Somryst®

Clinician Instructions for Use

Somryst® Prescription Digital Therapeutic

Somryst Clinician Instructions for Use

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Somryst App Version 2.x

Manufactured by:

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Rx Only
Caution: Federal Law restricts this device to sale by or on the order of a licensed healthcare professional in accordance with the law of the state in which that person practices to use or order the use of the device.

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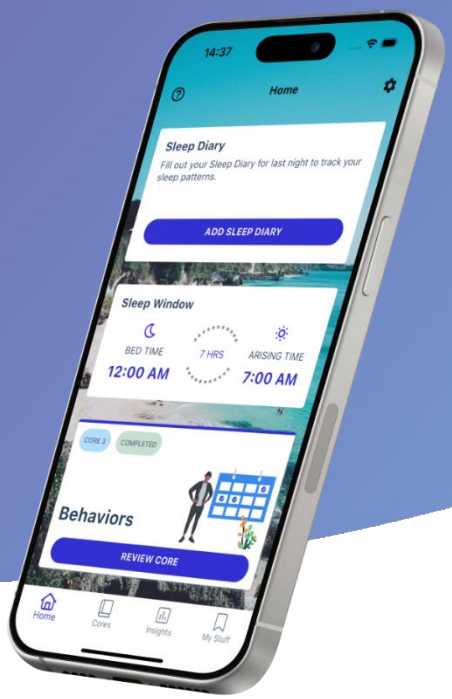
Somryst®, a mobile app is a 9-week Prescription Digital Therapeutic (PDT) for chronic insomnia.



Somryst® Product Overview

Somryst is a 9-week Prescription Digital Therapeutic (PDT) for chronic insomnia. Somryst can be used on a mobile device, such as a smartphone or tablet. Somryst is available by prescription only. A licensed Health Care Provider (HCP) must prescribe Somryst and use of Somryst should be undertaken only under the supervised care of a Health Care Provider.

Somryst delivers digital Cognitive Behavioral Therapy for Insomnia (CBT-I) therapeutic content. CBT-I is a neurobehavioral treatment that focuses on addressing the maladaptive behaviors, routines, and dysfunctional thoughts that perpetuate sleep problems, regardless of the original source of the sleep problem.

CBT-I is typically delivered by a specialty-trained clinician, either 1:1 or in group format. Standard delivery of CBT-I usually occurs in weekly sessions over 6-8 weeks. CBT-I can be conceptualized as six sessions or Cores that deliver proven behavioral and cognitive treatment strategies. Somryst delivers treatment with the following 6 treatment Cores:

1. **Get Ready:** This Core sets the stage for the therapeutic experience. It lets patients know what they will need to learn and do to improve sleep.
2. **Sleep Window:** This Core is one of the most important ones. The patient will receive their first Sleep Window — a recommended Bedtime and Arising Time.
3. **Behaviors:** This Core helps patients identify and change certain habits and behaviors that can interfere with sleep. It establishes the key guidelines of CBT for insomnia
4. **Thoughts:** This Core explains how a patient's thinking can contribute to insomnia. The patient will learn to identify and shift problematic thought patterns.
5. **Education:** This Core helps patients figure out what changes in their lifestyle and environment can promote better sleep.
6. **Looking Ahead:** This Core pulls together what patients have learned, prepares patients for the future, and teaches them what to do if they experience a relapse.

The Cores typically follow this structure:

- **Review:** Review of the previous week's sleep (after the first Core, "Get Ready"), as collected in a sleep diary, and of homework (practiced strategies) from the previous week
- **Session Objectives:** Provides the rationale for the new treatment Core
- **Main Content:** Introduces new treatment content and strategies
- **Summary:** Wraps up the session by recapping above
- **Assignment:** Assignment of homework/strategies for upcoming week

Somryst includes a daily Sleep Diary in which patients record information about their sleep. The My Stuff section provides selected resources and elements from each Core for review. The My Stuff section for each Core is available after the Core is completed.

Intended Use / Indications for Use

Somryst is a prescription-only digital therapeutic intended to provide a neurobehavioral intervention (CBT-I) to patients 22 years of age and older with chronic insomnia. Somryst treats patients with chronic insomnia by improving a patient's insomnia symptoms.

Who Should Use Somryst

The intended **patient** group includes people that:

- Are 22 years of age or older with chronic insomnia
- Are able to read and understand English
- Have regular access to a mobile device (such as smartphone or tablet)
- Are familiar with how to use mobile apps (applications)
- Are able to upload data periodically, i.e., have internet/wireless connection access
- Are under the supervision of a Health Care Provider

The intended **operators** are health care providers who treat patients with chronic insomnia. The patient follows the treatment at home after having been granted access and introduction to the digital therapeutic device by a health care provider.

Who Should Not Use Somryst
(Contraindications)

Somryst uses sleep restriction and consolidation, limiting the time a patient spends in bed to match the amount of time they sleep. This treatment technique can increase risks to some patients whose pathophysiology may be worsened. Because of this, it is not appropriate for everyone.

Patients with the following conditions or disorders should not use Somryst:

- Any disorder exacerbated by sleep restriction (e.g. bipolar disorder, schizophrenia, other psychotic spectrum disorders)
- Untreated obstructive sleep apnea
- Parasomnias
- Epilepsy
- Individuals at high risk of falls
- Individuals who are pregnant
- Individuals who have any other unstable or degenerative illness judged to be worsened by sleep restriction delivered as part of CBT-I

The Benefits of Somryst

Use of Somryst can result in significant and lasting improvements to insomnia symptoms for your patients. Results from the Somryst Pivotal Studies showed patients experience a significant reduction in severity of insomnia after treatment, with more than 40% of the patient group no longer meeting the criteria for insomnia.

Therapeutic benefits from the use of Somryst are only possible for your patients if they follow the instructions and practice the exercises and strategies provided in the program. Treatment results may vary for your patients.

Risks associated with using Somryst are described in the “Safety Information and Warnings” section on next page.

Safety Information and Warnings

Somryst is not for everyone. Please use your clinical judgment to determine whether Somryst is right for your patient.

- Somryst is not for emergency use. Please instruct patients to dial 911 or go to the nearest emergency room in the event of a medical emergency.
- Patients should be clearly instructed not to use Somryst to communicate severe, critical, or urgent information to their Health Care Provider.
- Somryst is meant to be used as treatment with supervision of a Health Care Provider.
- Somryst is not meant to be a substitute for any treatment medication.
- Somryst contains sensitive medical information. Please instruct patients to protect their information by password-protecting their smartphone or tablet, and ensuring no one else may access their device
- Sleep Restriction (and Consolidation) within Somryst can cause sleepiness, especially in the early stages of using the PDT. Somryst should not be used if the patient needs to be alert or cautious to avoid serious accidents in their job or daily life. Examples include:
  - — Long-haul truck drivers
  - — Long-distance bus drivers
  - — Air traffic controllers
  - — Operators of heavy machinery
  - — Some assembly line jobs
- The usage data collected in therapy lessons by Somryst are not intended to be used as a standalone assessment of treatment progress.

Note: In the early stages of treatment, increased daytime sleepiness may be expected, but is usually temporary. Please instruct the patient to consult with their HCP if these experiences do not go away over a few weeks, as it may indicate that they have another sleep disorder or medical condition other than insomnia. Please instruct the patient that if they have trouble staying awake while performing potentially dangerous tasks (like driving) at any point in the treatment, to avoid these dangerous tasks or stop following the sleep restriction component of the therapy.

Note: For operational support, in case of use errors, cybersecurity events or other type of events, please contact support@noxmedical.com.

Please instruct the patient to read and follow the instructions provided in each module, and to stay with the therapy until the end to achieve the best results with Somryst. Please instruct the patient that it is important to give honest and accurate answers when reporting sleep results.

Somryst Product Description

Downloading Somryst

Your patients will have to download Somryst to access the product. Below are instructions needed to obtain access to Somryst:

To download Somryst on the **iPhone or iPad**:

- Tap the App Store icon on the home screen
- Tap the search icon and type “Somryst”
- Tap the “Get” button. The patient may need to enter their Apple ID and Password, or use Touch ID or Face ID to approve the download
- When Somryst is downloading, the Somryst icon will be visible on the home screen. Download progress is indicated within the icon
- Tap the Somryst icon to open the app when download completes

To download Somryst on an **Android** phone or tablet:

- Tap on the Play Store app on the Android device
- Tap on the search bar and type “Somryst”
- Tap “Install”
- When Somryst is downloaded, either tap “Open” in the Play Store or, go to the home screen and tap the Somryst icon

Compatible Devices

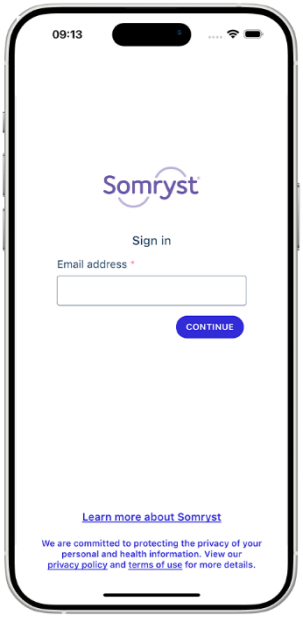
Somryst is compatible with smartphone and tablet devices running:

- iOS version 15 or higher
- Android version 8 or higher

Please ensure your patient’s smartphone or tablet is running an Operating System (OS) version matching those above. If not, then please instruct the patient to update their software version before downloading and using Somryst.

The Patient Therapeutic Mobile Application

Getting Started

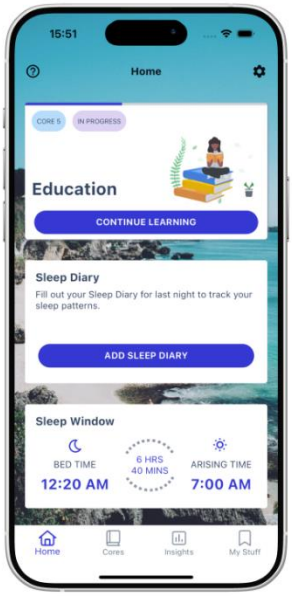


When Somryst is prescribed, the patient will receive an email to activate the Somryst prescription. The patient must launch the Somryst therapeutic software application. Somryst will show the log-in screen. The patient's email address and password can be used to log-in. During the initial onboarding, the patient's device must be connected to the Internet.

When logging in for the first time, the patient will be asked to enable fingerprint or face recognition for Somryst. This will allow the patient to quickly log in and access Somryst offline. This allows the patient to quickly re-authorize access to Somryst. If biometrics (fingerprint or face recognition) are not supported o the patient's mobile device, a passcode or pattern set on the device can be used instead.

Getting Around

This section describes how to navigate between the different areas of Somryst.



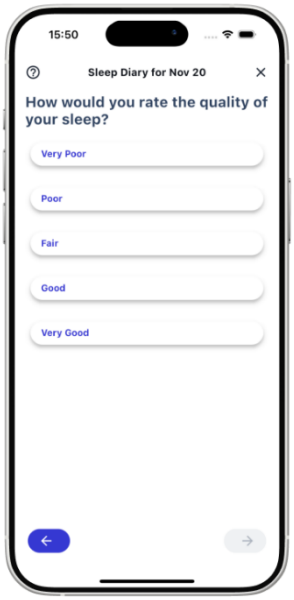
Basic Navigation

Instruct the patient to use the tab bar at the bottom of the screen to move between the main sections of Somryst. The active section will be highlighted.

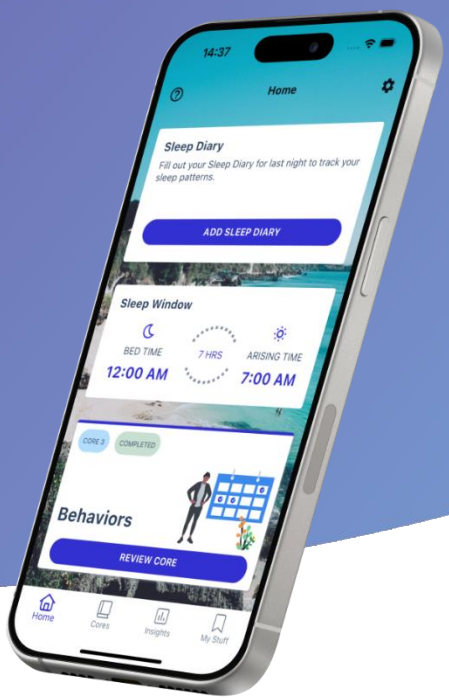
The arrows at the bottom of the screen lets the patient turn pages to read through the Core lessons. They can move forward or backward when the arrow is shown on the right or left side of the screen.

Access Help from the top of the home screen. The Help section contains information about how to use Somryst, including the directions for use.

The **Settings** section allows the patient to log out of Somryst, reset password, enable biometrics or device credentials to unlock the app, and delete the account.



Use the tab bar icons to move easily between different sections of Somryst.



Using the Tab Bar

The tab bar allows the patient to move easily between different sections of Somryst.

Home

Tapping the **Home icon** takes the patient to the home screen. Tap this icon from anywhere in Somryst to go home.

Cores

The **Cores icon** takes the patient to the list of Core modules. If a Core is available, it will be listed in blue. Unavailable Cores are shown in gray text with a lock icon.

Insights

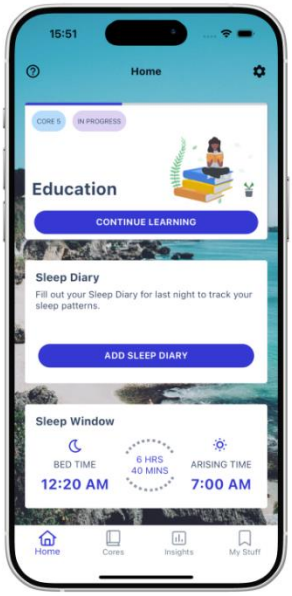
The **Insights icon** takes the patient to the Sleep Diary and Wake charts. This section also contains other useful information from their Sleep Diaries.

My Stuff

Tap the **My Stuff icon** to review important information from each Core.

Somryst Features

The most important sections of Somryst are described in the following pages.

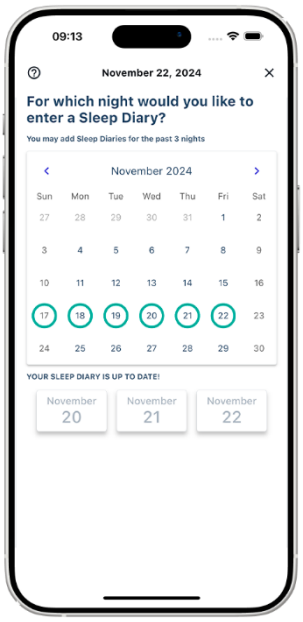


Home

On the Home screen, patients will find important information about their progress in the program and what they should do next. When a Sleep Window is available, patients can see their assigned bedtime and arising time. The number of sleep diaries entered for the week is also shown. Patients can also read an explanation of this week's Core.

Sleep Diaries

By entering Sleep Diaries, the patient collects important information about their sleep patterns, and track their progress in the program. To provide Somryst the most accurate information, patients complete the Sleep Diary every day. If possible, the Sleep Diary should be completed within one hour of getting out of bed. Patients can enter Sleep Diaries for the current day and the previous two days. The Sleep Diary can always be accessed from the home screen.



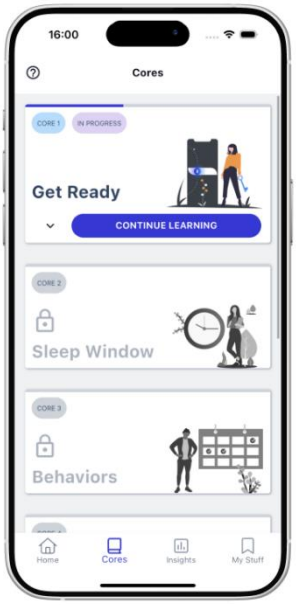
The Sleep Diary can be used to track sleep for people who are awake or asleep at unusual times. In the Sleep Diary, the word "day" refers to the time when your patient is awake. The term "bed" refers to when your patient usually sleeps. Patients should not worry about giving exact times and should not watch the clock. Patients should just give their best estimate when completing the Sleep Diary.

Cores

The Cores screen shows the 6 Cores of Somryst.

Cores provide new treatment techniques. When Cores are available, patients will see a button that, when tapped, will begin the Core. Tapping the icon will show a list of the topics in each Core. Cores that are not yet available show a gray lock icon.

If patients leave the Core, they can pick up again where they left off. Cores that patients need more time to complete show a progress bar at the top.



Insights

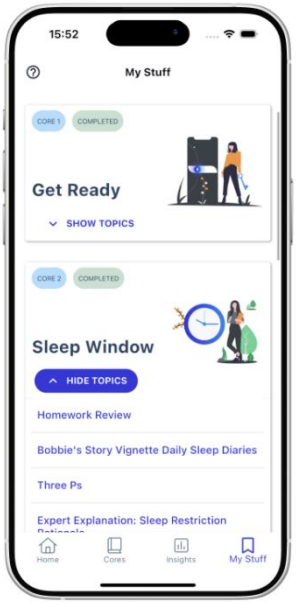
The Sleep and Wake Charts show your patients sleep pattern for the previous seven days. The patient can also view important information from their Sleep Diary, such as the quality of your sleep and any sleep medicines logged for the week.

Patients can use the arrows at the top of the screen to show data for previous weeks.

My Stuff

My Stuff allows the patient to easily review important information from Cores they have already finished. The patient can always revisit this information from within the Core, but My Stuff provides a shortcut.

Each Core's My Stuff information is unlocked after patients have completed that Core.



Notifications

Somryst will send patients notifications to help keep themon track. They will receive reminders to log their daily Sleep Diary, as well as notifications when new Cores are available.

Notifications help patients stay on track and make progress in sleep therapy.

Mobile Application Support

Security

Please remind patients that it is their responsibility to secure their mobile device (smartphone or tablet). If the patient uses an iPhone or iPad, they should use a passcode known only to them. If available, Touch ID or Face ID should be used. If the patient uses an Android phone or tablet, they should use a passcode or pattern, and enable face or fingerprint-unlock if available.

It is the patient's responsibility to update their phone or tablet operating system when recommended by the platform vendor (Apple or Google). Important security updates are included in operating system upgrades. The vendor will do this by notifying the patient on their device that an update is available for download and install.

Replacing A Device

If the patient needs to replace their smartphone or tablet, they should download Somryst again from the Apple Appstore or Google Play store and log in with their email address and password. The patient's progress in the program is saved with the Somryst prescription, so the patient will be returned to the place where he or she left off.

Updating Somryst

If an update is available for Somryst, an alert will appear when the patient next opens Somryst. To update:

- Tap "Upgrade Now" to confirm that you would like to install the update
- The patient will be taken to the Somryst app in the Apple App Store or Google Play Store
- Select "Update" next to the Somryst App
- Tap the icon to open Somryst.

Updating Somryst (continued)

For instructions on how to set up automatic app updates on a phone or smart device, visit the following web pages:

- Apple Support
- Google Play Support

For instructions on how to update the operating system (iOS or Android) of the phone or smart device, visit the following web pages:

- iOS Updates
- Android Updates

Traveling with Somryst

When traveling, the patient should follow the instructions below to ensure use of Somryst:

- Date and Time settings should be automatic. When connecting to a new network, the phone or smart device updates the time zone.
- If the time zone does not automatically adjust, go to the date and time settings to find the correct time zone, or to set the time zone back to automatic.
- Turning off cellular data will allow Somryst to be used without a network. An internet connection is required to login with an email address and password, and to update the server with new data, including Sleep Diaries and Sleep Window. Before turning off the cellular data, the patient must be logged in to the app and make sure that biometrics or device credentials (passcode or pattern) are enabled in the app.
- Somryst cannot be updated unless the mobile device (smartphone or tablet) is connected to Internet (e.g., cellular data or Wi-Fi).

Additional Support

For additional support the patient can contact their Health Care Provider, or contact Nox Medical support at support@noxmedical.com.

Somryst Prescriptions

Dose and Frequency

Patients should be clearly instructed to complete a dose of all 6 treatment Cores. Patients who have completed all 6 Cores have shown the best outcomes.

Each core should be completed on a frequency of one core every 7 days.

Patients should complete their Sleep Diary daily and follow the sleep restriction window recommendations provided by Somryst.

Duration and Extension

Patient access to Somryst will automatically discontinue after 9 weeks (63 days).The prescription will end automatically based on the start date. Additional 9-week use of the therapy may benefit the patient, as insomnia is achronic disease.

Decommissioning and Disposal

To delete Somryst from an **iPhone** or **iPad**:

- Touch and hold the app.
- Tap Remove App.
- Tap Delete App, then tap Delete to confirm.

To delete Somryst from an **Android** phone or tablet:

- Tap on the Play Store app on your Android device.
- At the top right, tap the Profile icon.
- Tap Manage apps & devices and select Manage.
- Select the Somryst app.
- Tap “Uninstall”.

For further instructions on how to delete the application, visit the following web pages

- Apple Support
- Google Play Support

If there are any questions or assistance is required regarding the decommissioning and/or disposal process, including the retrieval or deletion of user data, please contact support@noxmedical.com.

Security Information

Somryst complies with the following security standards and guidelines:

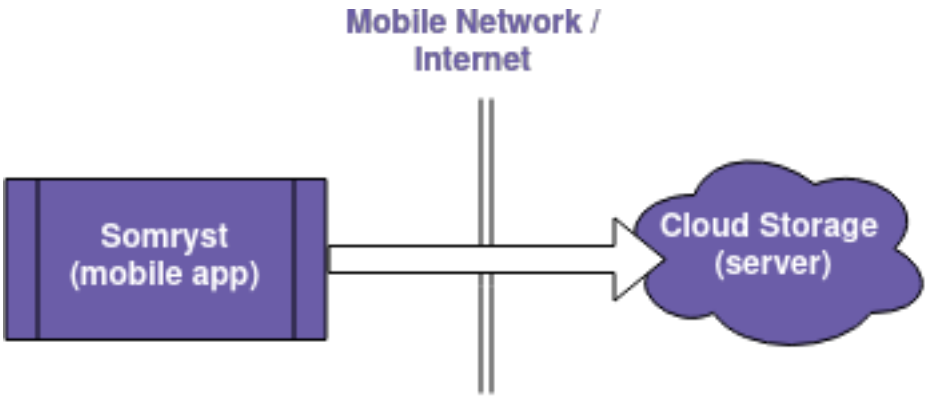
- IEC 81001-5-1:2021 Health software and health IT systems safety, effectiveness and security – Security - Activities in the product life cycle
- IEC 82304-1:2016 Health Software – General requirements for product safety
- ANSI/AAMI SW96:2023 Standard for Medical Device Security – Security Risk Management for Device Manufacturers

The data storage on the cloud server has the following certifications:

- ISO 27001
- SOC2
- HITRUST

Somryst Ecosystem

Somryst ecosystem consists of a mobile application (Somryst) and Cloud Storage. Data is sent from the mobile device to the cloud storage for review.



Data at Rest

The Cloud Storage is encrypted. The encryption used is an industry standard AES-256 data encryption.

Data in Transit

All Mobile Network/Internet data is transferred using encrypted endpoints (on port 443). No non-encrypted endpoints are provided for data communication.

The endpoint encryption uses TLS 1.2. The connection is encrypted using 256-bit encryption. SHA1 is used for message authentication and DHE_RSA as the key exchange mechanism.

Cloud Backups

All data is backed up both fully and incrementally. Incremental backups are performed daily, weekly and monthly with full recovery at least annually. Backups are tested at regular intervals to ensure successful recovery of data.

Cloud System Monitoring

Best practices for system monitoring are employed to ensure the security and stability of the system. AWS Inspector, CloudWatch and CloudTrail are used to monitor the systems for vulnerabilities, unusual activities and performance issues. Wazuh is used to monitor the logs for unusual activities or unauthorized file system changes. All these systems can generate alerts and block potentially threatening IP addresses.

Cloud Intrusion Detection and Prevention

To ensure that unauthorized people and services do not gain access to the platform, several intrusion detection and prevention measures have been implemented.

Log files are monitored to detect and prevent brute force attacks. Log files are monitored to detect multiple failed attempts to try to access the system and then block the IP of the calling system when this occurs.

User Configuration

To ensure seamless operation of the Somryst mobile application, the following security measures may need to be implemented by the user in case the mobile device or the home network is protected with e.g. a firewall application:

- Whitelisting of *.noxhealth.com (the asterisk means that subdomains shall be included) in the user's local firewall configuration
- Allowing outgoing traffic on port 443 to *.noxhealth.com in the user's local firewall configuration

Security Updates

All vulnerabilities notified / detected are assessed using the CVSS1. The score ranges between 0 and 10 and Security Updates are issued according to the following:

- CVSS 9.0-10.0: Critical – turn off service until the vulnerability has been patched.
- CVSS 7.0-8.9: High – Fix within 2 days.
- CVSS 4.0-6.9: Medium – Fix within 1 week.

[1] The Common Vulnerability Scoring System (CVSS) is a method used to supply a qualitative measure of severity.

- CVSS 0.1-3.9: Low – Fix within 4 weeks.
- CVSS 0: None – No action.

Security updates are delivered via Google Play Store / Apple App Store. All installation packages are digitally signed by Nox Medical to guarantee the security and integrity of their content.

Vulnerabilities

No vulnerabilities have been identified that can affect the cybersecurity or safety of the device.

The vulnerability process used complies with the ANSI/AAMI SW96:2023 Standard for medical device security using methods described in the AAMI TIR57:2016 guidance – Principles for medical device security.

Software Bill of Materials (SBOM)

Please reach out to support@noxmedical.com for full disclosure of the latest version of the Software Bill of Material for the product. The Software Bill of Material is updated with every product release / patch / vulnerability detection and is available both in a human readable and a machine-readable format.

Clinical Studies

The therapeutic content in Somryst was evaluated in two randomized clinical trials to demonstrate safety and effectiveness.

The GoodNight Study

Therapeutic content delivered in Somryst was validated in multiple randomized clinical trials. This data set includes “The Good Night Study,” a large randomized controlled trial sponsored by the National Health and Medical Research Council (NHMRC) of Australia (ACTRN12611000121965)[1,2,3]. The Somryst PDT was tested as equivalent clinical content, under the name Sleep Healthy Using the Internet (SHUTi), which was accessed via a browser[1,2]. Somryst delivers equivalent Therapeutic content via a native mobile software application.

The study was designed after prior clinical trials to further evaluate, among other things, Somryst in a population of patients with chronic insomnia.

Study participants (n=1149) were between the ages of 18-64, with symptoms of depression (PHQ-9 score between 4 and 20), with insomnia symptoms as documented by a score of 3 or above on at least one of the first four items of the Bergen Insomnia Scale (BIS) and score of 3 or above on at least one of the last 2 items and met criteria for chronic insomnia per Modified Morin’s Insomnia Interview. Participants with Major Depressive Disorder were excluded from this study.

All study participants received usual care (UC) consisting of behavioral treatment, pharmacotherapy and/or self-treatment (e.g., visit to a general practitioner for sleep and/or mood problems, pharmacotherapy (e.g., for sleep and/or mood problems), over-the-counter sleep aids, visit to a sleep specialist, visit to a mental health provider).

Participants were randomized 1:1 to 9 weeks of treatment with the following:

- UC+SHUTi: Usual Care + SHUTi (now known as Somryst)
- UC+Control: Usual Care + Attention-matched, Digital Control

The Digital Control intervention (HealthWatch) was an interactive health and lifestyle web program that contained information about a range of health content (e.g., environmental health, nutrition, activity, medication) but had no specific mental health or sleep-related content. HealthWatch also administered weekly surveys on these topics to match for interaction required in the treatment group.

Participants in the UC+SHUTi group (n=574) were asked to complete all six Cores within the 9-week treatment period. Participants randomized to UC+Control (n=575) were asked to complete nine internet-delivered modules within the 9-week treatment

program, thus matching the attention components of SHUTi. Insomnia symptoms were evaluated for all participants at baseline, the end of the 9-week treatment period and the 6-month, 12-month, and 18-month follow-up via the Insomnia Severity Index (ISI) and sleep diaries. Sleep diaries were administered online and collected for a period of 10 days (within a 2-week window), at each assessment time point. Sleep diaries were used to calculate diary-derived composite variables, including sleep onset latency (SOL, minutes to fall asleep) and wake after sleep onset (WASO, minutes awake during the night).

Endpoint Analysis: Insomnia Severity and Symptomatology

Insomnia severity was assessed using the ISI. ISI scores were analyzed using a mixed model repeated measures ANOVA with factors for treatment, time, and treatment time interaction. Least-Squares (LS) mean ISI scores for each treatment group were compared at baseline, at the end of the treatment (week 9), and at month 6, and month 12 follow-up. The analysis included all available data for participants randomized in the trial.

Table 1. Effect of therapy on insomnia symptoms (ISI) by assessment timepoint.

Timepoint	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
	Number of Subjects	LS Mean	Number of Subjects	LS Mean		
Baseline	574	15.92	575	16.23	-0.31 (-0.81, 0.18)	0.2120
End of Treatment Period (Week 9)	250	7.23	342	13.18	-5.94 (-6.72, -5.61)	<0.0001
Month 6 Follow-up	226	7.65	280	12.13	-4.48 (-5.30, -3.67)	<0.0001
Month 12 Follow-up	162	7.62	230	11.40	-3.77 (-4.69, -2.85)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

A comparison of LS mean ISI scores is shown in Table 1. Insomnia severity symptoms were comparable across treatment groups at baseline (p=0.2120). LS mean ISI scores were in the clinical insomnia range (score > 15). Insomnia severity symptoms were reduced at week 9 (p<0.0001), month 6 (p<0.0001), and month 12 (p<0.0001) follow-up among participants who received UC+SHUTi as compared to UC+Control.

To evaluate the change in insomnia severity symptoms over baseline, the change in ISI score from baseline to week 9, month 6, and month 12 follow-up were analyzed for each treatment group (Table 2). The average reduction in ISI score was greater at week 9, month 6, and month 12 for the UC+SHUTi group (mean -8.63, -8.17, and -8.21, respectively) than the UC+Control group (mean -2.85, -3.86, and -4.63). The difference between groups was significant at each timepoint (p<0.0001).

Table 2. Effect of therapy on change from baseline (ISI) by assessment timepoint.

Timepoint	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
	Number of Subjects	LS Mean	Number of Subjects	LS Mean		
End of Treatment Period (Week 9)	250	-8.63	342	-2.85	-5.78 (-6.50, -5.06)	<0.0001
Month 6 Follow-up	226	-8.17	280	-3.86	-4.31 (-5.09, -3.53)	<0.0001
Month 12 Follow-up	162	-8.21	230	-4.63	-3.59 (-4.46, -2.71)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

Improved insomnia symptom severity was observed in the intent-to-treat study population, demonstrating efficacy of UC+SHUTi in reducing chronic insomnia symptoms. Participants who received UC+SHUTi showed statistically significant improvement in overall insomnia symptom scores, as well as the within group change in insomnia symptom scores, over UC+Control. Insomnia symptom severity was improved at the end of the treatment period and this effect was maintained to month 12 for the participants randomized to UC+SHUTi.

Participants randomized to UC+SHUTi demonstrated more than a 7-point reduction in insomnia symptom score on average, representing a clinically significant change in insomnia severity. Furthermore, by the end of the treatment period participants receiving SHUTi no longer met the threshold for clinical insomnia. This effect of treatment was maintained up to the month 12 follow-up. In contrast, participants receiving UC+Control maintained a symptom severity status registering above “no clinically significant” insomnia, on average, at the end of the treatment period and at the month 6 follow-up.

Additional Insomnia Analysis: Insomnia Severity Symptoms During Intervention (Weeks 2, 4, 6, and 8)

An analysis of insomnia severity symptoms measured every other week during the treatment period was performed. The LS mean ISI scores for the UC+SHUTI and UC+Control groups are shown for each timepoint during the intervention period in Table 3.

Table 3. Effect of therapy on insomnia symptoms (ISI) during the intervention period.

Timepoint	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
	Number of Subjects	LS Mean	Number of Subjects	LS Mean		
Baseline	574	15.92	575	16.23	-0.31 (-0.81, 0.18)	0.2120
Week 2	277	13.16	438	14.59	-1.43 (-2.00, -0.86)	<0.0001
Week 4	233	10.04	384	13.56	-3.52 (-4.19, -2.85)	<0.0001
Week 6	195	8.08	324	13.32	-5.24 (-5.97, -4.51)	<0.0001
Week 8	162	6.88	273	13.06	-6.18 (-6.96, -5.39)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

A comparison of the LS mean change from baseline to weeks 2, 4, 6, and 8 is presented in Table 4.

Table 4. Effect of therapy on change from baseline insomnia symptoms (ISI) during intervention.

Timepoint	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
	Number of Subjects	LS Mean	Number of Subjects	LS Mean		
Week 2	277	-2.85	438	-1.59	-1.26 (-1.75, -0.76)	<0.0001
Week 4	233	-5.97	384	-2.62	-3.35 (-3.96, -2.74)	<0.0001
Week 6	195	-7.92	324	-2.87	-5.05 (-5.73, -4.37)	<0.0001
Week 8	162	-9.11	273	-3.13	-5.98 (-6.73, -5.24)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

Insomnia symptoms were reduced in the UC+SHUTi group in comparison to UC+Control at Weeks 2, 4, 6, and 8 ($p<0.0001$). Likewise, there was a significant difference between treatment groups in mean change from baseline ISI score beginning at Week 2 ($p<0.0001$) that was sustained at Weeks 4, 6, and 8 ($p<0.0001$).

Additional Insomnia Analysis: Insomnia Treatment Response and Remission

An analysis of the proportion of study participants deemed treatment responders and remitters was performed using the ISI data. Responders were defined by demonstration of an ISI score reduction of > 7 points clinically. A reduction of 7 or more points is considered optimal to detect treatment responders as it represents a threshold change in insomnia severity category[4]. Remitters were defined as participants achieving an ISI score of < 8, a validated cutoff score for insomnia remission[4]. As defined by the ISI, a score ranging between 0 – 7 indicates 'no clinically significant insomnia', a score 8 – 14 indicates 'mild or subthreshold insomnia', a score 15 -21 indicates 'clinical insomnia (moderate severity)' and a score 22 – 28 indicates "clinical insomnia (severe)'[4,5].

The proportion of participants in each treatment group deemed treatment responders at week 9, month 6, and month 12 were compared using a chi-square test. Likewise, the proportion of participants in each treatment group deemed treatment remitters at week 9, month 6, and month 12 were compared using a chi-square test.

The proportion of treatment responders identified in each treatment group and their comparison at each timepoint is shown in Table 5. Using criteria of insomnia treatment response (reduction of > 7 points on the ISI from baseline), 62.8% of the UC+SHUTi group were deemed treatment responders from baseline to week 9 compared with 14.0% of the UC+Control group. At the 6 months follow-up, 56.2% of the UC+SHUTi group and 18.9% of the UC+Control group were considered responders. At month 12 follow-up, 59.3% of the UC+SHUTi group and 25.2% of the UC+Control were deemed treatment responders. The difference between treatment groups was significant at all timepoints evaluated ($p<0.0001$).

Table 5. Comparison of proportion of ISI responders (reduction in ISI score > 7 points from baseline) by timepoint.

Time of Assessment	UC+SHUTi Proportion	UC+Control Proportion	P value
End of Treatment Period (Week 9)	157 (62.8%)	48 (14.0%)	<0.0001
Month 6 Follow-up	127 (56.2%)	53 (18.9%)	<0.0001
Month 12 Follow-up	96 (59.3%)	58 (25.2%)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

A similar pattern was observed for insomnia remitters (Table 6). Using an ISI score of <8 as a cutoff point, 61.6% of the UC+SHUTi group at week 9, 63.7% at month 6, and 63.0% at month 12 were considered insomnia remitters compared with 14.9% of the UC+Control group at week 9, 20.4% at month 6, 25.7% at month 12. The difference between treatment groups (using criteria of either <10 or <8) was significant at every assessment timepoint analyzed (p<0.0001).

Table 6. Comparison of proportion of ISI remitters (ISI score of < 8) by timepoint

Time of Assessment	UC+SHUTi Proportion	UC+Control Proportion	P value
End of Treatment Period (Week 9)	154 (61.6%)	51 (14.9%)	<0.0001
Month 6 Follow-up	144 (63.7%)	57 (20.4%)	<0.0001
Month 12 Follow-up	102 (63.0%)	59 (25.7%)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

The percentage of participants that achieved a clinically meaningful insomnia treatment response or remission was higher among participants using UC+SHUTi, demonstrating efficacy of UC+SHUTi, compared to UC+Control.

A statistically significance difference in percentage of participants deemed treatment responders at the end of the intervention period was observed in favor of UC+SHUTi over UC+Control. This finding was sustained at follow-up time points (months 6 and 12) following the end of the intervention period. Similarly, a significant difference in the percentage of participants deemed to have achieved insomnia remittance was higher among participants receiving UC+SHUTi than UC+Control. The effect was observed at the end of the intervention period and was sustained 6- and 12-months. Insomnia severity scores of participants deemed to have achieved insomnia remittance were on

average, below the clinically validated cutoff score reflecting remission of clinically significant insomnia (score of < 8).

Additional Insomnia Analysis: Sleep Onset Latency and Wake After Sleep Onset

Sleep onset latency (SOL) was analyzed using a mixed model repeated measures ANOVA with factors for treatment, time, and treatment*time interaction. This analysis was similar to that done for ISI. Least-Squares (LS) mean SOL values for each treatment group were compared at baseline, at the end of the treatment (week 9), and at month 6, and month 12 follow-up. The analysis included all available data for participants randomized in the trial.

Table 7. Effect of therapy on SOL (minutes) by assessment timepoint.

Timepoint	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
	Number of Subjects	LS Mean	Number of Subjects	LS Mean		
Baseline	574	49.12	574	50.00	-0.88 (-5.28, 3.52)	0.6948
End of Treatment Period (Week 9)	124	25.50	131	47.92	-22.4 (-29.7, -15.1)	<0.0001
Month 6 Follow-up	161	25.38	201	40.53	-15.1 (-21.2, -9.09)	<0.0001
Month 12 Follow-up	130	20.48	191	37.65	-17.2 (-23.0, -11.3)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

A comparison of LS mean SOL values is shown in Table 7. SOL was comparable across treatment groups at baseline (p=0.6948). SOL scores were reduced at week 9 (p<0.0001), month 6 (p<0.0001), and month 12 (p<0.0001) among participants who received UC+SHUTi as compared to UC+Control.

To evaluate the change in SOL over baseline, the change in SOL values from baseline to week 9 and to month 6, and month 12 follow-up were analyzed for each treatment group (Table 8). The average reduction in SOL was greater at week 9 and month 6 for the UC+SHUTi group (mean -22.7 and -22.6 respectively) than the UC+Control group (mean -0.46 and -7.88). Similarly, the average reduction in ISI score was greater at month 12 for the UC+SHUTi group (mean -27.6) than the UC+Control group (mean -10.8). The difference between groups was significant at each timepoint (p<0.0001).

Table 8. Effect of therapy on change from baseline (SOL) by assessment timepoint.

Timepoint	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
	Number of Subjects	LS Mean	Number of Subjects	LS Mean		
End of Treatment Period (Week 9)	124	-22.7	131	-0.46	-22.3 (-29.2, -15.3)	<0.0001
Month 6 Follow-up	161	-22.6	201	-7.88	-14.7 (-20.4, -8.96)	<0.0001
Month 12 Follow-up	130	-27.6	191	-10.8	-16.7 (-22.2, -11.3)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

An analysis of the proportion of study participants deemed treatment remitters according to their SOL values was also performed. The proportion of participants in each treatment group deemed treatment remitters (defined by demonstration of SOL ≤30 minutes)[6] at week 9, month 6, and month 12 were compared using a chi-square test.

Table 9. Comparison of proportion of SOL remitters (SOL ≤30 minutes) by timepoint.

Time of Assessment	UC+SHUTi Proportion	UC+Control Proportion	P value
End of Treatment Period (Week 9)	163 (92.6%)	138 (64.5%)	<0.0001
Month 6 Follow-up	181 (88.7%)	179 (73.7%)	<0.0001
Month 12 Follow-up	131 (90.3%)	164 (75.9%)	0.0005

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

The proportion of treatment remitters identified in each treatment group and their comparison at each timepoint is shown in Table 9. Using criteria of SOL remittance (SOL ≤30 minutes), 92.6% of the UC+SHUTi group were deemed treatment remitters from baseline to week 9 compared with 64.5% of the UC+Control group. At the 6 months follow-up, 88.7% of the UC+SHUTi group and 73.7% of the UC+Control group were considered remitters. At month 12 follow-up, 90.3% of the UC+SHUTi group and 72.8% of the UC+Control were deemed remitters. The difference between treatment groups was significant at all timepoints evaluated. The percentage of participants that achieved clinically meaningful remission was higher among participants using UC+SHUTi, demonstrating efficacy of UC+SHUTi, compared to UC+Control.

Wake after sleep onset (WASO) was analyzed using a mixed model repeated measures ANOVA with factors for treatment, time, and treatment*time interaction. This analysis was similar to that done for ISI and SOL. Least-Squares (LS) mean WASO values for each treatment group were compared at baseline, at the end of the treatment (week 9), and at month 6, and month 12 follow-up. The analysis included all available data for participants randomized in the trial.

Table 10. Effect of therapy on WASO (minutes) by assessment timepoint.

Timepoint	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
	Number of Subjects	LS Mean	Number of Subjects	LS Mean		
Baseline	574	49.44	574	50.22	-0.79 (-5.32, 3.75)	0.7341
End of Treatment Period (Week 9)	124	22.95	131	41.80	-18.8 (-24.7, -13.0)	<0.0001
Month 6 Follow-up	161	24.04	201	39.67	-15.6 (-21.1, -10.1)	<0.0001
Month 12 Follow-up	130	25.86	191	42.34	-16.5 (-23.1, -9.91)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

A comparison of LS mean WASO values is shown in Table 10. WASO was comparable across treatment groups at baseline (p=0.7341). WASO values were reduced at week 9 (p<0.0001), month 6 (p<0.0001), and month 12 (p<0.0001) among participants who received UC+SHUTi as compared to UC+Control.

To evaluate the change in WASO over baseline, the change in WASO score from baseline to week 9 and to month 6, and month 12 follow-up were analyzed for each treatment group (Table 11). The average reduction in WASO was greater at week 9 and month 6 for the UC+SHUTi group (mean -28.7 and -27.6 respectively) than the UC+Control group (mean -11.0 and -12.5). Similarly, the average reduction in WASO was greater at month 12 follow-up for the UC+SHUTi group (mean -25.1) than the UC+Control group (mean -9.36). The difference between groups was significant at each timepoint (p<0.0001).

Table 11. Effect of therapy on change from baseline (WASO) by assessment timepoint.

Timepoint	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
	Number of Subjects	LS Mean	Number of Subjects	LS Mean		
End of Treatment Period (Week 9)	124	-28.8	131	-11.0	-17.8 (-23.4, -12.3)	<0.0001
Month 6 Follow-up	161	-27.6	201	-12.5	-15.2 (-20.2, -10.1)	<0.0001
Month 12 Follow-up	130	-25.1	191	-9.36	-15.8 (-21.8, -9.80)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

An analysis of the proportion of study participants deemed treatment remitters was also performed. The proportion of participants in each treatment group deemed treatment remitters (defined by demonstration of WASO ≤ 30 minutes) [6] at week 9, month 6, and month 12 were compared using a chi-square test.

Table 12. Comparison of proportion of WASO remitters (WASO ≤30 minutes) by timepoint.

Time of Assessment	UC+SHUTi Proportion	UC+Control Proportion	P value
End of Treatment Period (Week 9)	151 (85.8%)	135 (63.1%)	<0.0001
Month 6 Follow-up	165 (80.9%)	159 (65.4%)	0.0003
Month 12 Follow-up	119 (82.1%)	131 (60.6%)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

The proportion of treatment remitters identified in each treatment group and their comparison at each timepoint is shown in Table 12. Using criteria of WASO remittance (WASO ≤30 minutes), 85.8% of the UC+SHUTi group were deemed treatment remitters from baseline to week 9 compared with 63.1% of the UC+Control group. At the 6 months follow-up, 80.9% of the UC+SHUTi group and 65.4% of the UC+Control group were considered remitters. At month 12 follow-up, 82.1% of the UC+SHUTi group and 60.6% of the UC+Control were deemed treatment remitters. The difference between treatment groups was significant at all timepoints up to 12 months. The percentage of participants that achieved a clinically meaningful treatment remission was higher among participants using UC+SHUTi, demonstrating efficacy of UC+SHUTi, compared to UC+Control.

Effectiveness Outcomes Summary

A summary of the effect of therapy on change from baseline for chronic insomnia outcomes (is provided in Table 13 below).

Table 13. Summary of effect of therapy on change from baseline at the end of the treatment period (week 9) and follow-ups (6 & 12 months).

Assess-ment	Timepoint	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
		Number of Subjects	LS Mean	Number of Subjects	LS Mean		
ISI	End of Treatment Period (Week 9)	250	-8.63	342	-2.85	-5.78 (-6.50, -5.06)	<0.0001
	Month 6 Follow-up	226	-8.17	280	-3.86	-4.31 (-5.09, -3.53)	<0.0001
	Month 12 Follow-up	162	-8.21	230	-4.63	-3.59 (-4.46, -2.71)	<0.0001
SOL	End of Treatment Period (Week 9)	124	-28.8	131	-11.0	-22.4 (-29.7, -15.1)	<0.0001
	Month 6 Follow-up	161	-27.6	201	-12.5	-15.1 (-21.2, -9.09)	<0.0001
	Month 12 Follow-up	130	-25.1	191	-9.36	-17.2 (-23.0, -11.3)	<0.0001
WASO	End of Treatment Period (Week 9)	124	-28.8	131	-11.0	-18.8 (-24.7, -13.0)	<0.0001
	Month 6 Follow-up	161	-27.6	201	-12.5	-15.6 (-21.1, -10.1)	<0.0001
	Month 12 Follow-up	130	-25.1	191	-9.36	-16.5 (-23.1, -9.91)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

Secondary Endpoint Analysis: Safety

Safety was assessed by adverse events (AE). Adverse event reporting was initiated afterparticipant consent and lasted until participation in the study concluded. No participant- reported AEs were identified during the study.

The were no significance differences in AE rate between the UC+SHUTi and UC+Control groups, as no AEs were identified for either treatment group of the study.

Based on these data, SHUTi/Somryst® can be considered as safe as standard treatment for individuals with chronic insomnia.

The UVA Study

Therapeutic content delivered by Somryst® was validated in multiple randomized clinical trials including “The UVA Study” RCT sponsored by National Institute of Mental Health (NCT01438697) and conducted at the University of Virginia[7]. Note that the Somryst prescription digital therapeutic was tested as equivalent clinical content, under the name Sleep Healthy Using the Internet (SHUTi), which was accessed via a browser. Somryst delivers equivalent content via a native mobile software application.

The study was designed after previous clinical studies to further evaluate, among other things, Somryst in a population of patients with chronic insomnia.

Study participants (n=303) were between the ages of 21-65, with sleep-onset insomnia and/or sleep maintenance insomnia (>30 minutes for at least 3 nights/week), insomnia symptoms lasting at least 6 months, an average total sleep time ≤ 6.5 hours per night, and reported significant distress or impairment in social, occupational, or other areas of functioning caused by sleep disturbances (or associated daytime fatigue).

All study participants received Usual Care (UC) consisting of behavioral treatment, pharmacotherapy and/or self-treatment (e.g., visit to a general practitioner for sleep and/or mood problems, pharmacotherapy (e.g., for sleep and/or mood problems), over-the-counter sleep aids, visit to a sleep specialist, visit to a mental health provider. The Digital Control program provided access to nontailored and fixed digital material about insomnia symptoms; the effect, prevalence, and causes of insomnia; when to see a physician; and basic lifestyle, environmental, and behavioral strategies to improve sleep.

The evaluation of safety and effectiveness of SHUTi to improve sleep, perceived health status, and overall quality of life was evaluated. Participants were randomized 1:1 to 9 weeks of treatment with one of the following:

- UC+SHUTi: Usual Care + SHUTi
- UC+Control: Usual Care + digital patient education for insomnia

Participants in the UC+ SHUTi group (n=151) were asked to complete all six Cores within the 9-week treatment period. Participants randomized to UC+Control (n=152) were able to read the patient education material immediately upon completion of the baseline assessments and could log in to review the material as often as they desired throughout the treatment period. Insomnia symptoms were evaluated for all participants at baseline, the end of the 9-week treatment period and the 6- and 12-month follow-up via the ISI and sleep diaries. Sleep diaries were administered online and collected for a period of 10 days (within a 2-week window), at each assessment time point. Diaries were used to calculate diary-derived variables, including SOL and WASO.

The primary outcome measures of the study were insomnia symptoms, SOL, and WASO measured via ISI and daily sleep diary data at the end of the 9-week treatment period and the 6- and 12-month follow-up.

Endpoint Analysis: Insomnia Severity and Symptomatology

Insomnia symptoms were assessed using the ISI. ISI scores were analyzed using a mixed model repeated measures ANOVA with factors for treatment, time and treatment*time interaction. Least-Squares (LS) mean ISI scores for each treatment group were compared at baseline, at the end of the treatment period (week 9), and at month 6 and month 12 follow ups. The analysis included all available data for participants randomized in the trial.

A comparison of the Least Squares (LS) mean ISI scores for each treatment group and time point is shown in Table 14.

Table 14. Effect of therapy on ISI by assessment timepoint.

Time of Assessment	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
	Number of Subjects	LS Mean	Number of Subjects	LS Mean		
Baseline	151	17.03	152	17.80	-0.77 (-1.68, 0.14)	0.0976
End of Treatment Period (Week 9)	133	9.34	142	14.70	-5.36 (-6.64, -4.08)	<0.0001
Month 6 Follow-up	114	8.65	129	12.29	-3.64 (-5.00, -2.28)	<0.0001
Month 12 Follow-up	122	7.60	128	11.60	-4.00 (-5.42, -2.59)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

Insomnia symptoms were comparable across treatment groups at baseline (p=0.0976). LS mean ISI scores were in the clinical insomnia range. Insomnia symptoms were reduced at week 9 (p<0.0001), month 6 (p<0.0001) and month 12 (p<0.0001) among participants who received UC+SHUTi as compared to UC+Control. LS mean ISI scores for the UC+SHUTi group registered in the 'mild or subthreshold' insomnia range at week 9 and month 6 follow up, and below the range for 'mild or subthreshold' insomnia at month 12 follow up. While insomnia symptoms were reduced for the UC+Control group at each time point, they remained higher in the 'mild or subthreshold' insomnia range than the UC+ SHUTi group.

To evaluate the change in insomnia symptoms over baseline, the change in ISI score from baseline to week 9, to month 6 and to month 12 were analyzed for each treatment group (Table 15). The average reduction in ISI score was greater at week 9, month 6 and month 12 for the UC+SHUTi group (mean -7.83, -8.52, and -9.57 respectively) than the UC+Control group (mean -2.94, -5.36, and -6.04). The difference between groups was significant at each time point (p<0.0001).

Table 15. Effect of therapy on change from baseline in ISI score by assessment timepoint.

Time of Assessment	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
	Number of Subjects	LS Mean	Number of Subjects	LS Mean		
End of Treatment Period (Week 9)	133	-7.83	142	-2.94	-4.89 (-6.02, -3.75)	<0.0001
Month 6 Follow-up	114	-8.52	129	-5.36	-3.16 (-4.41, -1.91)	<0.0001
Month 12 Follow-up	122	-9.57	128	-6.04	-3.52 (-4.87, -2.18)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

Improved insomnia symptom severity was observed in the intent-to-treat study population, demonstrating effectiveness of UC+SHUTi over UC+Control. Participants who received UC+SHUTi showed significant improvement in overall insomnia symptom scores, as well as the within group change in insomnia symptom scores, over UC+Control. Insomnia symptom severity was improved at the end of the treatment period and this effect was maintained to months 6 and 12 following treatment for the participants that received UC+SHUTi.

Participants randomized to UC+SHUTi demonstrated more than a 7-point reduction in insomnia symptom score on average, representing a clinically significant change in insomnia severity. Furthermore, by the end of the treatment period participants receiving SHUTi no longer met the threshold for clinically significant insomnia and on average, maintained a symptom score below the threshold score for clinically significant insomnia at the 12- month follow-up. In contrast, participants randomized to UC+Control maintained an average symptom score above the ‘no clinically significant’ insomnia range on average across all timepoints.

Additional Insomnia Analysis: Insomnia Severity Symptoms During Intervention (Cores 1-6)

An analysis of insomnia severity as measured prior to the initiation of each Core during the treatment period was performed. Summary statistics were calculated to describe insomnia severity among participants receiving UC+SHUTi at each time point. For the UC+Control arm, insomnia severity was not collected from these participants during the treatment period.

Mean ISI scores of participants in the UC+SHUTi arm before and during the intervention period were: 17.026 (±4.0066) at baseline, 15.637 (±4.3784) at Core 1, 15.104 (±4.7371) at Core 2, 12.508 (±4.6484) at Core 3, and 10.963 (±4.8761) at Core 4, 9.673 (±4.5566) at Core 5, and 9.031 (±4.7677) at Core 6. The mean ISI score for the UC+Control arm at baseline was 17.796 (±4.0532).

These data show that UC+SHUTi produced continuous improvements in insomnia symptomology throughout the treatment period.

Additional Insomnia Analysis: Insomnia Treatment Response and Remission

An analysis of the proportion of study participants deemed treatment responders and remitters was performed using the ISI data. Responders were defined by demonstration of an ISI score reduction of > 7 points clinically. A reduction of 7 or more points is considered optimal to detect treatment responders as it represents a threshold change in insomnia severity category [4]. Remitters were defined as participants achieving an ISI score of < 8, a validated cutoff score for insomnia remission [4]. As defined by the ISI, a score ranging between 0 – 7 indicates 'no clinically significant insomnia', a score 8 – 14 indicates 'mild or subthreshold insomnia', a score 15 -21 indicates 'clinical insomnia (moderate severity)' and a score 22 - 28 indicates 'clinical insomnia (severe)'[4,5].

The proportion of participants in each treatment group deemed treatment responders at week 9, month 6, and month 12 were compared using a chi-square test. Likewise, the proportion of participants in each treatment group deemed treatment remitters at week 9, month 6, and month 12 were compared using a chi-square test.

The proportion of treatment responders identified in each treatment arm and their comparison at each time point is shown in Table 16. Using criteria of insomnia treatment response (reduction of >7 points on the ISI from baseline), 52.6% of the UC+SHUTi arm were deemed treatment responders at week 9 compared with 16.9% of the UC+Control arm. At month 6 follow-up, 59.6% of the UC+SHUTi arm and 35.7% of the UC+Control arm were considered responders. At month 12 follow-up, 69.7% of the UC+SHUTi arm and 43.0% of the UC+Control arm were deemed treatment responders. The difference between treatment groups was significant at all timepoints evaluated.

Table 16. Comparison of proportion of ISI responders (reduction in ISI score > 7 points from baseline) by timepoint.

Time of Assessment	UC+SHUTi Proportion	UC+Control Proportion	P value
End of Treatment Period (Week 9)	70 (52.6%)	24 (16.9%)	<0.0001
Month 6 Follow-up	68 (59.6%)	46 (35.7%)	0.0002
Month 12 Follow-up	85 (69.7%)	55 (43.0%)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

A similar pattern was observed for insomnia remittance (Table 17). Using an ISI score of <8 as a cutoff point, 40.6% of the UC+SHUTi arm at week 9, 49.1% at month 6, and 56.6% at month 12 were considered insomnia remitters compared with 11.3% of the UC+Control arm at week 9, 24.0% at month 6, and 27.3% at month 12. The difference between treatment groups (using criteria of either <10 or <8) was significant at every assessment timepoint analyzed.

Table 17. Comparison of proportion of ISI remitters (ISI score of < 8) by timepoint.

Time of Assessment	UC+SHUTi Proportion	UC+Control Proportion	P value
End of Treatment Period (Week 9)	54 (40.6%)	16 (11.3%)	<0.0001
Month 6 Follow-up	56 (49.1%)	31 (24.0%)	<0.0001
Month 12 Follow-up	69 (56.6%)	35 (27.3%)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

The percentage of participants that achieved a clinically meaningful insomnia treatment response or remission was higher among participants using UC+SHUTi, demonstrating efficacy of UC+SHUTi, compared to UC+Control.

A statistically significance difference in percentage of participants deemed treatment responders at the end of the intervention period was observed in favor of UC+SHUTi over UC+Control. This finding was sustained at all follow-up time points (months 6 and 12) following the end of the intervention period. Similarly, a significant difference in the percentage of participants deemed to have achieved insomnia remittance was higher among participants receiving UC+SHUTi than UC+Control. The effect was observed at the end of the intervention period and was sustained at 6- and 12-months. Insomnia severity scores of participants deemed to have achieved insomnia remittance were on average, below the clinically validated cutoff score reflecting remission of insomnia (score of < 8).

Additional Insomnia Analysis: Sleep Onset Latency and Wake After Sleep Onset

Sleep onset latency (SOL) was analyzed using a mixed model repeated measures ANOVA with factors for treatment, time, and treatment*time interaction. This analysis was similar to that done for ISI. Least-Squares (LS) mean SOL values for each treatment group were compared at baseline, at the end of the treatment (week 9), and at month 6 and month 12 follow-up. The analysis included all available data for participants randomized in the trial.

Table 18. Effect of therapy on SOL (minutes) by assessment timepoint.

Timepoint	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
	Number of Subjects	LS Mean	Number of Subjects	LS Mean		
Baseline	151	43.66	149	52.02	-8.36 (-16.5, -0.25)	0.0434
End of Treatment Period (Week 9)	128	24.01	130	41.55	-17.5 (-25.1, -10.0)	<0.0001
Month 6 Follow-up	113	24.33	123	36.38	-12.0 (-20.2, -3.85	0.0041
Month 12 Follow-up	121	21.82	127	33.98	-12.2 (-19.8, -4.48)	0.0020

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

A comparison of LS mean SOL values is shown in Table 18. SOL was reduced at week 9 ($p<0.0001$), month 6 ($p=0.0014$), and month 12 ($p=0.0020$) among participants who received UC+SHUTi as compared to UC+Control. Given a difference in baseline values, the analysis of change in values from baseline was particularly important.

To evaluate the change in SOL over baseline, the change in SOL from baseline to week 9 and to month 6, and month 12 follow-up was analyzed for each treatment group (Table 19). The average reduction in SOL was greater at week 9, month 6 and month 12 for the UC+SHUTi group (mean -21.5, -21.1, and -23.7 respectively) than the UC+Control group (mean -8.84, -13.9, and -16.3). The difference between groups was significant at each timepoint

Table 19. Effect of therapy on change from baseline (SOL) by assessment timepoint.

Timepoint	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
	Number of Subjects	LS Mean	Number of Subjects	LS Mean		
End of Treatment Period (Week 9)	128	-21.5	129	-8.84	-12.6 (-18.3, -6.92)	<0.0001
Month 6 Follow-up	113	-21.1	121	-13.9	-7.25 (-13.9, -0.62)	0.0323
Month 12 Follow-up	121	-23.7	124	-16.3	-7.32 (-13.7, -0.90)	0.0255

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

An analysis of the proportion of study participants deemed treatment remitters was also performed. The proportion of participants in each treatment group deemed treatment remitters (defined by demonstration of SOL ≤30 minutes) at week 9, month 6, and month 12 were compared using a chi-square test [6].

Table 20. Comparison of proportion of SOL remitters (SOL ≤30 minutes) by timepoint.

Time of Assessment	UC+SHUTi Proportion	UC+Control Proportion	P value
End of Treatment Period (Week 9)	114 (89.1%)	85 (63.0%)	<0.0001
Month 6 Follow-up	99 (87.6%)	94 (74.6%)	0.0134
Month 12 Follow-up	112 (92.6%)	100 (78.7%)	0.0021

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

The proportion of treatment remitters identified in each treatment group and their comparison at each timepoint is shown in Table 20. Using criteria of SOL remittance (SOL ≤30 minutes), 89.1% of the UC+SHUTi group were deemed treatment remitters from baseline to week 9 compared with 63.0% of the UC+Control group. At the 6 months follow-up, 87.6% of the UC+SHUTi group and 74.6% of the UC+Control group were considered remitters. At month 12 follow-up, 92.6% of the UC+SHUTi group and 78.7% of the UC+Control were deemed remitters. The difference between treatment groups was significant at all timepoints evaluated. The percentage of participants that achieved clinically meaningful remission was higher among participants using UC+SHUTi, demonstrating efficacy of UC+SHUTi, compared to UC+Control.

Wake after sleep onset (WASO) was also analyzed using a mixed model repeated measures ANOVA with factors for treatment, time, and treatment*time interaction. This analysis was similar to that done for ISI and SOL. Least-Squares (LS) mean WASO values for each treatment group were compared at baseline, at the end of the treatment (week 9), and at month 6, and month 12 follow-up. The analysis included all available data for participants randomized in the trial.

Table 21. Effect of therapy on WASO (minutes) by assessment timepoint.

Time of Assessment	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
	Number of Subjects	LS Mean	Number of Subjects	LS Mean		
Baseline	151	46.19	149	49.11	-2.92 (-11.5, 5.69)	0.5050
End of Treatment Period (Week 9)	128	22.14	130	39.30	-17.2 (-24.3, -9.97)	<0.0001
Month 6 Follow-up	113	22.98	123	35.06	-12.1 (-19.2, -5.01)	0.0009
Month 12 Follow-up	121	18.46	127	31.14	-12.7 (-18.9, -6.51)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

A comparison of LS mean WASO values is shown in Table 21. WASO was comparable across treatment groups at baseline (p=0.5050). WASO scores were reduced at week 9 (p<0.0001), month 6 (p=0.0009), and month 12 (p<0.0001) among participants who received UC+SHUTi as compared to UC+Control.

To evaluate the change in WASO over baseline, the change in WASO from baseline to week 9 and to month 6, and month 12 follow-up were analyzed for each treatment group (Table 22). The average reduction in WASO was greater at week 9, month 6, and month 12 for the UC+SHUTi group (mean -24.9, -23.9, -28.4 respectively) than the UC+Control group (mean -8.46, -12.9, and -16.8). The difference between groups was significant at all post-baseline timepoints (p<0.001).

Table 22. Effect of therapy on change from baseline (WASO) by assessment timepoint.

Timepoint	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
	Number of Subjects	LS Mean	Number of Subjects	LS Mean		
End of Treatment Period (Week 9)	128	-24.9	129	-8.46	-16.4 (-22.4, -10.5)	<0.0001
Month 6 Follow-up	113	-23.9	121	-12.9	-11.0 (-17.2, -4.80)	0.0006
Month 12 Follow-up	121	-28.4	124	-16.8	-11.6 (-16.9, -6.27)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

An analysis of the proportion of study participants deemed treatment remitters was also performed. The proportion of participants in each treatment group deemed treatment remitters (defined by demonstration of WASO ≤ 30 minutes) [6] at week 9, month 6, and month 12 were compared using a chi-square test.

Table 23. Comparison of proportion of WASO remitters (WASO ≤30 minutes) by timepoint.

Time of Assessment	UC+SHUTi Proportion	UC+Control Proportion	P value
End of Treatment Period (Week 9)	107 (83.6%)	83 (61.5%)	<0.0001
Month 6 Follow-up	98 (86.7%)	88 (69.8%)	0.0018
Month 12 Follow-up	111 (91.7%)	92 (72.4%)	0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

The proportion of treatment remitters identified in each treatment group and their comparison at each timepoint is shown in Table 23. Using criteria of WASO remittance (WASO ≤30 minutes), 83.6% of the UC+SHUTi group were deemed treatment remitters from baseline to week 9 compared with 61.5% of the UC+Control group. At the 6 months follow-up, 86.7% of the UC+SHUTi group and 69.8% of the UC+Control group were considered remitters. At month 12 follow-up, 91.7% of the UC+SHUTi group and 72.4% of the UC+Control were deemed treatment remitters. The difference between treatment groups was significant at all timepoints evaluated. The percentage of participants that achieved a clinically meaningful treatment remission was higher among participants using UC+SHUTi, demonstrating efficacy of UC+SHUTi, compared to UC+Control.

Effectiveness Outcomes Summary

A summary of effect of therapy on change from baseline outcomes is provided in Table 24 below.

Table 24. Summary of effect of therapy on change from baseline at End of Treatment (Week 9) and Follow-ups (6 & 12 months).

Assess-ment	Timepoint	UC+SHUTi		UC+Control		LS Mean Differences (95% CI)	P value
		Number of Subjects	LS Mean	Number of Subjects	LS Mean		
ISI	End of Treatment Period (Week 9)	133	-7.83	142	-2.94	-4.89 (-6.02, -3.75)	<0.0001
	Month 6 Follow-up	114	-8.52	129	-5.36	-3.16 (-4.41, -1.91)	<0.0001
	Month 12 Follow-up	122	-9.57	128	-6.04	-3.52 (-4.87, -2.18)	<0.0001
SOL	End of Treatment Period (Week 9)	128	-21.5	130	-8.84	-12.6 (-18.3, -6.92)	<0.0001
	Month 6 Follow-up	113	-21.1	123	-13.9	-7.25 (-13.9, -0.62)	0.0323
	Month 12 Follow-up	121	-23.7	127	-16.3	-7.32 (-13.7, -0.90)	0.0255
WASO	End of Treatment Period (Week 9)	128	-24.9	130	-8.46	-17.2 (-24.3, -9.97)	<0.0001
	Month 6 Follow-up	113	-23.9	123	-12.9	-12.1 (-19.2, -5.01)	0.0006
	Month 12 Follow-up	121	-28.4	127	-16.8	-12.7 (-18.9, -6.51)	<0.0001

Note: p values are not adjusted for multiplicity and analyses are based on available patient data.

Secondary Endpoint Analysis: Safety

Recording and reporting of unanticipated problems and adverse events was initiated once a participant signed informed consent and ended upon completion of participation in the protocol. No AEs were identified for either treatment group of the study, and thus, no significant differences in AE rate between the UC+SHUTi and UC+Control groups were found. Based on these data, SHUTi/Somryst® can be considered as safe as standard treatment for individuals with insomnia.

Citations

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Description of Symbols and Abbreviations

AE	-	Adverse Event
BIS	-	Bergen Insomnia Scale
CBT-I	-	Cognitive Behavioral Therapy for Insomnia
HCP	-	Health Care Provider
ISI	-	Insomnia Severity Index
LS	-	Least-Squares
OS	-	Operating System
PDT	-	Prescription Digital Therapeutic
PHQ-9	-	Patient Health Questionnaire 9-item
Rx Only	-	US federal law restricts this device to sale by or on the order of a licensed medical practitioner.
SHUTi	-	Sleep Health Using the Internet
SOL	-	Sleep Onset Latency, minutes to fall asleep
UC	-	Usual Care
UDI: (01)15694311112112(8012)VVvvrr	-	Unique Device Identifier (UDI): the Application Identifier (01) indicates the device identifier (DI) (i.e. “15694311112112”), the Application Identifier (8012) indicates the software version (i.e. “VVvvrr”)
WASO	-	Wake after sleep onset, minutes awake during the night