Clinical trial results:
TREATMENT OF SLEEP DISTURBANCES IN TRAUMA-AFFECTED REFUGEES – A RANDOMISED CONTROLLED TRIAL

Summary

EudraCT number	2015-004153-40
Trial protocol	DK
Global end of trial date	18 March 2020

Results information

Result version number	v1 (current)
This version publication date	01 April 2021
First version publication date	01 April 2021

Trial information

Trial identification

Sponsor protocol code	PTF5

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Ethics committe: H-15014503

Notes:

Sponsors

Sponsor organisation name	Competence centre for Transcultural Psychiatry
Sponsor organisation address	Maglevaenget 21, Ballerup, Denmark, 2750
Public contact	Hinuga Sandahl, Competence Centre for Transcultural Psychiatry, 45 26847112, hinuga.sandahl.01@regionh.dk
Scientific contact	Hinuga Sandahl, Competence Centre for Transcultural Psychiatry, 45 26847112, hinuga.sandahl.01@regionh.dk
Sponsor organisation name	Competence Centre for Transcultural Psychiatry
Sponsor organisation address	Maglevaenget 21, Ballerup, Denmark, 2750
Public contact	Jessica Carlsson, Competence Centre for Transcultural Psychiatry, 45 38646180, jessica.carlsson.lohmann@regionh.dk
Scientific contact	Jessica Carlsson, Competence Centre for Transcultural Psychiatry, 45 38646180, jessica.carlsson.lohmann@regionh.dk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall aim of this study is to examine sleep enhancing treatment in refugees with PTSD in a randomised controlled trial.
The objectives are:
1. To estimate treatment effects of IRT and mianserin on sleep quality, sleep length and nightmares compared to treatment as usual (TAU) at CTP (Se description below)
2. To study the relation between enhanced sleep, PTSD-symptoms, observer rated functioning and self-rated quality of life
3. To examine predictors for positive outcome of treatment

Protection of trial subjects:	
None	
Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	01 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 219
Worldwide total number of subjects	219
EEA total number of subjects	219

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	217
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In the period from March 2016 to April 2018, 1125 patients consecutively referred to treatment at Competence Centre for Transcultural Psychiatry were screened for the study and 240 patients were randomized.

Pre-assignment

Screening details:

A total of 21 participants, equally distributed in the intervention groups, were excluded from analysis due to withdrawal of informed consent, error in error in eligibility assessment, or due to emergence of pregnancy or psychosis during the study. The modified intention-to-treat sample hence consisted of 219 participants.

Period 1

Period 1 title	overall period (pre-post treatment)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

Blinded assessors performed the HAM-D and HAM-A ratings pre- and post-treatment. Asessors were blinded for intervention group and pre/post and 6-months follow-up time.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment as usual (TAU)

Arm description:

TAU was an interdisciplinary treatment approach, covering a period of 8-12 months, with medicine according to standard at CTP (best clinical practice in the field), physiotherapy, psychoeducation (including sleep hygiene education and relaxation techniques), and manual-based CBT. The treatment was two-phased, phase one: 2-4 months treatment provided by physician and physiotherapist, phase two: 4-8 months of combined treatment provided by both physician and psychologist. For a detailed description of TAU, please see study protocol (Sandahl, Jennum, et al., 2017). Experienced interpreters were present in sessions, if needed, and during conduction of ratings, as required.

5 patients withdrawn, please see publiction for reason

Arm type	Treatment as usual

No investigational medicinal product assigned in this arm

Arm title	Mianserin

Arm description:

Mianserin was prescribed and delivered to the participant by the treating physician and initiated at 10 mg before bedtime. The dose could be increased gradually to a maximum dosage of 30 mg adjusted according to effect and side effects. At each session with the physician, the participants were asked to report whether they had taken their medication as prescribed, and the current dose of mianserin was registered. Adherence was monitored by measuring the plasma concentration of mianserin after phase one and phase two (post-treatment).

6 patients withdrawn, please see publiction for reason

Arm type	Experimental
Investigational medicinal product name	Mianserin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10-30 mg

Arm title	Imagery Rehearsal Therapy

Arm description:

IRT was integrated in six sessions of manual-based CBT in sessions administered by a psychologist. The sessions IRT treatment consisted of three components 1) psychoeducation on disturbing dreams, nightmares and sleep as well as exercises in cognitive restructuring and 2) imaginationimagery education and positive imagery exercises, enabling the patient to transform the 3) imagery rescripting of the disturbing dream or nightmare and rehearsal of into a new and non-disturbing dream. The manual was developed to accommodate for individual differences in the participants and allowed the therapist flexibility in sequencing of components. However, positive imagery exercises had to be performed prior to initiating imagery rescripting. The number of sessions devoted to each component was flexible and accustomed to the individual participant.
All psychologists were trained and supervised in this specific method, described in detail in the IRT manual available at ctp-net.dk.

Arm type	Experimental
Investigational medicinal product name	IRT (therapy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear ointment
Routes of administration	Other use

Dosage and administration details:

Pharmaceutical form not relevant for therapy

Arm title	IRT + mianserin

Arm description:

4 patients withdrawn, please see publiction for reason

Arm type	Experimental
Investigational medicinal product name	Mianserin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10-30 mg

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Blinded assessors performed the HAM-D and HAM-A ratings pre- and post-treatment. Asessors were blinded for intervention group and pre/post and 6-months follow-up time.

Number of subjects in period 1	Treatment as usual (TAU)	Mianserin	Imagery Rehearsal Therapy
Started	55	54	56
Completed	55	54	56

Number of subjects in period 1	IRT + mianserin
Started	54
Completed	54

Baseline characteristics

Reporting groups	
Reporting group title	overall period (pre-post treatment)

Reporting group description: -

Reporting group values	overall period (pre-post treatment)	Total	
Number of subjects	219	219	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	44.4		
standard deviation	± 10.4	-	
Gender categorical Units: Subjects			
Female	109	109	
Male	110	110	

End points

End points reporting groups

Reporting group title	Treatment as usual (TAU)

Reporting group description:

TAU was an interdisciplinary treatment approach, covering a period of 8-12 months, with medicine according to standard at CTP (best clinical practice in the field), physiotherapy, psychoeducation (including sleep hygiene education and relaxation techniques), and manual-based CBT. The treatment was two-phased, phase one: 2-4 months treatment provided by physician and physiotherapist, phase two: 4-8 months of combined treatment provided by both physician and psychologist. For a detailed description of TAU, please see study protocol (Sandahl, Jennum, et al., 2017). Experienced interpreters were present in sessions, if needed, and during conduction of ratings, as required.

5 patients withdrawn, please see publiction for reason

Reporting group title	Mianserin

Reporting group description:

Mianserin was prescribed and delivered to the participant by the treating physician and initiated at 10 mg before bedtime. The dose could be increased gradually to a maximum dosage of 30 mg adjusted according to effect and side effects. At each session with the physician, the participants were asked to report whether they had taken their medication as prescribed, and the current dose of mianserin was registered. Adherence was monitored by measuring the plasma concentration of mianserin after phase one and phase two (post-treatment).

6 patients withdrawn, please see publiction for reason

Reporting group title	Imagery Rehearsal Therapy

Reporting group description:

IRT was integrated in six sessions of manual-based CBT in sessions administered by a psychologist. The sessions IRT treatment consisted of three components 1) psychoeducation on disturbing dreams, nightmares and sleep as well as exercises in cognitive restructuring and 2) imaginationimagery education and positive imagery exercises, enabling the patient to transform the 3) imagery rescripting of the disturbing dream or nightmare and rehearsal of into a new and non-disturbing dream. The manual was developed to accommodate for individual differences in the participants and allowed the therapist flexibility in sequencing of components. However, positive imagery exercises had to be performed prior to initiating imagery rescripting. The number of sessions devoted to each component was flexible and accustomed to the individual participant.
All psychologists were trained and supervised in this specific method, described in detail in the IRT manual available at ctp-net.dk.

Reporting group title	IRT + mianserin

Reporting group description:

4 patients withdrawn, please see publiction for reason

Primary: Pittsburgh Sleep Quality Index

End point title	Pittsburgh Sleep Quality Index[1]

End point description:

End point type	Primary

End point timeframe:

Timepoint pre-treatment, after 2-3 months of treatment, post-treatment and follow-up.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Please see attached table and publication for statistical analysis.

End point values	Treatment as usual (TAU)	Mianserin	Imagery Rehearsal Therapy	IRT + mianserin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	54	56	54
Units: Scale points				
arithmetic mean (standard error)	15.60 (± 0.41)	16.42 (± 0.38)	16.58 (± 0.39)	16.42 (± 0.42)

Attachments (see zip file)	Table S2 Mixed model analyses intention-to-treat sample four

Statistical analyses

No statistical analyses for this end point

Secondary: Harvard Trauma Questionnaire

End point title	Harvard Trauma Questionnaire

End point description:

End point type	Secondary

End point timeframe:

pre-treatment, after 2-3 months of treatment, post-treatment and follow-up.

End point values	Treatment as usual (TAU)	Mianserin	Imagery Rehearsal Therapy	IRT + mianserin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	54	56	54
Units: scale points				
arithmetic mean (standard error)	2.84 (± 0.10)	3.15 (± 0.07)	2.86 (± 0.10)	2.89 (± 0.10)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event were reported post-treatment.

Adverse event reporting additional description:

The participants were asked about adverse events in each session with a physician and events were registered in accordance with definitions and current legislation by the Danish Medicines Agency (Medicines Agency, n.d.). In addition, all discomfort in connection with psychotherapy was registered.

Assessment type	Systematic

Dictionary used

Dictionary name	No Dictionary
Dictionary version	1

Reporting groups

Reporting group title	Treatment as usual (TAU)

Reporting group description:

TAU was an interdisciplinary treatment approach, covering a period of 8-12 months, with medicine according to standard at CTP (best clinical practice in the field), physiotherapy, psychoeducation (including sleep hygiene education and relaxation techniques), and manual-based CBT. The treatment was two-phased, phase one: 2-4 months treatment provided by physician and physiotherapist, phase two: 4-8 months of combined treatment provided by both physician and psychologist. For a detailed description of TAU, please see study protocol (Sandahl, Jennum, et al., 2017). Experienced interpreters were present in sessions, if needed, and during conduction of ratings, as required.

Reporting group title	Mianserin

Reporting group description:

Mianserin was prescribed and delivered to the participant by the treating physician and initiated at 10 mg before bedtime. The dose could be increased gradually to a maximum dosage of 30 mg adjusted according to effect and side effects. At each session with the physician, the participants were asked to report whether they had taken their medication as prescribed, and the current dose of mianserin was registered. Adherence was monitored by measuring the plasma concentration of mianserin after phase one and phase two (post-treatment).

Reporting group title	Imagery Rehearsal Therapy

Reporting group description:

IRT was integrated in six sessions of manual-based CBT in sessions administered by a psychologist. The sessions IRT treatment consisted of three components 1) psychoeducation on disturbing dreams, nightmares and sleep as well as exercises in cognitive restructuring and 2) imaginationimagery education and positive imagery exercises, enabling the patient to transform the 3) imagery rescripting of the disturbing dream or nightmare and rehearsal of into a new and non-disturbing dream. The manual was developed to accommodate for individual differences in the participants and allowed the therapist flexibility in sequencing of components. However, positive imagery exercises had to be performed prior to initiating imagery rescripting. The number of sessions devoted to each component was flexible and accustomed to the individual participant.
All psychologists were trained and supervised in this specific method, described in detail in the IRT manual available at ctp-net.dk.

Reporting group title	IRT + mianserin

Reporting group description: -

Serious adverse events	Treatment as usual (TAU)	Mianserin	Imagery Rehearsal Therapy
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 55 (1.82%)	0 / 54 (0.00%)	0 / 56 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Injury, poisoning and procedural complications			
Suicidal ideation			
subjects affected / exposed	0 / 55 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium tremens			
subjects affected / exposed	1 / 55 (1.82%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	IRT + mianserin		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 54 (1.85%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Suicidal ideation			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium tremens			
subjects affected / exposed	0 / 54 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment as usual (TAU)	Mianserin	Imagery Rehearsal Therapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 55 (5.45%)	32 / 54 (59.26%)	2 / 56 (3.57%)
Nervous system disorders			
Fatigue			
subjects affected / exposed	2 / 55 (3.64%)	20 / 54 (37.04%)	1 / 56 (1.79%)
occurrences (all)	2	20	1
Dizziness			

subjects affected / exposed	0 / 55 (0.00%)	6 / 54 (11.11%)	0 / 56 (0.00%)
occurrences (all)	0	6	0
Somnolence			
subjects affected / exposed	0 / 55 (0.00%)	11 / 54 (20.37%)	0 / 56 (0.00%)
occurrences (all)	0	11	0
Headache			
subjects affected / exposed	1 / 55 (1.82%)	3 / 54 (5.56%)	0 / 56 (0.00%)
occurrences (all)	1	3	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal discomfort	Additional description: Desciption of heavy body		
subjects affected / exposed	0 / 55 (0.00%)	2 / 54 (3.70%)	0 / 56 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Weight increased			
subjects affected / exposed	0 / 55 (0.00%)	4 / 54 (7.41%)	0 / 56 (0.00%)
occurrences (all)	0	4	0
Dry mouth			
subjects affected / exposed	0 / 55 (0.00%)	4 / 54 (7.41%)	1 / 56 (1.79%)
occurrences (all)	0	4	1

Non-serious adverse events	IRT + mianserin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 54 (55.56%)		
Nervous system disorders			
Fatigue			
subjects affected / exposed	14 / 54 (25.93%)		
occurrences (all)	14		
Dizziness			
subjects affected / exposed	7 / 54 (12.96%)		
occurrences (all)	7		
Somnolence			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Musculoskeletal and connective tissue			

disorders			
Musculoskeletal discomfort	Additional description: Desciption of heavy body		
subjects affected / exposed	6 / 54 (11.11%)		
occurrences (all)	6		
Metabolism and nutrition disorders			
Weight increased			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Dry mouth			
subjects affected / exposed	7 / 54 (12.96%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33529449