and can evoke a sense of empowerment in patients [18], [19], [20].

The aim of the RCT presented here was to examine the effectiveness of the self-guided, Internet-based intervention program *somnovia* when used adjunctively to TAU compared to TAU only.

3. Investigational device and methods

somnovia is a self-guided, Internet-based intervention program based on CBT for patients with insomnia. *somnovia* follows the guideline recommendation regarding CBT-I, providing respective psychoeducation and psychotherapeutic exercises, methods and techniques (see table 1). Content is presented playfully and tailored to the user's reported needs and interests.

somnovia has one main function and several supporting secondary functions. The main function consists of a "simulated dialogue". This means that *somnovia* presents the user brief text passages, and users then select a response option that interests them most or best suits their individual situation. *somnovia* then responds emphatically to this response and conveys the next piece of information, to which the user can then respond in turn, and so on. In this way, a communication dynamic evolves. Patients are also motivated to complete simple homework tasks. Users can pause *somnovia* at any time and continue from the point where they left off. Users are reminded regularly to take breaks.

In addition to the dialogues, which are at the core of the program, *somnovia* offers a range of features including media such as audio recordings to guide therapeutic exercises or explain specific content in more detail and PDF-materials (worksheets and summary sheets), tailored motivational short text messages delivered as SMS (optional) or via email, as well as self-monitoring questionnaires to track target behaviors.

The content of somnovia is presented in table 1.

Table 1 | Content of *somnovia.*

Assessment of sleeping problems and sleep-related habits. Incl. sleeping patterns, sleep-related beliefs, sleep-related habits etc.
Psychoeducation. Basic knowledge about physiological and psychological aspects of sleep; main ingredients of the "vicious circle of insomnia"; interactive explanation of cognitive, emotional, behavioral, habit-related patterns adding to the development and maintenance of insomnia.
Sleep restriction. Assess the individual bed time needed by the patient and contrast it with their current habit. Set up a plan on how to stick to the recommended bedtime even in changing everyday circumstances.
Sleep hygiene. Identify sleep-damaging behaviors and set the goal to reduce them.
Reduction of alcohol use at night. Urge surfing and imaginary distancing against alcohol craving.
Improvement of exercise behavior. Use implementation intentions to improve exercise behavior if needed.

Relaxation techniques. Teach patient techniques to relax and reduce stress during daytime and in order to fall asleep by using Relaxation techniques, gratitude interventions, mindfulness techniques.

Cognitive techniques. Alleviating the circle of insomnia by using cognitive techniques to address catastrophization, ruminating thoughts and negative focus on negative effects of sleep problems. Creating positive sleep thoughts.

Reducing rumination. Strategies to deal with excessive ruminating thoughts. Assessment of immediacy and actionability of worries via a decision tree; Rumination-Stop via conditioning and relaxation techniques.

3.2 Intended purpose

somnovia is intended to provide therapeutic methods and exercises based on evidence-based psychological and psychotherapeutic therapies for patients with insomnia disorder, to help them managing their insomnia disorder.

somnovia is intended as a self-application for patients 18 years of age or older.

somnovia is neither intended to replace treatment provided by a health care provider nor to provide information which is used to make decisions with diagnosis or therapeutic purposes.

4. Clinical investigation plan

4.1 Clinical investigation objectives

The primary objective of this study was to evaluate the effectiveness of the self-guided digital health application *somnovia* in improving insomnia symptoms in patients with insomnia disorder in addition to usual care. Moreover, the effects of *somnovia* were examined in terms of improvements in depression, anxiety, and social and work-related functioning.

4.2 Clinical investigation design

- pragmatic
- randomized (simple randomization)
- controlled (two arms)
- online

4.3 Clinical investigation endpoints

4.3.1 Primary endpoint

- Insomnia severity (assessed with the ISI total score [22], [23])

4.3.2 Secondary endpoints

- Depression (assessed with the PHQ-9 total score [24], [25])
- Anxiety (assessed with the GAD-7 total score [26], [27])
- Social and work-related functioning (assessed with the WSAS total score [28])
- Responder Rate (calculated based on ISI total score [21])
- Remission Rate (calculated based on ISI total score [22])

4.4 Control group

Participants in the control group received usual medical care in consultation with their respective treating team. Following the pragmatic study design, usual medical care was supposed to reflect the reality of care, and may therefore have comprised all forms of outpatient care, including treatment by a primary care physician or specialist, psychotherapy (such as CBT), and no treatment at all [29], [30].

4.5 Ethical considerations

This study was reviewed and approved by the ethics committee of the Medical Faculty of the Christian-Albrecht University of Kiel (reference number D 495/22).

4.6 Data quality assurance

Data were collected online using a secure, internationally recognized survey software (easyfeedback.de). The survey software was programmed such that valid possible responses and response ranges were predefined for every question. Quality of the data and procedures were checked every week (e.g., participants were contacted in time to complete the questionnaires). Regular record-checking took place using a codebook with appropriate metadata. In addition, a daily backup of the data was performed. These were stored in anonymized form after the study was completed. The data will be retained for 10 years.

4.7 Subject population for the clinical investigation

Inclusion criteria:

- women, men, non-binary
- age ≥ 18 years
- diagnosis of chronic insomnia (ICD-11: 7A00 Chronic insomnia, which corresponds to ICD-10 G47.0/F51.0; assessed via online questionnaire and structured telephone interview)[1]
- impaired quality of sleep (cut-off) of ≥ 10 on the ISI
- consent to participation

Exclusion criteria: None.

4.8 Treatment allocation schedule

Simple randomization (no blocked randomization, no stratification) was performed automatically and concealed from study staff.

4.9 Concomitant medications/treatment

All participants received usual medical care in consultation with their respective treating physician. Following the pragmatic study design, usual medical care should reflect the reality of care, and may therefore include all forms of outpatient care, including treatment by a primary care physician or specialist, psychotherapy (such as CBT), and no treatment at all [29], [30].

4.10 Duration of follow-up

The total duration of follow-up was 6 months.

[1] The confirmation of the diagnosis was established through a structured telephone interview administered by trained psychological staff. This interview was conducted with individuals whose screening questionnaire indicated the presence of chronic insomnia, along with baseline ISI total scores ≥ 10. The specific questions for the telephone interview were based on the diagnostic criteria for chronic insomnia outlined in the ICD-11 [31]. Unclear cases were discussed in regular supervision meetings with PD Dr. Gitta Jacob.

4.11 Statistical design

Analysis of intervention effects at the 3-month time point was performed by calculating an ANCOVA: the respective outcome at 3 months served as the dependent variable, the treatment condition (intervention vs. control group) as the independent variable, and the baseline values of the respective outcome as the covariate. Treatment effects (independent variable: treatment condition), i.e., baseline-adjusted mean group differences between the intervention and control group in the respective outcome variable at 3 months, are reported on the original scale, along with the corresponding 95%-CI. The corresponding *p*-value of the treatment effect from the ANCOVA was used to determine statistical significance of the results.

Between-group effects (Cohen's *d* [32], [33]) were determined based on the difference in unadjusted mean values between the intervention group and the control group at 3 months, respectively.

The primary analysis was performed as an ITT analysis with multiple imputation under 'missing at random' (MAR) assumption [34], [35]. The ITT analysis provides an estimation of the treatment effect for all subjects randomized [34]. In addition, a conservative sensitivity analysis based on reference-based multiple imputation (J2R imputation, with the control group serving as the reference) and a complete-case sensitivity analysis were calculated.

In the ITT analysis, missing data points at the 3-month survey time point were imputed using the respective variable values at baseline as well as group membership and other sociodemographic and clinical variables (age, sex, familial status, education, employment status, and psychotherapy at baseline). The ITT analysis was implemented following a computationally efficient implementation for bootstrapped maximum likelihood multiple imputation by von Hippel and Bartlett (2021) [36] using the *R* packages *bootImpute* [36] and *mice* [37]. The relevant outcome variable was imputed using the *mice* package with default settings (i.e., using the predictive mean matching method with a pool of 5 candidate values drawn at random), as recommended.

These procedures were analogously employed in the per-protocol (PP) analysis, which encompassed all participants from the control group and those from the intervention group who had used *somnovia* on a minimum of two different days.

As part of a conservative sensitivity analysis, these results were compared to a J2R imputation. Under reference-based imputation, patients who drop out of the intervention group are assumed to no longer participate in the intervention and their outcomes from that point on are assumed to be the same as those of the control group [38], [39]. J2R sensitivity analysis was implemented with a computationally efficient implementation for bootstrapped maximum likelihood multiple imputation by von Hippel and Bartlett (2021) [36] using the *bootImpute* package in *R*.

For ITT, PP and J2R sensitivity analysis, ANCOVA was performed on each imputed data set as described above and parameters of interest were aggregated by pooling [36], [40]. Cohen's *d*

was calculated analogously within the ITT, PP and J2R analyses for each imputed data set and then pooled as well [36], [40].

In addition to the PP and J2R analyses, only study participants who had provided complete information at the 3-month time point (CC analysis) were included within a further sensitivity analysis. The modeling strategy was identical to that of the primary analysis; however, a CC analysis inherently omits estimation and pooling of model parameters in multiply imputed data.

Analogously, all analyses (ITT, J2R and CC) were performed for the 6-month time point to assess the durability of effects.

Operationally, all results were considered statistically significant at the two-sided 5% level. This is equivalent to using a one-sided *p*-value (nominal $\alpha = 0.025$) and a one-sided 2.5% overall significance level [41]. All analyses were performed with *R*, version 4.2.1 [42]. No correction for multiple testing was applied.

4.12 Amendments to the CIP

Not applicable.

5. Results

5.1 Clinical investigation initiation date

- First Patient First Visit: 2022-11-08

5.2 Clinical investigation completion/suspension date

- Last Patient Last Visit: 2023-09-18

5.3 Disposition of subjects

Recruitment of patients was through an online campaign. 801 people were screened for participation. Of these, 290 met all specified inclusion criteria and were randomized to the intervention (*n* = 149) und control group (*n* = 141). The investigational device *somnovia* was provided free of charge by its developer and manufacturer, GAIA. The intervention group received access immediately after randomization, while the control group was offered access to *somnovia* after 6 months. *somnovia* is an Internet-based application that does not require any installation. However, Internet access and an up-to-date Internet browser are required to use *somnovia*.

5.4 Accountability of subjects

Figure 1 summarizes the flow of participants through the study. In the ITT analysis, missing data points at the 3-month survey time point were imputed using the respective variable values at baseline as well as group membership and other sociodemographic and clinical variables (age, familial status, education, employment status, and psychotherapy at baseline). The ITT analysis was implemented following a computationally efficient implementation for bootstrapped maximum likelihood multiple imputation by von Hippel and Bartlett (2021) [36] using the *R* packages *bootImpute* [36] and *mice* [37]. The relevant outcome variable was imputed using the *mice* package with default settings (i.e., using the predictive mean matching method with a pool of 5 candidate values drawn at random), as recommended.

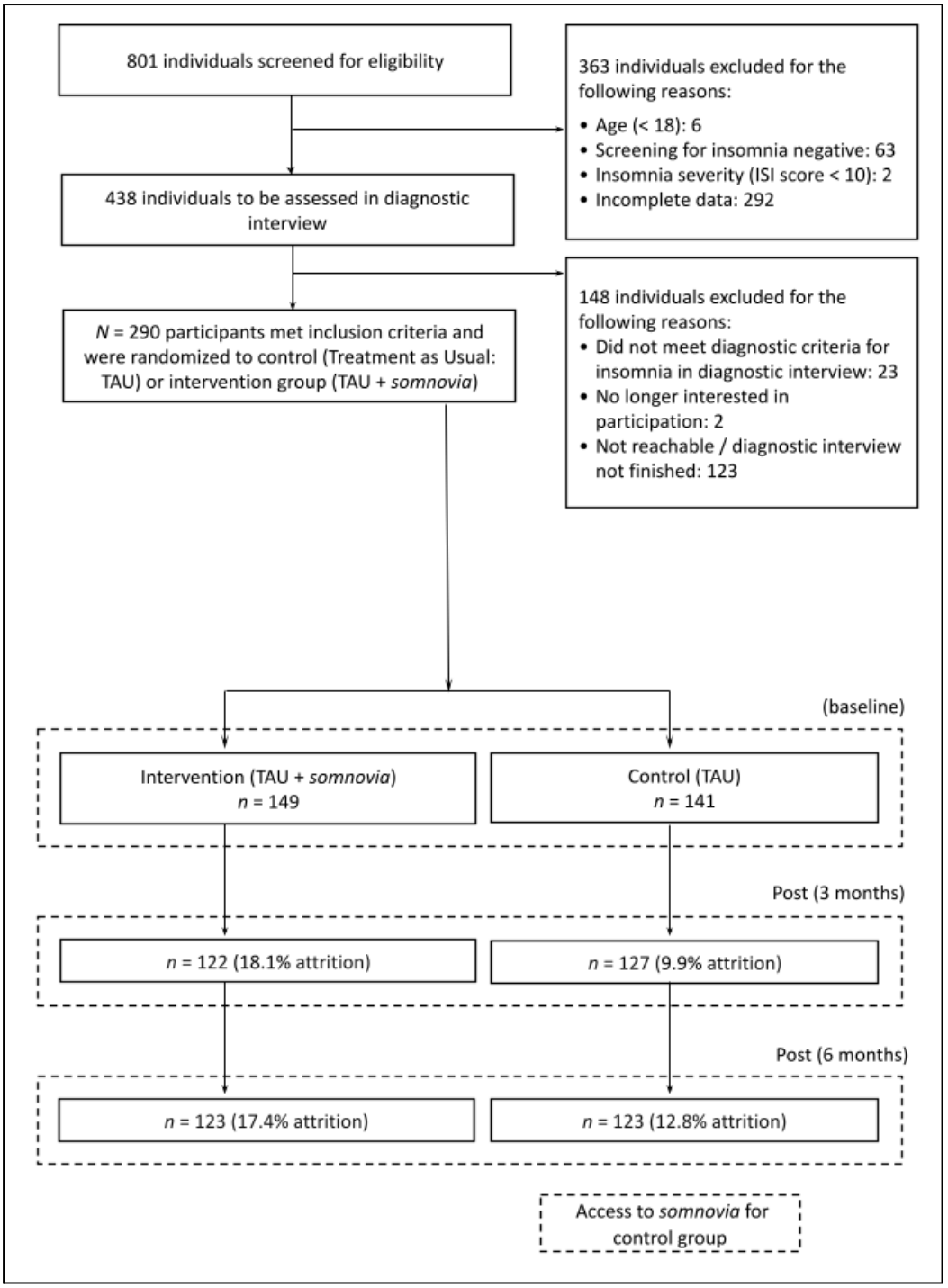

Figure 1 | Flow of participants through the study.

5.4.1 Subjects who did not pass the screening test

A total of 801 people were initially screened for eligibility. Of these, 363 had to be excluded in the online questionnaire for the following reasons:

- Age (< 18): 6
- Screening for insomnia negative: 63
- Insomnia severity (ISI score < 10): 2

- Incomplete data: 292

Thus, 438 people were to be assessed for eligibility in a diagnostic interview conducted via telephone. Of these, 148 were excluded for the following reasons:

- Did not meet diagnostic criteria for insomnia in diagnostic interview: 23
- No longer interested in participation: 2
- Not reachable / structured clinical interview not finished: 123

5.4.2 Subjects lost to follow-up

Table 2 | Number of patients lost to follow-up by time point and study group.

Time point	Control	*somnovia*
up to T1	10	24
up to T2	12	22

5.4.3 Subjects withdrawn from the clinical investigation

Table 3 | Number of patients withdrawn from the clinical investigation by time point and study group.

Time point	Control	*somnovia*
up to T1	4	3
up to T2	6	4

5.4.4 Comparison of dropouts and completers

Table 4 | Comparison of baseline characteristics of dropouts and completers (up to T1).

	Dropouts	Completers	Statistical comparison
	n = 41	n = 249	
Age	47.74 (16.50)	50.17 (13.69)	t = -0.89, p = 0.375
Sex (n [%])			χ^2 = 0.45, p = 0.504
male	9 (22.0)	67 (26.9)	
female	32 (78.0)	182 (73.1)	
intersexual	0 (0)	0 (0)	
Family situation (n [%])			χ^2 = 4.49, p = 0.344
single	10 (24.4)	46 (18.5)	

	Dropouts	Completers	Statistical comparison
living in partnership	12 (29.3)	55 (22.1)	
married / registered civil partnership	12 (29.3)	115 (46.2)	
divorced / registered partnership annulled	6 (14.6)	25 (10.0)	
widowed / registered partner deceased	1 (2.4)	8 (3.2)	
Education (n [%])			$\chi^2 = 9.63$, $p = 0.086$
Hauptschulabschluss	0 (0.0)	1 (0.4)	
Realschulabschluss	2 (4.9)	20 (8.0)	
Fachhochschulreife	4 (9.8)	13 (5.2)	
Abitur (A-levels)	6 (14.6)	25 (10.0)	
completed vocational training	14 (34.1)	46 (18.5)	
completed university studies	15 (36.6)	144 (57.8)	
Employment (n [%])			$\chi^2 = 1.56$, $p = 0.980$
not employed	9 (22.0)	54 (21.7)	
employed irregularly	0 (0.0)	2 (0.8)	
marginal employment	1 (2.4)	4 (1.6)	
employed part-time	8 (19.5)	63 (25.3)	
employed full-time	22 (53.7)	119 (47.8)	
in vocational training	0 (0.0)	1 (0.4)	
on parental leave	1 (2.4)	5 (2.0)	
partial retirement	0 (0.0)	1 (0.4)	
In shift work (n [%])	2 (4.9)	10 (4.0)	$\chi^2 = 0$, $p = 1$
Sick days (last 3 months; n [%])			$\chi^2 = 6.14$, $p = 0.105$
0 sick days	26 (63.4)	119 (47.8)	
1-5 sick days	3 (7.3)	59 (23.7)	
6-10 sick days	4 (9.8)	24 (9.6)	
> 10 sick days	8 (19.5)	47 (18.9)	
Diagnosis (ICD-10 G47.0 or F51.0, n [%])	41 (100%)	249 (100%)	n/a
Screening for mental disorders (WSQ; multiple answers possible; n [%])			

	Dropouts	Completers	Statistical comparison
Depression	12 (29.3)	39 (15.7)	$\chi^2 = 4.50$, $p = 0.034$
Generalized Anxiety Disorder	27 (65.9)	133 (53.4)	$\chi^2 = 2.20$, $p = 0.138$
Panic Disorder	13 (31.7)	52 (20.9)	$\chi^2 = 2.37$, $p = 0.124$
Panic Disorder with Agoraphobia	4 (9.8)	14 (5.6)	$\chi^2 = 0.45$, $p = 0.505$
Agoraphobia	7 (17.1)	19 (7.6)	$\chi^2 = 3.85$, $p = 0.050$
Specific phobia	17 (41.5)	84 (33.7)	$\chi^2 = 0.93$, $p = 0.336$
Social phobia	20 (48.8)	105 (42.2)	$\chi^2 = 0.63$, $p = 0.428$
Post Traumatic Stress Disorder	24 (58.5)	118 (47.4)	$\chi^2 = 1.75$, $p = 0.186$
Obsessive Compulsive Disorder	9 (22.0)	48 (19.3)	$\chi^2 = 0.16$, $p = 0.690$
Alcohol Abuse/Dependence	5 (12.2)	5 (2.0)	$\chi^2 = 8.13$, $p = 0.004$
ISI sum score	20.32 (3.90)	19.11 (3.95)	$t = 1.84$, $p = 0.072$
PHQ-9 sum score	12.20 (5.07)	11.20 (4.46)	$t = 1.19$, $p = 0.241$
GAD-7 sum score	9.20 (4.01)	8.32 (4.44)	$t = 1.27$, $p = 0.208$
WSAS sum score	17.66 (9.42)	17.22 (8.46)	$t = 0.28$, $p = 0.783$
Currently in psychotherapy (n [%])	13 (31.7)	52 (20.9)	$\chi^2 = 2.37$, $p = 0.124$
Currently taking any psycholeptic / psychoanaleptic medication[a] (n [%])	20 (48.8)	112 (45.0)	$\chi^2 = 0.21$, $p = 0.651$
Regular medication (multiple answers possible; n [%])			
Antipsychotics	0 (0.0)	12 (4.8)	$\chi^2 = 2.06$, $p = 0.151$
Anxiolytics	2 (4.9)	3 (1.2)	$\chi^2 = 1.05$, $p = 0.304$
Hypnotics and sedatives	2 (4.9)	24 (9.6)	$\chi^2 = 0.48$, $p = 0.488$
Antidepressants	10 (24.4)	38 (15.3)	$\chi^2 = 2.12$, $p = 0.145$
Psychostimulants	1 (2.4)	4 (1.6)	$\chi^2 = 0$, $p = 1$
Medication as needed (multiple answers possible; n [%])			
Antipsychotics	0 (0.0)	6 (2.4)	$\chi^2 = 1.01$, $p = 0.315$
Anxiolytics	3 (7.3)	6 (2.4)	$\chi^2 = 1.42$, $p = 0.233$
Hypnotics and sedatives	10 (24.4)	55 (22.1)	$\chi^2 = 0.11$, $p = 0.743$
Antidepressants	5 (12.2)	13 (5.2)	$\chi^2 = 1.87$, $p = 0.172$

	Dropouts	Completers	Statistical comparison
Psychostimulants	0 (0.0)	2 (0.8)	$\chi^2 = 0$, $p = 1$

[a] ATC classification codes N05 / N06.

Abbreviations: GAD-7 = Generalized Anxiety Disorder-7; ISI = Insomnia Severity Index; PHQ-9: Patient Health Questionnaire-9; WSAS = Work and Social Adjustment Scale; WSQ = Web Screening Questionnaire.

Among participants of the intervention group, the average weekly active use time in *somnovia* was significantly higher in completers (mean = 60.4 minutes, SD = 53.3) than in drop-outs (mean = 33.2 minutes, SD = 14.8; $t = 4.78$, $p < 0.001$) up to T1.

5.4.5 Per Protocol Dataset

In adherence to the predetermined criteria for inclusion in the PP analyses, 136 out of 149 participants (91.3%) in the intervention group showed a minimum usage of *somnovia* on at least two days. Consequently, the PP dataset comprised a total of 277 participants, with 136 from the intervention group and all 141 participants from the control group.

5.5 Subject demographics and clinical characteristics

Table 5 below presents an overview of the participants' characteristics. On average, participants in this study were women aged 50, predominantly in partnerships or marriages. The majority of participants had completed either vocational training or university studies, with most working either part-time or full-time. Approximately 4% of participants reported working on a shift basis. In terms of health-related information, half of the participants reported no sick days in the last 3 months. Approximately one-fifth reported 1 to 5 sick days, roughly 10% reported 6 to 10 sick days, and another fifth reported more than 10 sick days. The screening for mental disorders revealed that generalized anxiety disorder and post-traumatic stress disorder were the most common positive results, with around half of the participants screening positive for each. Notably, approximately one-fifth of participants reported being in psychotherapy, and just under 50% reported taking any psycholeptic or psychoanaleptic medication.

Table 5 | Subject demographics and clinical characteristics at baseline. Values represent mean (SD) unless stated otherwise.

	Control	*somnovia*	Total
	n = 141	n = 149	N = 290
Age	49.75 (13.55)	49.90 (14.67)	49.83 (14.12)
Age category (n [%])			
18-25 years	3 (2.1)	6 (4.0)	9 (3.1)
26-35 years	25 (17.7)	23 (15.4)	48 (16.6)
36-45 years	27 (19.1)	27 (18.1)	54 (18.6)

	Control	*somnovia*	Total
46-55 years	29 (20.6)	30 (20.1)	59 (20.3)
56-65 years	36 (25.5)	46 (30.9)	82 (28.3)
> 65 years	21 (14.9)	17 (11.4)	38 (13.1)
Sex (n [%])			
male	37 (26.2)	39 (26.2)	76 (26.2)
female	104 (73.8)	110 (73.8)	214 (73.8)
intersexual	0 (0)	0 (0)	0 (0)
Family situation (n [%])			
single	30 (21.3)	26 (17.4)	56 (19.3)
living in partnership	30 (21.3)	37 (24.8)	67 (23.1)
married / registered civil partnership	61 (43.3)	66 (44.3)	127 (43.8)
divorced / registered partnership annulled	16 (11.3)	15 (10.1)	31 (10.7)
widowed / registered partner deceased	4 (2.8)	5 (3.4)	9 (3.1)
Education (n [%])			
Hauptschulabschluss	1 (0.7)	0 (0.0)	1 (0.3)
Realschulabschluss	13 (9.2)	9 (6.0)	22 (7.6)
Fachhochschulreife	12 (8.5)	5 (3.4)	17 (5.9)
Abitur (A-levels)	13 (9.2)	18 (12.1)	31 (10.7)
completed vocational training	25 (17.7)	35 (23.5)	60 (20.7)
completed university studies	77 (54.6)	82 (55.0)	159 (54.8)
Employment (n [%])			
not employed	31 (22.0)	32 (21.5)	63 (21.7)
employed irregularly	1 (0.7)	1 (0.7)	2 (0.7)
marginal employment	0 (0.0)	5 (3.4)	5 (1.7)
employed part-time	38 (27.0)	33 (22.1)	71 (24.5)
employed full-time	66 (46.8)	75 (50.3)	141 (48.6)
in vocational training	0 (0.0)	1 (0.7)	1 (0.3)
on parental leave	4 (2.8)	2 (1.3)	6 (2.1)

	Control	*somnovia*	Total
partial retirement	1 (0.7)	0 (0.0)	1 (0.3)
In shift work (n [%])	8 (5.7)	4 (2.7)	12 (4.1)
Sick days (last 3 months; n [%])			
0 sick days	72 (51.1)	73 (49.0)	145 (50.0)
1-5 sick days	30 (21.3)	32 (21.5)	62 (21.4)
6-10 sick days	14 (9.9)	14 (9.4)	28 (9.7)
> 10 sick days	25 (17.7)	30 (20.1)	55 (19.0)
Diagnosis (ICD-10 G47.0 or F51.0, n [%])	141 (100%)	149 (100%)	290 (100%)
Screening for mental disorders (WSQ; multiple answers possible; n [%])			
Depression	26 (18.4)	25 (16.8)	51 (17.6)
Generalized Anxiety Disorder	78 (55.3)	82 (55.0)	160 (55.2)
Panic Disorder	31 (22.0)	34 (22.8)	65 (22.4)
Panic Disorder with Agoraphobia	10 (7.1)	8 (5.4)	18 (6.2)
Agoraphobia	16 (11.3)	10 (6.7)	26 (9.0)
Specific phobia	42 (29.8)	59 (39.6)	101 (34.8)
Social phobia	64 (45.4)	61 (40.9)	125 (43.1)
Post Traumatic Stress Disorder	74 (52.5)	68 (45.6)	142 (49.0)
Obsessive Compulsive Disorder	30 (21.3)	27 (18.1)	57 (19.7)
Alcohol Abuse/Dependence	4 (2.8)	6 (4.0)	10 (3.4)
ISI sum score	19.77 (3.92)	18.81 (3.95)	19.28 (3.96)
PHQ-9 sum score	11.52 (4.43)	11.17 (4.68)	11.34 (4.55)
GAD-7 sum score	8.49 (4.24)	8.40 (4.54)	8.44 (4.39)
WSAS sum score	17.52 (8.17)	17.07 (8.99)	17.29 (8.59)
Currently in psychotherapy (n [%])	28 (19.9)	37 (24.8)	65 (22.4)
Currently taking any psycholeptic / psychoanaleptic medication[a] (n [%])	66 (46.8)	66 (44.3)	132 (45.5)

	Control	*somnovia*	Total
Regular medication (multiple answers possible; n [%])			
Antipsychotics	8 (5.7)	4 (2.7)	12 (4.1)
Anxiolytics	3 (2.1)	2 (1.3)	5 (1.7)
Hypnotics and sedatives	18 (12.8)	8 (5.4)	26 (9.0)
Antidepressants	22 (15.6)	26 (17.4)	48 (16.6)
Psychostimulants	4 (2.8)	1 (0.7)	5 (1.7)
Medication as needed (multiple answers possible; n [%])			
Antipsychotics	3 (2.1)	3 (2.0)	6 (2.1)
Anxiolytics	5 (3.5)	4 (2.7)	9 (3.1)
Hypnotics and sedatives	31 (22.0)	34 (22.8)	65 (22.4)
Antidepressants	7 (5.0)	11 (7.4)	18 (6.2)
Psychostimulants	2 (1.4)	0 (0.0)	2 (0.7)

[a] ATC classification codes N05 / N06.

Abbreviations: GAD-7 = Generalized Anxiety Disorder-7; ISI = Insomnia Severity Index; PHQ-9: Patient Health Questionnaire-9; WSAS = Work and Social Adjustment Scale; WSQ = Web Screening Questionnaire.

Table 6 | Relevant treatment characteristics over the course of the clinical investigation.

	Control	*somnovia*	Statistical comparison
T1	n = 127	n = 122	
Currently in psychotherapy (n [%])	26 (20.5)	31 (25.4)	$\chi^2 = 0.86$, $p = 0.354$
Currently taking any psycholeptic / psychoanaleptic medication[a] (n [%])	61 (48.0)	48 (39.3)	$\chi^2 = 1.91$, $p = 0.167$
Regular medication (multiple answers possible; n [%])			
Antipsychotics	7 (5.5)	4 (3.3)	$\chi^2 = 0.30$, $p = 0.583$
Anxiolytics	2 (1.6)	0 (0.0)	$\chi^2 = 0.46$, $p = 0.495$
Hypnotics and sedatives	21 (16.5)	6 (4.9)	$\chi^2 = 8.69$, $p = 0.003$
Antidepressants	20 (15.7)	17 (13.9)	$\chi^2 = 0.16$, $p = 0.688$
Psychostimulants	4 (3.1)	0 (0.0)	$\chi^2 = 2.17$, $p = 0.141$
Medication as needed (multiple			

	Control	*somnovia*	Statistical comparison
answers possible; n [%])			
Antipsychotics	2 (1.6)	2 (1.6)	$\chi^2 = 0$, $p = 1$
Anxiolytics	4 (3.1)	1 (0.8)	$\chi^2 = 0.74$, $p = 0.391$
Hypnotics and sedatives	23 (18.1)	26 (21.3)	$\chi^2 = 0.40$, $p = 0.525$
Antidepressants	4 (3.1)	7 (5.7)	$\chi^2 = 0.47$, $p = 0.493$
Psychostimulants	2 (1.6)	0 (0.0)	$\chi^2 = 0.46$, $p = 0.495$
	Control	***somnovia***	**Statistical comparison**
T2	n = 123	n = 123	
Currently in psychotherapy (n [%])	26 (21.1)	29 (23.6)	$\chi^2 = 0.21$, $p = 0.646$
Currently taking any psycholeptic / psychoanaleptic medication* (n [%])	57 (46.3)	46 (37.4)	$\chi^2 = 2.02$, $p = 0.155$
Regular medication (multiple answers possible, % yes)			
Antipsychotics	6 (4.9)	5 (4.1)	$\chi^2 = 0$, $p = 1$
Anxiolytics	1 (0.8)	0 (0.0)	$\chi^2 = 0$, $p = 1$
Hypnotics and sedatives	19 (15.4)	8 (6.5)	$\chi^2 = 5.03$, $p = 0.025$
Antidepressants	20 (16.3)	19 (15.4)	$\chi^2 = 0.03$, $p = 0.861$
Psychostimulants	2 (1.6)	0 (0.0)	$\chi^2 = 0.50$, $p = 0.478$
Medication as needed (multiple answers possible; n [%])			
Antipsychotics	1 (0.8)	2 (1.6)	$\chi^2 = 0$, $p = 1$
Anxiolytics	2 (1.6)	1 (0.8)	$\chi^2 = 0$, $p = 1$
Hypnotics and sedatives	20 (16.3)	20 (16.3)	$\chi^2 = 0$, $p = 1$
Antidepressants	4 (3.3)	7 (5.7)	$\chi^2 = 0.38$, $p = 0.537$
Psychostimulants	2 (1.6)	0 (0.0)	$\chi^2 = 0.50$, $p = 0.478$

[a] ATC classification codes N05 / N06.

Table 7 | Newly initiated treatments over the course of the clinical investigation.

	Control	*somnovia*
T1	n = 127	n = 122
Started psychotherapy since T0 (n [%])	11 (8.7)	3 (2.4)
Started regular medication since T0 (multiple answers possible; n [%])		
Antipsychotics	0 (0.0)	0 (0.0)
Anxiolytics	1 (0.8)	0 (0.0)
Hypnotics and sedatives	6 (4.7)	1 (0.8)
Antidepressants	4 (3.1)	2 (1.6)
Psychostimulants	0 (0)	0 (0.0)
Started medication as needed since T0 (multiple answers possible; n [%])		
Antipsychotics	1 (0.8)	0 (0.0)
Anxiolytics	1 (0.8)	0 (0.0)
Hypnotics and sedatives	1 (0.8)	1 (0.8)
Antidepressants	2 (1.6)	0 (0)
Psychostimulants	0 (0)	0 (0.0)
T2	n = 119	n = 114
Started psychotherapy since T1 (n [%])	6 (5.0)	2 (1.8)
Started regular medication since T1 (multiple answers possible; n [%])		
Antipsychotics	0 (0.0)	0 (0.0)
Anxiolytics	0 (0.0)	0 (0.0)
Hypnotics and sedatives	3 (2.5)	2 (1.8)
Antidepressants	4 (3.1)	2 (1.6)
Psychostimulants	0 (0)	0 (0.0)
Started medication as needed since T1 (multiple answers possible; n [%])		
Antipsychotics	0 (0.0)	0 (0.0)
Anxiolytics	0 (0.0)	0 (0.0)
Hypnotics and sedatives	1 (0.8)	0 (0.0)
Antidepressants	2 (1.6)	2 (1.6)
Psychostimulants	1 (0.8)	0 (0.0)

[a] ATC classification codes N05 / N06.

5.6 CIP compliance

The CIP was complied with throughout the duration of the investigation.

5.7 Analysis

The means at follow-ups (T1 and T2) presented in tables 8-11 are unadjusted for baseline. For baseline-adjusted means, see tables 22-25 in the appendix.

5.7.1 Primary endpoint

- Insomnia severity (assessed with the ISI total score)

Table 8 | Results of the primary endpoint insomnia severity.

Time		**Control**			***somnovia***			**ANCOVA**				
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*F(df)*	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	141	19.8	3.9	149	18.8	3.9	-	-	-	-	-
	T1	141	16.0	5.4	149	12.1	5.5	-3.3 (-4.5, -2)	*F*(1, 287) = 76.9	< 0.001	0.10	0.71 (0.44, 0.98)
	T2	141	14.6	5.7	149	11.2	5.8	-2.8 (-4.2, -1.5)	*F*(1, 287) = 57.0	< 0.001	0.07	0.59 (0.33, 0.85)
J2R	T0	141	19.8	3.9	149	18.8	3.9	-	-	-	-	-
	T1	141	15.9	5.3	149	12.7	5.7	-2.6 (-3.6, -1.6)	*F*(1, 287) = 76.5	< 0.001	0.07	0.58 (0.37, 0.80)
	T2	141	14.6	5.6	149	11.7	5.9	-2.3 (-3.3, -1.3)	*F*(1, 287) = 65.9	< 0.001	0.05	0.50 (0.29, 0.71)
CC	T0	141	19.6	3.9	149	18.5	3.9	-	-	-	-	-
	T1	127	15.9	5.4	122	12.0	5.5	-3.2 (-4.5, -2)	*F*(1, 246) = 64.9	< 0.001	0.09	0.71 (0.45, 0.97)
	T2	123	14.5	5.7	123	11.1	5.9	-2.7 (-4.1, -1.3)	*F*(1, 243) = 48.2	< 0.001	0.06	0.60 (0.34, 0.85)
PP	T0	141	19.8	3.9	136	18.7	3.9	-	-	-	-	-
	T1	141	15.9	5.4	136	12.0	5.5	-3.3 (-4.5, -2)	*F*(1, 274) = 72.2	< .001	0.10	0.72 (0.45, 0.99)
	T2	141	14.6	5.7	136	11.1	5.8	-2.9 (-4.3, -1.6)	*F*(1, 274) = 55.8	< .001	0.07	0.62 (0.35, 0.89)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.
[b] based on unadjusted values; positive values show effects in favor of the intervention group.

5.7.2 Secondary endpoints

- Depression (assessed with the PHQ-9 total score)

Table 9 | Results of the secondary endpoint depression.

Time	**Control**			***somnovia***			**ANCOVA**				
	n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*F(df)*	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]

ITT	T0	141	11.6	4.4	149	11.2	4.7	-	-	-	-	-
	T1	141	10.2	4.9	149	7.3	3.9	-2.7 (-3.6, -1.8)	$F(1, 287) = 128.4$	< 0.001	0.12	0.66 (0.41, 0.90)
	T2	141	9.6	5.0	149	6.9	4.3	-2.5 (-3.5, -1.4)	$F(1, 287) = 85.8$	< 0.001	0.08	0.57 (0.32, 0.82)
J2R	T0	141	11.5	4.4	149	11.2	4.7	-	-	-	-	-
	T1	141	10.2	4.9	149	7.9	4.3	-2.1 (-2.9, -1.3)	$F(1, 287) = 141.9$	< 0.001	0.07	0.50 (0.3, 0.71)
	T2	141	9.5	4.9	149	7.4	4.5	-2.0 (-2.7, -1.2)	$F(1, 287) = 93.0$	< 0.001	0.06	0.45 (0.26, 0.65)
CC	T0	141	11.5	4.3	149	10.9	4.6	-	-	-	-	-
	T1	126	10.2	4.9	122	7.2	3.9	-2.6 (-3.6, -1.7)	$F(1, 245) = 106.2$	< 0.001	0.11	0.68 (0.42, 0.93)
	T2	122	9.5	5.0	123	6.8	4.3	-2.4 (-3.5, -1.4)	$F(1, 242) = 67.1$	< 0.001	0.08	0.59 (0.33, 0.84)
PP	T0	141	11.5	4.4	136	11.0	4.5	-	-	-	-	-
	T1	141	10.2	4.9	136	7.1	3.8	-2.7 (-3.7, -1.8)	$F(1, 274) = 123.4$	< .001	0.12	0.70 (0.46, 0.93)
	T2	141	9.5	5.0	136	6.7	4.2	-2.5 (-3.6, -1.5)	$F(1, 274) = 80.5$	< .001	0.09	0.61 (0.35, 0.86)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.

[b] based on unadjusted values; positive values show effects in favor of the intervention group.

To evaluate the clinical significance of the findings, we performed an exploratory analysis of responders at the 3-month time point (T1) using an MCID of 5 points in the PHQ-9 total score [43], utilizing complete case data. A significantly higher proportion of participants in the intervention group reached this criterion than in the control group (46/122 [37.7%] versus 24/126 [19.0%]; $\chi^2 = 10.65$, $p = 0.001$; OR = 2.57, 95% CI = [1.44, 4.58]). Thus, the responder analysis confirmed that the additional use of *somnovia* was more likely to result in clinically relevant reductions in depression compared with TAU alone.

Additionally, we assessed how many participants experienced relevant clinical deterioration (defined as an increase of at least 5 points in the PHQ-9 total score [MCID] from baseline to T1): 0/122 patients (0%) in the intervention group versus 7/126 (6%) patients in the control group were classified as deteriorators, respectively.

Finally, we assessed how many participants had no clinically relevant improvement or deterioration in depressive symptoms from baseline to T1. This applied to 76/122 (62.3%) participants in the intervention group, and to 95/126 (75.4%) of participants in the control group ($\chi^2 = 4.97$, $p = 0.026$; OR = 0.54, 95% CI = [0.31, 0.93]).

The same analyses were repeated in the ITT population and showed comparable results: 59/149 (39.6%) patients and 28/141 (19.9%) patients were classified as responders in the intervention group and control group, respectively ($\chi^2 = 13.44$, $p < 0.001$; OR = 2.65, 95% CI = [1.56, 4.49]). One patient in the intervention group (0.7%) and 9 patients in the control group (6.4%) were classified as deteriorators ($\chi^2 = 5.49$, $p = 0.019$; OR = 0.10, 95% CI = [0.01, 0.79]). Finally, 89/149 (59.7%) patients in the intervention group and 104/141 (73.8%) patients in the control group showed no clinically relevant improvement or deterioration ($\chi^2 = 6.40$, $p = 0.011$; OR = 0.53, 95% CI = [0.32, 0.87]).

- Anxiety (assessed with the GAD-7 total score)

Table 10 | Results of the secondary endpoint anxiety.

	Time	Control			*somnovia*			ANCOVA				
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*F(df)*	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	141	8.5	4.2	149	8.4	4.5	-	-	-	-	-
	T1	141	7.8	4.4	149	5.6	3.7	-2.2 (-3, -1.4)	*F*(1, 287) = 151.6	< 0.001	0.10	0.56 (0.32, 0.81)
	T2	141	7.4	4.4	149	5.4	3.7	-2.0 (-2.9, -1.2)	*F*(1, 287) = 90.3	< 0.001	0.08	0.51 (0.27, 0.76)
J2R	T0	141	8.5	4.2	149	8.4	4.5	-	-	-	-	-
	T1	141	7.9	4.4	149	6.1	4.0	-1.8 (-2.4, -1.1)	*F*(1, 287) = 155.5	< 0.001	0.07	0.44 (0.22, 0.65)
	T2	141	7.4	4.3	149	5.8	4.0	-1.5 (-2.2, -0.8)	*F*(1, 287) = 111.4	< 0.001	0.04	0.37 (0.17, 0.57)
CC	T0	141	8.4	4.3	149	8.3	4.6	-	-	-	-	-
	T1	126	7.8	4.4	122	5.5	3.7	-2.2 (-3, -1.3)	*F*(1, 245) = 131.1	< 0.001	0.10	0.55 (0.30, 0.81)
	T2	122	7.4	4.4	122	5.3	3.7	-2.0 (-2.9, -1.1)	*F*(1, 241) = 80.5	< 0.001	0.07	0.53 (0.27, 0.78)
PP	T0	141	8.5	4.2	136	8.3	4.4	-	-	-	-	-
	T1	141	7.9	4.4	136	5.5	3.6	-2.3 (-3.1, -1.5)	*F*(1, 274) = 141.6	< .001	0.11	0.60 (0.35, 0.85)
	T2	141	7.4	4.4	136	5.3	3.7	-2.1 (-3.0, -1.2)	*F*(1, 274) = 85.6	< .001	0.08	0.53 (0.27, 0.79)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.
[b] based on unadjusted values; positive values show effects in favor of the intervention group.

To evaluate the clinical significance of the findings, we performed an exploratory analysis of responders at the 3-month time point (T1) using an MCID of 4 points in the GAD-7 total score [44], utilizing complete case data. A significantly higher proportion of participants in the intervention group reached this criterion than in the control group (46/122 [37.7%] versus 25/126 [19.8%]; $\chi^2 = 9.68$, $p = 0.002$; OR = 2.45, 95% CI = [1.38, 4.33]). Thus, the responder analysis confirmed that the additional use of *somnovia* was more likely to result in clinically relevant reductions in anxiety compared with TAU alone.

Additionally, we assessed how many participants experienced relevant clinical deterioration (defined as an increase of at least 4 points in the GAD-7 total score [MCID] from baseline to T1): 7/122 patients (5.7%) in the intervention group versus 15/126 (11.9%) patients in the control group were classified as deteriorators, respectively ($\chi^2 = 2.20$, $p = 0.138$; OR = 0.45, 95% CI = [0.18, 1.15]).

Finally, we assessed how many participants had no clinically relevant improvement or deterioration in anxiety symptoms from baseline to T1. This applied to 69/122 (56.6%) participants in the intervention group, and to 86/126 (68.3%) of participants in the control group ($\chi^2 = 3.62$, $p = 0.057$; OR = 0.61, 95% CI = [0.36, 1.02]).

The same analyses were repeated in the ITT population and showed comparable results: 60/149 (40.3%) patients and 29/141 (20.6%) patients were classified as responders in the intervention group and control group, respectively ($\chi^2 = 13.22$, $p < 0.001$; OR = 2.60, 95% CI = [1.54, 4.39]). 8 patients in the intervention group (5.4%) and 18 patients in the control group

(12.8%) were classified as deteriorators (χ^2 = 3.99, p = 0.046; OR = 0.39, 95% CI = [0.16, 0.92]). Finally, 81/149 (54.4%) patients in the intervention group and 94/141 (66.7%) patients in the control group showed no clinically relevant improvement or deterioration (χ^2 = 4.58, p = 0.032; OR = 0.60, 95% CI = [0.37, 0.96]).

- Social and work-related functioning (assessed with the WSAS total score)

Table 11 | Results of the secondary endpoint social and work-related functioning.

	Time	**Control**			***somnovia***			**ANCOVA**				
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*F(df)*	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	141	17.5	8.1	149	17.1	8.9	-	-	-	-	-
	T1	141	16.0	8.7	149	11.8	8.4	-4.0 (-5.7, -2.2)	*F*(1, 287) = 160.5	< 0.001	0.08	0.50 (0.24, 0.76)
	T2	141	14.5	8.9	149	10.3	8.0	-3.9 (-5.7, -2.2)	*F*(1, 287) = 133.7	< 0.001	0.08	0.50 (0.24, 0.76)
J2R	T0	141	17.5	8.1	149	17.1	8.9	-	-	-	-	-
	T1	141	16.0	8.7	149	12.6	8.8	-3.2 (-4.6, -1.8)	*F*(1, 287) = 176.3	< 0.001	0.05	0.39 (0.18, 0.61)
	T2	141	14.4	8.7	149	11.0	8.3	-3.1 (-4.5, -1.8)	*F*(1, 287) = 148.2	< 0.001	0.05	0.40 (0.19, 0.61)
CC	T0	141	17.6	8.1	149	16.8	8.9	-	-	-	-	-
	T1	125	16.0	8.7	122	11.6	8.5	-3.9 (-5.7, -2.2)	*F*(1, 244) = 133.9	< 0.001	0.07	0.51 (0.26, 0.77)
	T2	122	14.5	8.9	121	10.0	7.9	-4 (-5.8, -2.2)	*F*(1, 240) = 111.2	< 0.001	0.07	0.54 (0.28, 0.79
PP	T0	141	17.5	8.1	136	16.9	8.7	-	-	-	-	-
	T1	141	16.1	8.7	136	11.5	8.3	-4.2 (-6.0, -2.4)	*F*(1, 274) = 151.3	< .001	0.09	0.54 (0.27, 0.80)
	T2	141	14.5	8.9	136	10.1	8.0	-4.0 (-5.8, -2.3)	*F*(1, 274) = 124.4	< .001	0.08	0.52 (0.27, 0.77)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.

[b] based on unadjusted values; positive values show effects in favor of the intervention group.

To assess the clinical significance of the findings, we conducted an exploratory analysis to identify responders at the 3-month time point (T1), utilizing complete case data. Given the absence of universally accepted criteria for categorizing responders in the context of work-related and social functioning, as assessed by the WSAS, we used the Reliable Change Index (RCI) to define responders [45]. Specifically, we classified a participant as a responder if the RCI value surpassed a critical z-score of 1.96 for a 95% confidence interval. The reliability estimate necessary for RCI calculations was obtained from [46].

A significantly higher proportion of participants in the intervention group demonstrated reliable improvements, as defined by the RCI, compared to the control group (22/122 [18.0%] versus 8/125 [6.4%]; χ^2 = 6.78, p = 0.009; OR = 3.22, 95% CI = [1.37, 7.54]). Additionally, we assessed how many participants experienced relevant clinical deterioration from baseline to T1, as defined by the RCI: 2/122 patients (1.6%) in the intervention group

versus 3/125 (2.4%) patients in the control group were classified as deteriorators, respectively ($\chi^2 < 0.001$, $p = 1$; OR = 0.68, 95% CI = [0.11, 4.13]).

Finally, we assessed how many participants had no clinically relevant improvement or deterioration in work-related and social functioning, as defined by the RCI, from baseline to T1. This applied to 98/122 (80.3%) participants in the intervention group, and to 114/125 (91.2%) of participants in the control group ($\chi^2 = 6.00$, $p = 0.014$; OR = 0.39, 95% CI = [0.18, 0.85]). The same analyses were repeated in the ITT population and showed comparable results: 29/149 (19.5%) patients in the intervention group and 10/141 (7.1%) patients in the control group experienced reliable improvements ($\chi^2 = 9.53$, $p = 0.002$; OR = 3.17, 95% CI = [1.48, 6.77]). 3 patients in the intervention group (2.0%) and 4 patients in the control group (2.8%) were classified as deteriorators ($\chi^2 = 0.01$, $p = 0.941$; OR = 0.70, 95% CI = [0.15, 3.20]). Finally, 117/149 (78.5%) patients in the intervention group and 127/141 (90.1%) patients in the control group showed no clinically relevant improvement or deterioration ($\chi^2 = 7.24$, $p = 0.007$; OR = 0.40, 95% CI = [0.20, 0.79]).

As an alternative way to define response, we employed the criterion of achieving a minimum 50% improvement in work-related and social functioning from baseline to T1. Significantly more participants in the intervention group showed clinically relevant improvements based on this criterion than in the control group (63/122 [51.6%] versus 35/125 [28.0%]; $\chi^2 = 14.4$, $p < 0.001$; OR = 2.75, 95% CI = [1.62, 4.66]). The same analysis was repeated in the ITT population and showed comparable results: 77/149 (51.7%) patients in the intervention group and 40/141 (28.4%) patients in the control group experienced reliable improvements ($\chi^2 = 16.35$, $p < 0.001$; OR = 2.70, 95% CI = [1.66, 4.40]).

Thus, the responder analyses confirmed that the additional use of *somnovia* was more likely to result in clinically relevant improvements in social and work-related functioning compared with TAU alone.

- Responder Rate of insomnia symptoms

Statistical comparison of the number of responders (defined as a reduction in insomnia symptoms, assessed with the ISI total score, of at least 6 points [MCID] from baseline to T1 [21]) based on complete cases showed that clinically relevant effects on insomnia symptoms were more frequent in the intervention group than in the control group: 63/122 patients (51.6%) in the intervention group versus 40/127 (31.5%) patients in the control group were classified as responders, respectively ($\chi^2 = 10.41$, $p = 0.001$; OR = 2.32, 95% CI = [1.39, 3.89]; see also table 12). This pattern of results corresponds to an NNT of 5. Thus, the responder analysis confirmed that the additional use of *somnovia* was more likely to result in clinically relevant reductions in insomnia symptoms compared with TAU alone.

Additionally, we explored how many participants experienced relevant clinical deterioration (defined as an increase in insomnia symptoms, assessed with the ISI total score, of at least 6 points [MCID] from baseline to T1 [21]): 0/122 patients (0%) in the intervention group versus 1/127 (0.1%) patients in the control group were classified as deteriorators, respectively (see also table 12).

Finally, we explored how many participants had no clinically relevant improvement or deterioration in insomnia symptoms from baseline to T1. This applied to 59/122 (48.4%)

participants in the intervention group, and to 86/127 (67.7%) of participants in the control group (χ^2 = 9.58, *p* = 0.002; OR = 0.45, 95% CI = [0.27, 0.75]).

The same analyses were performed in an exploratory manner for T2 (see table 12 for results). All aforementioned analyses were repeated in the ITT population and showed comparable results than in the CC population (see table 12).

For a visual representation of the responder analyses presented in a Sankey Diagram, please refer to figures 2 and 3. These diagrams specifically encompass only participants who have data available at both T1 and T2.

Table 12| Responder Rate of insomnia symptoms at T1 and T2 by study group.

		Control	***somnovia***	Statistical comparison	Odds Ratio (95% CI)[a]
	T1	n = 127	n = 122		
	responder (n [%])	40 (31.5)	63 (51.6)	χ^2 = 10.41, *p* = 0.001	2.32 (1.39, 3.89)
CC	deteriorator (n [%])	1 (0.8)	0 (0)	n/a	n/a
	no clinically relevant change (n [%])	86 (67.7)	59 (48.4)	χ^2 = 9.58, *p* = 0.002	0.45 (0.27, 0.75)
	T2	n = 123	n = 123		
	responder (n [%])	56 (45.5)	72 (58.5)	χ^2 = 4.17, *p* = 0.041	1.69 (1.01, 2.80)
CC	deteriorator (n [%])	0 (0)	1 (0.8)	n/a	n/a
	no clinically relevant change (n [%])	67 (54.4)	50 (40.7)	χ^2 = 4.71, *p* = 0.030	0.57 (0.35, 0.95)
	T1	n = 141	n = 149		
	responder (n [%])	46 (32.6)	80 (53.7)	χ^2 = 13.09, *p* < 0.001	2.39 (1.49, 3.86)
ITT	deteriorator (n [%])	1 (0.7)	1 (0.8)	χ^2 < 0.001, *p* = 1	0.95 (0.06, 15.27)
	no clinically relevant change (n [%])	94 (66.7)	68 (45.6)	χ^2 = 13.0, *p* < 0.001	0.42 (0.26, 0.68)
	T2	n = 141	n = 149		
	responder (n [%])	64 (45.4)	91 (61.2)	χ^2 = 7.16, *p* = 0.007	1.89 (1.18, 3.01)
ITT	deteriorator (n [%])	1 (0.7)	1 (0.8)	χ^2 < 0.001, *p* = 1	0.95 (0.06, 15.27)
	no clinically relevant change (n [%])	76 (53.9)	57 (38.3)	χ^2 = 7.14, *p* = 0.008	0.53 (0.33, 0.85)

[a] calculated using unconditional maximum likelihood estimation (Wald). An Odds Ratio (OR) > 1 signifies a higher likelihood of the event occurring in the intervention group.

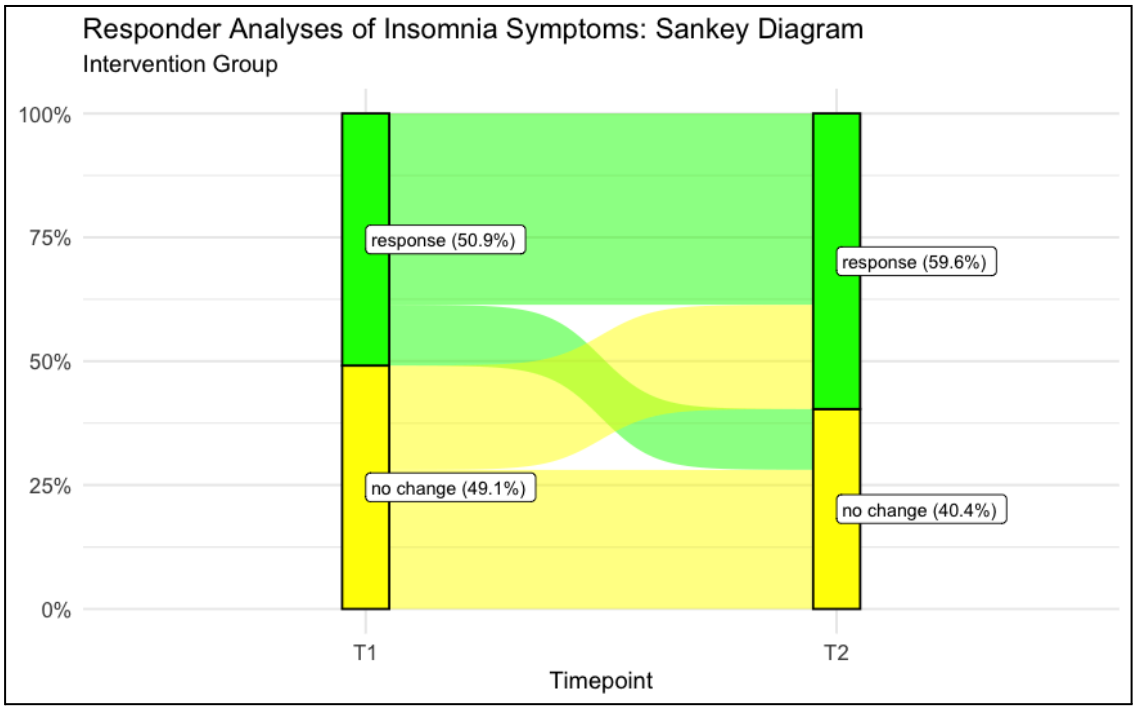

Figure 2 | Sankey Diagram illustrating Responder Analyses of Insomnia Symptoms in the Intervention Group. The depicted data represent only participants with available data at both T1 and T2. Response, no change, and deterioration were categorized using the MCID of the ISI total score. Further details on the computation are provided in the accompanying text above.

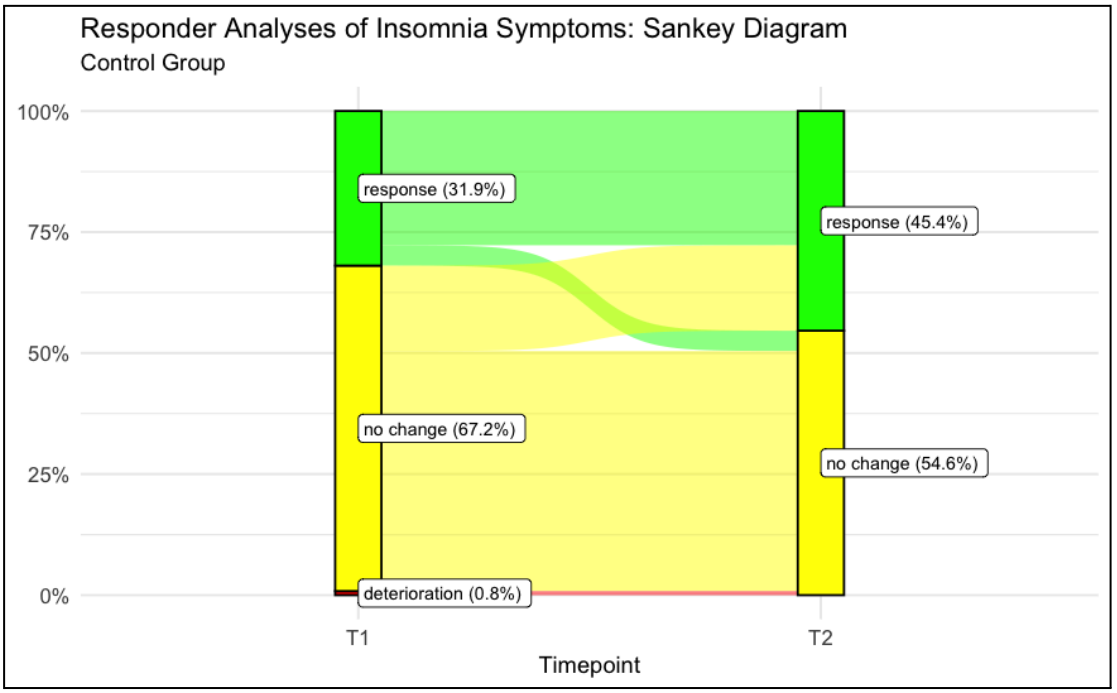

Figure 3 | Sankey Diagram illustrating Responder Analyses of Insomnia Symptoms in the Control Group. The depicted data represent only participants with available data at both T1 and T2. Response, no change, and deterioration were categorized using the MCID of the ISI total score. Further details on the computation are provided in the accompanying text above.

- Remission Rate of insomnia symptoms

Statistical comparison of the number of patients in remission (defined as an ISI total score < 8 at T1) based on complete cases demonstrated that remission was more frequent in the intervention group than in the control group: 22/122 patients (18.0%) versus 10/127 (7.9%) patients were classified as in remission, respectively (χ^2 = 5.73, *p* = 0.017; OR = 2.57, 95% CI = [1.16, 5.69]). The same analysis was performed in the ITT population and showed comparable results (see table 13).

Thus, the remission analysis confirmed that the additional use of *somnovia* was more likely to result in remission of insomnia symptoms compared with TAU alone.

Table 13 | Remission Rate of insomnia symptoms at T1 by study group.

		Control	***somnovia***	Statistical comparison	Odds Ratio (95% CI)[a]
CC	in remission (n [%])	n = 122 10 (7.9)	n = 122 22 (18.0)	χ^2 = 5.73, *p* = 0.017	2.57 (1.16, 5.69)
ITT	in remission (n [%])	n = 141 12 (8.5)	n = 149 27 (18.1)	χ^2 = 5.75, *p* = 0.017	2.38 (1.15, 4.91)

[a] calculated using unconditional maximum likelihood estimation (Wald). An Odds Ratio (OR) > 1 signifies a higher likelihood of the event occurring in the intervention group.

- Use of *somnovia*

Virtually all patients in the intervention group (146/149, 98.0%) registered to use *somnovia*. Among those registered, a significant majority (106, 72.6%) completed all 6 treatment modules of *somnovia;* the average number of modules completed was 5.0 (SD = 1.8). Registered patients demonstrated an average of 13.5 days (SD = 18.0) with active use in the program up to T1.

- User Satisfaction

User satisfaction was assessed with the Net Promoter Score (NPS). After 3 months of access to *somnovia*, participants were asked how likely they were to recommend the program to a friend or colleague [47]. Responses were scored on an 11-point Numerical Rating Scale, ranging from 0 = “I definitely do not recommend the program” to 10 = “I definitely recommend the program.” The traditional approach to calculating the NPS yielded a score of 7, indicating good user satisfaction.

The ZUF-8 was evaluated as an alternative measure of user satisfaction in the intervention group. After 3 months, the mean total score on this measure was 20.1 (SD = 1.3), which translates to a mean item score of 2.5, again reflecting a generally positive evaluation of *somnovia* (item scores range from 1 to 4 and are oriented from negative to positive).

5.7.3 Adverse events and adverse device effects

No adverse events or device effects were observed.

5.8 Device deficiencies and serious adverse events

Device deficiencies or serious adverse events were not observed.

5.9 Subgroup analyses for special populations

5.9.1 Subgroup analyses

Subgroup analyses were performed on multiply imputed data following the ITT-principle for the primary endpoint insomnia symptoms (ISI total score) for the subgroup analyses presented in tables 14-17. The analyses presented in tables 18-21 are based on complete cases, as the subgroups were defined using treatment use data from follow-ups (T1 and T2), which ensures complete data by definition. An overview of the results of the subgroup analyses presented in tables 14-17 in the form of a forest plot is given in figure 4. The means at T1/T2 presented in tables 14-21 are unadjusted for baseline.

- Age

Table 14 | Subgroup analysis based on age for the primary endpoint insomnia severity at T1.

	Time	**Control**			***somnovia***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
18-65 years (n = 252)	T0	120	19.6	4.1	132	18.7	3.9	-	-	-
	T1	120	15.8	5.3	132	11.7	5.3	-3.6 (-5, -2.3)	< 0.001	0.78 (0.49, 1.07)
> 65 years (n = 38)	T0	21	21.1	2.4	17	19.3	4.2	-	-	-
	T1	21	16.8	5.3	17	15.3	5.4	-0.3 (-3.3, 2.8)	0.856	0.28 (-0.37, 0.94)

[a] Group difference on original scale 3 months after baseline, adjusted for baseline scores.
[b] based on unadjusted values; positive values show effects in favor of the intervention group.

- Sex

Table 15 | Subgroup analysis based on sex for the primary endpoint insomnia severity at T1.

Time	**Control**			***somnovia***			**ANCOVA**		
	n	mean	SD	n	mean	SD	Treatment	*p*-value	Cohen's *d*

								effect (95% CI)[a]		(95% CI)[b]
Women (n = 214)	T0	104	20.2	3.6	110	19.1	4.1	-	-	-
	T1	104	15.8	5.2	110	12.3	5.7	-2.9 (-4.3, -1.4)	< 0.001	0.65 (0.34, 0.96)
Men (n = 76)	T0	37	18.7	4.4	39	17.9	3.3	-	-	-
	T1	37	16.3	5.7	39	11.6	4.6	-4.3 (-6.5, -2.1)	< 0.001	0.92 (0.43, 1.42)

[a] Group difference on original scale 3 months after baseline, adjusted for baseline scores.
[b] based on unadjusted values; positive values show effects in favor of the intervention group.

- Psychotherapy status

Table 16 | Subgroup analysis based on psychotherapy status at baseline for the primary endpoint insomnia severity at T1.

	Tim	**Control**			***somnovia***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
In psychotherapy (n = 65)	T0	28	19.7	3.6	37	19.1	3.9	-	-	-
	T1	28	15.2	5.3	37	12.1	6.4	-2.8 (-5.4, -0.2)	0.032	0.55 (0.06, 1.04)
Not in psychotherapy (n = 225)	T0	113	19.8	3.9	112	18.7	3.9	-	-	-
	T1	113	16.1	5.3	112	12.1	5.1	-3.4 (-4.7, -2.1)	< 0.001	0.77 (0.47, 1.07)

[a] Group difference on original scale 3 months after baseline, adjusted for baseline scores.
[b] based on unadjusted values; positive values show effects in favor of the intervention group.

- Medication

Table 17 | Subgroup analysis based on psycholeptic / psychoanaleptic medication at baseline for the primary endpoint insomnia severity at T1.

	Time	**Control**			***somnovia***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
On medication[c] (n = 132)	T0	66	19.9	3.8	66	19.8	3.7	-	-	-
	T1	66	16.0	5.5	66	12.9	6.1	-3.1 (-5, -1.1)	0.002	0.55 (0.16, 0.94)
Not on medication[c] (n = 158)	T0	75	19.7	3.9	83	18.0	3.9	-	-	-
	T1	75	15.9	5.3	83	11.5	4.8	-3.4 (-4.8, -2.0)	< 0.001	0.88 (0.54, 1.22)

[a] Group difference on original scale 3 months after baseline, adjusted for baseline scores.
[b] based on unadjusted values; positive values show effects in favor of the intervention group.
[c] ATC classification codes N05 / N06.

- Use of any therapy at T1 / T2

Table 18 | Subgroup analysis based on use of any therapy (psychotherapy and/or psycholeptic / psychoanaleptic medication) at T1 for the primary endpoint insomnia severity at T1.

	Time	**Control**			***somnovia***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
In any therapy[c] at T1 (n = 130)	T0	70	19.9	4.0	60	19.8	3.9	-	-	-
	T1	70	15.8	5.5	60	12.8	6.2	-2.8 (-4.7, -0.9)	0.003	0.50 (0.15, 0.85)
Not in any therapy[c] at T1 (n = 119)	T0	57	19.3	3.8	62	17.4	3.6	-	-	-
	T1	57	16.0	5.2	62	11.2	4.7	-3.7 (-5.4, -2.0)	< 0.001	0.98 (0.60, 1.36)

[a] Group difference on original scale 3 months after baseline, adjusted for baseline scores.
[b] based on unadjusted values; positive values show effects in favor of the intervention group.
[c] includes psychotherapy and psycholeptic / psychoanaleptic medication (ATC classification codes N05 / N06).

Table 19 | Subgroup analysis based on use of any therapy (psychotherapy and/or psycholeptic / psychoanaleptic medication) at T2 for the primary endpoint insomnia severity at T2.

	Time	**Control**			***somnovia***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
In any therapy[c] at T2 (n = 125)	T0	66	20.1	3.8	59	20.1	3.7	-	-	-
	T2	66	14.2	5.6	59	12.1	6.6	-2.1 (-4.1, -0.002)	0.049	0.34 (-0.01, 0.69)
Not in any therapy[c] at T2 (n = 121)	T0	57	19.4	3.8	64	17.0	3.4	-	-	-
	T2	57	14.9	5.8	64	10.1	5.0	-3.3 (-5.2, -1.4)	< 0.001	0.90 (0.53, 1.28)

[a] Group difference on original scale 6 months after baseline, adjusted for baseline scores.
[b] based on unadjusted values; positive values show effects in favor of the intervention group.
[c] includes psychotherapy and psycholeptic / psychoanaleptic medication (ATC classification codes N05 / N06).

- Use of any therapy at any time during the course of the study

Table 20 | Subgroup analysis based on use of any therapy (psychotherapy and/or psycholeptic / psychoanaleptic medication) at any time during the course of the study up to T1 for the primary endpoint insomnia severity at T1.

	Time	**Control**			***somnovia***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
In any therapy[c] up to T1 (n = 130)	T0	75	19.8	4.0	64	19.8	3.8	-	-	-
	T1	75	15.5	5.5	64	12.7	6.2	-2.8 (-4.6, -1.0)	0.003	0.49 (0.15, 0.82)
Not in any therapy[c] up to T1 (n = 119)	T0	52	19.4	3.8	58	17.2	3.6	-	-	-
	T1	52	16.4	5.2	58	11.3	4.6	-3.8 (-5.5, -2.0)	< 0.001	1.06 (0.66, 1.46)

[a] Group difference on original scale 3 months after baseline, adjusted for baseline scores.
[b] based on unadjusted values; positive values show effects in favor of the intervention group.
[c] includes psychotherapy and psycholeptic / psychoanaleptic medication (ATC classification codes N05 / N06).

Table 21 | Subgroup analysis based on use of any therapy (psychotherapy and/or psycholeptic / psychoanaleptic medication) at any time during the course of the study up to T2 for the primary endpoint insomnia severity at T2.

	Time	**Control**			***somnovia***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
In any therapy[c] up to T2 (n = 137)	T0	74	20.0	3.9	63	19.7	3.8	-	-	-
	T2	74	14.2	5.5	63	11.4	6.2	-2.6 (-4.5, -0.8)	0.006	0.48 (0.14, 0.82)
Not in any therapy[c] up to T2 (n = 96)	T0	45	19.3	3.7	51	16.7	3.5	-	-	-
	T2	45	14.9	6.0	51	10.0	4.8	-3.3 (-5.4, -1.1)	0.003	0.92 (0.49, 1.34)

[a] Group difference on original scale 6 months after baseline, adjusted for baseline scores.
[b] based on unadjusted values; positive values show effects in favor of the intervention group.
[c] includes psychotherapy and psycholeptic / psychoanaleptic medication (ATC classification codes N05 / N06).

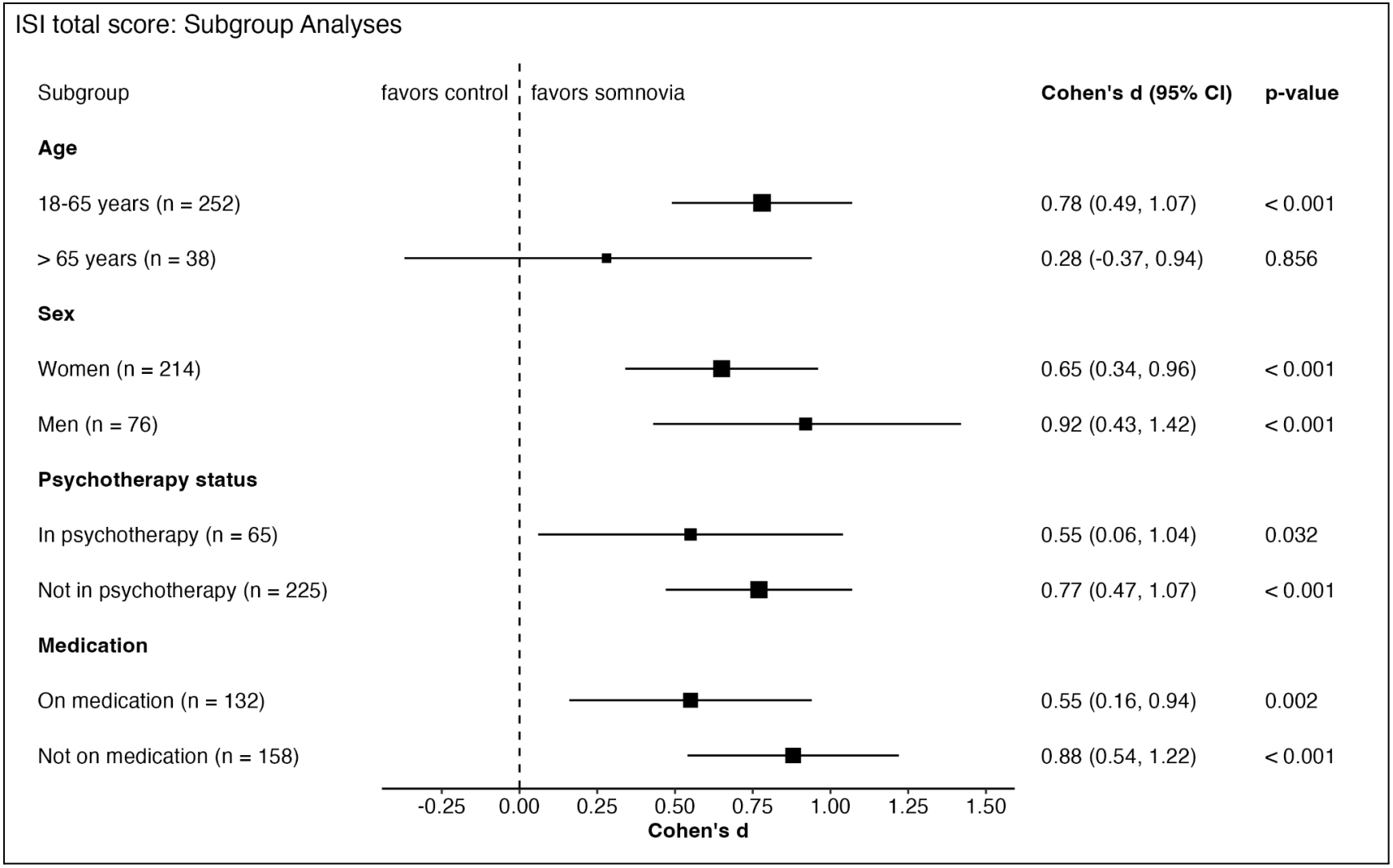

Figure 4 | Forest plot of effect sizes (Cohen's *d*) for the primary endpoint insomnia severity, assessed with the ISI total score. *p*-values are derived from the ANCOVA.

5.10 Exploratory moderation analyses

As specified in the CIP, exploratory moderation analyses were performed for the following variables: currently attending psychotherapy, depressive symptoms (PH9-9), anxiety (GAD-7) and social functioning (WSAS). Analyses in participants with complete data showed that none of these variables significantly moderated the effectiveness of *somnovia* after 3 months (all *p*s > 0.149).

5.11 Listings of deaths and reasons for deaths

Deaths and reasons thereof were not recorded during this clinical investigation.

6. Discussion and overall conclusions

6.1 Clinical performance, effectiveness and safety results

After 3 months, the *somnovia* intervention group displayed significantly lower levels of insomnia symptoms than the control group. Responder and remission analyses verified the clinical significance of these reductions. In addition, there were significant effects of *somnovia* on depression, anxiety, as well as social and work-related functioning. These intervention effects remained stable at the 6-month follow-up. The robustness of the results was confirmed by the conservative J2R sensitivity analysis and the CC-sensitivity analysis. Regarding the primary endpoint, i.e., insomnia symptoms, *somnovia* has an NNT of 5. No adverse events or device effects were observed. Patients rated their satisfaction with the program as good.

6.2 Assessment of benefits and risks

In this clinical investigation report, use of *somnovia* in addition to TAU was shown to be more effective in reducing insomnia symptoms in patients with insomnia disorder than TAU alone. Moreover, positive intervention effects on depression, anxiety and social and work-related functioning were observed. Furthermore, no adverse events or device events were observed. Therefore, the benefit-risk ratio can be rated as positive.

6.3 Discussion of the clinical relevance of the results

CBT-I, the treatment option with the highest level of recommendation in the European guideline for the treatment of insomnia [8], is hardly available in health care settings [10], [48], [49], [50]. Flexible and convenient to use, DiGAs represent valuable tools in narrowing this treatment gap [13], [14], [15], [16], [17], [50]. Specifically, for self-guided, Internet-based intervention programs based on CBT-I, a recent meta-analysis reports a medium-sized effect of d = 0.78 on insomnia severity post-treatment [10].

The results of the present RCT complement and extend these findings: Following a 3-month utilization of *somnovia*, the intervention group exhibited significantly reduced levels of insomnia symptoms in comparison to the control group, corresponding to a medium-sized effect of d = 0.71. Responder and remission analyses verified the clinical significance of these reductions. Moreover, significant effects of *somnovia* on depression, anxiety, and social and work-related functioning were observed. Intervention effects were maintained at the 6-month follow-up.

These findings, although highly promising, should be considered within the broader context of available treatment options, specifically face-to-face CBT-I, pharmacotherapy, and other DiGAs. We will discuss them separately for each confirmatory outcome.

Meta-analytic evidence suggests that CBT-I delivered by health-care professionals yields average improvements in insomnia severity in the range of d = 0.84–1.27 [10], [11], [51], [52]. However, the effective delivery of CBT-I typically requires special training for mental

health professionals. Consequently, the demand for appropriately qualified professionals far exceeds their availability [48], [49], [50]. Moreover, despite yielding descriptively larger effect sizes, a recent network meta-analysis found no evidence supporting the superiority of face-to-face delivery over unguided settings [10]. The literature concerning pharmacotherapy shows a mixed picture: While many licensed sleep medications prove effective in the acute treatment of insomnia (d = 0.36–0.83 [53]), they are often associated with adverse effects, such as dizziness, drowsiness, addiction, and relapse upon discontinuation. Furthermore, information about the long-term effects of these medications is either unavailable or insufficient, leading to the recommendation against their long-term use [8], [54], [55].

Therefore, given the substantial challenges in accessing CBT-I and the lack of evidence supporting the long-term use of pharmacotherapy, our study findings underscore the crucial role of self-guided, Internet-based CBT-I interventions such as *somnovia*. These interventions represent a valuable addition to the treatment spectrum for insomnia disorder, facilitating the dissemination of CBT-I. Their effectiveness, comparable to face-to-face delivery, addresses the needs of the many individuals with insomnia who might otherwise lack access to guideline-recommended care.

Meta-analytic evidence suggests a medium-sized effect of d = 0.78 (95% CI = [0.38; 1.18]) on insomnia severity post-treatment for self-guided, Internet-based intervention programs based on CBT-I [56]. To date, two interventions for people with chronic insomnia are already officially listed in the DiGA registry and can therefore be reimbursed by statutory health insurance in Germany: *somnio* and *HelloBetter Schlafen*. For admission into the DiGA registry, the manufacturer of *somnio* provided data from an RCT with 56 patients suffering from insomnia, which reported a between-group effect of d = 1.79 for the primary endpoint, the ISI [13]. The effect observed exceeds the meta-analytic mean by more than twofold and lies far outside the corresponding confidence interval, despite a shorter observation period of 6 weeks, contrasting with studies with observation periods up to 12 weeks, including the present study [57], [58], [59], [60]. Furthermore, the authors departed from common practice by using pre-post changes instead of post-treatment scores to calculate between-group effect sizes [61]. This led to an overestimation of the intervention effect due to significant group differences in baseline ISI scores: Given the intervention group's substantially higher baseline scores, a larger symptom reduction was expected regardless of intervention effectiveness, which can be attributed to regression to the mean [62]. Recalculating the effect size based on the more conventional approach, using post-treatment means and standard deviations reported in table 3, yielded d = 0.96, which is significantly lower than the reported d = 1.79. Thus, the significant baseline differences in the primary endpoint, likely a result of the small sample size, in combination with this methodological approach, resulted in an overestimation of the intervention effect [63]. Moreover, the study assessing *somnio*'s effectiveness involved intervention group participants completing a twice-daily sleep diary "to measure process parameters". Participants in the intervention group who failed to complete this sleep diary were sent email reminders. If they continued to miss completing the diary for three consecutive days, they were unable to proceed with the program. Importantly, participants of the control group did not fill out such a sleep diary. Given that intensive self-monitoring, such as keeping a sleep diary, already serves as an intervention itself [64], the intervention group received a combination of two separate

interventions - *somnio* and the twice-daily sleep diary. Therefore, the effectiveness of *somnio* without the addition of an extensive reminder and penalty scheme introduced by the sleep diary remains uncertain, and the reported effect size likely reflects the combined impact of *somnio* and this intensive diary-based self-monitoring intervention. By contrast, both groups in our study underwent identical sets of assessments, and no intensive reminder or self-monitoring scheme was used to support the intervention. In fact, those in the intervention group received only fully automated access to *somnovia,* without any additional support. Moreover, in contrast to the *somnio*-study, access to *somnovia* was not contingent upon completing any endpoint measurements.

Finally, we noted some inconsistencies in the *somnio* trial between the inclusion and exclusion criteria as stated in the study registration and those detailed in the published paper on *somnio*. Notably, there were fewer exclusion criteria specified in the registration compared to those presented in the paper. Overall, this suggests that the results of the *somnio* trial ought to be interpreted with caution.

HelloBetter Schlafen was investigated indirectly only, with an Individual Participant Data Meta-Analysis of 3 RCTs in different patient populations, which yielded an average between-group effect of d = 1.06. However, at least one of the available studies on *HelloBetter Schlafen* featured personal support for participants in the intervention group, provided by trained coaches, which makes it difficult to disentangle the effects of the digital intervention and the personal coaching [65]. Furthermore, the available evidence in the DiGA registry lacks sufficient detail for independent evaluation, leaving uncertainties regarding the relevance and adequacy of the described studies in assessing the treatment effect. Since the evidence from these studies did not meet the criteria for final inclusion in the DiGA directory, it suggests that substantial methodological limitations were present. Consequently, the effectiveness of *HelloBetter Schlafen* awaits confirmation through an ongoing RCT. Although our present study showed a slightly smaller effect on insomnia symptoms, the large sample size (N = 290) and its completely self-guided nature strengthen the evidence for *somnovia's* effectiveness, in contrast to *somnio* and *HelloBetter Schlafen*.

In the context of treating depressive symptoms in individuals with insomnia disorder, meta-analyses of unguided CBT-I interventions show an average effect size of d = 0.35-0.43 [56], [66], [67]. A comparable meta-analytic effect on depressive symptoms is documented for face-to-face delivery of CBT-I (d = 0.34 [68]). The average meta-analytic effect size for treating depressive symptoms with pharmacotherapy is reported at d = 0.30 [69]. *HelloBetter Schlafen* had an effect of d = 0.85 on depressive symptoms in one study that investigated its use in teachers with sleeping problems [70]; *somnio* reported a between-group effect of d = 1.01 [13]. Whereas both effects are thus larger than the one we observed for *somnovia,* again, the large sample size of the present RCT underlines the robustness of our findings. Therefore, the observed effect of somnovia in alleviating depressive symptoms among individuals with insomnia disorder (d = 0.66) seems highly favorable when considered in comparison to the existing evidence for alternative treatment approaches.

When considering the outcome anxiety in patients with insomnia disorder following treatment with CBT-I, meta-analyses report average effect sizes of *d* = 0.29-0.41 [56], [67], [71], [72]. The average meta-analytic effect size for treating anxiety symptoms with pharmacotherapy is reported at *d* = 0.33 [69]. The DiGA *somnio* did not have any significant effect on anxiety symptoms (*d* = 0.29, *p* = .290) [13]. Therefore, considering the available evidence, the effect size of *d* = 0.56 observed for *somnovia* in reducing anxious symptoms among individuals with insomnia disorder can be considered a very positive result.

When considering the outcome of psychosocial functioning in insomnia disorder, the data in the literature is very limited. One study showed that 8 weeks of face-to-face CBT-I significantly improve social and work-related functioning [73]. Meta-analytic evidence is only available for the related outcome quality of life, showing small to medium effects of face-to-face CBT-I (*d* = 0.46) and digital CBT-I compared to control groups (*d* = 0.46). Thus, the observed effect of *somnovia* on social and work-related functioning (*d* = 0.50) is comparable to the available data.

Analyzing the subgroup results, *somnovia* overall showed significant effects regardless of whether participants were using concomitant therapies (psychotherapy and/or psychotropic medication) at baseline or during the course of the study. The observed effects were descriptively somewhat larger in participants who were not using additional therapies, suggesting that *somnovia* may be more effective when it is used as standalone treatment. Conceptually, this finding is consistent with evidence suggesting that, following acute therapy, treatment with CBT-I alone is more effective than the combination of CBT-I and pharmacotherapy [74], [75]. Participants already receiving psychotherapy and/or psychotropic medication might have reached a level of “therapeutic saturation”, leaving less room for additional improvement from *somnovia*. However, even in these cases, *somnovia* has a significant add-on effect on the therapeutic outcome. Overall, the subgroup analyses demonstrate that *somnovia* is effective both as a standalone therapy and when used alongside other treatments, underscoring its potential for wide application in various therapeutic contexts.

In summary, *somnovia* stands out favorably when compared to existing treatment options, including the DiGAs already listed, for all tested outcomes in insomnia disorder. Although resource-intensive face-to-face CBT-I shows a slight descriptive advantage in reducing insomnia severity, its accessibility in practical care settings is very limited. Long-term use of pharmacotherapy is not recommended for managing insomnia, and its effects on the secondary endpoints of depression and anxiety are considerably smaller compared to the observed effects of *somnovia*. The evidence supporting *somnovia* also sets it apart from other listed DiGAs for chronic insomnia. Unlike studies on *somnio* and *HelloBetter Schlafen*, which relied on extensive reminder schemes and personal support, leaving the true effectiveness uncertain, *somnovia* was rigorously tested as the fully automated intervention it is. Furthermore, the *somnio* and *HelloBetter Schlafen* studies revealed additional methodological ambiguities, including uncommonly large effect sizes, significant baseline differences in the primary endpoint, and discrepancies between the methods described in the trial registry versus the published study report. In contrast, there are no such ambiguities in the *somnovia* trial, and its effect sizes closely align with established literature on unguided

insomnia interventions, affirming the credibility of the provided evidence. Moreover, the considerable sample size in the effectiveness trial enhances the robustness of *somnovia*'s evidence, consolidating its position as a promising, scalable solution for managing insomnia symptoms. Notably, *somnovia* also demonstrated significant effects on depression, anxiety, and psychosocial functioning, underscoring its multifaceted benefits for patients.

6.4 Specific benefits or special precautions required for individual subjects or groups considered to be at risk

Using *somnovia* in addition to TAU was found to be more effective in reducing insomnia symptoms compared to TAU alone. *somnovia* should only be used as an adjunct to usual care, not as a substitute for it.

6.5 Implications for the conduct of future clinical investigations

This clinical investigation affirms the feasibility of online studies assessing the efficacy of fully automated interventions for insomnia disorder. The user feedback highlights a willingness in the target population to embrace digital solutions. Future studies might explore whether certain patient profiles or care settings yield greater benefits from *somnovia*.

6.6 Limitations of the clinical investigation

Slight differences in dropout rates emerged between the intervention and control group. It is conceivable that some participants in the intervention group used *somnovia* until they perceived sufficient benefits, subsequently opting out of further study involvement—a phenomenon extensively documented as the “good enough” effect in psychotherapy research [78], [79]. Notwithstanding this limitation, our study establishes that *somnovia* reduces insomnia symptoms significantly and to a clinically relevant extent.

7. Abbreviated terms and definitions

ANCOVA	analysis of covariance
CBT-I	Cognitive behavioral therapy for insomnia
CC	complete case
CI	confidence interval
CIP	clinical investigation protocol
DiGA	“Digitale Gesundheitsanwedung”
GAD-7	Gesundheitsbogen für Patienten - 7 Items
ISI	Insomnia Severity Index
ITT	intent to treat
J2R	jump to reference
MCID	Minimal Clinically Important Difference
NPS	Net Promoter Score
NRS	Numeric Rating Scale
PDF	Portable Document Format
PHQ-9	Gesundheitsbogen für Patienten - 9 Items
PP	Per Protocol
RCI	Reliable Change Index
RCT	randomized controlled trial
SD	standard deviation
SE	standard error
SMS	Short Message Service
TAU	treatment as usual
WSAS	Work and Social Adjustment Scale

8. Ethics

This study was reviewed and approved by the ethics committee of the Medical Faculty of the Christian-Albrecht University of Kiel (reference number D 495/22). The clinical investigation was conducted in accordance with the ethical principles in the Declaration of Helsinki. Prior to participation, detailed patient information was provided and informed consent was obtained online.

9. Investigators and administrative structure of clinical investigation

This clinical investigation was primarily conducted as an online trial without a traditional physical investigation site. Study management including patient recruitment and data acquisition was conducted by the sponsor. No funding was provided by the sponsor.

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- role: trial management, online-data acquisition and analyses.

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- role: Key Opinion Leader, consulting cooperation partner to discuss trial design and analyses

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11. Appendix

Table 22 | Baseline-adjusted means derived from the ANCOVA model for the primary endpoint insomnia severity (ISI total score).

Time		Control		*somnovia*	
		mean	SE	mean	SE
ITT	T1	15.7	0.4	12.4	0.4
	T2	14.3	0.5	11.5	0.4
J2R	T1	15.6	0.4	13.0	0.4
	T2	14.3	0.4	12.0	0.4
CC	T1	15.6	0.4	12.3	0.5
	T2	14.2	0.5	11.4	0.5
PP	T1	15.6	0.4	12.3	0.4
	T2	14.3	0.5	11.4	0.5

Table 23 | Baseline-adjusted means derived from the ANCOVA model for the secondary endpoint depression (PHQ-9 total score).

Time		Control		*somnovia*	
		mean	SE	mean	SE
ITT	T1	10.1	0.3	7.4	0.3
	T2	9.5	0.3	7.0	0.3
J2R	T1	10.1	0.3	8.0	0.3
	T2	9.4	0.3	7.4	0.3
CC	T1	10.0	0.3	7.4	0.3
	T2	9.3	0.4	6.9	0.4
PP	T1	10.0	0.3	7.3	0.3
	T2	9.4	0.3	6.9	0.4

Table 24 | Baseline-adjusted means derived from the ANCOVA model for the secondary endpoint anxiety (GAD-7 total score).

Time		Control		*somnovia*	
		mean	SE	mean	SE
ITT	T1	7.8	0.3	5.6	0.3
	T2	7.4	0.3	5.4	0.3
J2R	T1	7.8	0.3	6.1	0.3
	T2	7.4	0.3	5.9	0.3

CC	T1	7.8	0.3	5.6	0.3
	T2	7.3	0.3	5.3	0.3
PP	T1	7.8	0.3	5.5	0.3
	T2	7.4	0.3	5.3	0.3

Table 25 | Baseline-adjusted means derived from the ANCOVA model for the secondary endpoint social and work-related functioning (WSAS total score).

Time		**Control**		***somnovia***	
		mean	SE	mean	SE
ITT	T1	15.9	0.6	11.9	0.6
	T2	14.3	0.6	10.4	0.6
J2R	T1	15.9	0.6	12.7	0.6
	T2	14.3	0.6	11.1	0.6
CC	T1	15.8	0.6	11.9	0.6
	T2	14.2	0.6	10.2	0.6
PP	T1	15.9	0.6	11.7	0.6
	T2	14.3	0.6	10.3	0.6