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An open-label trial to evaluate the safety and efficacy of chloral hydrate in patients with severe insomnia

Submission date
11/05/2023

Recruitment status
No longer recruiting

Registration date
04/09/2023

Overall study status
Completed

Last Edited
23/04/2025

Condition category
Nervous System Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Persistent insomnia affects approximately 10% of the adult population and is a risk factor for several mental and physical health problems. Severe insomnia can impair quality of life and performance of daily tasks, as well as increasing the risk of disorders such as depression, heart attack, stroke and diabetes.

Current sleep therapies include cognitive behavioural therapy (CBT), where access remains limited, and the use of hypnotics and (off-label) sedative antidepressants, which are associated with side-effects, tolerance and dependence. There is therefore a need to identify additional treatments especially where these treatments fail in cases where insomnia is severe.

Chloral Hydrate is a licensed treatment in the UK for the short-term treatment (2 weeks) in patients with severe insomnia which is interfering with normal daily life, and where other sleep therapies (behavioural and pharmacologic) have failed. However, despite having a long clinical experience, there is a lack of clinical evidence with Chloral Hydrate.

The main aim of this trial is to establish whether short-term Chloral Hydrate treatment (2 weeks) is effective in patients with severe insomnia, assessed by the Insomnia Severity Index (ISI).

Who can participate?
Patients with severe insomnia which is interfering with normal daily life, and where other behavioural and drug sleep therapies have not been successful, will be recruited to the trial. All potential participants in the UK can enrol through the trial website.

What does the study involve?
All enrolment (pre-screening, informed consent, assessment by a sleep specialist, eligibility review by a medical doctor, and collection of baseline data) and follow-up procedures (validated questionnaires, daily/weekly surveys, and safety assessments), during and after Chloral Hydrate

treatment will be conducted remotely via telephone/video calls and online questionnaires. An independent and medically qualified safety committee will oversee and monitor safety throughout the trial.

What are the possible benefits and risks of participating?
Benefits:
We do not know if the intervention being tested will have additional benefits. The intervention will help build the best evidence–based care for future patients with severe insomnia, and may or may not help participants in the trial.
Risks:
Side-effects
There are reported side-effects associated with chloral hydrate, although their frequency is unknown. These side-effects include: allergic skin reactions; high levels of ketones urine; psychiatric disorders: anxiety, hyperactivity, confusion, tolerance, dependence, delirium, abuse, chronic intoxication, withdrawal symptoms; headache; coordination impairment, shortness of breath, respiratory depression, abnormality of the heart's rhythm, gastrointestinal disorders: stomach lining irritation, abdominal distension, wind, gastric necrosis, gastric perforation, nausea, vomiting, gastritis, and medical kidney disease.

Participants will be asked to record the severity of known and unknown side-effects of the IMP, in their daily/weekly surveys and they can also inform the trial team via the freephone number or trial email address. The severity and causality of these AEs will be assessed by a medically qualified doctor. Additionally, a research nurse/sleep specialist/medically qualified doctor will be conducting a safety review during a video/telephone call with participants on Day 4 and 14. It will be left to the Investigator’s clinical judgment to decide whether or not an AE is of sufficient severity to require the participant’s removal from treatment. Participants may also voluntarily withdraw from treatment due to what they perceive as an intolerable AE.

Participants will also be provided with a Trial Wallet Emergency Card with a contact telephone line, answered by a member of the clinical team, enabling them to report AEs they experience whilst taking the drug. In the event of a medical emergency, trial participants will be instructed to show this card to the clinician they see. We will record SAEs and have an Independent Safety Committee in place to review ongoing safety events to reduce the risk to the participants.

Pregnancy
The trial medication is not suitable for pregnant or breastfeeding women due to associated risks to the baby. Participants will not be included in the study if they are pregnant, trying to become pregnant or are breastfeeding. Women of child-bearing potential will be asked to provide a urine pregnancy test, and confirmation of negative pregnancy test will be required before trial drugs can be started. If the participant becomes pregnant while taking part in the trial or begins breastfeeding, the trial medication will be immediately discontinued and the participant will be followed up on the progress of pregnancy until its resolution.

Dependence
Dependence has been reported with chloral hydrate. Individuals with a history of alcohol or drug abuse or dependence may be at greater risk of abuse and misuse of chloral hydrate. Patients with a history of alcohol and drug abuse will be excluded from the trial. The trial involves the short-term use of the IMP, and participants will be supplied with a 14 day supply only.

Drowsiness
Chloral hydrate may cause drowsiness and impair the ability to drive or use machinery. Participants will be informed of this possible side-effects in the IMP information leaflet.

Participants will also be required to not consume alcohol during the 14 day IMP treatment period, which may increase drowsiness when given with chloral hydrate.

Overdose
Prior to starting IMP, participants will be informed about the risk of overdose by a medically qualified doctor and provided with clear instructions for how to take the IMP and what to do in an emergency.

Where is the study run from?
Lindus Health (UK)

When is the study starting and how long is it expected to run for?
May 2023 to April 2024

Who is funding the study?
Pharmanovia (Atnahs Pharma UK Ltd)

Who is the main contact?
Dr Adrian Williams, ajwsleep@gmail.com

Contact information

Type(s)
Scientific

Contact name
Dr Stephen Deacon

Contact details
Sovereign House
Miles Gray Road
Basildon
United Kingdom
SS14 3FR
+44 1268 943700
stephen.deacon@pharmanovia.com

Type(s)
Principal investigator

Contact name
Dr Adrian Williams

Contact details
Queen Victoria Hospital NHS Foundation Trust
East Grinstead
United Kingdom
RH19 3DZ
-
ajwsleep@gmail.com

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1007757

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 1007757, CPMS 56181

Study information

Scientific Title
An open-label tRial to Evaluate the SafeTy and efficacy Of chloral hydrate in patients with seveRE insomnia (RESTORE)

Acronym
RESTORE

Study objectives
Primary objective:
To assess the effectiveness of chloral hydrate in reducing insomnia severity.

Secondary objectives:
To explore whether chloral hydrate will affect (1-6):
1. Insomnia severity
2. Daytime sleepiness
3. Health-related quality of life
4. Self-reported sleep
5. Anxiety and depression
6. Quality of sleep and sleep disturbances
7. To investigate the safety of chloral hydrate
8. To investigate intervention adherence
9. To assess tolerance of chloral hydrate
10. To determine any changes in the use of non-pharmacological sleep therapies
11. To determine any changes in:
- Concomitant prescribed medication
- Over-the-counter medication used to facilitate sleep
12. Medical doctor assessment of effectiveness of chloral hydrate

Exploratory objective:
13. To assess days off work

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 23/08/2023, North of Scotland Research Ethics Committee 1 (Summerfield House, 2 Eday Road, Aberdeen, AB15 6RE, United Kingdom; +44 1224 558458; gram.nosres@nhs.scot), ref: 23/NS/0054

Study design
Interventional non randomized

Primary study design
Interventional

Study type(s)
Treatment, Safety, Efficacy

Health condition(s) or problem(s) studied
Patients with severe insomnia which is interfering with normal daily life, and where other sleep therapies (behavioural and pharmacologic) have failed.

Interventions
The trial will have one treatment arm, where all trial participants will receive Chloral Hydrate oral solution daily for up to 2 weeks. Chloral Hydrate is licensed in the UK, for the short-term treatment (maximum 2 weeks) of severe insomnia, which is interfering with normal daily life and where other therapies (behavioural and pharmacologic) have failed.

Participants currently on maximum doses of drugs for the treatment of their insomnia will usually be commenced on the licensed dose of 860 mg of Chloral Hydrate, and participants on intermediate doses of drugs for the treatment of their insomnia will normally be commenced on the lowest recommended dose of 430 mg of Chloral Hydrate, though the medical assessor will have the discretion to use a different dose depending on the individual participants needs within the range 430 mg-860 mg (the maximal daily dose is 2 g, but recommended starting doses are 430-860 mg).

The occurrence of potential side effects will be collected in the participant's daily diaries, safety video/phone calls, or reported by the participant using the trial email or freephone number. If the participant experiences any side-effects, this may result in reducing the dose of Chloral Hydrate by the trial medical doctor, or complete withdrawal of the trial treatment.

For participants starting on 430 mg, if Chloral Hydrate is proving ineffective following medical assessment during the day 4 safety review call, the participant will be offered the option of persisting with the current dose for the remainder of the trial, or to be reassessed with the option of increasing the dose to 860 mg. All dose changes will be documented and approved by the trial medical doctor.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Chloral Hydrate 500 mg/5 ml Oral Solution

Primary outcome(s)
Change in self-rated insomnia severity, assessed using the Insomnia Severity Index at baseline and 2 weeks

Key secondary outcome(s))
1. Change in self-rated insomnia severity, assessed using the Insomnia Severity Index at Baseline, 1 and 6 weeks
2. Change in Epworth Sleepiness Scale (ESS) scores at Baseline, 1, 2 and 6 weeks
3. Change in health-related quality of life, measured using the ShortForm 36 Questionnaire (SF-36) and EQ-5D-5L at Baseline, 1, 2 and 6 weeks
4. Change in subjective sleep measured using the NHS sleep diary over 7 days, at baseline, 1, 2, 3 and 6 weeks
5. Change in Hospital Anxiety and Depression Scale (HADS) scores at Baseline, 1, 2 and 6 weeks
6. Change in Pittsburgh Sleep Quality Index (PSQI) scores at Baseline, 2 and 6 weeks
7. Evaluation of overall safety of chloral hydrate by the monitoring of AEs and SAEs over 6 week trial duration
8. Daily intervention adherence for the duration of the intervention (Days 1-14)
9. Number of participants withdrawn from the IMP due to an AE, during the 2 week treatment period
10. Change in use of non-pharmacological sleep therapies at Baseline, 1, 2 and 6 weeks
11. Change in:
- Concomitant medication at Baseline, 1, 2 and 6 weeks
- Over the counter medication used to facilitate sleep at Baseline, 1, 2 and 6 weeks
12. Clinical Global Impressions - Severity Scale (CGI-S) assessed at baseline, and Clinical Global Impressions – Improvement scale (CGI-I) assessed after IMP treatment by the medically qualified doctor at baseline, and CGI-I at 2 and 6 weeks

Exploratory end point
13. Change in percentage of days off work at 1 month and 12 months prior to baseline, and 2 and 6 weeks

Completion date
24/04/2024

Eligibility

Key inclusion criteria
1. Aged ≥18 years and ≤75 years
2. Participant is willing and able to give informed consent
3. Clinically significant impairment from severe insomnia (eg. ISI score 22-28)
4. Previous treatment with sleep therapies (behavioural and pharmacologic), which have failed. Defined as the presence of ongoing severe insomnia (ISI score 22-28), despite previous use of other sleep therapies.
5. Able to adhere to study procedures
6. Willingness to take a pregnancy test prior to starting IMP treatment (participants of childbearing potential)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
75 years

Sex
All

Total final enrolment
99

Key exclusion criteria
1. Pregnant or breastfeeding
2. Taking any substances that significantly affect sleep during the 2 week IMP treatment period
3. Starting any new behavioural sleep therapies* during the 2 week IMP treatment period
4. At point of enrolment taking substances that affects sleep at greater than maximum licensed doses
5. Other sleep diagnosed/suspected sleep disorders (restless legs, periodic limb movements, unusual sleep timings (indicative of advanced/delayed sleep, etc), parasomnias
6. Known severe hepatic impairment
7. Known moderate / severe renal impairment / eGFR <60
8. Known severe sleep apnea
9. Known severe cardiac disease
10. Known cardiac disease with QT prolongation
11. History of myocardial infarction in the last 12 months
12. History of stroke or TIA
13. Taking medication that may cause QT prolongation
14. Active gastritis, oesophagitis, gastric or duodenal ulcers or perforation
15. Susceptible to acute attacks of porphyria
16. Hypersensitivity to chloral hydrate or to any of the excipients (glycerol, liquid glucose, citric acid, sodium citrate, sodium benzoate, saccharin sodium, essence of passion fruit [containing natural flavouring, artificial flavouring, propylene glycol], and purified water)
17. Individuals with a history of alcohol or drug abuse or dependence
18. Patients taking antipsychotic medication in last 12 months
19. History of overdose or attempted overdose
20. History of significant psychiatric disease
21. Patients are taking one of the drugs listed as interacting with Chloral Hydrate and would need to continue taking these during the trial: alcohol, CNS depressants, antipsychotics, hypnotics, anxiolytics/sedatives, antidepressant agents, centrally acting muscle relaxants, narcotic, analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines, intravenous furosemide, anticoagulants.
22. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant’s ability to participate in the trial.

23. Participants who have participated in another research trial involving an investigational product in the past 4 months
24. Participants of childbearing potential (participants who are anatomically and physiologically capable of becoming pregnant), or have a partner of childbearing potential, not willing to use highly effective contraceptives** for the duration of the trial, and who do not confirm a negative pregnancy test prior to starting the drug.

*Participants currently undergoing behavioural sleep therapies, such as CBT, will continue on these during the trial, in line with the licensing for chloral hydrate licensing, where chloral hydrate should be used as an adjunct to behavioural therapies. However, they should not start any new behavioural sleep therapies during the 2 week IMP treatment period.

**Highly effective methods have typical-use failure rates of less than 1% and include sterilisation and long-acting reversible contraceptive (LARC) methods (intrauterine devices and implants) OR if a couple are using another method of contraception, such as a combined hormonal method, progestogen only pill or injection, they are only eligible if they are willing to use an additional barrier method (e.g. male condom) for the 28-day duration of follow-up in the trial. Note: a barrier method on its own is not sufficient.

Date of first enrolment
25/09/2023

Date of final enrolment
05/12/2023

Locations

Countries of recruitment
United Kingdom

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
Pharmanovia

Funder(s)

Funder type
Industry

Funder Name
Pharmanovia (Atnahs Pharma UK Ltd)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication.

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Plain English results		23/04/2025	23/04/2025	No	Yes