Clinical Trial Protocol

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Protocol for Digital Real-world Evidence trial for Adults with insomnia treated via Mobile (DREAM): an open-label trial of a prescription digital therapeutic for treating patients with chronic insomnia

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Background: Cognitive behavioral therapy for insomnia (CBT-I) is underused in healthcare settings and is challenging for people with insomnia to access because of uneven geographical distribution of behavioral sleep medicine providers. Prescription digital therapeutics can overcome these barriers. This study evaluates the effectiveness of a specific digital CBT-I therapeutic. **Materials & methods:** **D**igital **R**eal-world **E**vidence trial for **A**dults with insomnia treated via **M**obile (DREAM) is a 9-week, open-label, decentralized clinical trial to collect real-world evidence for a digital therapeutic (Somryst™) delivering CBT-I to patients with chronic insomnia. The primary objective is to examine the effectiveness of Somryst to reduce self-reported insomnia symptoms and severity in a real-world population (n = 350). **Conclusion:** This pragmatic study seeks to assess the potential benefits of treating insomnia with an asynchronous, mobile, tailored prescription digital therapeutic.

Clinical trial registration: NCT04325464 (ClinicalTrials.gov)

Lay abstract: Chronic insomnia is linked to a range of health problems, including heart disease, chronic pain, high blood pressure and depression. A behavioral treatment called cognitive behavioral therapy for insomnia (CBT-I) is considered the first choice for helping patients overcome insomnia and reduce their risks of insomnia-related problems. Although the benefits of CBT-I have been established, it can be difficult for patients to access trained CBT-I therapists. One possible solution is to use digital forms of CBT-I, which patients can access on mobile devices. Somryst™ is a prescription digital therapeutic, which means it is authorized by the US FDA and has been proven effective in carefully-controlled clinical trials. Less is known, however, about how well the prescription digital therapeutic works in real-world settings. The Digital Real-world Evidence trial for Adults with insomnia treated via Mobile study (DREAM) will explore this question by evaluating a range of symptoms and outcomes in at least 350 patients with chronic insomnia who will use Somryst and be followed for 1 year.

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Keywords: CBT-I • chronic insomnia • cognitive behavioral therapy for insomnia • digital therapeutics • insomnia • PDT • prescription digital therapeutic

Background & rationale

Approximately 30 million Americans suffer from chronic insomnia [1], a condition associated with significant impairment in health and functioning [2–4]. Conditions co-occurring with insomnia include psychiatric disorders, heart disease, chronic pain and hypertension [5]. The annual medical and socioeconomic costs of chronic insomnia are estimated at US$30–70 billion [6].

Future Medicine

Cognitive behavioral therapy for insomnia (CBT-I) is the guideline-recommended, first-line treatment approach for adults with chronic insomnia [7–10], based on robust evidence of long-term efficacy and significantly lower safety risks compared with pharmacologic treatment options, which are associated with adverse events (AEs) and dependence [11,12]. CBT-I has been shown to improve insomnia itself as well as co-occurring symptoms [13], functional health, psychological well-being and sleep-related quality of life [14]. CBT-I, however, remains underused in healthcare settings and is challenging for people with insomnia to access [15,16]. Barriers to increased use of CBT-I include a paucity of healthcare providers trained in behavioral sleep medicine, inconvenience for patients due to the limited geographic diversity of CBT-I providers across the US, and patient concerns about privacy [16].

Prescription digital therapeutics (PDTs) represent a promising clinical approach for treating insomnia that can overcome the barriers currently constraining the use of CBT-I. A PDT for treatment of adults with chronic insomnia was market cleared in March 2020 by the US FDA [17,18]. The Somryst™ PDT is a native mobile application adaptation (with identical therapeutic content) of Sleep Healthy Using the Internet (SHUTi) – a web-based CBT-I intervention accessed via a responsive browser that has been extensively evaluated in at least nine randomized trials with over 3000 patients [19,20]. A meta-analysis of randomized trials found that the efficacy of digitally-delivered CBT-I is comparable with that delivered via traditional face-to-face modalities [21].

The objective of the Digital Real-world Evidence trial for Adults with insomnia treated via Mobile (DREAM) study is to examine the effectiveness of a digital therapeutic to reduce insomnia symptoms and severity in a real-world population of participants with chronic insomnia. The pragmatic study is designed to improve the understanding of how a PDT is actually used outside of a clinical trial setting and to assess its impact on insomnia symptoms and other measures of neuropsychiatric mental health and well-being.

Design

Study design

Prospective, open-label clinical trial with no comparator group.

Study setting

The DREAM study is decentralized. All participants will be recruited from within the US from a study waiting list that includes: participants who expressed interest in a mobile version of SHUTi when it became available; participants referred by their clinician; and participants who searched the internet for insomnia treatment. Participants may also be recruited using online advertising on social media sites.

Eligibility criteria

The DREAM study platform has been programmed with the inclusion and exclusion requirements allowing the system to automatically determine participant eligibility.

Inclusion criteria:

- Provision of electronic informed consent (prior to study-specific assessments).
- Age between 22 and 75 years, inclusively.
- Insomnia as defined by a score of 8 or above on the Insomnia Severity Index (ISI).
- Insomnia symptoms for at least 3 months [22].
- Access to a mobile device (i.e., smartphone or tablet) running supported versions of iOS or Android for the duration of the trial (including continuous data plan/Wi-Fi access).
- Resident of the US and living in the US for the duration of the trial.

Exclusion criteria:

- Presence of an active and progressive physical illness (e.g., congestive-heart failure, chronic obstructiNve pulmonary disease, or acute pain), neurological disorder (e.g., epilepsy) or neurological degenerative disease (e.g., dementia and multiple sclerosis).
- Unstable medication regimen (change to schedule or dosage within the past 3 months).
- Diagnosis of a psychotic disorder, bipolar disorder or a medical condition contraindicated by sleep restriction.
- Family or work schedules that interfere with normal sleep schedules (i.e., normal routine considered to be bedtime between 8:00 p.m. and 2:00 a.m. and/or waking times between 4:00 and 10:00 a.m.).

- Need to be alert or cautious to avoid serious accidents in a job or daily life. Examples include: long-haul truck drivers, long-distance bus drivers, air traffic controllers, operators of heavy machinery and some assembly line jobs.
- Pregnancy or intent to become pregnant during the trial.
- Other untreated sleep disorders as self-reported by the participant (e.g., obstructive sleep apnea, periodic leg movements, or parasomnias).
- Participation in an investigational research study in the past 30 days.

Eligible participants will be contacted via email and given an access code that will enable them to create an account and access the Somryst program. Ineligible participants will be notified via email and receive referral information to other sleep websites. In the event of uncertainty about a participant's eligibility, the Principal Investigator will contact the participant and/or participant's treating clinician to confirm if they are eligible for the study.

Who will take informed consent?

Participants who initially meet eligibility will complete an electronic informed consent form (eICF). Once the eICF is signed by both the participant and the Principal Investigator, the participant will be invited to complete additional medical/medication history questions, the ISI, and the Short Form 12 Health Survey to further determine eligibility and provide baseline data for the study. All data provided during the prescreening and screening periods is self-reported. The eICF will be reviewed and approved by the Institutional Review Board (IRB) prior to the start of the study. A copy of the IRB approval letter of the protocol, any amendments and the eICF will be filed in the Trial Master File.

Study procedures

Intervention description

The intervention to be evaluated in the study is an FDA-market-cleared PDT (Somryst) that delivers digital CBT-I therapeutic content to a patient via a mobile device (smartphone or tablet). CBT-I focuses on addressing the maladaptive behaviors, routines, and dysfunctional thoughts that perpetuate sleep problems, regardless of the cause of the sleep problems. Digital CBT-I is modeled on face-to-face CBT-I, which is typically delivered in weekly sessions over 6–8 weeks. The study program delivers 6 treatment Cores (learning modules), covering the following specific CBT-I therapy content:

1. **Get ready.** This Core sets the stage for the therapeutic experience. It lets the participant know what they will need to learn and do to improve their sleep and set goals for success.
2. **Sleep window.** This Core focuses on the concept of sleep restriction and consolidation. Using the participant's own data, the PDT will identify a tailored Sleep Window (a recommended Bedtime and Arising Time) that the participant should follow.
3. **Behaviors.** This Core focuses on stimulus control and works to break the connection between bed/bedtime and being awake.
4. **Thoughts.** This Core explains how a participant's thinking can contribute to chronic insomnia. The participant will learn to identify and shift these thought patterns to promote better sleep.
5. **Education.** This Core helps the participant identify changes to target in their lifestyle and environment to achieve better sleep.
6. **Look ahead.** This Core pulls together what the participant has learned, prepares participants for the future and teaches them what to do if they experience a relapse.

Cores must be completed sequentially and take approximately 30–45 min to complete. Each new Core is made available one week after the completion of the previous Core. Between Cores 1 and 2, at least 5 daily sleep diaries (integrated into the program) within a 7-day period must also be entered to unlock the next Core. Going forward, the participant must complete 5 out of 7 sleep diaries between Cores in order to receive an updated Sleep Window. Participants will have access to the program for 9 weeks, after which time their access will expire. Although all Cores can be completed in as little as 6 weeks, the intervention is made available for 9 weeks prior to postassessment to allow users sufficient time to access all Core materials, as well as implement new behaviors, strategies and techniques.

Table 1. Study objectives and end points.

Primary objectives	Primary end points
1. To examine the effectiveness of a digital therapeutic to reduce insomnia severity in a real-world insomnia patient population	1. Change in ISI from baseline to end of treatment
Secondary objectives	**Secondary end points**
1. Evaluate engagement and adherence rates with the digital therapeutic in a real-world patient population	1. Findings from in-therapeutic software application data: a. Core completion rate b. Intervention sleep diary completion rate c. Number of times the digital therapeutic is opened
2. Examine change in depression symptoms	2. Change in PHQ-8 score from baseline to end of treatment
3. Examine change in anxiety symptoms	3. Change in GAD-7 score from baseline to end of treatment
4. Examine change in insomnia severity, depression and anxiety at follow-ups	4. Change in ISI, PHQ-8 and GAD-7 scores from baseline to day 243 (~35 weeks) and day 428 (~61 weeks)
Exploratory objectives	**Exploratory end points**
1. Examine insomnia response to treatment	1. A decrease in ISI score from baseline to end of treatment >7 points
2. Examine insomnia remission	2. A final ISI score <8 points
3. Examine relationship among engagement and outcomes	3. ISI, PHQ-8 and GAD-7 findings from in-therapeutic software application data (e.g., Core completion or minutes spent in the PDT)
4. Examine relationship among assessments across time	4. ISI, PHQ-8 and GAD-7 results at specified time points
5. Evaluate participant satisfaction, usability, context and longitudinal experience and acceptance of the digital therapeutic and digital CBT-I	5. User Experience Surveys: NPS and SUS, qualitative diary data, participant interviews)
6. Determine if there is change in daytime sleepiness	6. Change in ESS from baseline to end of treatment
7. Determine change in quality of life	7. Change in SF-12 from baseline to end of treatment
8. Determine change in work attendance and productivity	8. Change in presenteeism/absenteeism work questions from baseline through end of treatment, day 243 and day 428

CBT-I: Cognitive behavioral therapy for insomnia; ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; NPS: Net Promoter Score; PDT: Prescription digital therapeutic; SF-12: Short Form 12 Health Survey; SUS: System Usability Scale.

Criteria for discontinuing or modifying allocated interventions

There are no special criteria for discontinuing or modifying allocated interventions. Participants may choose to stop using the Somryst therapeutic at any point and do not need permission to do so.

Strategies to improve adherence to interventions

The Somryst therapeutic automatically reminds users to complete treatment and study procedures via email and push notifications. Study team members will also send manual emails to remind participants of study procedures during the study.

Outcomes

Table 1 details the primary, secondary and exploratory outcomes of the DREAM study and the assessment tools used to evaluate each end point.

Participant timeline

Participants will complete assessments at end of treatment (9 weeks/day 63), 6 month follow-up (day 243) and 12 month follow-up (day 428) (see Table 2 for details). A subset of approximately 34 participants will be asked to partake in an optional user experience sub study (see Table 3). Participants will be asked to sign an additional eICF for the sub-study. The user experience sub-study includes the following data collection components:

- Qualitative Diary Data collected from the participant over the course of 5 consecutive days starting in Core 2 and Core 4.
- Interviews conducted with the participant via Zoom interview at end of Core 4 and start of Core 6.

Sample size

This is an open access study and is expected to be overpowered for the primary end point based on previous trials with a similar product. A trial of Somryst's predecessor, SHUTi, reported an effect size of 1.90 or higher [19], which corresponds to a sample size of 6 (assuming 95% power at an alpha of 0.05). In order to better characterize

Table 2. Schedule of events.

Study phase	Prescreening	Screening	Treatment (Core)						End of treatment (Day 63)	Follow-up (Day 243)	Follow-up (Day 428)	Ref.
			1	2	3	4	5	6				
Procedures												
Informed consent		X										
Inclusion/exclusion	X	X										
Demography	X											
Medical/medication History		X							X	X	X	
Sleep restriction window				X	X	X	X	X				
Sleep diary			X	X	X	X	X	X				
ISI		X	X	X	X	X	X	X	X	X	X	[23]
PHQ-8		X	X		X		X		X	X	X	[24]
GAD-7		X	X		X		X		X	X	X	[25]
Epworth Sleepiness Scale		X		X	X	X	X	X	X	X	X	[26]
User Experience SUS & NPS						X	X					
Health economics and outcomes questions (survey)		X							X	X	X	
SF-12		X							X	X	X	[27]
Adverse events collection (self report)			X	X	X	X	X	X	X	X	X	

ISI: Insomnia Severity Index; NPS: Net Promoter Score; SF-12: Short Form 12 Health Survey; SUS: System Usability Scale.

Table 3. Optional user experience sub-study schedule of events.

Study phase	Treatment (Core)						End of treatment (Day 63)
	1	2	3	4	5	6	
Procedures							
Informed consent	X						
User experience diary data		X			X		
User experience interview				X		X	

the secondary end points, we expect to enroll approximately 350 participants. For the qualitative user experience substudy, a sample size of 34 participants was selected as that sample size should be adequate to reach saturation in the qualitative interviews [28].

Recruitment

As noted earlier, all participants will be recruited from the US from a study waiting list that includes: participants who previously used SHUTi (the web-based precursor of Somryst) who have expressed interest in the mobile version; participants referred by their clinician; and participants who searched the internet for insomnia treatment.

Data management

Oversight of data management, including electronic data collection, storage and export, security, tracking, data analysis and quality assurance will be the responsibility of Pear. The Principal Investigator will also be responsible for ensuring that all study staff adhere to human participants/IRB guidelines related to data management. Data files will be backed up at regular intervals and will be accessible only by trained study staff members.

Data collection

All participant data are collected within the study website and digital therapeutic and stored in the sponsor's database. Eligibility determinations and medical release waivers will be collected in the source records and maintained electronically. The eligibility determination will be documented in the study dashboard by the Principal Investigator or designee. All AEs will be collected by the contract research organization (CRO) and entered into an electronic case report form. The source data will be retained electronically at the clinical site until notification is given by Pear for destruction.

Monitoring

The study will be monitored remotely by Pear or its representative (the Study Monitor) to ensure it is conducted and documented according to the protocol, International Conference on Harmonisation/Good Clinical Practice (ICH/GCP) and all applicable regulatory requirements. The Investigator will work closely with the Study Monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

Quality assurance & quality control

Although Pear or its designee will perform the quality assurance and quality control activities of this study, responsibility for the accuracy, completeness and reliability of the study data presented to Pear will lie with the participants and Investigator. Prior to the study initiation, Pear will explain the protocol and instructions for using the study product to the Investigator assigned by the CRO. In addition, a Pear Clinical Operations Manager will be available to explain applicable regulations and to answer any questions regarding the conduct of the study. At its discretion, Pear may conduct audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP and all applicable regulatory requirements. The study center may also be compelled to an inspection by a Regulatory Authority.

Source data

Source data are defined as information in original records and certified copies of original records of clinical findings, observations, data or other activities in a clinical study necessary for the reconstruction and evaluation of the study. In this decentralized trial, data collected through the Somryst mobile program infrastructure and study website will be considered as source. In addition, source documentation will be maintained by the Principal Investigator for determination of participant eligibility and safety reporting.

Record keeping

The Investigator must arrange for retention of study records (Essential Documents for the Conduct of a Trial are listed in the ICH Guideline for Good Clinical Practice) at the site, in a secure location. Records will be kept for the duration of the product lifetime, per Pear's quality management system record retention requirements, or a period of 2 years after completion of the study, whichever is longer. These documents will be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with Pear. It is the responsibility of Pear to inform the Investigator/institution as to when these documents no longer need to be retained. The Investigator will take measures to prevent any accidental or premature destruction of these documents.

Confidentiality

The protection of patient privacy is of the utmost importance and is a principal consideration throughout the software design. The approaches to data security undertaken were based on a number of recommendations, principally National Institute of Standards and Technology Cybersecurity Practice Guide, Special Publication 1800–1: "Securing Electronic Health Records on Mobile Devices," and on guidance from a number of consultants and vendors.

Data transport & storage

All data collected by the device are hosted and stored in Amazon Web Services (AWS). AWS follows a variety of internationally recognized security standards such as the National Institute of Standards and Technology SP800–53 and Health Insurance Portability and Accountability. All participant information is automatically encrypted by AWS when it is entered into the system, allowing for secure data transfer and storage. All back-end services operate

in nonroutable IP space on dedicated instances, are only accessible to external callers through secured, software mediated interfaces and are only accessible via Hypertext Transfer Protocol Secure. All communications between subsystems (Data in Motion) are encrypted using Transport Layer Security. No access is provided to any subsystem via unencrypted protocols. All communication between the backend, service layer and the mobile application is further secured through Advanced Encryption Standard-encrypted session tokens, used to identify all actors in the system without providing any data visibility to any third party, intentionally or otherwise.

Data stored in the service layer are encrypted according to the Advanced Encryption Standard. A cryptographically secure pseudo-random number generator is used to generate the encryption key for mobile app storage. All use data within the mobile application are stored in an encrypted queue and flushed to the Backend Services securely over Hypertext Transfer Protocol Secure whenever internet connectivity is available.

Data segregation

In order to limit access to Protected Health Information (PHI) and Personally Identifiable Information (PII), we maintain completely isolated infrastructure for the Production Environment and provide a functionally identical Development, Staging and QA environment for software development, user story acceptance and testing. Access to the Production Environment is limited to quality controlled and audited software developed by the Pear Therapeutics team and is further limited to a set of authorized users, with limited access for environment management and maintenance purposes. Production Data, including all PHI and PII, is maintained in the Production Environment only; it cannot enter the Development, Staging and QA environment, nor can it be copied for any purpose to desktop or laptop computers used for development. These environments are maintained in separate accounts, to prevent access to anyone other than minimum authorized administrators, and to prevent system-level attacks or inadvertent access to PHI or PII.

Statistical methods

Statistical methods for primary & secondary outcomes

The Intention-to-Treat population will serve as the primary population for the analysis of efficacy and safety data in this trial. The Intention-to-Treat consists of all participants who have a baseline observation for the analysis end point. The per-protocol set will include all participants who complete the 6 CBT-I cores.

Descriptive statistics will be used to evaluate the enrolled population and the population at risk for each of the 6 Cores as well as at end of treatment (day 63) and follow-up (day 243 and day 428). Categorical data will be presented as frequencies and percentages of participants at risk at baseline. For continuous data, mean, standard deviation, median, first and third quartile, minimum and maximum will be presented.

Primary end point analysis

The primary efficacy end point in this study is the ISI score measured at baseline, day 63, day 243 and day 428. The ISI score will be analyzed using a mixed-effects model for repeated measure (MMRM) including the fixed categorical effect of visit with subject as a random effect. An unstructured correlation matrix will be used to model the within-subject errors. The primary hypothesis to be tested is that the study PDT reduces insomnia severity, as measured by change in ISI, from baseline to end of treatment (day 63) and to follow-up assessments (day 243 and day 428). Significance will be evaluated with a two-tailed p-value of 0.05. To control for multiplicity end of treatment will be evaluated first and if significant days 243 and 428 will be evaluated. In addition, estimated marginal means ± 95% CIs will be calculated for each assessment point and Cohen's d will be used as an estimate of effect size for the change from baseline to each assessment point.

Secondary end point analysis

Engagement with the study PDT will be estimated from the rate of core completion, the rate of sleep diary completion and the number of times the PDT is opened. These variables will be summarized using descriptive statistics. As an exploratory end point, minutes spent in the PDT will also be captured. Change in patient health questionnaire 8 (PHQ-8) and general anxiety disorder 7 (GAD-7), will also be analyzed with an MMRM analysis in a manner consistent with ISI. The significance test will be carried out on a visit effect using a one-sided alpha of 0.05/2 = 0.025 to control for multiplicity if the primary end point is significant with end of treatment being evaluated first in both cases. In addition, estimated marginal means ± 95% CIs will be calculated for each visit and Cohen's d will be used as an estimate of effect size for each time point.

Qualitative user experience analysis

The qualitative interviews with participants are open-ended interviews. With participant permission, interviews are recorded and transcribed verbatim (single coder). A trained user experience researcher then serves as the coder of the transcribed interview to categorize the data gathered, aiming to discover major themes that emerge from the data. *A priori* codes are used to denote challenges, motivations and other contexts in the data. These processes follow grounded theory which provides a common data analysis method for qualitative data across human computer interactions [29–31].

Interim analyses

Interim analyses, after all participants complete post-treatment, may be conducted upon IRB review and approval of interim analysis plans.

Methods for additional analyses (e.g., subgroup analyses)

For exploratory end point analyses, insomnia responders (decrease in ISI score from baseline to end of treatment >7) and remitters (final ISI score <8) will be counted and tabulated. Correlations between engagement and clinical outcomes will be evaluated using both Pearson's correlation coefficient and Spearman's rank correlation as follows. Change from baseline (follow-up – baseline) will be calculated for ISI, PHQ-8, GAD-7 and Epworth Sleepiness Scale at both the end of treatment and the end of follow-up. These will be correlated with core completion rates, sleep diary completion rate and the number of times the PDT is opened. In addition, correlations among the engagement variables and among the clinical outcomes will also be evaluated.

User experience surveys, qualitative diary data and participant interviews will be summarized using descriptive statistics. Change in Epworth Sleepiness Scale and Short Form 12 Health Survey will be analyzed with an MMRM analysis consistent with ISI, PHQ-8 and GAD-7. All four clinical outcomes can be expressed as clinical categories of severity. For example, an ISI score of 22–28 corresponds to severe insomnia, 15–21 moderate insomnia, 8–14 subthreshold insomnia and 0–7 no insomnia. Similar categories exist for the three other clinical metrics. Clinical improvement in outcomes will be summarized using shift tables from baseline categories to the end of treatment and the end of follow-up.

Methods in analysis to handle protocol nonadherence & any statistical methods to handle missing data

Participants with missing data will initially be evaluated assuming data are missing at random in the MMRM. Sensitivity to this assumption will be evaluated with multiple imputation, last observation carried forward imputation and evaluation of the per protocol core 6 completers which should reduce the amount of missing data and will be detailed in the statistical analysis plan prior to database lock.

Oversight & monitoring

Composition of the coordinating center & trial steering committee

Operational activities and processes are completed through rigorous management and trial oversight of a CRO under supervision of a site Principal Investigator. In addition, a cross-functional team for the Sponsor meets weekly or bi-weekly to review study status, including recruitment, participant support, study milestones and any safety concerns that may arise.

Composition of the data monitoring committee, its role & reporting structure

A data monitoring committee is not required for this study because Somryst is an FDA-cleared medical device. All AEs and serious AEs (SAEs) and tracked and reported as detailed below.

AE reporting & harms

AEs will be self-reported by participants throughout the study, beginning at the time the participant gives informed consent through the last follow-up period. Participants will be provided with telephone and email contacts for the investigator and/or study support to address any health or technical related questions. Participants are also given instructions within the PDT that it is not intended for emergencies and to contact 911 or go to the nearest emergency room for all emergent concerns. The Investigator or designee and research site staff are responsible for the documentation, classification, reporting and follow-up of events meeting the definition of an AE or SAE.

Risks & benefits

Somryst therapeutic content has demonstrated significant benefits to participants with chronic insomnia and chronic insomnia with depression [19,20]. More specifically, compared with comparison conditions, participants experienced:

- Significant improvement in insomnia severity (as measured by clinically validated and standardized instruments, including the ISI).
- Significant improvement in symptoms of depression (as measured by clinically validated and standardized instruments, including the patient health questionnaire 9 [PHQ-9]).
- Significant reductions in symptoms of anxiety (as measured by clinically validated and standardized instruments, GAD-7).

The following risks are associated with use of Somryst:

- Digital concerns: Some participants may feel uncomfortable providing data electronically and may have concerns about the confidentiality of their digital data. They may also have concerns about the legitimacy of a digital therapeutic.
  Security measures to protect participant data include the fact that the PDT requires a username and password for access. Users set up a 4-digit PIN and have the option to grant permission to use biometric features (Face ID or Touch ID on iPhone, Fingerprint on Android phones).
- Sleep restriction (and consolidation) within Somryst can cause sleepiness, especially in the early stages of use. Increased daytime sleepiness is normal and expected, but it is also temporary. Sleepiness that persists after a few weeks of treatment may indicate the presence of another sleep disorder or medical condition other than insomnia.

Definitions

An AE is any untoward medical occurrence in a participant or clinical investigation and may not necessarily have a causal relationship with the administered treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory abnormality, for example), symptom or disease temporally associated with the use of a treatment whether or not related to the treatment itself. Pre-existing conditions, diseases or disorders are not considered AEs unless there is a change in intensity, frequency or quality.

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening (at the time of the event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A suspected unexpected serious adverse reaction is an SAE that is not identified in nature, intensity or frequency in the risk information set out in the risks and benefit section of this protocol.

Classification of AE intensity

The Investigator or designee is responsible for making an assessment as to the seriousness, intensity, causality and outcome of an AE. The Investigator will determine causality as either related or unrelated to Somryst. For each recorded AE or SAE, the investigator or designee must assess intensity based on the criteria listed in Table 4 and follow the classification schemes detailed in Tables 5 & 6. If there is insufficient information to determine intensity, the AE must still be reported.

AEs will be followed up per the site's standard operating procedures requirements.

Table 4. Adverse event classifications.

Classification	Definition
Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the participant.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living or significantly affects clinical status. The event poses a significant risk of harm to the participant and hospitalization may be required.

Table 5. Classification of adverse event causality.

Classification	Definition
Unrelated	The AE or SAE is judged to be clearly and incontrovertibly due only to extraneous causes (e.g., disease, environment) and does not meet the criteria for study product relationship listed under probable, possible or unlikely.
Unlikely	The AE or SAE is unlikely related to the study product when the AE or SAE: • Does not follow a reasonable temporal sequence from administration of the study product • May readily have been produced by the participant's clinical state, environmental or toxic factors, drugs or other modes of therapy administered to the participant • Does not follow a known pattern of response to the study product • Does not reappear or worsen when the study device is re-administered
Possible	The AE or SAE is possibly related to the study product when the connection to the study product appears unlikely but cannot be ruled out with certainty. This causal relationship is assigned when the AE or SAE: • Follows a reasonable temporal sequence from administration of the study product • May have been produced by the participant's clinical state, environmental or toxic factors, drugs or other modes of therapy administered to the participant • Follows a pattern of response to the suspected study product
Related	The AE or SAE is probably related to the study product when the connection to study product can be made with a high degree of certainty. This causal relationship is assigned when the AE or SAE: • Follows a reasonable temporal sequence from administration of the study product • Cannot be reasonably explained by the known characteristics of the participant's clinical state, environmental or toxic factors, drugs or other modes of therapy administered to the participant • Disappears or decreases upon cessation or reduction in product use (note that there are important exceptions when an AE or SAE does not disappear upon discontinuation of the study product, yet product relatedness clearly exists) • Follows a known pattern of response to the suspected study product • Reappears upon re-challenge

AE: Adverse event; SAE: Serious adverse event.

Table 6. Classification of adverse event outcomes.

Classification	Definition
Fatal	The participant died
Resolved	The AE or SAE has ended
Resolved with sequelae	The AE or SAE has ended but changes are noted from baseline
Unresolved	The AE has not ended. And AE outcome can only be categorized as unresolved if the AE is: • Ongoing at the end of the reporting period after the final follow-up visit, and the investigator deems that further follow-up is not medically required • Lost to follow-up after repeated unsuccessful attempts to contact the participant • Ongoing and referred to the participant's physician or a specialist

AE: Adverse event; SAE: Serious adverse event.

SAE reporting

The Investigator is required to contact Pear Therapeutics, Inc. (Pear) within 24 h of learning of any SAE.

Pear Therapeutics, Inc.:

Telephone: +1 833 ASK-PEAR (275 7327).

Email: pearconnect@peartherapeutics.com

If the SAE is fatal or life threatening, Pear must be informed immediately. For reporting of all SAEs, Investigator must scan/email all completed pages of the SAE report form within 24 h to the Medical Monitor. To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until the last study visit must be reported to Pear within 24 h of learning of its occurrence.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 h of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event. Note: SAEs, related or possibly related, to Somryst are subject to the SAE reporting requirements in this section.

Frequency & plans for auditing trial conduct

Teams from the Sponsor and research site meet weekly or bi-weekly to discuss trial recruitment, participant support any IRB-related requirements, study logistics and any safety concerns should they arise. In addition, documentation required by the IRB is developed and reviewed as required, including annual reports on study progress.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees)

Substantive changes in the protocol include changes that affect the safety of participants, and/or changes that alter the scope of the investigation or the scientific quality of the study. Such changes must be prepared as a protocol amendment and approved by the IRB prior to implementation. If a protocol amendment requires changes in the eICF, the revised eICF must also be approved by the IRB.

Conclusion

This pragmatic study is designed to mimic a real-world scenario to understand how Somryst is used by individuals with insomnia outside of a randomized clinical trial setting. The number of clinical assessments has been minimized in terms of frequency and type to reduce clinical trial burden. Clinical scales and surveys will be used to evaluate a range of efficacy, usability and health-related outcomes that will help further an understanding of the impact of insomnia and the potential benefits of treating insomnia with an asynchronous, contact-less prescription digital therapeutic.

Trial status

Study no.: PEAR-003-101, version 3.0, 12 May 2020. The DREAM study is currently recruiting and plans to recruit until the projected sample size is met.

Summary points

- Cognitive behavioral therapy for insomnia (CBT-I) is the guideline-recommended first-line treatment for patients with chronic insomnia but it is underused in healthcare settings and is challenging for patients to access.
- Prescription digital therapeutics may help expand access to cognitive behavioral therapy for insomnia and, not only improve insomnia symptoms, but also be connected to improvement in co-occurring physical and psychological illnesses.
- The prescription digital therapeutic Somryst™ has been proven effective in randomized controlled trials and is US FDA-approved for patients with chronic insomnia, but less is known about its effectiveness in real-world settings.
- Digital Real-world Evidence trial for Adults with insomnia treated via Mobile (DREAM) is a 9-week, open-label, decentralized clinical trial to collect evidence for Somryst in a real-world population of 350 patients with chronic insomnia.
- Outcomes to be evaluated include: insomnia symptoms; engagement with and adherence to the therapeutic; symptoms of depression and anxiety; and rates of insomnia response and remission.
- Outcomes will be assessed at the end of treatment (week 9) and again at 6 and 12-month follow-ups.

Author contributions

FP Thorndike and YA Maricich conceived the study concept and design for the Digital Real-world Evidence trial for Adults with insomnia treated via Mobile study. RB Berry is the site investigator and contributed to study design. R Gerwien is the biostatistician for the study and will perform the statistical analyses of study results. S Braun is a medical writer who wrote the first draft of this article. All named authors adhere to the authorship guidelines of *JCER*. All authors have agreed to publication.

Financial & competing interests disclosure

This study is funded entirely by Pear Therapeutics, Inc. The sponsor oversaw the study design; collection, management, analysis and interpretation of data; writing of the report; and the decision to submit the report for publication. FP Thorndike, R Gerwien,

S Braun and YA Maricich are employees of Pear Therapeutics, Inc., which develops the Somryst™ digital therapeutic discussed in this protocol. RB Berry is an employee of the University of Florida. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. The Investigator and sub-Investigators, as noted on the US FDA Form 1572, will provide Pear Therapeutics Inc. with sufficient accurate financial disclosure information to allow Pear to maintain complete and accurate certification or disclosure statements as required under 21 CFR Part 54. The Investigator shall promptly update this information if any relevant changes occur during the investigation and for 1 year following the completion of the study.

Editorial assistance on the writing of this paper was provided by N Enman and S Edington (employees of Pear Therapeutics, Inc.).

Ethical conduct of research

This study will be conducted in full accordance with all applicable Policies and Procedures and all applicable US federal and state laws and regulations including 45 Code of Federal Regulations (CFR) 46, and the Health Insurance Portability and Accountability (HIPAA) Privacy Rule. Any episode of noncompliance will be documented. The Investigator will perform the study in accordance with this protocol and will report unexpected problems in accordance with Institutional Review Board (IRB) procedures and all federal requirements. Collection, recording and reporting of data will be accurate and will ensure the privacy, health and welfare of research participants during and after the study. Participants have the right to withdraw from the study at any time and for any reason, and all participants are made aware that withdrawal will not affect their routine care.

Consent for publication is not applicable as there are no identifying images of other personal details of participants presented.

Data sharing statement

Any data required to support the protocol will be supplied on request. All information obtained as a result of this study or during the conduct of this study will be regarded as confidential. The requirements concerning dissemination of the information derived from this clinical trial are described in the Clinical Trial Agreement.

Open access

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