

Dronabinol for nightmares in post-traumatic stress disorder: a randomized controlled trial

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SUPPLEMENTARY APPENDIX

Supplement to: Dronabinol for nightmares in post-traumatic stress disorder: a randomized controlled trial

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Supplementary methods

Prohibited medication

Prohibited Drug Category	Restriction period
Cannabis-based medicine	Not permitted during the trial or within 3 months prior to screening.
Cannabis herb	Not permitted during the trial or within 3 months prior to screening.
Sleep medication (for example, all benzodiazepines, non-benzodiazepines [zaleplon, zolpidem, zopiclone], other sleep medication [chloral hydrate, melatonin, antihistaminergic agents [diphenhydramine, doxylamine, promethazine], mirtazapine, trazodone, trimipramine, doxepin, pipamperone and melperone])	Initiation of sleep medication 4 weeks prior to screening and during the trial is not allowed. Sleep medication that has been initiated 4 or more weeks before screening can be continued at stable dose during the trial.

Prohibited Drug Category	Restriction period
Alpha-adrenergic agents (for example, doxazosin, prazosin, terazosin and clonidine)	Alpha-adrenergic agents that have been initiated 4 or more weeks before screening can be continued at stable dose during the trial. Initiation of alpha-adrenergic agents 4 weeks prior to screening and during the trial is not allowed.

End points

Primary endpoint	Change in nightmare frequency and intensity on the Clinician-Administered PTSD Scale (CAPS-IV) B2 score (range, 0 to 8) from baseline to Week 10
Secondary endpoint	1. Change from baseline of the frequency and intensity of nightmares, measured with the Clinician-Administered PTSD Scale-IV (CAPS-IV) B2 score for the last week, range 0–8, at Week 1 – Week 8 2. Change from baseline of the CAPS-5 total score (overall PTSD symptoms, last week) at Week 6 and Week 10 3. Change from baseline of the Pittsburgh Sleep Quality Index-Addendum for PTSD (PSQI-A) (PTSD-related sleep symptoms) at Week 6 and Week 10 4. Change from baseline of the Montgomery-Åsberg Depression Rating Scale (MADRS, depressive symptoms) at Week 6 and Week 10 5. Weekly change from baseline of the patients' daily total sleep time (in minutes), sleep onset latency at night (in minutes), recuperation of night sleep (5-point Likert scale, 1 = very much; 5 = not at all), and time awake at night (in minutes), number of nightmares last night (0, 1, 2, 3, 4 or more) and intensity of nightmares (5-point Likert scale, 0 = not at all; 4 = extreme) assessed with sleep diaries during Week 1 – Week 10 6. Change from baseline of PTSD symptoms assessed with the PTSD Checklist for DSM-5 (PCL-5) at Week 6 and Week 10 7. Change from baseline of the Borderline Symptom List 23 (BSL-23) score at Week 6 and Week 10 8. Change from baseline of the Health-Related Quality of Life (EQ-5D) score at Week 6 and Week 10 9. Overall patient status measured by the Patient Global Impression of Change (PGIC) at Week 6 and Week 10 10. Change from baseline of the Social and Occupational Functioning Assessment Scale (SOFAS) at Week 6 and Week 10 11. Change from baseline of the Pittsburgh Sleep Quality Index (PSQI) at Week 6 and Week 10 12. Change from baseline of symptoms of PTSD and complex PTSD according to ICD-11 assessed with the International Trauma Questionnaire (ITQ) at Week 6 and Week 10 13. Change from baseline of THC withdrawal symptoms assessed with the Marijuana Withdrawal Checklist (MWC) at Week 6, Week 10, and Week 12 14. Responder analysis: proportion of patients showing improvement in nightmares (change from baseline) defined as decrease of CAPS-IV B2 $\geq 50\%$ assessed at the end of treatment (Week 10) 15. Remitter analysis: proportion of patients showing full remission of nightmares defined as CAPS-IV B2 = 0, assessed at the end of treatment (Week 10)

Supplementary Tables

Table S1. Baseline values of secondary outcomes.^a

Outcome	Dronabinol	Placebo	Total	Between-group differences (95% CI) ^b
PSQI-A ^c	11.87 (3.42)	12.61 (3.41)	12.23 (3.42)	-0.75 (-1.81 to 0.31)
N (%)	82 (94.3)	80 (97.6)	162 (95.9)	
PCL-5 ^d	49.22 (13.03)	51.75 (10.51)	50.46 (11.89)	-2.53 (-6.21 to 1.15)
N (%)	82 (94.3)	79 (96.3)	161 (95.3)	
PSQI ^e	13.42 (3.50)	13.93 (2.95)	13.67 (3.24)	-0.50 (-1.57 to 0.57)
N (%)	73 (83.9)	69 (84.1)	142 (84)	
BSL-23 ^f	35.45 (19.50)	37.14 (18.50)	36.28 (18.97)	-1.69 (-7.57 to 4.19)
N (%)	83 (95.4)	80 (97.6)	163 (96.4)	
ITQ ^g	46.63 (13.68)	49.24 (11.54)	47.88 (12.73)	-2.61 (-6.62 to 1.39)
N (%)	81 (93.1)	74 (90.2)	155 (91.7)	
EQ-5D TTO ^h	0.74 (0.26)	0.68 (0.27)	0.71 (0.27)	0.10 (-0.01 to 0.14)
N (%)	84 (96.6)	82 (100)	166 (98.2)	
EQ-5D VAS ⁱ	56.11 (21.84)	52.34 (21.65)	54.26 (21.76)	3.77 (-2.96 to 10.50)
N (%)	83 (95.4)	80 (97.6)	163 (96.4)	
SOFAS ^j	57.36 (13.46)	56.7 (12.55)	57.04 (12.99)	0.66 (-3.29 to 4.61)
N (%)	87 (100)	82 (100)	169 (100)	

^a Data from the full analysis set. Values are means (SD). Baseline values of primary and key secondary outcomes are provided in Table 1.

^b Between-group differences are shown with 95% confidence intervals; details of the analysis of the EQ-5D TTO index are provided below.

^c Pittsburgh Sleep Quality Index-Addendum for PTSD (PSQI-A) assesses frequency of disruptive nocturnal behaviors related to PTSD (including nightmares and nocturnal distress); scores range from 0 to 21, with higher scores indicating greater severity of trauma-related sleep disturbances.

^d PTSD Checklist for DSM-5 (PCL-5) assesses severity of post-traumatic stress disorder (PTSD) symptoms according to DSM-5; scores range from 0 to 80, with higher scores indicating greater symptom severity.

^e Pittsburgh Sleep Quality Index (PSQI) assesses subjective sleep quality and sleep disturbances; scores range from 0 to 21; higher scores indicate poorer sleep quality.

^f Borderline Symptom List 23 (BSL-23) assesses severity of borderline personality disorder symptoms; scores range from 0 to 92, with higher scores indicating greater symptom severity.

^g International Trauma Questionnaire (ITQ) assesses symptoms of PTSD and disturbances in self-organization according to ICD-11 criteria; scores range from 0 to 72, with higher scores indicating greater symptom severity.

^h Health-Related Quality of Life (EQ-5D-3L) assesses health-related quality of life across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each rated on three levels (no problems, some problems, extreme problems), generating a preference-based index score derived from time trade-off (TTO) valuation; TTO scores typically range from values below 0 to 1. For the EQ-5D TTO index (non-normally distributed), the between-group difference is the difference in medians, with a 95% CI derived by BCa bootstrap (9,999 replications); descriptive values are shown as means (SD).

ⁱ EQ-5D-3L visual analog scale (VAS) assesses perceived level of health; scores range from 0 to 100 with higher scores indicating better perceived health

^j Social and Occupational Functioning Assessment Scale (SOFAS) assesses level of social and occupational functioning; scores range from 0 to 100 with higher scores indicating better social and occupational functioning.

Table S2. Comorbid psychiatric disorders^a

Disorder	Dronabinol (n = 87)	Placebo (n = 82)	Total (N = 169)
Major depression (current) – no. (%)	36 (41.4)	32 (39)	68 (40.2)
Depression (lifetime) – no. (%)	81 (93.1)	70 (85.4)	151 (89.3)
Panic disorder (current) – no. (%)	8 (9.2)	7 (8.5)	15 (8.9)
Panic disorder (lifetime) – no. (%) ^b	21 (24.4)	24 (29.3)	45 (26.8)
Agoraphobia (current) – no. (%)	20 (23)	18 (22)	38 (22.5)
Social anxiety disorder (current) – no. (%) ^c	17 (19.5)	14 (17.3)	31 (18.5)
OCD (current) – no. (%) ^d	8 (9.2)	11 (13.4)	19 (11.2)
Alcohol use disorder (past 12 Months) – no. (%)	2 (2.3)	4 (4.9)	6 (3.6)
Substance use disorder (past 12 Months) – no. (%)	2 (2.3)	1 (1.2)	3 (1.8)
Bulimia nervosa (current) – no. (%)	4 (4.6)	6 (7.3)	10 (5.9)
Binge eating disorder (current) – no. (%)	2 (2.3)	4 (4.9)	6 (3.6)
GAD (current) – no. (%) ^e	7 (8)	3 (3.7)	10 (5.9)
Borderline personality disorder – no. (%) ^f	16 (19.3)	14 (17.9)	30 (18.6)

^a Patient data from the full analysis set. Mini International Neuropsychiatric Interview for DSM-5 (MINI-5) was performed.

^b Dronabinol Group had one missing patient value for panic disorder (lifetime)

^c Placebo Group had one missing patient value for social anxiety disorder

^d OCD = obsessive-compulsive disorder

^e GAD = generalized anxiety disorder

^f Dronabinol Group had four missing patient values and the Placebo Group had four missing patient values for borderline personality disorder

Table S3. Concomitant Medications Across Groups Based on ATC Level 2 Classification ^a

	Dronabinol n = 87	Placebo n = 82	Total N = 169
Anti-acne preparations	1 (1.1)	0 (0)	1 (0.6)
Analgesics	18 (20.7)	13 (15.9)	31 (18.3)
Other nervous system drugs	0 (0)	1 (1.2)	1 (0.6)
Antianemic preparations	2 (2.3)	0 (0)	2 (1.2)
Drugs used in diabetes	2 (2.3)	4 (4.9)	6 (3.6)
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	2 (2.3)	0 (0)	2 (1.2)
Antiemetics and antinauseants	1 (1.1)	0 (0)	1 (0.6)
Antiepileptics	4 (4.6)	0 (0)	4 (2.4)
Antihistamines for systemic use	3 (3.4)	2 (2.4)	5 (3)
Antihypertensives	2 (2.3)	4 (4.9)	6 (3.6)
Antifungals for dermatological use	0 (0)	1 (1.2)	1 (0.6)
Anti-Parkinson drugs	5 (5.7)	2 (2.4)	7 (4.1)
Anti-inflammatory and antirheumatic products	9 (10.3)	12 (14.6)	21 (12.4)
Antipsoriatics	0 (0)	1 (1.2)	1 (0.6)
Antithrombotic agents	3 (3.4)	4 (4.9)	7 (4.1)
Beta blocking agents	6 (6.9)	4 (4.9)	10 (5.9)
Calcium channel blockers	3 (3.4)	2 (2.4)	5 (3)
Diuretics	4 (4.6)	2 (2.4)	6 (3.6)
Drugs for gout	0 (0)	1 (1.2)	1 (0.6)
Cardiac therapy	0 (0)	1 (1.2)	1 (0.6)
Cough and cold preparations	1 (1.1)	0 (0)	1 (0.6)
Immunosuppressants	1 (1.1)	3 (3.7)	4 (2.4)
Drugs for functional gastrointestinal disorders	3 (3.4)	0 (0)	3 (1.8)
Drugs for obstructive airway diseases	4 (4.6)	4 (4.9)	8 (4.7)
Drugs for acid related disorders	8 (9.2)	10 (12.2)	18 (10.7)
Drugs for constipation	0 (0)	0 (0)	0 (0)
Agents acting on the renin–angiotensin system	10 (11.5)	14 (17.1)	24 (14.2)
Drugs for treatment of bone diseases	1 (1.1)	0 (0)	1 (0.6)
Lipid modifying agents	2 (2.3)	5 (6.1)	7 (4.1)
Muscle relaxants	0 (0)	1 (1.2)	1 (0.6)
Ophthalmologicals	1 (1.1)	0 (0)	1 (0.6)
Psychoanaleptics	53 (60.9)	52 (63.4)	105 (62.1)
Psycholeptics	19 (21.8)	24 (29.3)	43 (25.4)
Nasal preparations	1 (1.1)	0 (0)	1 (0.6)
Thyroid therapy	13 (14.9)	7 (8.5)	20 (11.8)
Sex hormones and modulators of the genital system	15 (17.2)	5 (6.1)	20 (11.8)
Urologicals	0 (0)	2 (2.4)	2 (1.2)
Vitamins	8 (9.2)	6 (7.3)	14 (8.3)
Wound and ulcer treatment preparations	0 (0)	1 (1.2)	1 (0.6)

^a Patient data from the full analysis set. Values are n (%). ATC = Anatomical Therapeutic Chemical classification system; multiple entries per individual were possible.

Table S4. Baseline primary and key secondary outcomes by current depression status^a

Outcome	No depression n = 101	Depression n = 68
CAPS-IV B2 ^b	6.78 (0.92)	6.69 (0.95)
CAPS-5 ^c	36.6 (9.66)	44.97 (10.38)
MADRS ^d	16.1 (5.88)	23.29 (4.45)

^a Data from the full analysis set. Values are means (SD).

^b The Clinician-Administered posttraumatic stress disorder (PTSD) Scale for DSM-IV (CAPS-IV) B2 item assesses frequency and intensity of nightmares; scores range from 0 to 8, with higher scores indicating greater symptom severity.

^c CAPS-5 is the updated version for DSM-5 criteria assessing PTSD symptoms (range 0–80), with higher scores indicating greater symptom severity.

^d The Montgomery–Åsberg Depression Rating Scale (MADRS) ranges from 0 to 60, with higher scores indicating more severe depression.

Table S5. Descriptive Measures of Traumatic Events and Childhood Trauma^a

Characteristic	Dronabinol n = 87	Placebo n = 82	Total N = 169
LEC-5 Item^b			
Natural disaster	20 (23.0)	20 (24.4)	40 (23.7)
Fire or explosion	24 (27.6)	35 (42.7)	59 (34.9)
Transportation accident	48 (55.2)	45 (54.9)	93 (55.0)
Serious accident at work, home, or during recreation	29 (33.3)	32 (39.0)	61 (36.1)
Exposure to toxic substance	7 (8.0)	9 (11.0)	16 (9.5)
Physical assault	67 (77.0)	63 (76.8)	130 (76.9)
Assault with a weapon	38 (43.7)	44 (53.7)	82 (48.5)
Sexual assault	71 (81.6)	65 (79.3)	136 (80.5)
Other unwanted or uncomfortable sexual experience	61 (70.1)	63 (76.8)	124 (73.4)
Combat or exposure to a war zone	17 (19.5)	15 (18.3)	32 (18.9)
Captivity	14 (16.1)	17 (20.7)	31 (18.3)
Life-threatening illness or injury	43 (49.4)	46 (56.1)	89 (52.7)
Severe human suffering	50 (57.5)	47 (57.3)	97 (57.4)
Sudden violent death	41 (47.1)	44 (53.7)	85 (50.3)
Sudden accidental death	28 (32.2)	27 (32.9)	55 (32.5)
Serious injury, harm, or death you caused to someone else	12 (13.8)	9 (11.0)	21 (12.4)
Any other very stressful event or experience	41 (47.1)	49 (59.8)	90 (53.3)
How the traumatic events were experienced			
Personal Experience	85 (97.7)	80 (97.6)	165 (97.6)
Witnessed	52 (59.8)	53 (64.6)	105 (62.1)
Heard about it	43 (49.4)	54 (65.9)	97 (57.4)
Part of my job	16 (18.4)	22 (26.8)	38 (22.5)
CTQ^c subscale			
Emotional abuse ^d	17.7 (6.5)	17.38 (6.02)	17.54 (6.25)
Physical abuse ^e	10.99 (5.79)	11.98 (6.24)	11.48 (6.02)
Sexual abuse ^f	12.11 (7.4)	13.28 (7.13)	12.69 (7.27)
Emotional neglect ^g	17.37 (5.24)	17.15 (5.33)	17.26 (5.27)
Physical neglect ^h	12.45 (5.39)	12.23 (5.11)	12.34 (5.24)

^a Patient data from the full analysis set.

^b LEC-5 = Life Events Checklist for DSM-5. Values are n (%). Events are reported when participants indicated in the Life Events Checklist (LEC-5) that the event was experienced as personal experience, witnessed, heard about it or part of their job. Responses categorized as “Unsure” were not included.

^c CTQ = Childhood Trauma Questionnaire. Values are mean (SD).

^d Four Emotional Abuse subscale values were missing in the dronabinol group and one in the placebo group.

^e Four Physical Abuse subscale values were missing in the dronabinol group and one in the placebo group.

^f Four Sexual Abuse subscale values were missing in the dronabinol group and one in the placebo group.

^g Four Emotional Neglect subscale values were missing in the dronabinol group and one in the placebo group.

^h Two Physical Neglect subscale values were missing in the dronabinol group and one in the placebo group.

Table S6. Maintenance Dose of the Investigational Medicinal Product^a

Characteristic	Dronabinol (n = 87)	Placebo (n = 82)	Total (N = 169)
Mean (SD), Hub ^b	15.85 (3.74)	17.55 (2.03)	16.66 (3.15)
Median (IQR), Hub ^b	18 (15 – 18)	18 (18 – 18)	18 (18 – 18)
Range, Hub ^b	3 – 18	3 – 18	3 – 18
Dose level — no. (%) ^c			
3	2 (2.5)	1 (1.4)	3 (1.9)
6	2 (2.5)	0 (0)	2 (1.3)
9	5 (6.2)	0 (0)	5 (3.2)
12	7 (8.6)	2 (2.7)	9 (5.8)
15	11 (13.6)	2 (2.7)	13 (8.4)
18	54 (66.7)	69 (93.2)	123 (79.4)

^a Patient data from the full analysis set. Maintenance dose available from 81 participants in the dronabinol group and 74 participants in the placebo group.

^b Mean, median, and range values are reported in “Hub”, corresponding to the number of device activations per day. 3 Hub $\approx$ 2.5 mg dronabinol.

^c The dose level is expressed in “Hub,” corresponding to the number of device activations per day. 3 Hub $\approx$ 2.5 mg dronabinol. Percentages use the number of participants with available data for maintenance dose as the denominator in each group.

Table S7. Sleep-Diary Outcomes^a

Outcome	Dronabinol (n = 87)	Placebo (n = 82)	Between-group difference (95% CI)
Total sleep time ^b wk 1 [min]	372.07 (103.53)	360.92 (100.21)	11.15 (-23.68 to 45.98)
No. (%)	70 (80.5)	64 (78)	---
Total sleep time ^b wk 2 [min]	384.35 (97.84)	372.18 (103.64)	12.18 (-23.39 to 47.74)
No. (%)	64 (73.6)	62 (75.6)	---
Total sleep time ^b wk 3 [min]	410.49 (97.01)	362.59 (101.76)	47.90 (12.76 to 83.05)
No. (%)	66 (75.9)	60 (73.2)	---
Total sleep time ^b wk 4 [min]	422.76 (94.66)	391.02 (88.6)	31.74 (-0.98 to 64.46)
No. (%)	63 (72.4)	60 (73.2)	---
Total sleep time ^b wk 5 [min]	424.83 (101.58)	389.39 (87.61)	35.44 (1.36 to 69.51)
No. (%)	63 (72.4)	58 (70.7)	---
Total sleep time ^b wk 6 [min]	434.41 (104.79)	398.26 (92.54)	36.15 (0.17 to 72.13)
No. (%)	63 (72.4)	55 (67.1)	---
Total sleep time ^b wk 7 [min]	429.1 (96.5)	395.32 (103.39)	33.79 (-2.62 to 70.19)
No. (%)	65 (74.7)	55 (67.1)	---
Total sleep time ^b wk 8 [min]	432.52 (94.28)	409.06 (82.55)	23.46 (-9.80 to 56.73)
No. (%)	59 (67.8)	52 (63.4)	---
Total sleep time ^b wk 9 [min]	425.35 (94.19)	409.06 (88.18)	16.30 (-18.76 to 51.35)
No. (%)	59 (67.8)	48 (58.5)	---
Total sleep time ^b wk 10 [min]	421.42 (90.06)	397.83 (93.66)	23.59 (-12.84 to 60.02)
No. (%)	54 (62.1)	47 (57.3)	---
Sleep-onset latency ^c wk 1 [min]	54.28 (43.17)	58.89 (43.58)	-4.61 (-18.89 to 9.66)
No. (%)	77 (88.5)	68 (82.9)	---
Sleep-onset latency ^c wk 2 [min]	52.39 (49.31)	55.01 (48.84)	-2.62 (-19.03 to 13.80)
No. (%)	73 (83.9)	67 (81.7)	---
Sleep-onset latency ^c wk 3 [min]	46.72 (42.06)	50.11 (44.44)	-3.38 (-17.91 to 11.15)
No. (%)	75 (86.2)	65 (79.3)	---
Sleep-onset latency ^c wk 4 [min]	44.89 (46.07)	45.61 (39.05)	-0.72 (-15.05 to 13.61)
No. (%)	73 (83.9)	65 (79.3)	---
Sleep-onset latency ^c wk 5 [min]	44.94 (43.83)	46.55 (41.28)	-1.62 (-16.02 to 12.78)
No. (%)	74 (85.1)	63 (76.8)	---
Sleep-onset latency ^c wk 6 [min]	38.54 (40.51)	42.92 (38.07)	-4.38 (-17.83 to 9.08)
No. (%)	73 (83.9)	61 (74.4)	---
Sleep-onset latency ^c wk 7 [min]	42.29 (43.8)	40.98 (47.76)	1.31 (-14.69 to 17.31)
No. (%)	72 (82.8)	59 (72)	---
Sleep-onset latency ^c wk 8 [min]	43.19 (38.23)	40.67 (37.43)	2.51 (-10.81 to 15.84)
No. (%)	69 (79.3)	58 (70.7)	---
Sleep-onset latency ^c wk 9 [min]	41.11 (39.1)	42.2 (42.71)	-1.09 (-15.75 to 13.57)
No. (%)	69 (79.3)	56 (68.3)	---
Sleep-onset latency ^c wk 10 [min]	43.91 (47.15)	48.3 (52.32)	-4.39 (-22.65 to 13.88)
No. (%)	65 (74.7)	54 (65.9)	---
Time awake at night ^d wk 1 [min]	46.42 (40.6)	47.66 (34.66)	-1.24 (-13.73 to 11.25)
No. (%)	75 (86.2)	67 (81.7)	---
Time awake at night ^d wk 2 [min]	39.58 (40.65)	43.39 (40.4)	-3.81 (-17.52 to 9.89)
No. (%)	71 (81.6)	66 (80.5)	---
Time awake at night ^d wk 3 [min]	31.7 (34.35)	40.48 (38.93)	-8.78 (-21.30 to 3.75)

Outcome	Dronabinol (n = 87)	Placebo (n = 82)	Between-group difference (95% CI)
No. (%)	72 (82.8)	64 (78)	---
Time awake at night ^d wk 4 [min]	27.5 (37.35)	35.63 (35.2)	-8.13 (-20.53 to 4.27)
No. (%)	70 (80.5)	64 (78)	---
Time awake at night ^d wk 5 [min]	34.42 (50.32)	31.54 (29.67)	2.88 (-11.00 to 16.76)
No. (%)	72 (82.8)	63 (76.8)	---
Time awake at night ^d wk 6 [min]	28.36 (36.44)	36.83 (34.96)	-8.47 (-20.78 to 3.84)
No. (%)	71 (81.6)	61 (74.4)	---
Time awake at night ^d wk 7 [min]	28.28 (38.3)	33.23 (34.67)	-4.94 (-17.83 to 7.94)
No. (%)	69 (79.3)	57 (69.5)	---
Time awake at night ^d wk 8 [min]	28.41 (38.81)	34.47 (38.56)	-6.06 (-19.81 to 7.69)
No. (%)	68 (78.2)	57 (69.5)	---
Time awake at night ^d wk 9 [min]	32.31 (45.63)	32.32 (35.96)	-0.01 (-14.58 to 14.56)
No. (%)	67 (77)	56 (68.3)	---
Time awake at night ^d wk 10 [min]	24.88 (32.74)	33.6 (34.29)	-8.72 (-21.13 to 3.69)
No. (%)	63 (72.4)	53 (64.6)	---
Sleep recuperation ^e wk 1 [1 to 5]	3.34 (0.53)	3.33 (0.62)	0.01 (-0.18 to 0.20)
No. (%)	77 (88.5)	68 (82.9)	---
Sleep recuperation ^e wk 2 [1 to 5]	3.02 (0.63)	3.12 (0.79)	-0.10 (-0.34 to 0.14)
No. (%)	75 (86.2)	67 (81.7)	---
Sleep recuperation ^e wk 3 [1 to 5]	2.78 (0.64)	2.98 (0.65)	-0.21 (-0.42 to 0.01)
No. (%)	76 (87.4)	65 (79.3)	---
Sleep recuperation ^e wk 4 [1 to 5]	2.72 (0.72)	2.98 (0.71)	-0.26 (-0.50 to -0.02)
No. (%)	76 (87.4)	65 (79.3)	---
Sleep recuperation ^e wk 5 [1 to 5]	2.52 (0.68)	2.95 (0.69)	-0.43 (-0.66 to -0.19)
No. (%)	75 (86.2)	63 (76.8)	---
Sleep recuperation ^e wk 6 [1 to 5]	2.58 (0.74)	2.91 (0.66)	-0.33 (-0.57 to -0.09)
No. (%)	75 (86.2)	62 (75.6)	---
Sleep recuperation ^e wk 7 [1 to 5]	2.48 (0.73)	2.89 (0.76)	-0.41 (-0.67 to -0.16)
No. (%)	74 (85.1)	60 (73.2)	---
Sleep recuperation ^e wk 8 [1 to 5]	2.51 (0.73)	2.75 (0.68)	-0.24 (-0.48 to 0.01)
No. (%)	71 (81.6)	59 (72)	---
Sleep recuperation ^e wk 9 [1 to 5]	2.5 (0.69)	2.84 (0.76)	-0.35 (-0.60 to -0.09)
No. (%)	71 (81.6)	58 (70.7)	---
Sleep recuperation ^e wk 10 [1 to 5]	2.49 (0.71)	2.96 (0.73)	-0.47 (-0.73 to -0.21)
No. (%)	66 (75.9)	55 (67.1)	---
No. of nightmares ^f – wk 1	1.21 (0.83)	1.55 (0.91)	-0.34 (-0.63 to -0.05)
No. (%)	77 (88.5)	68 (82.9)	---
No. of nightmares ^f – wk 2	0.93 (0.81)	1.31 (0.88)	-0.38 (-0.66 to -0.10)
No. (%)	75 (86.2)	68 (82.9)	---
No. of nightmares ^f – wk 3	0.71 (0.72)	1.16 (0.88)	-0.44 (-0.71 to -0.17)
No. (%)	76 (87.4)	66 (80.5)	---
No. of nightmares ^f – wk 4	0.6 (0.67)	1.11 (0.88)	-0.52 (-0.78 to -0.25)
No. (%)	75 (86.2)	66 (80.5)	---
No. of nightmares ^f – wk 5	0.6 (0.77)	0.97 (0.81)	-0.36 (-0.63 to -0.10)
No. (%)	73 (83.9)	64 (78)	---
No. of nightmares ^f – wk 6	0.58 (0.8)	1.07 (0.85)	-0.49 (-0.77 to -0.21)
No. (%)	74 (85.1)	62 (75.6)	---
No. of nightmares ^f – wk 7	0.54 (0.85)	0.95 (0.83)	-0.41 (-0.70 to -0.12)
No. (%)	73 (83.9)	59 (72)	---
No. of nightmares ^f – wk 8	0.56 (0.87)	1 (0.89)	-0.44 (-0.75 to -0.12)
No. (%)	71 (81.6)	57 (69.5)	---
No. of nightmares ^f – wk 9	0.57 (0.84)	1.01 (0.95)	-0.44 (-0.76 to -0.12)
No. (%)	70 (80.5)	58 (70.7)	---
No. of nightmares ^f – wk 10	0.53 (0.76)	1.01 (0.97)	-0.49 (-0.81 to -0.16)
No. (%)	66 (75.9)	53 (64.6)	---
Intensity of nightmares ^g – wk 1 [0-4]	1.67 (0.85)	2.08 (0.86)	-0.40 (-0.69 to -0.12)
No. (%)	77 (88.5)	67 (81.7)	---
Intensity of nightmares ^g – wk 2 [0-4]	1.39 (0.96)	1.84 (1.03)	-0.45 (-0.78 to -0.12)
No. (%)	75 (86.2)	67 (81.7)	---
Intensity of nightmares ^g – wk 3 [0-4]	1.13 (0.95)	1.72 (0.93)	-0.60 (-0.91 to -0.28)
No. (%)	76 (87.4)	64 (78)	---
Intensity of nightmares ^g – wk 4 [0-4]	0.93 (0.94)	1.55 (0.96)	-0.62 (-0.94 to -0.31)
No. (%)	74 (85.1)	66 (80.5)	---
Intensity of nightmares ^g – wk 5 [0-4]	0.92 (1.05)	1.44 (0.93)	-0.52 (-0.86 to -0.19)
No. (%)	72 (82.8)	64 (78)	---
Intensity of nightmares ^g – wk 6 [0-4]	0.88 (1.06)	1.5 (0.92)	-0.62 (-0.96 to -0.28)

Outcome	Dronabinol (n = 87)	Placebo (n = 82)	Between-group difference (95% CI)
No. (%)	73 (83.9)	61 (74.4)	---
Intensity of nightmares ^g – wk 7 [0-4]	0.79 (1.01)	1.46 (1.01)	-0.67 (-1.02 to -0.32)
No. (%)	72 (82.8)	58 (70.7)	---
Intensity of nightmares ^g – wk 8 [0-4]	0.85 (1.01)	1.36 (0.98)	-0.51 (-0.87 to -0.16)
No. (%)	70 (80.5)	56 (68.3)	---
Intensity of nightmares ^g – wk 9 [0-4]	0.83 (1.05)	1.53 (1.12)	-0.70 (-1.09 to -0.32)
No. (%)	69 (79.3)	57 (69.5)	---
Intensity of nightmares ^g – wk 10 [0-4]	0.81 (1.03)	1.47 (0.99)	-0.65 (-1.02 to -0.28)
No. (%)	66 (75.9)	53 (64.6)	---

^a Data from the full analysis set of 169 participants. Values are mean (SD) and n (%), indicating number of participants with available data per group. Sleep diary assessments commenced on the day of randomization and first study drug administration; therefore, no pre-randomization baseline sleep diary data were available. Consequently, change-from-baseline analyses could not be performed.

^b Values reported in minutes. Morning self-report in response to the question, 'How long did you sleep in total?'

^c Values reported in minutes. Morning self-report in response to the question, 'How long did it take you to fall asleep after turning off the lights?'

^d Values reported in minutes. Morning self-report in response to the question, 'For how long do you estimate that you were awake?'

^e Morning self-report on a five-point Likert scale in response to the question, 'How restorative was your sleep?' (1 = very; 2 = quite; 3 = moderate; 4 = hardly; 5 = not at all).

^f Morning self-report assessed in response to the question, 'Did you have nightmares?' (0 = none; 1 = once; 2 = twice; etc.).

^g Morning self-report in response to the question, 'How much distress or discomfort did these dreams cause?' (0 = not at all; 1 = mild: minimal distress, awakened once; 2 = moderate: awakened but fell asleep again quickly; 3 = severe: distressing, difficulty falling asleep again; 4 = extreme: overwhelming distress, did not fall asleep again).

Table S8. Marijuana Withdrawal Symptoms assessed with the Marijuana Withdrawal Checklist (MWC)^a

Outcome	Dronabinol Mean (SD)	Dronabinol N (%)	Placebo Mean (SD)	Placebo N (%)	Adjusted LS mean difference (95% CI)	P ^b Value
Change from BL to wk6	-6.05 (8.69)	65 (74.7)	-2.47 (7.24)	62 (75.6)	-2.66 (-4.95 to -0.37)	0.02
Change from BL to wk10	-6.67 (8.34)	63 (72.4)	-3.86 (7.84)	58 (70.7)	-2.61 (-4.87 to -0.35)	0.02
Change from BL to wk 12	-5.44 (9.56)	55 (63.2)	-3.98 (6.91)	50 (61.0)	-1.50 (-3.90 to 0.90)	0.22
Change from wk10 to wk12	1.29 (9.15)	55 (63.2)	-0.14 (7.25)	44 (53.7)	1.11 (-1.72 to 3.95)	0.44

^a Data from the full analysis set. Data are observed mean changes from baseline (SD). Treatment effects represent least-squares mean differences from the mixed model for repeated measures; missing data were handled by reference-based multiple imputation (jump-to-reference).

^b P values are uncorrected for multiple testing.

Table S9. Treatment-emergent Adverse Events by Treatment Group and Sex.^a

System Organ Class/ Term	Dronabinol			Placebo		
	Female n = 73	Male n = 14	Total n = 87	Female n = 62	Male n = 21	Total n = 83
Any treatment-emergent adverse event	66 (90.4)	12 (85.7)	78 (89.7)	50 (80.6)	14 (66.7)	64 (77.1)
Nervous system disorders	36 (49.3)	3 (21.4)	39 (44.8)	22 (35.5)	4 (19)	26 (31.3)
Headache	12 (16.4)	2 (14.3)	14 (16.1)	16 (25.8)	3 (14.3)	19 (22.9)
Dizziness	19 (26.0)	1 (7.1)	20 (23)	12 (19.4)	0 (0)	12 (14.5)
Disturbance in attention	4 (5.5)	0 (0)	4 (4.6)	2 (3.2)	1 (4.8)	3 (3.6)
Memory impairment	2 (2.7)	0 (0)	2 (2.3)	0 (0)	1 (4.8)	1 (1.2)
Somnolence	2 (2.7)	0 (0)	2 (2.3)	1 (1.6)	0 (0)	1 (1.2)
Paresthesia	1 (1.4)	0 (0)	1 (1.1)	1 (1.6)	0 (0)	1 (1.2)
Restless legs syndrome	2 (2.7)	0 (0)	2 (2.3)	0 (0)	0 (0)	0 (0)
Traumatic brain injury	1 (1.4)	0 (0)	1 (1.1)	1 (1.6)	0 (0)	1 (1.2)
Dysgeusia	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Hypoesthesia	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Neuralgia	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Synesthesia	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Tremor	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Psychiatric disorders	26 (35.6)	4 (28.6)	30 (34.5)	15 (24.2)	6 (28.6)	21 (25.3)
Depression	5 (6.8)	1 (7.1)	6 (6.9)	5 (8.1)	3 (14.3)	8 (9.6)

Table S9. Treatment-emergent Adverse Events by Treatment Group and Sex.^a

System Organ Class/ Term	Dronabinol			Placebo		
	Female n = 73	Male n = 14	Total n = 87	Female n = 62	Male n = 21	Total n = 83
Anxiety/restlessness	6 (8.2)	0 (0)	6 (6.9)	0 (0)	4 (19.0)	4 (4.8)
Sleep disorder	3 (4.1)	0 (0)	3 (3.4)	4 (6.5)	2 (9.5)	6 (7.2)
Self-injurious behavior	0 (0)	0 (0)	0 (0)	1 (1.6)	2 (9.5)	3 (3.6)
Dissociation	2 (2.7)	1 (7.1)	3 (3.4)	1 (1.6)	1 (4.8)	2 (2.4)
Thinking abnormal	3 (4.1)	1 (7.1)	4 (4.6)	1 (1.6)	0 (0)	1 (1.2)
Irritability	0 (0)	0 (0)	0 (0)	3 (4.8)	0 (0)	3 (3.6)
Other: drive reduction	2 (2.7)	0 (0)	2 (2.3)	1 (1.6)	0 (0)	1 (1.2)
Other: lack of drive	2 (2.7)	1 (7.1)	3 (3.4)	0 (0)	0 (0)	0 (0)
Panic attack	2 (2.7)	0 (0)	2 (2.3)	1 (1.6)	0 (0)	1 (1.2)
Suicidal ideation	0 (0)	0 (0)	0 (0)	2 (3.2)	1 (4.8)	3 (3.6)
Emotional lability	1 (1.4)	0 (0)	1 (1.1)	1 (1.6)	0 (0)	1 (1.2)
Abnormal dreams	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Apathy	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Bruxism	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Drug abuse	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Drug overdose	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Other: mood swing	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Other: reduced inhibition level	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Other: withdrawal Symptoms	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Post-traumatic stress disorder	1 ^b (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	27 (37.0)	4 (28.6)	31 (35.6)	15 (24.2)	4 (19.0)	19 (22.9)
Nausea	7 (9.6)	0 (0)	7 (8)	10 (16.1)	1 (4.8)	11 (13.3)
Diarrhea	10 (13.7)	0 (0)	10 (11.5)	1 (1.6)	2 (9.5)	3 (3.6)
Dry mouth	7 (9.6)	1 (7.1)	8 (9.2)	1 (1.6)	0 (0)	1 (1.2)
Vomiting	1 (1.4)	0 (0)	1 (1.1)	2 (3.2)	2 (9.5)	4 (4.8)
Constipation	3 (4.1)	1 (7.1)	4 (4.6)	0 (0)	0 (0)	0 (0)
Abdominal pain upper	2 (2.7)	0 (0)	2 (2.3)	1 (1.6)	0 (0)	1 (1.2)
Toothache	1 (1.4)	1 (7.1)	2 (2.3)	0 (0)	0 (0)	0 (0)
Abdominal discomfort	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Anal bleeding	0 (0)	1 (7.1)	1 (1.1)	0 (0)	0 (0)	0 (0)
Esophagitis	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Flatulence	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Hypersalivation	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Stomatitis	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
General disorders and administration site conditions	13 (17.8)	6 (42.9)	19 (21.8)	16 (25.8)	3 (14.3)	19 (22.9)
Tiredness	8 (11.0)	2 (14.3)	10 (11.5)	11 (17.7)	2 (9.5)	13 (15.7)
Feeling abnormal	1 (1.4)	1 (7.1)	2 (2.3)	3 (4.8)	0 (0)	3 (3.6)
Vaccination reaction	3 (4.1)	1 (7.1)	4 (4.6)	1 (1.6)	0 (0)	1 (1.2)
Pain	0 (0)	2 (14.3)	2 (2.3)	1 (1.6)	0 (0)	1 (1.2)
Fatigue	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Heat exhaustion	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Oropharyngeal discomfort	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.8)	1 (1.2)
Infections and infestations	12 (16.4)	5 (35.7)	17 (19.5)	9 (14.5)	2 (9.5)	11 (13.3)
SARS-CoV-2 infection	8 (11.0)	3 (21.4)	11 (12.6)	1 (1.6)	1 (4.8)	2 (2.4)
Upper respiratory infection	3 (4.1)	2 (14.3)	5 (5.7)	7 (11.3)	1 (4.8)	8 (9.6)
Common cold	0 (0)	0 (0)	0 (0)	2 (3.2)	0 (0)	2 (2.4)
Gastroenteritis	1 (1.4)	0 (0)	1 (1.1)	1 (1.6)	0 (0)	1 (1.2)
Herpes labialis	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Pneumonia	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders	17 (23.3)	3 (21.4)	20 (23)	7 (11.3)	2 (9.5)	9 (10.8)
Increased appetite	11 (15.1)	3 (21.4)	14 (16.1)	6 (9.7)	1 (4.8)	7 (8.4)
Loss of appetite	5 (6.8)	0 (0)	5 (5.7)	0 (0)	1 (4.8)	1 (1.2)
Hypercholesterolemia	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Other: ferritin decreased	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Weight increased	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Cardiac disorders	5 (6.8)	1 (7.1)	6 (6.9)	4 (6.5)	1 (4.8)	5 (6)
Tachycardia	4 (5.5)	1 (7.1)	5 (5.7)	3 (4.8)	1 (4.8)	4 (4.8)
Atrial fibrillation	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)

Table S9. Treatment-emergent Adverse Events by Treatment Group and Sex.^a

System Organ Class/ Term	Dronabinol			Placebo		
	Female n = 73	Male n = 14	Total n = 87	Female n = 62	Male n = 21	Total n = 83
Right bundle branch block	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Ear and labyrinth disorders	5 (6.8)	0 (0)	5 (5.7)	4 (6.5)	0 (0)	4 (4.8)
Vertigo	3 (4.1)	0 (0)	3 (3.4)	2 (3.2)	0 (0)	2 (2.4)
Tinnitus	1 (1.4)	0 (0)	1 (1.1)	2 (3.2)	0 (0)	2 (2.4)
Ear pain	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders	5 (6.8)	0 (0)	5 (5.7)	5 (8.1)	1 (4.8)	6 (7.2)
Sweating	4 (5.5)	0 (0)	4 (4.6)	3 (4.8)	0 (0)	3 (3.6)
Alopecia	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Eczema	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.8)	1 (1.2)
Erythema migrans	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Local hypersensitivity reactions	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Pruritus	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Musculoskeletal and connective tissue disorders	1 (1.4)	0 (0)	1 (1.1)	3 (4.8)	6 (28.6)	9 (10.8)
Arthralgia	0 (0)	0 (0)	0 (0)	2 (3.2)	3 (14.3)	5 (6)
Back pain	1 (1.4)	0 (0)	1 (1.1)	1 (1.6)	0 (0)	1 (1.2)
Myalgia	0 (0)	0 (0)	0 (0)	1 (1.6)	1 (4.8)	2 (2.4)
Gout arthritis	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.8)	1 (1.2)
Muscle tightness	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.8)	1 (1.2)
Renal and urinary disorders	5 (6.8)	1 (7.1)	6 (6.9)	2 (3.2)	0 (0)	2 (2.4)
Urinary tract infection	3 (4.1)	1 (7.1)	4 (4.6)	2 (3.2)	0 (0)	2 (2.4)
Dysuria	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Urinary urgency	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	4 (5.5)	0 (0)	4 (4.6)	3 (4.8)	0 (0)	3 (3.6)
Dry nose	1 (1.4)	0 (0)	1 (1.1)	1 (1.6)	0 (0)	1 (1.2)
Sore throat	1 (1.4)	0 (0)	1 (1.1)	1 (1.6)	0 (0)	1 (1.2)
Allergic rhinitis	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Dyspnea	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Hoarseness	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Eye disorders	3 (4.1)	0 (0)	3 (3.4)	2 (3.2)	1 (4.8)	3 (3.6)
Blurred vision	1 (1.4)	0 (0)	1 (1.1)	0 (0)	1 (4.8)	1 (1.2)
Dry eye	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Eyelid function disorder	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Other: eye Irritation	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Other: red eye	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Reproductive system and breast disorders	2 (2.7)	0 (0)	2 (2.3)	3 (4.8)	0 (0)	3 (3.6)
Amenorrhea	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Breast pain	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Dysmenorrhea	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Erectile dysfunction	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Pelvic pain	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Vascular disorders	2 (2.7)	0 (0)	2 (2.3)	2 (3.2)	0 (0)	2 (2.4)
Hypotension	0 (0)	0 (0)	0 (0)	2 (3.2)	0 (0)	2 (2.4)
Hot flashes	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Hypertension	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Endocrine disorders	0 (0)	1 (7.1)	1 (1.1)	1 (1.6)	0 (0)	1 (1.2)
Hyperthyroidism	0 (0)	1 (7.1)	1 (1.1)	1 (1.6)	0 (0)	1 (1.2)
Immune system disorders	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Allergic reaction	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Injury, poisoning and procedural complications	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Insect bite	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.2)
Investigations	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Lipase increased	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Other: meningioma	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Surgical and medical procedures	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
Hiatus hernia repair	1 ^c (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)

^a Data from the safety analysis set. Values are n (%). Percentages refer to the respective sex- and treatment-specific denominators.

^b The patient was hospitalized for elective, preplanned inpatient psychotherapy for the treatment of PTSD.

^c The patient was hospitalized for elective hiatal hernia repair.

Table S10. Laboratory Parameters^a

Parameter	Screening		Week 10	
	Dronabinol (n = 87)	Placebo (n = 83)	Dronabinol (n = 87)	Placebo (n = 83)
Hemoglobin [g/dL] ^b	13.7 (1.01)	13.51 (1.46)	13.71 (1.1)	13.54 (1.6)
No. (%)	87 (100)	83 (100)	77 (88.5)	71 (85.5)
Hematocrit [L/L] ^c	0.4 (0.03)	0.4 (0.04)	0.4 (0.03)	0.4 (0.04)
No. (%)	87 (100)	83 (100)	77 (88.5)	71 (85.5)
WBC [$\times 10^9/L$] ^d	7.21 (1.9)	7 (1.52)	7.1 (2.04)	6.85 (1.74)
No. (%)	87 (100)	83 (100)	77 (88.5)	71 (85.5)
RBC [$\times 10^{12}/L$] ^e	4.56 (0.33)	4.6 (0.51)	4.54 (0.35)	4.61 (0.51)
No. (%)	87 (100)	83 (100)	77 (88.5)	71 (85.5)
PLT [$\times 10^9/L$] ^f	277.67 (67.58)	269.9 (64.35)	275.56 (68.51)	271.76 (70.13)
No. (%)	87 (100)	83 (100)	77 (88.5)	71 (85.5)
Serum sodium [mmol/L] ^g	139.6 (1.82)	139.51 (2)	140.31 (1.93)	139.5 (1.83)
No. (%)	86 (98.9)	83 (100)	77 (88.5)	70 (84.3)
Serum potassium [mmol/L] ^h	4.35 (0.41)	4.23 (0.38)	4.32 (0.32)	4.27 (0.34)
No. (%)	87 (100)	83 (100)	78 (89.7)	71 (85.5)
Serum chloride [mmol/L] ⁱ	103.75 (2.91)	104 (3.06)	104.84 (2.52)	104 (2.97)
No. (%)	84 (96.6)	80 (96.4)	73 (83.9)	68 (81.9)
Serum calcium [mmol/L] ^j	2.37 (0.1)	2.37 (0.1)	2.37 (0.09)	2.35 (0.1)
No. (%)	86 (98.9)	80 (96.4)	75 (86.2)	71 (85.5)
AST [U/L] ^k	25.16 (7.66)	25.07 (12.42)	23.04 (6.26)	24.38 (9.63)
No. (%)	87 (100)	81 (97.6)	76 (87.4)	71 (85.5)
ALT [U/L] ^l	24.61 (12.25)	28.47 (23.87)	21.08 (9.9)	27.55 (24.89)
No. (%)	87 (100)	83 (100)	76 (87.4)	69 (83.1)
GGT [U/L] ^m	24.6 (19.29)	25.99 (26.53)	22.62 (17.04)	24.94 (22.79)
No. (%)	84 (96.6)	83 (100)	77 (88.5)	70 (84.3)
Serum alkaline phosphatase [U/L] ⁿ	72.45 (20.17)	76.44 (22.81)	73.47 (21.44)	78.01 (27.87)
No. (%)	84 (96.6)	82 (98.8)	74 (85.1)	68 (81.9)
Serum lipase [U/L] ^o	35.68 (15.22)	36.65 (20.08)	36.18 (16.89)	36.24 (15.88)
No. (%)	78 (89.7)	78 (94)	72 (82.8)	69 (83.1)
Serum bilirubin [mg/dL] ^p	0.46 (0.21)	0.46 (0.29)	0.46 (0.22)	0.46 (0.37)
No. (%)	86 (98.9)	82 (98.8)	75 (86.2)	71 (85.5)
Serum creatinine [mg/dL] ^q	0.76 (0.12)	0.77 (0.14)	0.79 (0.15)	0.78 (0.14)
No. (%)	83 (95.4)	83 (100)	78 (89.7)	67 (80.7)
TSH [mU/L] ^r	1.71 (0.82)	1.72 (1.17)	1.53 (0.73)	1.74 (1.19)
No. (%)	84 (96.6)	82 (98.8)	73 (83.9)	70 (84.3)

^a Data from Safety Analysis Set. Values are means (SD) and n (%), number of participants with available data. Blood sample of week 10 was taken earlier if the participant terminated the study prematurely.

^b Range 13.5 – 17 (M); 12 – 15.6 (F)

^c Range 0.395 – 0.505 (M); 0.355 – 0.455 (F)

^d WBC = White blood cell count; Range 3.9 – 10.5 (M); 3.9 – 10.5 (F)

^e RBC = Red blood cell count; Range 4.3 – 5.8 (M); 3.9 – 5.2 (F)

^f PLT = Platelet count; Range 150 – 370 (M, F)

^g Range 136 – 145 (M, F)

^h Range 3.5 – 5.1 (M, F)

ⁱ Range 98 – 107 (M, F)

^j Range 2.15 – 2.5 (M, F)

^k AST = Aspartate aminotransferase; Range < 50 (M); < 35 (F)

^l ALT = Alanine aminotransferase; Range < 42 (M); < 31 (F)

^m GGT = γ -Glutamyltransferase; Range 8 – 61 (M); 5 – 36 (F)

ⁿ Range 40 – 130 (M); 35 – 105 (F)

^o Range 13 – 60 (M, F)

^p Range < 1.2 (M, F)

^q Range 0.7 – 1.2 (M); 0.5 – 0.9 (F)

^r TSH = Thyroid-stimulating hormone; Range 0.27 – 4.2 (M, F)

Table S11. Subgroup analysis by treatment-assignment guess

Contrast	Estimate	Lower 95% CI	Upper 95% CI	Standard Error	P value
Difference between treatment-guess subgroups ^a	0.68	-1.15	2.51	0.92	0.46
Participants guessing dronabinol: Dronabinol vs placebo	-1.11 ^b	-2.18	-0.03	0.54	
Participants guessing placebo: Dronabinol vs placebo	-1.79 ^b	-3.30	-0.28	0.76	

^a Corresponds to the treatment × time × treatment-guess interaction effect from the MMRM model.

^b Negative values indicate lower CAPS-IV B2 scores in the dronabinol group relative to placebo.

Table S12. Impact of medication with potential effect on dreaming and nightmares^a on treatment response

Contrast	Estimate	95% CI	P value
Effect of medication ^a (overall)	-0.02	-1.59 to 1.54	0.98
Effect of medication ^a within the dronabinol group	-0.20	-1.30 to 0.90	0.72
Effect of medication ^a within the placebo group	-0.17	-1.31 to 0.96	0.76
Treatment effect (dronabinol vs placebo) in patients taking medication ^a	-1.50	-2.72 to -0.28	0.016
Treatment effect (dronabinol vs placebo) in patients not taking medication ^a	-1.48	-2.49 to -0.47	0.004

^a Medication was defined based on published reports linking specific pharmacological classes to increased dream intensity, vivid or abnormal dreams, and nightmares. The following drug classes and active substances used in the study were considered: lipophilic β-blockers (metoprolol); selective serotonin reuptake inhibitors (sertraline, escitalopram, fluoxetine, citalopram); serotonin–norepinephrine reuptake inhibitors (venlafaxine, duloxetine); noradrenergic and specific serotonergic antidepressant (mirtazapine); tricyclic antidepressants (doxepin, amitriptyline, trimipramine); non-benzodiazepine hypnotics (zopiclone); dopaminergic antiparkinsonian agents (levodopa); dopamine agonists (pramipexole); central nervous system stimulants (methylphenidate, lisdexamfetamine); norepinephrine–dopamine reuptake inhibitors (bupropion); and sedating antihistamines (promethazine). Supporting references are provided in the main manuscript.

Table S13. Supportive analysis using the CAPS-5 B2 item (“recurrent distressing dreams”)^a

Sample	Outcome	Estimate	95% confidence interval		P value
			CI-Lower	CI-Upper	
Complete Cases set	CAPS-5 B2 score from BL to wk 10	-0.54	-0.96	-0.11	0.014
Full Analysis Set	CAPS-5 B2 score from BL to wk 10	-0.46	-0.88	-0.05	0.028
Per Protocol Set	CAPS-5 B2 score from BL to wk 10	-0.57	-1.08	-0.07	0.026

^a Results from MMRM analyses analogous to the primary analysis using the CAPS-IV B2 item. CAPS-5 B2 uses a scoring range of 0–4 compared with 0–8 for CAPS-IV B2.

Table S14. Change from baseline to week 10 in primary and key secondary outcomes by current depression status^a

Outcome	Dronabinol		Placebo	
	No depression	Depression	No depression	Depression
CAPS-IV B2 ^b	-4.24 (2.52)	-2.87 (2.45)	-2.67 (2.43)	-1.56 (2.47)
N	45	31	42	27
CAPS-5 ^c	-11.44 (13.04)	-7.84 (13.72)	-6.17 (10.59)	-8.30 (10.91)
N	43	31	41	27
MADRS ^d	-4.07 (8.03)	-3.30 (8.09)	-1.46 (7.98)	-0.81 (7.68)
N	45	30	41	27

^a Data from the full analysis set. Values are means (SD). N = Patients with available data.

^b The Clinician-Administered posttraumatic stress disorder (PTSD) Scale for DSM-IV (CAPS-IV) B2 item assesses frequency and intensity of nightmares; scores range from 0 to 8, with higher scores indicating greater symptom severity.

^c CAPS-5 is the updated version for DSM-5 criteria assessing PTSD symptoms (range 0–80), with higher scores indicating greater symptom severity.

^d The Montgomery–Åsberg Depression Rating Scale (MADRS) ranges from 0 to 60, with higher scores indicating more severe depression.

Table S15. Assessment instruments

Instrument	Description
The Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV) B2 item	DSM-IV-based assessment of frequency (subscore ranges from 0 to 4) and intensity (subscore ranges from 0 to 4) of nightmares; scores range from 0 to 8, with higher scores indicating greater symptom severity. Before study initiation, all raters evaluated 21 example videos. Interrater reliability was assessed with an intraclass correlation coefficient (ICC[3,1]) of 0.96 (95% CI, 0.93 to 0.98).
The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)	Assessing PTSD symptoms according to DSM-5; scores range from 0 to 80, with higher scores indicating greater symptom severity.
Montgomery-Åsberg Depression Rating Scale (MADRS)	Assesses severity of depressive symptoms using a clinician-administered interview across 10 items, each rated on a 7-point Likert scale (0–6); total scores range from 0 to 60, with higher scores indicating greater depressive symptom severity.
Patient Global Impression of Change (PGIC)	Assesses patients' global perception of change since initiation of study medication in overall clinical status using a single-item self-report measure rated on a 7-point Likert scale (1–7); scores range from 1 (“very much improved”) to 7 (“very much worse”), with lower scores indicating greater perceived improvement.
Pittsburgh Sleep Quality Index-Addendum for PTSD (PSQI-A)	Assesses frequency of disruptive nocturnal behaviors related to PTSD (including nightmares and nocturnal distress) over the past four weeks using a self-report questionnaire across seven items; each item is rated on a 4-point scale (0–3). Total scores range from 0 to 21, with higher scores indicating greater severity of trauma-related sleep disturbances.
PTSD Checklist for DSM-5 (PCL-5)	Assesses severity of post-traumatic stress disorder (PTSD) symptoms according to DSM-5 criteria using a self-report questionnaire across 20 items, each rated on a 5-point Likert scale (0–4); total scores range from 0 to 80, with higher scores indicating greater symptom severity.
Pittsburgh Sleep Quality Index (PSQI)	Assesses subjective sleep quality and sleep disturbances over the past month using a self-report questionnaire across 19 items, generating seven component scores (each ranging from 0 to 3) and a global score ranging from 0 to 21; higher scores indicate poorer sleep quality.
Sleep diary	Participants completed a daily sleep diary throughout the study, adapted from the Consensus Sleep Diary. Each morning, they reported total sleep time in minutes in response to the question, “How long did you sleep in total?”, sleep-onset latency in minutes (“How long did it take you to fall asleep after turning off the lights?”), and the estimated duration of time awake during the night in minutes (“For how long do you estimate that you were awake?”). Subjective sleep recuperation was assessed on a five-point Likert scale in response to the question, “How restorative was your sleep?”, with response options ranging from 1 (very) to 5 (not at all). Nightmare frequency was recorded in response to the question, “Did you have nightmares?”, with responses ranging from none to multiple occurrences. Participants also rated the distress or discomfort caused by nightmares on a five-point scale ranging from 0 (not at all) to 4 (extreme, overwhelming distress with inability to fall asleep again).
Borderline Symptom List 23 (BSL-23)	Assesses severity of borderline personality disorder symptoms using a self-report questionnaire across 23 items, each rated on a 5-point Likert scale (0–4); total scores range from 0 to 92, with higher scores indicating greater symptom severity.
International Trauma Questionnaire (ITQ)	Assesses symptoms of post-traumatic stress disorder (PTSD) and disturbances in self-organization (DSO) according to ICD-11 criteria using a self-report questionnaire across 18 items, each rated on a 5-point Likert scale (0–4); PTSD and DSO symptom severity scores are

	calculated, and PTSD or complex PTSD (cPTSD) diagnoses are assigned based on ICD-11 diagnostic algorithms. The current analyses were based on the summed score (ITQ) of PTSD and DSO, with a range from 0 to 72.
Health-Related Quality of Life (EQ-5D-3L)	Assesses health-related quality of life using a self-report questionnaire across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each rated on three levels (no problems, some problems, extreme problems), generating a preference-based index score derived from time trade-off (TTO) valuation; TTO scores typically range from values below 0 to 1, with higher scores indicating better health-related quality of life. Additionally, a self-rated health score is obtained using a vertical visual analog scale (VAS), with scores ranging from 0 to 100 and higher scores indicating better perceived health.
Social and Occupational Functioning Assessment Scale (SOFAS)	Assesses level of social and occupational functioning using a clinician-rated scale ranging from 0 to 100; higher scores indicate better social and occupational functioning.
Marijuana Withdrawal Checklist (MWC)	Assesses severity of cannabis withdrawal symptoms in the last week using a self-report questionnaire across 15 items, each rated on a 4-point Likert scale (0–3); total scores range from 0 to 45, with higher scores indicating greater withdrawal symptom severity.
Childhood Trauma Questionnaire (CTQ)	Assesses exposure to childhood maltreatment using a self-report questionnaire across 28 items covering five subscales—emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect—each rated on a 5-point Likert scale (1–5); subscale scores range from 5 to 25, with higher scores indicating greater severity of childhood trauma within each domain.
Mini-International Neuropsychiatric Interview (MINI)	Assesses current and lifetime psychiatric disorders according to DSM-5 criteria using a structured clinician-administered diagnostic interview.

“Treating Nightmares in Posttraumatic Stress Disorder with Dronabinol: A Randomized Controlled Study (THC PTSD-trial)”

Protocol code number: THC-PTSD
EudraCT-Number: 2019-002211-25

Protocol

Version 1.3 / 24.01.2020

Sponsor of the Clinical Study

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The following persons accept the content of this protocol and confirm to conduct this study in compliance with Good Clinical Practice and applicable regulatory requirements.

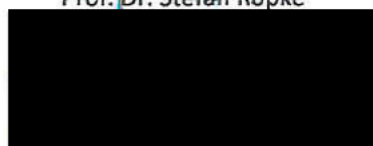
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- Confidential -

The information contained in this protocol has to be kept strictly confidential. Therefore the protocol is only provided to Investigators in confidence for review, to study staff, Independent Ethics Committee/Institutional Review Board, regulatory authorities and CROs (or KKS) and for obtaining written informed consent from patients.

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Abbreviations

ADL	Activities of daily living
ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	Analysis of Covariance
BSL-23	Borderline Symptom List 23
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
CAPS-IV B2	Clinician-Administered PTSD Scale for DSM-IV score for Item B2
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CTFG	Clinical Trial Facilitation Group
CTQ	Childhood Trauma Questionnaire
DALY	disability-adjusted life year
DSM-5	Diagnostic and Statistical Manual of Mental Disorders DSM-5
eCRF	electronic Case Report Form
ECG	Electrocardiogram
EWR	Europäischer Wirtschaftsraum
EQ-5D	Health Related Quality of Life
FPI	Last Patent out
GCP	Good Clinical Practice
ICH	International Conference of Harmonisation
IEC	Ethic Committee
IMP	Investigational Medicinal Product
ITT	Intent to treat Population
ITI	International Trauma Interview
ITQ	International Trauma Questionnaire
KKS	Koordinierungszentrum für Klinische Studien
LPO	Last Patient out
MADRS	Montgomery-Åsberg Depression Rating Scale
MWC	Marijuana Withdrawal Checklist
PCL-5	PTSD Checklist for DSM-5
PGIC	Patient Global Impression of Change
PPP	Per protocol population
PSQI-	Pittsburgh Sleep Quality Index
PSQI-A	Pittsburgh Sleep Quality Index-Addendum for PTSD
PTSD	Posttraumatic Stress Disorder
SAE	Serious Adverse Event
SCID-5	Structured Clinical Interview for DSM-5
SDV	Source Data Verification
SOFAS	Social and Occupational Functioning Assessment Scale
SSL	Secure Socket Layer
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
WHO	World Health Organization
WOCBP	women of childbearing potential

1 Synopsis

Study title	Treating Nightmares in Posttraumatic Stress Disorder with Dronabinol: A Randomized Controlled Study (THC-PTSD-trial)
EudraCT Number	2019-002211-25
Study design	Multi-centric, double-blind, randomized, placebo-controlled, parallel group, interventional exploratory phase II trial
Medical Condition	Posttraumatic Stress Disorder
Sponsor	Charité – Universitätsmedizin Berlin Charitéplatz 1, D-10117 Berlin
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Hypothesis	Dronabinol (2.5-15 mg) improves nightmares in patients with PTSD to a greater extent than placebo as measured by the CAPS-IV B2 score (intensity and frequency of nightmares) after 10 weeks of treatment in a parallel group design.
Rationale	No pharmacological agent has been approved to treat nightmares associated with PTSD in Europe. First empirical evidence shows that nightmares, other PTSD related sleep symptoms, hyperarousal, and other PTSD symptoms can be treated with dronabinol. This randomized controlled trial will test the hypothesis that oral dronabinol improves nightmares (primary outcome), other PTSD symptoms and psychopathology (secondary outcomes) to a greater extent than placebo over a ten week intervention phase in a parallel group design.
Primary objective	To examine whether oral dronabinol (2.5 to 15 mg) reduces nightmares to a greater extent than placebo in patients with posttraumatic stress disorder
Primary endpoint	Primary efficacy endpoint: Frequency and intensity of nightmares, measured with the Clinician-Administered PTSD Scale-IV (CAPS-IV) B2 score for the last week, range 0–8, directly after last intervention (10 weeks, Visit 8). A lower score indicates less frequent and/or intense nightmares.

Secondary objectives	Secondary objectives of the study are to examine the efficacy of oral dronabinol in reducing other PTSD-specific symptoms, general sleep parameters and depressive symptoms in patients with posttraumatic stress disorder
Key secondary endpoint(s)	1. Change from baseline of the frequency and intensity of nightmares, measured with the Clinician-Administered PTSD Scale-IV (CAPS-IV) B2 score for the last week, range 0–8, at Visit 3 – Visit 7 2. Change from baseline of the CAPS-5 total score (overall PTSD symptoms, last week) at Visit 6 and Visit 8 3. Change from baseline of the Pittsburgh Sleep Quality Index-Addendum for PTSD (PSQI-A) (PTSD related sleep symptoms) at Visit 2 – Visit 8 4. Change from baseline of the Montgomery-Åsberg Depression Rating Scale (MADRS, depressive symptoms) at Visit 6 and Visit 8 5. Weekly mean of change from baseline of the patients daily total sleep time (in minutes), sleep onset latency at night (in minutes), recuperation of night sleep (5-point Likert scale, 1 = very much; 5 = not at all), and time awake at night (in minutes), number of nightmares last night (0, 1, 3, 4 or more) and intensity of nightmares (5-point Likert scale, 0 = not at all; 5 = extreme) assessed with sleep diaries during Visit 2 – Visit 8 6. Change from baseline of PTSD symptoms assessed with the PTSD Checklist for DSM-5 (PCL-5) at Visit 6 and Visit 8 7. Change from baseline of the Borderline Symptom List 23 (BSL-23) score at Visit 6 and Visit 8 8. Change from baseline of the Health-Related Quality of Life (EQ-5D) score at Visit 6 and Visit 8 9. Overall patients status measured by the Patient Global Impression of Change (PGIC) at Visit 6 and Visit 8 10. Change from baseline of the Social and Occupational Functioning Assessment Scale (SOFAS) at Visit 6 and Visit 8 11. Change from baseline of the Pittsburgh Sleep Quality Index (PSQI) at Visit 6 and Visit 8 12. Change from baseline of symptoms of PTSD and complex PTSD according to ICD-11 assessed with the International Trauma Questionnaire (ITQ) at Visit 6 and Visit 8 13. Change from baseline of THC withdraw symptoms assessed with the Marijuana Withdrawal Checklist (MWC) at Visit 6, Visit 8, and Visit 9 14. Responder analysis: proportion of patients showing improvement in nightmares (change from baseline) defined as decrease of CAPS-IV B2 $\geq 50\%$ assessed at the end of treatment (Visit 8) 15. Remitter analysis: proportion of patients showing full remission of nightmares defined as CAPS-IV B2 = 0, assessed at the end of treatment (Visit 8)

Inclusion criteria	1. Diagnosis of posttraumatic stress disorder (PTSD) according to DSM-5 with a 20 item CAPS-5 total score ≥ 26 2. At least two nightmares a week, an intensity score ≥ 2, with a CAPS-IV B2 (frequency and intensity for the last week) score ≥ 5 3. Men and women between 18 and 65 years of age 4. Written informed consent 5. The patient has the capacity to give consent (He/she is able to understand the nature and anticipated effects/side effects of the proposed medical intervention) 6. The patient is not breastfeeding 7. Women of child-bearing potential must have a negative urine or serum pregnancy test 8. All participants must use highly effective contraception 9. The patient received stable pharmacological medication for at least 4 weeks prior to study entry (any changes in medication dose or frequency of therapy must be answered with no)
Exclusion criteria	1. Lifetime cannabis use disorder 2. Current substance/alcohol use disorder (≤ 3 months); 3. Acute suicidality; 4. Psychotic disorder; 5. Bipolar disorder; 6. Current anorexia nervosa; 7. Current major depressive episodes and a MADRS score > 29; 8. Dementia; 9. Trauma-focused psychotherapy four weeks before the trial 10. Initiation of sleep medication 4 weeks prior screening or initiation of alpha adrenergic agents 4 weeks prior to screening 11. Acute or unstable medical illness. 12. Epilepsy 13. Relevant heart diseases 14. Known HIV- and/or active Hepatitis-B- or Hepatitis-C-infection 15. Current or past malignant illness 16. The patient is unwilling to consent to saving, processing and propagation of pseudonymized medical data for study reasons 17. Patients, who may be dependent on the sponsor, the investigator or the trial sites, have to be excluded from the trial 18. The patient is legally detained in an official institution 19. The patient does have a known allergy or contraindication against Dronabinol 20. The patient does have clinically significant abnormalities in 12-lead ECG 21. The patient does have clinically significant laboratory abnormalities 22. The patient did participate in other interventional trials during the 3 months before and at the time of this trial

Visit and documentation schedule	Eligible patients will be screened up to 10 days prior to randomization. After baseline assessment, patients will be randomized and receive either 2.5 mg oral dronabinol (oily solution) per day before bedtime or undistinguishable placebo (cannabis aroma). Oral dronabinol will be titrated with the goal of complete elimination of trauma nightmares to up to 15 mg/day in first four weeks. Until week 4 one visit per week will take place. Dose increase in steps of 2.5 mg every 3-4th day according to effect (complete elimination of nightmares) and side effect over the first 4 weeks (titration period). If side effects occur (ADRs), dose will be decreased to the lower prior dose (in steps of 2.5 mg) until next trial visit. The intervention phase will be 10 weeks, i.e., 4 weeks titration phase and 6 weeks maintenance phase, when dronabinol dose (or placebo) will be kept stable. Beside assessment of primary and secondary endpoints, adverse events will be monitored. There will be a post-trial follow-up visit at week 12. See also Table 1 ("Outline of trial visits") at the end of the synopsis.
Safety Assessment	Assessment of blood pressure and heart rate at every visit. Assessment of laboratory parameters - safety laboratory - at screening and end of trial (visit 8 in week 10); physical examination at screening and end of trial; ECG at screening, end of trial and in case of significant abnormal ECG findings at visit 8 (week 10) a further ECG at follow-up (visit 9, week 12). Urinary pregnancy test (women only) at screening, baseline, visit 3 (week 2), visit 5 (week 4), visit 6 (week 6), visit 7 (week 8), and visit 8 (week 10). Standard procedures for reporting of adverse events will be used. Adverse events will be assessed at every visit starting at visit 2.
Safety and Discontinuation Criteria	<u>The following events must cause premature termination of the individual subject:</u> • Unblinding in case of a medical emergency • The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study • Pregnancy • Consent withdrawn by patient • CTCAE catalogue (Common Terminology Criteria for Adverse Events, Version 5.0) score > 3 • Complete missing of two consecutive visits <u>Premature termination of the clinical trial:</u> • Unjustifiable risk and negative risk-benefit analysis (decision taken by the sponsor) • New scientific evidence provided during the study that could affect the patient's safety (benefit-risk analysis no longer positive) • Decision of the sponsor, the coordinating investigator, by request of an authority or because of withdrawal of a positive vote by a responsible ethics committee.

	<u>Sponsor may terminate the trial at an individual study centre, if:</u> • the investigator no longer considers the risk-benefit ratio to be reasonable, • the centre's recruitment rate is too low, • the drop-out rate is unusually high, or • the investigator does not comply with the protocol or other regulations with the necessary care.																
Study medication	BX-1 is an oily solution containing 25 mg/ml dronabinol.																
Placebo/ Reference Medication	Oily Placebo Solution (cannabis aroma)																
Pharmacological-toxicological evaluation	Dronabinol is in medical use for several years in Germany. A number of clinical trials proved tolerability, safety and low incidence of side effects.																
Trial Duration	<table border="0" style="width: 100%;"> <tr> <td>Study set up</td><td style="text-align: right;">6 months</td></tr> <tr> <td>FPI to Last Patient Out (Visite 8)</td><td style="text-align: right;">24 months</td></tr> <tr> <td>LPO to Data Base Closure</td><td style="text-align: right;">2 months</td></tr> <tr> <td>DBC to first results available</td><td style="text-align: right;">2 months</td></tr> <tr> <td>DBC to Clinical Study Report</td><td style="text-align: right;">4 months</td></tr> <tr> <td> Estimated total duration of the trial (FPI to Clinical Study Report)</td><td style="text-align: right;"> 32 months</td></tr> <tr> <td> Planned FPI (First Patient in):</td><td style="text-align: right;"> approximately Jan 2020</td></tr> <tr> <td>Planned LPO (Last Patient out):</td><td style="text-align: right;">approximately Dec 2021</td></tr> </table>	Study set up	6 months	FPI to Last Patient Out (Visite 8)	24 months	LPO to Data Base Closure	2 months	DBC to first results available	2 months	DBC to Clinical Study Report	4 months	 Estimated total duration of the trial (FPI to Clinical Study Report)	 32 months	 Planned FPI (First Patient in):	 approximately Jan 2020	Planned LPO (Last Patient out):	approximately Dec 2021
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Duration of Intervention per Patient	10 weeks (4 weeks titration, 6 weeks observation)																
Follow- up per Patient	2 weeks																
Total number of patients	to be assessed for eligibility (n = 450) To be enrolled into trial (n = 176) To be analyzed (n = 158 in full analysis set, excluding patients that are randomized but never received study medication, n = 18, ≈10%)																
Statistical analysis	<u>Primary analysis:</u> Confirmatory analysis will be conducted based on the full analysis set consisting of all randomized patients which received the study medication at least once. The aim is to show that scores at 10 weeks are lower in the intervention group (I) than the control group (C). An ANCOVA model including the baseline score, will be applied (Hauschke et al. 2007). The global two-sided significance level will be 0.05. Missing values will be replaced using multiple imputation (van Buuren 2012). <u>Secondary analyses:</u> Descriptive methods will be used to analyze secondary outcomes, including appropriate summary measures of the empirical distribution as well as 95% confidence intervals and																

	descriptive two-sided p-values. Safety analysis will include calculation of frequencies and rates of adverse and serious adverse events. Additionally, sensitivity will analyzed in different populations (per-protocol population, patients with complete cases). Further statistical methods will be used to assess data quality. All analyses will be done using validated statistical software.
Participating Organization	• please refer to appendix 1
Funding	Bionorica SE, Kerschensteinerstrasse 11-15, 92318 Neumarkt (Bionorica provides the IMP and financial resources as funding)

Table 1: Outline of trial visits

Assessments	SC	BL Visit 1 W 0	Visit 2 W 1	Visit 3 W 2	Visit 4 W 3	Visit 5 W 4	Visit 6 W 6	Visit 7 W 8	Visit 8 W 10	FU Visit 9 W 12
Screening and consent										
Inclusion/exclusion criteria	X									
Informed consent	X									
Physical examination ¹	X								X	
Prior and concomitant medication and non-drug therapy	X	X	X	X	X	X	X	X	X	X
Medical history	X									
IMP dispersion		X	X	X	X	X	X	X		
IMP return			X	X	X	X	X	X	X	
Safety										
Blood test ²	X								X	
Cannabis test	X									
Pregnancy test	X	X		X		X	X	X	X	
ECG	X								X	(X) ³
Blood pressure, pulse	X	X	X	X	X	X	X	X	X	X
Weight	X	X					X		X	X
Adverse event recording			X	X	X	X	X	X	X	X
Effectiveness										
primary										
CAPS-IV B2									X	
secondary										
CAPS-IV B2	X	X	X	X	X	X	X	X		
CAPS-5	X ^a	X ^b					X ^b		X ^b	
PSQI-A		X	X	X	X	X	X	X	X	
MADRS	X	X				X			X	
Sleep diary		X	X	X	X	X	X	X	X	
PCL-5		X					X		X	
BSL-23		X					X		X	
EQ-5D		X					X		X	
PGIC							X		X	
SOFAS		X					X		X	
PSQI		X					X		X	
ITQ		X					X		X	
MWC		X					X		X	X
others										
Demographics	X									
CTQ	X									
MINI-5	X									
ITI	X									

Note: SC = screening, W. = week +/- 3 days, BL = baseline and randomization, FU = post-trial follow-up, CAPS-IV B2 = B2 score of the Clinician-Administered PTSD Scale for DSM-IV (frequency and intensity of nightmares), CAPS-5 = Clinician-Administered PTSD Scale for DSM-5 (a = last month version, b = last week version), PSQI-A = Pittsburgh Sleep Quality Index-Addendum for PTSD, MADRS = Montgomery-Åsberg Depression Rating Scale, PCL-5 = PTSD Checklist for DSM-5, BSL-23 = Borderline Symptom List 23, EQ-5D = Health-Related Quality of Life, PGIC = Patient Global Impression of Change, SOFAS = Social and Occupational Functioning Assessment Scale, PSQI = Pittsburgh Sleep Quality Index, ITQ = international trauma questionnaire, MWC = Marijuana Withdrawal Checklist, CTQ = Childhood trauma questionnaire, MINI-5 = The Mini International Neuropsychiatric Interview for DSM-5, ITI = International Trauma Interview. 1 Physical examination includes height and weight of the patient and the skin, abdomen, respiratory system, head and extremities will be examined, 2: blood test s include haematology (erythrocytes, haemoglobin, haematocrit, platelets, leukocytes (including neutrophils, eosinophils, basophils, lymphocytes, monocytes) and serum chemistry (sodium, potassium, chloride, calcium, creatinine, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, aspartate aminotransferase, bilirubin, lipase, thyroid stimulating hormone), 3. In case of significant abnormal ECG findings at the visit 8 (week 10), a further ECG will be recorded at the follow-up visit.

2 Introduction

2.1 Introduction and background

PTSD is associated with serious disability, medical illness, and a severely impaired quality of life (Monson, Caron, McCloskey, & Brunet, 2017; Shalev, Liberzon, & Marmar, 2017). The WHO has reported an overall disability-adjusted life year (DALY) rate per 100,000 inhabitants of Germany of 54 for PTSD; 80 in women, 28 in men (WHO 2004). PTSD places a high socioeconomic burden on patients with marked reductions in household income (Sareen, Afifi, McMillan, & Asmundson, 2011). More than 50% of PTSD patients suffer from comorbid mood, anxiety, and substance-use disorders (Pietrzak, Goldstein, Southwick, & Grant, 2011b). Various medical comorbidities are very common in PTSD patients with cardiovascular diseases among the most prevalent (Pietrzak, Goldstein, Southwick, & Grant, 2011a). Distressing nightmares are an independent risk factor for comorbidity and severity in PTSD patients. Nightmares also contribute to alcohol and substance abuse, suicidal ideation, and even completed suicide (Raskind et al., 2007). Further, distress related to insomnia is one of the most common residual symptoms after specific psychotherapy for PTSD (Larsen *et al.*, 2018). Only SSRIs (in Germany paroxetine) are currently approved as pharmacological treatment for PTSD with low response and remission rates (Cukor, Olden, Lee, & Difede, 2010). Further, there is no evidence that SSRIs can treat nightmares in PTSD (Brownlow, Harb, & Ross, 2015). Accumulating clinical data indicate that cannabinoid agonists (e.g., dronabinol) can improve nightmare symptomatology and overall PTSD symptoms in patients with PTSD (Wilkinson, Radhakrishnan, & D'Souza, 2016). First, many patients with PTSD cite motives of self-medication for continued use of cannabis due to its ability to promote relaxation and sleep, and reduce anxiety symptoms and hyperarousal (Betthausen, Pilz, & Vollmer, 2015; Bonn-Miller, Vujanovic, Feldner, Bernstein, & Zvolensky, 2007; Bremner, Southwick, Darnell, & Charney, 1996). Second, an uncontrolled open-label study of nabilone (0.5-6mg/day) at bedtime reduced nightmares in patients with PTSD, 34 out of 47 patients exhibiting either total cessation or significant reduction in nightmares (Fraser, 2009). Third, a retrospective chart review showed that nabilone (mean dose 4 mg/day) treatment was associated with a significant improvement in sleep and a reduction in nightmares (severity and frequency) as well as a general reduction in PTSD symptom severity (Cameron, Watson, & Robinson, 2014). Fourth, an open label, uncontrolled pilot study examined the impact of adding 5 mg of $\Delta(9)$ -THC twice a day as add-on treatment onto existing medications in PTSD patients and found that THC consumption specifically improved sleep quality, reduced nightmares, and reduced symptoms of hyperarousal (Roitman, Mechoulam, Cooper-Kazaz, & Shalev, 2014). Fifth, a small, randomized, double-blind, placebo controlled crossover study assessed nabilone (3 mg daily) and found significant reduction in severity and frequency of nightmares, and increased general well-being (Jetly, Heber, Fraser, & Boisvert, 2015). Further, no negative results of cannabinoid-agonists in PTSD treatments are published to date.

Currently are three ongoing randomized clinical trials of THC treatment in patients with PTSD registered at clinicaltrials.gov (NCT02759185, NCT02517424, NCT03251326). None of these studies is in direct concurrence with the current trial proposal.

2.2 Rationale

No pharmacological agent has been approved to treat nightmares associated with PTSD in Europe. First empirical evidence shows that nightmares, other PTSD related sleep symptoms, hyperarousal, and other PTSD symptoms can be treated with dronabinol (see background

information). This randomized controlled exploratory phase II trial will test the hypothesis that oral dronabinol improves nightmares (primary outcome) and other PTSD symptoms (secondary outcomes) to a greater extent than placebo over a ten week intervention phase in a parallel group design.

3 Study objectives

3.1 Primary endpoint

Primary objective of the study is to examine the efficacy of oral dronabinol over placebo in reducing nightmares in patients with posttraumatic stress disorder.

Primary efficacy endpoint: Frequency and intensity of nightmares, measured with the Clinician-Administered PTSD Scale (CAPS-IV) B2 score for the last week, range 0–8 (Blake et al., 1995) directly after last intervention (10 weeks).

3.2 Secondary endpoints

Secondary objectives of the study are to examine the efficacy of oral dronabinol in reducing disorder-specific symptoms in patients with posttraumatic stress disorder, and to examine the efficacy of oral dronabinol in reducing sleep disturbance in patients with posttraumatic stress disorder.

Secondary endpoints:

1. Change from baseline of the frequency and intensity of nightmares, measured with the Clinician-Administered PTSD Scale-IV (CAPS-IV) B2 score for the last week, range 0–8, at Visit 3 – Visit 7
2. Change from baseline of the CAPS-5 total score (overall PTSD symptoms, last week) at Visit 6 and Visit 8
3. Change from baseline of the Pittsburgh Sleep Quality Index-Addendum for PTSD (PSQI-A) (PTSD related sleep symptoms) at Visit 2 – Visit 8
4. Change from baseline of the Montgomery-Åsberg Depression Rating Scale (MADRS, depressive symptoms) at Visit 6 and Visit 8
5. Weekly change from baseline of the patients daily total sleep time (in minutes), sleep onset latency at night (in minutes), recuperation of night sleep (5-point Likert scale, 1 = very much; 5 = not at all), and time awake at night (in minutes), number of nightmares last night (0, 1, 3, 4 or more) and intensity of nightmares (5-point Likert scale, 0 = not at all; 5 = extreme) assessed with sleep diaries during Visit 2 – Visit 8
6. Change from baseline of PTSD symptoms assessed with the PTSD Checklist for DSM-5 (PCL-5) at Visit 6 and Visit 8
7. Change from baseline of the Borderline Symptom List 23 (BSL-23) score at Visit 6 and Visit 8
8. Change from baseline of the Health-Related Quality of Life (EQ-5D) score at Visit 6 and Visit 8
9. Overall patients status measured by the Patient Global Impression of Change (PGIC) at Visit 6 and Visit 8
10. Change from baseline of the Social and Occupational Functioning Assessment Scale (SOFAS) at Visit 6 and Visit 8
11. Change from baseline of the Pittsburgh Sleep Quality Index (PSQI) at Visit 6 and Visit 8
12. Change from baseline of symptoms of PTSD and complex PTSD according to ICD-11 assessed with the International Trauma Questionnaire (ITQ) at Visit 6 and Visit 8

13. Change from baseline of THC withdraw symptoms assessed with the Marijuana Withdrawal Checklist (MWC) at Visit 6, Visit 8, and Visit 9
14. Responder analysis: proportion of patients showing improvement in nightmares (change from baseline) defined as decrease of CAPS-IV B2 $\geq 50\%$ assessed at the end of treatment (Visit 8)
15. Remitter analysis: proportion of patients showing full remission of nightmares defined as CAPS-IV B2 = 0, assessed at the end of treatment (Visit 8)

Descriptive methods (see above) will be used to analyze secondary outcomes, including appropriate summary measures of the empirical distribution as well as 95% confidence intervals and descriptive two-sided p-values. Safety analysis will include calculation of frequencies and rates of adverse and serious adverse events. Additionally, sensitivity will be analyzed in different populations (per-protocol population, patients with complete cases). Further statistical methods will be used to assess data quality. All analyses will be done using validated statistical software.

3.3 Study design

The study is a multi-centric, double-blind, randomized, placebo-controlled, parallel group interventional exploratory phase II trial.

3.4 Timetable

Study set up (signed contract to First Patient In)	6 months
FPI to Last Patient Out (Visit 8)	24 months
LPO to Data Base Closure	2 months
DBC to first results available	2 months
DBC to Clinical Study Report	4 months
Estimated total duration of the trial (FPI to Clinical Study Report)	32 months
Planned FPI (First Patient in):	approximately Jan 2020
Planned LPO (Last Patient out):	approximately Dec 2021

4 Study population

176 patients will be enrolled (sample size estimation, see chapter 14.1). There will be no specific gender distribution as no gender specific differences concerning efficacy and safety of the investigational product are expected (see GCP-V § 7 (2) No. 12).

4.1 Inclusion criteria

Obligatory inclusion criteria:

1. Diagnosis of posttraumatic stress disorder (PTSD) according to DSM-5 with a 20 item CAPS-5 total score ≥ 26
2. At least two nightmares a week, an intensity score ≥ 2 , with a CAPS-IV B2 (frequency and intensity for the last week) score ≥ 5
3. Men and women between 18 and 65 years of age
4. Written informed consent
5. The patient has the capacity to give consent (He/she is able to understand the nature and anticipated effects/side effects of the proposed medical intervention)
6. The patient is not breastfeeding
7. Women of child-bearing potential must have a negative urine or serum pregnancy test
8. All participants must use highly effective contraception
9. The patient received stable pharmacological medication for at least 4 weeks prior to study entry (any changes in medication dose or frequency of therapy must be answered with no)

4.2 Exclusion criteria

The following exclusion criteria are obligatory.

1. Lifetime cannabis use disorder
2. Current substance/alcohol use disorder (≤ 3 months);
3. Acute suicidality;
4. Psychotic disorder;
5. Bipolar disorder;
6. Current anorexia nervosa;
7. Current major depressive episodes and a MADRS score > 29 ;
8. Dementia;
9. Trauma-focused psychotherapy four weeks before the trial
10. Initiation of sleep medication 4 weeks prior screening or initiation of alpha adrenergic agents 4 weeks prior to screening
11. Acute or unstable medical illness
12. Epilepsy
13. Relevant heart diseases
14. Known HIV- and/or active Hepatitis-B- or Hepatitis-C-infection
15. current or past malignant illness

16. The patient is unwilling to consent to saving, processing and propagation of pseudonymized medical data for study reasons
17. Patients, who may be dependent on the sponsor, the investigator or the trial sites, have to be excluded from the trial
18. The patient is legally detained in an official institution
19. The patient does have a known allergy or contraindication against Dronabinol
20. The patient does have clinically significant abnormalities in 12-lead ECG
21. The patient does have clinically significant laboratory abnormalities
22. The patient did participate in other interventional trials during the 3 months before and at the time of this trial

4.3 Contraception and WOCBP

Study participants with reproductive capacity (both: male and female) have to use highly effective methods of contraception according to the guideline of the Clinical Trial Facilitation Group (CTFG) (Sep 2014):

- Highly effective contraception for both male and female subjects throughout the study and for at least 30 days after the last IMP treatment
- A female subject is eligible to enter the study if she is:
 - Not pregnant or nursing
 - Of non-childbearing potential (i.e., post-menopausal defined as having been amenorrheic for at least 1 year prior to screening, or has had bilateral tubal ligation at least 6 months prior to administration of study drug or bilateral oophorectomy or complete hysterectomy)
 - Women of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test prior to drug administration and be using a highly effective means of contraception during study participation and until 1 month after the last dose of study drug. Highly effective contraception methods include:
 - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
 - In case hormonal contraception is used the second method of contraception must be a barrier method.
 - Combination of any two of the following (i+ii or i+iii, or ii+iii):
 - use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.
 - placement of an intrauterine device (IUD) or intrauterine system (IUS)
 - barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps)
 - In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Definition of Women of childbearing potential (WOCBP):

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.

According to the recommendations of the CTFG, the use of condoms is regarded as a contraceptive method in male study participants.

5 Plan for medical treatment

5.1 Description of study medication / investigational medicinal product

BX-1 is an oily solution containing 25 mg/ml dronabinol. Dronabinol ((-)-trans- Δ^9 -Tetrahydrocannabinol, Δ^9 -THC) is the major psychoactive constituent of *Cannabis sativa* L.. Dronabinol is a clear to amber resin. It is highly lipid soluble. Dronabinol is thermolabile, photolabile and susceptible to oxidation.

5.1.1 Adverse drug reactions and restrictions, contra-indications, drug interactions

Expected adverse reactions are: anxiety/restlessness, depression, euphoria, sleep disorder, thinking abnormal, dizziness, headache, disturbance in attention, memory impairment, speech difficulties, tremor, vertigo, tachycardia, hypertension, hypotonia, dry nose, dyspnea, tiredness, asthenia/muscular weakness, feeling abnormal, nausea, constipation, diarrhoea, abdominal pain upper, dry mouth, flatulence, vomiting, hypoaesthesia oral, increased appetite, loss of appetite, sweating, local hypersensitivity reactions, pressure behind the eyes, dry eye, abnormal sensation in eye. In case of occurrence of intolerable side effects dosages should be adjusted.

In case of overdose of BX-1 the patient must be closely monitored. Overdose treatment should be based on symptomatic treatment of adverse reactions. A potentially serious overdose of BX-1, if recent, should be treated with gut decontamination. In unconscious patients with a secure airway, activated carbon should be administered via a nasogastric tube (30 to 100 g for adults). A saline laxative or sorbitol may be added to the first dose of activated carbon. Patients who show depressive, hallucinatory or psychotic reactions must be placed in a quiet room and calmed by persuasion. Benzodiazepines (1 to 2.5 mg lorazepam p.o.) can be used to treat extreme agitation. Hypotension usually responds to the Trendelenburg position and i.v. fluid. Vasopressors are rarely necessary. Tachycardia can be treated with beta blockers. Due to the initial half-life time of dronabinol and its active metabolite, it is expected that the effect of BX-1 is significantly reduced after 8 hrs. BX-1 should be administered with caution to patients with mania, depression or schizophrenia, heart diseases, history of seizure-related diseases and history of substance abuse. If seizures are occurring, treatment with BX-1 should be immediately discontinued. There might be additional or synergistic effects in patients treated concomitantly with sedative, hypnotic or other psychoactive medicinal products on central nervous system adverse reactions.

The probability of occurrence of withdrawal symptoms after discontinuation of BX-1 in the allowed dosage as well as the development of tolerance and dependence is quite low in the allowed dosages. Furthermore, it is not expected that BX-1 is abused after chronic intake if the patient has no history of drug abuse. Nevertheless, if there is suspicion of such symptoms the patient must be closely monitored and if deemed necessary the treatment should be discontinued. Non-clinical studies showed that dronabinol has no mutagenic, genotoxic, carcinogen, and teratogenic effect. Nevertheless, in animals it negatively affected fertility and caused embryo- and/or fetal toxicity. Therefore, BX-1 should not be administered to pregnant or breastfeeding women.

Patients should be warned not to drive or engage in activities requiring unimpaired judgement and coordination until it is established that they are able to tolerate the drug and to perform such tasks safely. Alcohol may interact with dronabinol, particularly in affecting coordination, concentration and ability to respond quickly.

Please refer also to Table 9: Reported adverse reactions in Bionorica sponsored clinical trials (IB of BX-1, Ed.3.0, 27.Sep 20189), Section 7 “Risk-benefit-assessment” of this Protocol.

5.1.2 Rational for selection of doses

The detailed dosage schedule is described in section 5.1.3.

Due to the experience in previous trials with cannabis based medicine in healthy individuals and clinical groups, including patients with PTSD, the daily dose was determined between 2.5 mg per day to 15 mg per day (single administration) with an increase in dose by 2.5 mg every third/fourth day (see Investigators Brochure, Edition Number Final 3.0, Date of release: 27SEP2019, page 30ff, 6. Effects in Humans). The Investigators Brochure recommends 30 mg dronabinol per day as maximal dose. As single dosing will be applied in this study the maximal daily dose of dronabinol has been restricted to 15 mg which also corresponds to our clinical experience. Effects of THC on nightmares in PTSD have been found in an open label pilot study with 10 mg per day of THC (5 mg twice a day), starting with 5 mg per day (2.5 mg twice a day) (Roitman et al., 2014). However, pharmacokinetic parameters of dronabinol show high intra-individual variability. To determine the optimal individual dose with respect to efficacy (decrease of intensity and frequency of nightmares) and side effects, up-titration in steps of 2.5 mg dronabinol per day will be performed with an increase every third/fourth day. Alternating increase every third and every fourth day has been chosen to take into account that the clinical visits will be take place every seventh day (once a week) in the up-titration period (first four weeks of treatment, Visit 1 to Visit 5). Comparable titration schemas have been used in previous and ongoing trials with dronabinol in other indications (e.g., NCT03756974) and correspond to our clinical experience.

5.1.3 Treatment schedule

The trial comprises 2 phases: screening period of up to 10 days (Visit 0 to Visit 1) and intervention period of 10 weeks, i.e., titration period of 4 weeks (Visit 1 to Visit 5) and maintenance period of 6 weeks (Visit 5 to Visit 8). This is followed by a safety follow-up period of 2 weeks (Visit 8 to Visit 9).

Trial design

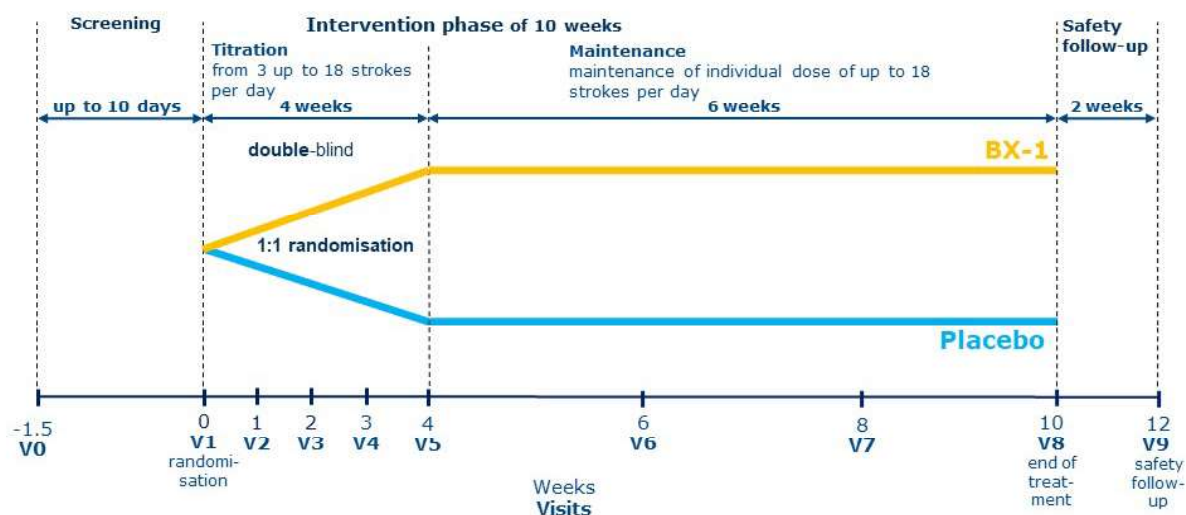


Figure 1: treatment schedule

Screening period

Eligible patients will be screened up to 10 days prior to randomization. No treatment during the screening period is administered.

Titration period

At baseline (Visit 1), patients will be randomised in 1:1 ratio to one of the 2 treatment groups (BX-1 or placebo). The titration period lasts 4 weeks and is performed double-blinded, neither the patient nor the investigator/sponsor knows the identity of the IMP.

All patients start with 3 strokes per day (corresponding to 2.5 mg THC in the active treatment group) and keep the dosage constant for 4 days. On the following day (day 5) an increase with additional 3 strokes (corresponding to 5 mg THC in the active treatment group) should be done. This should be repeated on day 8, day 12, day 15 and day 19 until the maximum dosage of 18 strokes per day (corresponding to 15 mg THC in the active treatment group) is reached. Day of up-titration differs between 3 and 4 days due to the weekly visits during up-titration. See also Figure 2 for a titration schedule.

day of titration period	1	2	3	4	5	6	7	8	9	10	11	12	13	14
No. of strokes/night	3	3	3	3	6	6	6	9	9	9	9	12	12	12
IMP per day [mg THC]	2.5	2.5	2.5	2.5	5	5	5	7.5	7.5	7.5	7.5	10	10	10

day of titration period	15	16	17	18	19	20	21	22	23	24	25	26	27	28
No. of strokes/night	15	15	15	15	18	18	18	18	18	18	18	18	18	18
IMP per day [mg THC]	12.5	12.5	12.5	12.5	15	15	15	15	15	15	15	15	15	15

Figure 2: Titration schedule

However, 18 strokes as the maximal number of strokes per day is **not the treatment goal** of this trial. Patients should not be instructed to reach the maximum dosage, but the **optimal dosage**. The optimal dose is reached if nightmares are completely eliminated. It should therefore be noted, that the instructions above are only a suggested titration scheme. Only the starting dose of 3 strokes at night is fixed. Uptitration should only be based on tolerability and stopped if intolerable side effects appear. In case that nightmares reappear during titration phase, uptitration has to be continued.

In case of intolerable side effect, the increase of doses can be interrupted, delayed or the dose may be decreased in steps of 3 strokes per day until side effects are on an acceptable level. Further increases in steps of 3 strokes per day are allowed if study medication is well tolerated again and if the desired effect is not reached. These cycles might be repeated within the titration period until the optimal dose is obtained. If the optimal dosage is reached it should be continued until the end of the titration period.

It should be noted, however, that the appearance of an adverse event does not necessarily qualify for a down-titration as not all adverse events are an intolerable side effect at the same time. It is in the responsibility of the investigator to define an intolerable side effect together with the patient. A close interaction between investigator and patient has to be established in order to define the individual optimal daily dosage.

Maintenance and treatment period

The individually established daily dosage, i.e. the daily dosage established at day 28, should be maintained throughout the 6 weeks double-blinded maintenance and treatment period.

Safety follow-up period

No treatment during the 2 week lasting safety follow-up period is administered.

Instructions for application:

The solution is taken as follows: IMP has to be placed on a spoon and taken without any additional fluid. To place the oily drops of IMP on the spoon the bottle has to be placed head first and the pump-fed needs to be pressed strongly. The IMP is for oral application only, NOT nasal application! Before first use of the bottle, the pump-fed needs to be pressed several times until the first drop flows. The first drop needs to be discarded. The patients will receive an intake instruction and the correct use will be demonstrated with help of a demo-kit.

5.1.4 Storage requirements and administration (distribution and return of study drug)

IMP has to be stored between 15 and 25°C in the folding box separately from normal practice stocks of marketed drugs or any other IMPs, in a safe (250 kg of weight) with restricted access. The applicable regulatory requirements for controlled drugs have to be considered.

The temperature has to be controlled using calibrated thermometers for this specific trial or by another temperature control system approved by the sponsor in advance. The minimum and maximum temperature of the respective storage condition must be recorded at site on a daily basis (working days). Site staff has to reset daily the minimum temperature as well as the maximum temperature. Temperature of IMP storage must be documented at least until last patient of the site has finished Visit 8.

IMP shipments will be performed under controlled conditions (between 15 and 25°C) by using an electronic temperature data logger. The whole IMP return process will be managed by the pharmacy (St-Hubertus Apotheke) until receipt and reconciliation of IMP at the depot.

5.1.5 Treatment compliance

Compliance will be checked for each patient at Visits 2-8 by weighing the bottles when returned by the patient with a calibrated balance. The weight of each bottle is to be documented as source data in the eCRFs. Based on a mean weight for full bottles the system calculates the medication intake. In order to have the correct calculation it must be marked if the cap is on the bottle or not.

The compliance of the patient will be calculated for each visit and for the complete trial. Patients are non-compliant for the complete trial if less than 80% or more than 120% of the individually established dosage (Visit 5) was taken.

If IMP was lost or broken an intake has to be assumed. Therefore, the patient should be asked if the IMP was full, partially used or empty when broken or lost. If the IMP was full it is assumed that there was no intake, if the IMP was empty it is assumed that complete IMP was taken. If the IMP was partially used it is assumed that half was taken (125 mg dronabinol).

5.2 Placebo / reference medication

There is no discernible difference between BX-1 and the corresponding placebo with regard to colour, taste, and appearance, thus ensuring the trials double-blind character. However, batch-specific variations of odour and colour may occur. In addition, all medications for the double-blind period will be labelled with a common batch number.

Trial treatments are double-blinded. The medication list and the randomisation list are stored at the pharmacy (St-Hubertus Apotheke) and the allocation to treatment groups will be managed by the pharmacy (St-Hubertus Apotheke) and will not be known to the investigator or any other person involved in the conduct of the trial until completion of the trial, except in case of an emergency (see 5.5).

5.3 Concomitant medication / concomitant therapy

In general, concomitant medications and non-drug therapies should be kept to a minimum during the trial and if any is necessary a stable dose should be taken. If the administration of any concomitant treatment becomes necessary, it must be reported in the patient's medical file and the eCRF.

All previous medications taken within 4 weeks or other (non-trauma focused) therapies applied within two-weeks before the start of the trial must also be documented in the medical file and eCRF. All medications or other therapies being taken by the patient on entry to the trial or at any time during the trial in addition to the IMP are regarded as concomitant treatments and must be documented in the patient's medical file and the eCRF.

Concomitant therapy with any medication not listed under "not permitted concomitant pharmacotherapy" is allowed. Trauma-focused psychotherapy is not allowed 4 weeks prior to the trial and during the entire trial.

Treatments specified here are only allowed if stable in the defined timeframe prior to the trial and unaltered during the trial.

Pharmacotherapy

All psychotropic medication needs to be stable at least 4 weeks prior to the start of the study (baseline) and has to remain stable over the 12-week study period. All other non-psychiatric medication has to be stable at least 4 weeks prior to baseline and during the entire trial with some exceptions. Medications for minor transient non-psychiatric medical conditions (e.g., common cold and menstrual cramps) such as NSAIDs are allowed. Pharmacotherapy with alpha-2-agonists, alpha-1-antagonists will not be allowed (see 'not permitted concomitant pharmacotherapy'). Trauma-focused psychotherapy is not allowed 4 weeks prior to and during the trial. Non-trauma-focused psychotherapy is allowed during the trial in stable doses. All clinical exacerbation requiring prescription of other psychotropic drugs will be considered a serious adverse event (SAE).

Not permitted concomitant pharmacotherapy

The following concomitant therapy that interferes with the treatment evaluation of the Investigational Medicinal Product (IMP) is not permitted:

(1) Cannabis-based medicine

Dronabinol or other cannabis-based medicine is not permitted during the trial or within 3 months prior to screening. The intake of such medication has to be clarified with the patient in an interview. In addition, drug abuse screening test is performed. The investigator may not apply such medication during the course of the trial and has to inform the patient that it is not allowed during the trial.

(2) Cannabis herb

Consumption of cannabis herb/marijuana is not permitted during the trial or within 3 months prior to Visit 0. The consumption has to be clarified with the patient in an interview. In addition, drug screening test is performed at screening. The investigator should inform the patient that the consumption is not allowed during the trial.

(3) Sleep medication

Sleep medication that has been initiated 4 or more weeks before screening can be continued at stable dose during the trial.

Initiation of sleep medication 4 weeks prior screening and during the trial is not allowed. I.e., initiation of all benzodiazepines, non-benzodiazepines and other sleep medication are not allowed 4 weeks prior to screening and during the trial.

As examples the following active ingredients (not trade names) are considered as non-benzodiazepines and other sleep medication. Please note that this list is not extensive:

- All benzodiazepines
- Non-benzodiazepines: zaleplon, zolpidem, zopiclon,
- Other sleep medication: Chloralhydrate, Melatonin, Antihistaminergic agents (diphenhydramine, doxylamine, promethazine), mirtazapine, trazodone, trimipramine, doxepin, pipamperon, melperon)

(4) Alpha adrenergic agents (where some evidence of effect on nightmares in PTSD patients has been shown)

Alpha adrenergic agents that has been initiated 4 or more weeks before screening can be continued at stable dose during the trial.

Initiation of alpha adrenergic agents 4 weeks prior screening and during the trial is not allowed.

As examples the following active ingredients (not trade names) are considered as alpha or beta adrenergic agents. Please note that this list is not extensive:

- Doxazosin, prazosin, terazosin, clonidine

Psychotherapy

Non-trauma-focused psychotherapy is allowed if initiated 2 weeks prior to screening and at stable dose during the trial. Psychotherapy frequency has to be documented in the medical file and eCRF.

Trauma-focused psychotherapy is not allowed 4 weeks prior to the trial and during the entire trial.

5.4 Blinding procedures and emergency envelopes

Treatment is blinded by use of a matching placebo. The Sponsor, study personnel, and subjects will be blinded to treatment until the database is locked. Emergency envelopes will be provided by the pharmacy and will be stored in the trial sites. These emergency envelopes could then be used by investigators in case of emergencies.

5.5 Procedures in case of emergency and unblinding

In the case of an emergency, access to the study treatment code for an individual subject will be possible at the trial sites. Emergency envelopes will be stored at the trial sites.

Every trial patient will receive a patient ID card where the address and telephone number of the responsible investigator in case of emergency and the complete address of the trial site will be indicated. The patient ID card contains information that the patient is participating in a clinical trial involving exposure to BX-1 with dronabinol as the active ingredient or corresponding placebo.

A patient's investigational product assignment can be unblinded by a study center when knowledge of the investigational product assignment is essential for the care of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. The Sponsor may unblind a subject's investigational product assignment for safety reporting as required by regulatory authorities.

Whenever the treatment assignment of a subject is unblinded, the reason, the date and time of the unblinding must be included in source documentation. The name of the individual who broke the blind must be included in the site's source documentation as well.

The decision about necessity of unblinding lies in the responsibility of the investigator or the authorised person. However, the investigator should promptly document and explain to the sponsor any premature unblinding.

6 Study procedures

6.1 Recruitment / screening procedures

Patient's will be recruited via the in- and outpatients center at the recruiting centers. Flyer, advertising the study, will be distributed at other treatment centers and private practice for psychiatry and psychotherapy.

A recruitment period of 21 months is planned

Eligible patients will be screened up to 10 days prior to randomization.

The following will be collected at screening:

- Signed informed consent form
- Review of study eligibility (inclusion and exclusion criteria)
- Physical examination
- Blood pressure, pulse, weight
- Prior and concomitant medication and non-drug therapy
- Medical history
- Blood test
- Urinary or serum cannabis test
- Pregnancy test
- ECG
- Blood pressure, pulse
- CAPS-IV B2score
- CAPS-5
- MADRS
- Demographics
- CTQ
- MINI-5
- ITI

6.2 Methods of obtaining informed consent

Every study site will assess patients for eligibility to enroll into the study. Before enrolment, every patient will receive full oral and written information about the nature, purpose, expected advantages and possible risks of the trial. The patient will agree to participate in the trial by signing the informed consent form. Patients must be given an opportunity to enquire about details of the study. After a sufficient period of time for the individual's consideration and decision, comprehension and consent shall be documented on the consent form by the dated signature of the patient and the Investigator. If a patient is able to consent but cannot sign himself/herself, oral information and written consent need to be testified and signed by a witness.

The subject must read, sign, and date the informed consent form before entering in the trial, takes study treatment or undergoes any study-specific procedures. The entry into this trial is defined as the patient's signature of the consent. The final versions of patient information and consent will be presented to the Ethics Committee. Both the patient information and the patient consent form are produced in duplicate. One of each form for the Investigator, a

duplicate will be handed to the patient. Twice the patient informed consent form are signed. One of each form is for the patient file, another will be handed to the patient. Patients will not have any disadvantage by not participating in the study. Patients have the right to withdraw from the study at any time for any reason after giving informed consent.

6.3 Methods of avoiding simultaneous enrolment in other trials

Those patients recruited in the present study could not be recruited in other clinical interventional trials. They will not receive any other investigational drug. The investigator will register in the medical records of the patient that he/she has been included in a clinical trial and the expected duration of it. Patients are informed that they may not enter into other interventional trials. A patient study card will be given to each patients informing about the participation in this trial.

6.4 Enrolment and randomisation (assignment of study medication)

Patients, who meet all inclusion criteria and who have given their written informed consent will be randomised for study treatment in one of the two study arms. The patients receive a 5-digit randomization number (= subject ID). The study medication is provided by the pharmacy with kit numbers. The pharmacy allocates the kit-numbers (study medication) to the patients on the basis of a randomisation plan. Patient data will be captured in the medical files (source data) and are consecutively transferred pseudonymized to the eCRF.

6.5 Clinical examinations and trial-related deviations from clinical practice

6.5.1 Screening

The following examinations will be performed at screening: evaluation of inclusion/exclusion Criteria, Informed consent, Physical examination, blood pressure, pulse, weight, assessment of prior and concomitant medication and non-drug therapy, assessment of medical history, blood test, urinary or serum cannabis test, urinary or serum pregnancy test, ECG recording, blood pressure and pulse measurement, assessment of CAPS-IV B2, CAPS-5, MADRS, Demographics, CTQ, MINI-5, and ITI.

6.5.2 Examinations during trial

At baseline, assessment includes prior and concomitant medication and non-drug therapy, blood test (see 6.5.5 Laboratory assessments), urinary or serum cannabis test, urinary or serum pregnancy test, ECG, blood pressure and pulse, weight, adverse event recording, CAPS-IV B2, CAPS-5, PSQI-A, MADRS, Sleep diary, PCL-5, BSL-23, EQ-5D, PGIC, SOFAS, PSQI, ITQ, MWC. Further assessments during the trial will be performed at visit 2 (week 1), visit 3 (week 2), visit 4 (week 3), visit 5 (week 4), visit 6 (week 6), visit 7 (week 7), and the final examination (visit 8 in week 10). At visit 2 (week 1), visit 3 (week 2), visit 4 (week 3), visit 5 (week 4), and visit 7 (week 7), concomitant medication and non-drug therapy, blood pressure and pulse, Adverse event recording, CAPS-IV B2, PSQI-A and Sleep diary will be assessed.

At visit 6 (week 6), concomitant medication and non-drug therapy, blood pressure and pulse, weight, adverse event recording, CAPS-IV B2, PSQI-A, Sleep diary, CAPS-5, PCL-5, BSL-23, EQ-5D, PGIC, SOFAS, PSQI, ITQ, and MWC will be assessed.

Table 1: Outline of trial visits

Assessments	SC	BL Visit 1 W 0	Visit 2 W 1	Visit 3 W 2	Visit 4 W 3	Visit 5 W 4	Visit 6 W 6	Visit 7 W 8	Visit 8 W 10	FU Visit 9 W 12
Screening and consent										
Inclusion/exclusion criteria	X									
Informed consent	X									
Physical examination ¹	X								X	
Prior and concomitant medication and non-drug therapy	X	X	X	X	X	X	X	X	X	X
Medical history	X									
IMP dispersion		X	X	X	X	X	X	X		
IMP return			X	X	X	X	X	X	X	
Safety										
Blood test ²	X								X	
Cannabis test	X									
Pregnancy test	X	X		X		X	X	X	X	
ECG	X								X	(X) ³
Blood pressure, pulse	X	X	X	X	X	X	X	X	X	X
Weight	X	X					X		X	X
Adverse event recording			X	X	X	X	X	X	X	X
Effectiveness										
primary										
CAPS-IV B2									X	
secondary										
CAPS-IV B2	X	X	X	X	X	X	X	X		
CAPS-5	X ^a	X ^b					X ^b		X ^b	
PSQI-A		X	X	X	X	X	X	X	X	
MADRS	X	X				X			X	
Sleep diary		X	X	X	X	X	X	X	X	
PCL-5		X					X		X	
BSL-23		X					X		X	
EQ-5D		X					X		X	
PGIC							X		X	
SOFAS		X					X		X	
PSQI		X					X		X	
ITQ		X					X		X	
MWC		X					X		X	X
others										
Demographics	X									
CTQ	X									
MINI-5	X									
ITI	X									

Note: SC = screening, W. = week +/- 3 days, BL = baseline and randomization, FU = post-trial follow-up, CAPS-IV B2 = B2 score of the Clinician-Administered PTSD Scale for DSM-IV (frequency and intensity of nightmares), CAPS-5 = Clinician-Administered PTSD Scale for DSM-5 (a = last month version, b = last week version), PSQI-A = Pittsburgh Sleep Quality Index-Addendum for PTSD, MADRS = Montgomery-Åsberg Depression Rating Scale, PCL-5 = PTSD Checklist for DSM-5, BSL-23 = Borderline Symptom List 23, EQ-5D = Health-Related Quality of Life, PGIC = Patient Global Impression of Change, SOFAS = Social and Occupational Functioning Assessment Scale, PSQI = Pittsburgh Sleep Quality Index, ITQ = international trauma questionnaire, MWC = Marijuana Withdrawal Checklist, CTQ = Childhood trauma questionnaire, MINI-5 = The Mini International Neuropsychiatric Interview for DSM-5, ITI = International Trauma Interview. 1 Physical examination includes height and weight of the patient and the skin, abdomen, respiratory system, head and extremities will be examined, 2: blood tests include haematology (erythrocytes, haemoglobin, haematocrit, platelets, leukocytes (including neutrophils, eosinophils, basophils, lymphocytes, monocytes) and serum chemistry (sodium, potassium, chloride, calcium, creatinine, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, aspartate aminotransferase, bilirubin, lipase, thyroid stimulating hormone), 3. In case of significant abnormal ECG findings at the visit 8 (week 10), a further ECG will be recorded at the follow-up visit.

6.5.3 Final examination

The final examination will be performed at visit 8 (week 10) and include a physical examination, concomitant medication and non-drug therapy recording, IMP return, blood tests, urinary or serum pregnancy tests, ECG, measurement of blood pressure and pulse, weight, adverse event recording, assessment of CAPS-IV B2, PSQI-A, MADRS, sleep diary, PCL-

5, BSL-23, EQ-5D, PGIC, SOFAS, PSQI, ITQ, MWC. Further, number of remitters (defined as CAPS-IV B2 = 0) and responders (defined as decrease of CAPS-IV B2 $\geq 50\%$) from baseline to week 10 will be determined.

6.5.4 Follow-up examination

A follow-up visit will take place at Visit 9 (W12) and include blood pressure, pulse, and weight assessment, adverse event recording, and concomitant medication and non-drug therapy. In case of significant abnormal ECG findings at visit 8 (week 10), a further ECG will be recorded at the follow-up visit.

6.5.5 Laboratory assessments

Laboratory assessments of blood parameters will be performed at screening and at Visit 8 (w10). Blood tests include haematology (erythrocytes, haemoglobin, haematocrit, platelets, leukocytes (including neutrophils, eosinophils, basophils, lymphocytes, monocytes) and serum chemistry (sodium, potassium, chloride, calcium, creatinine, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, aspartate aminotransferase, bilirubin, lipase, thyroid stimulating hormone).

6.6 Individual trial duration

After screening (10 days maximum), patients will be randomized and allocated to IMP or placebo. The individual patient will be treated for 10 weeks and a follow-up visit will take place after 2 weeks.

7 Risk-benefit-assessment

Risks, adverse reactions, stresses, advantages and disadvantages for the participants
 In general, dronabinol is well tolerated, but the patient's individual maximum dosage is limited by adverse reactions. Expected adverse reactions are listed in the table below.

System Organ Class	Adverse Reactions	Frequency
Psychiatric disorders	Anxiety/restlessness, depression, euphoria, sleep disorder	Common
	Thinking abnormal	Uncommon
Nervous system disorders	Dizziness, headache, disturbance in attention, memory impairment, speech difficulties	Common
	Tremor	Uncommon
Ear and labyrinth disorders	Vertigo	Common
Cardiac disorders	Tachycardia	Uncommon
Vascular disorders	Hypertension, hypotonia	Uncommon
Respiratory, thoracic and mediastinal disorders	Dry nose	Common
	Dyspnoea	Uncommon
General disorders and administration site conditions	Tiredness	Very common
	Asthenia/muscular weakness, feeling abnormal	Common
Gastrointestinal disorders	Nausea, constipation, diarrhoea, abdominal pain upper, dry mouth	Common
	Flatulence, vomiting, hypoaesthesia oral	Uncommon
Metabolism and nutrition disorders	Increased appetite, loss of appetite	Common
Skin and subcutaneous tissue disorders	Sweating, local hypersensitivity reactions	Common
Eye disorders	Pressure behind the eyes	Common
	Dry eye, abnormal sensation in eye	Uncommon

Table 2: Reported adverse reactions in Bionorica sponsored clinical trials

(IB of BX-1, Ed.3.0, 27.Sep 2019; please refer to table 9 of the IB)

The following frequency categories are used for the evaluation of these adverse reactions:

Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$)

Due to the known effects of dronabinol, BX-1 should be administered with caution to patients with mania, depression or schizophrenia, heart diseases, history of seizure-related diseases and history of substance abuse. There might be additional or synergistic effects on central nervous system adverse reactions in patients treated concomitantly with sedative, hypnotic or other psychoactive medicinal products. BX-1 is not intended for the use in pregnant or breastfeeding women.

In order to minimize the risk for patients, patient groups with a significant risk are excluded from trial participation.

In addition to the risks related to the investigational medicinal product, there is a trial procedure related risk. Blood sampling might be painful, or the patients might temporarily become dizzy. Patients may also experience intermittent complaints like re-bleeding or puncture site bruises, blood clot (thrombus) in the punctured vessel (rarely), puncture site infections (rarely) or mechanical nerve damage (very rarely). After initial irritation, vein puncturing for blood sampling is usually painless and hardly noticeable.

The total volume of blood sampling during the entire clinical trial will be approximately 18 ml within approximately 14 weeks and is far below the volume of a normal blood donation. However, in single cases it might be necessary to repeat single blood sampling, e.g. an additional sample has to be taken due to re-measurements of clinical laboratory samples or due to bad vein conditions and a new sample must be taken from another vein, etc. Thus, the total blood volume may deviate in single cases by a small amount. No safety related risk is expected from this blood sampling.

In case of emergency, standard emergency procedures will be employed. The responsible investigator is to be consulted and informed immediately. He/she will provide all the necessary emergency equipment and specially trained staff to handle emergency events during this clinical trial. All cases of emergency have to be immediately reported as required to the sponsor comprising legal stipulations.

Benefits

There is no current approved medication to treat nightmares in patients with PTSD. Distressing nightmares are an independent risk factor for comorbidity and severity in PTSD patients. Nightmares also contribute to alcohol and substance abuse, suicidal ideation, and even suicide (Raskind et al., 2007). There is initial evidence for dronabinol either in combination with other active ingredients or as the sole active ingredient having a clinically relevant effect on nightmares in patients with nightmares and PTSD (Roitman et al., 2014; Wilkinson et al., 2016). For example, an open label, uncontrolled pilot study examined the impact of adding 5 mg of $\Delta(9)$ -THC twice a day as add-on treatment onto existing medications in PTSD patients and found that THC consumption specifically improved sleep quality, reduced nightmares, and reduced symptoms of hyperarousal (Roitman et al., 2014). Further, no negative results of cannabinoid-agonists in PTSD treatments are published to date.

Conclusion

Based on available literature data and trial conceptual design a positive benefit-risk balance is expected for BX-1 in this trial.

8 Termination and subsequent treatment

8.1 Premature termination of the individual participant

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled. Withdrawal from the study will not jeopardize their future medical care or relationship with the investigator. Subjects will be asked to specify the reason for their termination, but have the right not to answer.

The investigator may decide to withdraw a subject from the study at any time with reasonable rationale. The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the study until completion of the study.

The reason for withdrawal of a patient should be recorded, if possible, in the eCRF and in the subject's records (Withdrawal of Consent Form).

A subject who withdraws Informed Consent before randomization or who develops a condition infringing with selection criteria before randomization is defined as a screening failure. No follow-up of screening failures will be performed.

The following events must cause premature termination of the individual subject:

- Unblinding in case of a medical emergency
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study
- Pregnancy
- Consent withdrawn by patient
- Events with a score > 3 according to the CTCAE catalogue (Common Terminology Criteria for Adverse Events, Version 5.0)
- Complete missing of two consecutive visits

8.2 Premature termination of the clinical study

The following events must cause premature termination of the clinical trial:

- Unjustifiable risk and negative risk-benefit analysis (decision taken by the sponsor)
- New scientific evidence provided during the study that could affect the patient's safety (benefit-risk analysis no longer positive)
- Decision of the Sponsor or the Competent Authority that the study should be discontinued or because of withdrawal of a positive vote by a responsible ethics committee.

Sponsor may terminate the trial at an individual study centre, if

- the investigator no longer considers the risk-benefit ratio to be reasonable,
- the centre's recruitment rate is too low,
- the drop-out rate is unusually high, or
- the investigator does not comply with the protocol or other regulations with the necessary care.

8.3 Follow-up and continuing treatment after regular / premature termination

After the end of the trial, the patients will be treated according to local standard practice. No further post-trial therapy will be offered by the sponsor.

In the case of premature termination, the reason for withdrawal must be entered on the appropriate case report form (CRF) page and must be followed for safety and efficacy until 8 days (five times half-life of 36 h) after discontinuation.

9 Adverse events

9.1 Definitions (according to guideline 2001/20/EG)

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE could be diseases, signs or symptoms which occur or worsen after enrolment of the patient in the clinical trial.

Serious Adverse Event (SAE)

A 'serious adverse event or serious adverse reaction' is any untoward medical occurrence or effect that at any dose

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- or is a congenital anomaly or birth defect;
- other medically important event (as described in 9.3.1)

Adverse Reactions

Adverse reactions are all untoward and unintended responses to an investigational medicinal product related to any dose administered.

Suspected Unexpected Serious Adverse Reactions (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is any suspected adverse reaction related to the study treatment that is both serious and unexpected.

"Unexpected" means that the nature and severity of the adverse reaction are not consistent with the information about the study medication in question set out in the reference safety information.

The evaluation of expectedness will be done by the sponsor.

9.2 Treatment of (S)AEs

All AEs should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization or any other medically required intervention.

9.3 Assessment of SAEs

As far as possible, each AE should be evaluated to determine:

1. the severity grade (CTCAE v5.0)
2. its relationship to the study drug (assessment of causality)
3. its duration (start and end dates or if continuing at final exam)

4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this AE; hospitalization)
5. whether it constitutes a serious adverse event (SAE)

9.3.1 Assessment of Seriousness

Seriousness shall be determined according to the definition above.

Furthermore medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room, or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug addiction or drug abuse.

9.3.2 Assessment of intensity

CTCAE grading:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

9.3.3 Assessment of causality

Causal relationship between the occurrence of an AE and the administration of the IMP as assessed by the investigator according to the available data:

Related: There is a reasonable causal relationship, which means that there is evidence to suggest a causal relationship. The adverse event could medically (pharmacologically/ clinically) be attributed to the investigational product under trial in this protocol.

Not related: There is no reasonable causal relationship, which means that there is no evidence to suggest a causal relationship. The adverse event could not medically (pharmacologically/ clinically) be attributed to the investigational product under trial in this protocol.

9.4 Documentation of AEs and SAEs

All Serious Adverse Events (SAEs) and all Adverse Events (AEs) need to be documented, no matter if the Investigator suspects a causal connection to the investigational product or not.

The documentation needs to include the type of event, start, duration, severity and causality, outcome, action taken.

Related signs, symptoms and laboratory changes should be summarized to a specific disease. The event will be recorded in the CRF SAEs need to be documented on a separate SAE form.

Out of normal range laboratory data need to be analysed concerning their clinical relevance by the Investigator – and if relevant documented as an AE itself. CTCAE criteria will be applied to laboratory values.

All adverse events need to be followed until they subside or stabilize.

The Sponsor will carefully document all SAEs reported by the Investigator. His documentation will be sent to the relevant regulatory authorities and to relevant authorities of other European member states and other contracting states of the EWR agreement, if the study is run in their territory and if they so request.

9.5 Reporting of SAEs

To ensure patient safety all SAEs occurring after the patient has provided informed consent must be reported, regardless of causality, by the local investigator to the Sponsor within 24 hours of learning its occurrence. The local Investigator is responsible for reporting all adverse events reported by the participant or detected by the study staff without delay and within 24 hours to the Sponsor's designee (KKS Charité, Pharmacovigilance Department). It has to be documented on the appropriate pages of the case report form (CRF).

The Investigator will report any Serious Adverse Event promptly after becoming aware to the Sponsor's designee (KKS Charité, Pharmacovigilance Department) and will afterwards send an extended written record.

This announcement will be done via fax or email to:

Pharmacovigilance, KKS Charité

Fax: +49 (0)30 – 450 7553-856

Email: pharmacovigilance-kks@charite.de

9.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor's designee (KKS Charité) will report all suspicious cases of Suspected Unexpected Serious Adverse Reactions (SUSARs) which had been occurred in one of clinical trials conducted by the same sponsor with the same drug substance/IMP to the relevant Ethics Committee, the relevant regulatory authorities and to relevant regulatory authorities of other European member states and other contracting states of the EWR agreement, if the study is run in their territory immediately, at the latest 15 days after it becomes known. He will also inform all Investigators involved in the trial.

In case of a fatal or life threatening SUSAR the Sponsor will report all information relevant for judging the event immediately, at the latest 7 days after the event becomes known to the relevant Ethics Committee, the relevant regulatory authorities and to relevant regulatory authorities of other European member states and other contracting states of the EWR agreement, if the study is run in their territory as well as to all Investigators involved in the trial. After a further 8 days all further relevant information must be available.

9.7 Other safety issues requiring expedited reporting

The Sponsor's designee will immediately, at the latest 15 days after it becomes known report all circumstances that require a revision of the risk-benefit analysis to the relevant Ethics Committee, the relevant regulatory authorities and to relevant regulatory authorities of other European member states and other contracting states of the EWR agreement, if the study is run in their territory. This especially includes:

- Singular cases of expected severe adverse events with an unexpected outcome.
- Increased incidence of expected severe adverse events that are judged as being clinically relevant.
- SUSARs which occur after termination of the clinical trial (up to 8 days (five times half-life of 36 h) after termination or exclusion)
- Events related to study procedures or development of the study medication, which could affect a subject's safety.

All person-related data will always be transmitted pseudonymised. Before reporting a SUSAR the subject will be unblinded.

9.8 Follow-up of adverse events

Once an AE is detected, it should be followed until its resolution or stabilisation, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study, the interventions required to treat it and the outcome.

Follow-up information is sent to the same address to which the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

For a follow-up report to the authorities, the investigator may be required to collect further information for a detailed description and a final evaluation of the case, including copies of hospital reports, autopsy reports, or other relevant documents.

9.9 Pregnancy

The investigator will collect pregnancy information on any female patient, who becomes pregnant while participating in this clinical trial. The investigator will record pregnancy information on the SAE form (under other medically important condition) and submit it to the sponsor immediately (i.e. within 24 hours after acknowledgment of a patient's pregnancy). The receipt of reports concerning pregnancy will be confirmed immediately, but not later than three (3) working days after the receipt. Without confirmation after three working days, the investigator has to transmit the report again on the following working day.

Any patient who becomes pregnant while participating in the trial should discontinue treatment immediately and will be withdrawn from the trial.

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Generally, follow-up will be no longer than 3 months following the estimated delivery date. Any follow-up information will be sent to the sponsor immediately (i.e. within 24 hours after acknowledgment).

Newly diagnosed pregnancy in a clinical trial patient is not considered to be an AE or SAE unless meeting seriousness criteria, or it is suspected that the IMP interacted with a contraceptive method and led to pregnancy.

Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Furthermore, any SAE occurring as in association with a pregnancy (in cases where the pregnancy occurred after the end of the trial participation of the patient) brought to the investigator's attention after the patient has completed the trial and considered by the investigator as reasonably related to the IMP must be promptly reported to the sponsor.

9.10 Contact for reporting

Name	Pharmacovigilance, KKS Charité
Study centre	Charité – Universitätsmedizin Berlin, Campus Charité Mitte
Address	Charitéplatz 1, 10117 Berlin
Fax:	+49-(0)30-450 7553-856
E-Mail:	pharmacovigilance-kks@charite.de

9.11 Annual Safety Reporting

Once a year throughout the clinical trial, the sponsor will provide the Member States in whose territory the clinical trial is being conducted and the relevant Ethics Committees with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.' For the format reference is made to the guideline ICH Topic E2F — Development Safety Update Report ('DSUR', hereinafter 'note for guidance ICH E2F').

10 Documentation

10.1 Case Report Forms (CRF)

Data collected on each subject will be captured in the medical files (source data) and are consecutively recorded in the eCRF (electronically).

10.2 Investigator Site File (ISF)

All essential documents will be kept in the Investigator Site File which will be stored at the study site in accordance with ICH GCP chapter 8.

10.3 Drug accountability / flow of study medication

IMP will be provided by Bionorica SE via the pharmacy “St. Hubertus Apotheke”. Labelling and secondary packaging for use in a clinical trial will be performed by the pharmacy “St. Hubertus Apotheke” under the responsibility of Bionorica SE.”. The pharmacy “St. Hubertus Apotheke” will provide study medication to the study centers. Emergency envelopes will also be sent to the study centers by the pharmacy “St. Hubertus Apotheke”. The study centers will provide study medication to the participants. IMP will be weighed after return of IMP at the study centers with an analytical balance. After return of study medication to the study centers IMP will be sent to the “St. Hubertus Apotheke”. Discreation of IMP will be performed at “St. Hubertus Apotheke”.

11 Quality management

11.1 Control of trial progress and data quality

11.1.1 Monitoring, Data Quality Assurance

The trial site will be monitored by KKS Charité to ensure the quality of the data collected. The objectives of the monitoring procedures are to ensure that the trial subject's safety and rights as a study participant are respected, that accurate, valid and complete data are collected, and that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation.

All investigators agree that the monitor regularly visits the trial site and assure that the monitor will receive appropriate support in his activities at the trial site.

The declaration of informed consent includes a statement to the effect that the monitor has the right – while observing the provisions of data protection legislation – to compare the case report forms (eCRFs) with the trial subject's medical records (doctor's notes, ECGs, laboratory printouts etc.). The investigator will secure access for the monitor to all necessary documentation for trial-related monitoring. The aims of the monitoring visits are as follows:

- To check the declarations of informed consent.
- To monitor trial subject safety (occurrence and documentation/reporting of AEs and SAEs).
- To check the completeness and accuracy of entries on the eCRF.
- To validate the entries on the eCRF against those in the source documents (source data verification, SDV).
- To evaluate the progress of the trial.
- To evaluate compliance with the trial protocol.
- To assess whether the trial is being performed according to GCP at the trial site.
- To discuss with the investigator aspects of trial conduct and any deficiencies found.

A monitoring visit report is prepared for each visit describing the progress of the clinical trial and any problems (e.g. refusal to give access to documentation).

11.1.2 Audits / inspections

Authorised representatives of the Sponsor, a regulatory authority, or an Independent Ethics Committee (IEC) may visit the centre to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements.

12 Data entry und data management

All patient related data will be recorded under a pseudonym. Every patient will receive a patient number / pseudonym which will be unique for this individual patient. The Investigator will compile a confidential list, which relates these patient numbers to the patient's full name. This list will only be accessible to the study team and the monitor. Original patient files may be viewed by monitors, auditors and inspectors.

12.1 Data collection/Case Report Form (CRF)

All data will be recorded in an electronic Case Report Form. The study software used is SecuTrial.

All data will be recorded online/offline and will be transmitted directly to the database of the study centre. Data will be transferred between the workstation computer at the study site and the study server via a secure connection (secure socket layer /SSL) so that the data cannot be manipulated.

All patient data will be saved under a pseudonym. The study software will automatically generate a pseudonym for every new patient/the pseudonym for new patients can be typed into the study software. A document for clear patient allocation will be printed and must be kept in a safe place.

12.2 Source Data and Patient Files

The information in original documents and records (e. g. patient files, laboratory notes) are defined as Source Data and will be reviewed by the Monitor for Source Data Verification. All patient data, including the weight of the bottles for documentation of treatment compliance, will be captured in the medical files (source data) and are consecutively transferred pseudonymized to the eCRF.

12.3 Data processing

The study centre / Sponsor / biometrical centre will file all data electronically. To verify accuracy of the data, range, validity and consistency checks will be performed. Implausible or missing data can be corrected or added after consulting the Investigator. Documentation for these corrections will be stored with the CRFs.

All validated data will be stored in a database Oracle.

After termination of the study and after all entries have been completed, the database will be closed for further entries. This process will be documented.

The analysis will be performed using the following commercial software SAS.

12.4 Generation of pseudonym

First, the patients will receive a screening number. With enrolment into the study, patients receive randomization numbers (subject IDs), which consist of a number for the study centers and a sequential number. The pseudonym for new patients can be typed into the study software. A document for clear patient allocation will be printed and must be kept in a safe place at the trial site.

13 Statistical Analysis

13.1 Sample size estimation

The sample size calculation is based on the primary endpoint “Clinician-Administered PTSD Scale-IV (CAPS-IV) B2 score at 10 weeks” in the ITT population including all randomized patients who received the study medication at least once. The aim is to show a lower average score at 10 weeks in the intervention group (I) than in the control group (C). Sample size calculation will be based on a two-sided, two-sample t-test. Adjustment for baseline scores in an ANCOVA model which is applied for the primary efficacy analysis will increase the power compared with a two-sample t-test, which ignores the influence of different baseline values. Therefore, this strategy for sample size calculation is a conservative procedure. In a recent random-effects meta-analysis of four RCTs investigating the effect of prazosin on PTSD nightmares, a combined standardized mean difference (Cohen’s d) of 0.5 (95% CI = 0.03–0.96) was observed (Augedal, Hansen, Kronhaug, Harvey, & Pallesen, 2013). We conservatively assume a standardized effect which is a little smaller and given by 0.45. This assumed effect can be considered as clinically relevant because distressing nightmares are an independent risk factor for comorbidity and severity in PTSD patients. Nightmares also contribute to alcohol and substance abuse, suicidal ideation, and even completed suicide (Raskind et al., 2007). As studies assessing minimal clinically important difference (MCID) for reduction of nightmares in PTSD are currently missing, clinical significance cannot be used to calculate sample size. The required sample size to detect this effect of 0.45 with a power of 0.8 is 158 (79 per group) calculated with nQuery Version 8.2.1.0. We conservatively assume that there will be no more than 10% of patients who are randomized but never get the study medication. Therefore the total number of patients to be recruited is 176 ($158/0.9=176$) or 88 per group.

13.2 Randomisation

Patients will be randomized at baseline in a 1:1 allocation using block randomization with fixed block lengths stratified by study center. Randomization will be performed by the pharmacy (St. Hubertus Apotheke).

13.3 Statistical analysis

13.3.1 Hypotheses

The null hypothesis states that the score at 10 weeks is higher on average in the intervention group (I) than the control group (C) whereas the alternative hypothesis states that the score at 10 weeks is lower on average in the intervention group (I) than the control group (C).

13.3.2 Definition of population for analysis

Confirmatory analysis will be conducted based on full analysis set.

Definition of the full analysis set: The full-analysis set consists of all randomized patients which received the study medication at least once. Patients are analysed as randomized. This is the population as close as possible to the intention-to-treat population. Exclusion of patients who never received the study medication is explicitly stated as an option in the ICH E) Guideline.

Definition of the per protocol set: The per-protocol population includes all patients without major protocol violations, to be defined in the statistical analysis plan which must be finalized before data base closure.

Definition of the safety set: The safety set as the basis for all safety analyses corresponds to the full analysis set.

We assume that 15% of patients who are randomized and received the study medication at least once will not finish the study as planned (non-completers). Non-complete cases will be subject to missing value imputation as specified below. Non-completers will not reduce the sample size of the primary analysis.

Sensitivity analyses will be conducted based on the per-protocol population including all patients without major protocol violations, to be defined in the statistical analysis plan which must be finalized before data base closure.

13.3.3 Analysis of primary and secondary endpoints

Primary analysis: The aim is to show that the score at 10 weeks is lower in the intervention group (I) than the control group (C). An ANCOVA model including the baseline score and adjusted for study center, will be applied for primary analysis. The global two-sided significance level will be 0.05.

Missing values for the analysis of the primary endpoint will be imputed as follows: If the follow-up assessment at 10 weeks is missing but the patient has at least one follow-up assessment after baseline, last observation carried forward will be used for missing value imputation. If the baseline visit is missing but follow-up assessments are available, the baseline value will be imputed using multiple imputation (van Buuren 2012).

Secondary analyses: Descriptive methods will be used to analyse secondary outcomes, including appropriate summary measures of the empirical distribution as well as 95% confidence intervals and descriptive two-sided p-values. For analyses the secondary endpoints considering the primary score at different follow-up times, the same imputation mechanisms as specified above will be applied. For all other secondary endpoints no imputation is planned. Additionally, sensitivity of the primary analysis will be analysed in different populations to assess the impact of the analysis population and of the imputation method (comparison to per-protocol population, patients with complete cases). All analyses will be done using validated statistical software.

13.3.4 Analysis of safety

Safety analysis will include (if appropriate) calculation of frequencies and rates of adverse and serious adverse events, adverse drug reaction and serious adverse drug reaction, laboratory parameters, vital signs, physical examinations, and ECGs.

13.3.5 Interim analyses and endpoints for premature study termination

No interim analyses will be conducted.

14 Reporting

14.1 Statistical report

The statistical analysis and composition of a biometrical report will be performed by Prof. Dr. Geraldine Rauch in cooperation with the Sponsor and the Principal Investigator. All data in this report is confidential.

14.2 Final report

After completion of the biometric evaluation, the sponsor will prepare a study report. The report will include all trial results, irrespective of whether favourable or not. Within 12 months after the end of the trial, the sponsor will submit a summary of the final report to the ethics committee and to the competent federal authorities. The summary will be prepared in the format provided for report synopses by the ICH Guideline E3, "Guidance on Structure and Content of Clinical Study Reports".

14.3 Publication (policy)

The study results will be published irrespective of the study outcome.

15 Ethical, legal and regulatory aspects

15.1 ICH-GCP-guidelines

This trial will be conducted in accordance with the current ICH-GCP-guidelines. Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

15.2 Legal requirements of the study

- Approval of Ethics Committee (according to AMG § 42 (1) and GCP-V § 7)
- Approval of competent authority (according to AMG § 42 (2) and GCP-V § 7)
- Approval of the competent authority (Bundesopiumstelle) (according to BtMG § 3)
- Notification to regional authorities (according to AMG § 67)
- Informed Consent
- Insurance
- Data privacy and confidentiality

15.2.1 Approval of Ethics Committee

Study protocol, patient information and consent form will be presented to the relevant Ethics Committee for survey. According to AMG § 42 (1) and GCP-V § 7 the study will only start after ethics approval has been granted. The Ethics Committee will immediately be informed (by the Sponsor) of all changes to the protocol (according to GCP-V § 10) and of all events that could affect a patients safety. The Ethics Committee will also be informed of all suspected SUSARs and of regular or premature termination of the study.

The Investigators have to register with the Ethics Committee (enter proof of qualification) before they enrol any patients.

15.2.2 Approval of competent authority

According to AMG § 42 (2), GCP-V § 7 and BtMG § 3 the trial will be submitted to the relevant federal authorities (BfArM, “Fachregistratur Klinische Prüfung” and “Bundesopiumstelle”) for approval. The trial will only start after approval has been granted.

15.2.3 Notification to regional authorities

According to AMG § 67 and GCP-V § 12 Abs. 1-3 the trial will be submitted to the relevant state authorities. The Sponsor and all Investigators will be reported by full name.

15.2.4 Patient information and informed consent

Patient Information

Before enrolment every patient will receive full oral and written information about the nature, purpose, expected advantages and possible risks of the trial. (see 6.2).

Consent to participation in the trial:

The patient will agree to participation in the trial by signing the informed consent form. Patients must be given an opportunity to enquire about details of the study. After a sufficient period of time for the individual’s consideration and decision, comprehension and consent

shall be documented on the consent form by the dated signature of the patient and the Investigator/ treating doctor. If a patient is able to consent but cannot sign himself/herself, oral information and written consent need to be testified and signed by a witness.

Adults who cannot give their consent must be represented by a legal carer.

Design and language will be adjusted to the study site's needs. The final versions of patient information and consent will be presented to the Ethics Committee. Both the patient information and the patient consent form are prepared in duplicate. One of each form for the Investigator, a duplicate will be handed to the patient.

15.2.5 Patient insurance

For participating patients, an insurance (gem. AMG § 40 Absatz 1 Satz 3 Nr. 8) has been established. The insurance (HDI Global SE, Am Schönenkamp 45, 40599 Düsseldorf), policy number 4312562503674 will cover for incidents from the commencement of the study. The insurance is limited to a maximum of 500.000 Euro per patient.

15.2.6 Data Privacy and confidentiality

The participants' data will be saved in a pseudonymous form, which will neither contain initials nor full date of birth. All regulative requirements applying to data protection will be met. Re-identification of a participant subject's name is possible from the patient identification log, which is kept in a locked research office at the Trial site where access is only possible by the principal Investigator or persons authorised by the principal Investigator.

Patients will be informed that their disease-related data will be saved for scientific purpose (Publication, etc.) using a pseudonym. Consenting patients have got the right to be informed about the data recorded. Patients will also be informed that their pseudonymised data will be forwarded to the 'Bundesoberbehörde' (BfArM) and to the Ethics Committee responsible, in accordance with legal notification obligation for drug safety. Patients, who disagree with this process of data transfer, are not allowed to participate in this study.

15.3 Archiving of data / access to records

Originals of all study-related report forms will be stored in the study headquarters at the trial site for at least 10 years after completion of the trial (GCP-V § 13(10)).

The Investigator / principle Investigator stores all administrative documents (correspondence with the Ethics Committee, the Supervising Authority, trial centre, study site), patient identification log, the signed patient consent forms, copies of the data documentation form and common study documentation (protocol, amendments) for the duration mentioned above. Original data of study patients (medical records) will be stored for at least 10 years.

A list allowing patient identification will be kept for 15 years (directive 2001/83/EG).

15.4 Financing

The trial is funded by **Bionorica SE**, Kerschensteinerstrasse 11-15, 92318 Neumarkt. Bionorica provides the IMP and financial resources as funding.

16 References

- Augedal, A. W., Hansen, K. S., Kronhaug, C. R., Harvey, A. G., & Pallesen, S. (2013). Randomized controlled trials of psychological and pharmacological treatments for nightmares: a meta-analysis. *Sleep Med Rev*, 17(2), 143-152. doi:10.1016/j.smrv.2012.06.001
- Betthausen, K., Pilz, J., & Vollmer, L. E. (2015). Use and effects of cannabinoids in military veterans with posttraumatic stress disorder. *Am J Health Syst Pharm*, 72(15), 1279-1284. doi:10.2146/ajhp140523
- Bonn-Miller, M. O., Vujanovic, A. A., Feldner, M. T., Bernstein, A., & Zvolensky, M. J. (2007). Posttraumatic stress symptom severity predicts marijuana use coping motives among traumatic event-exposed marijuana users. *Journal of Traumatic Stress*, 20(4), 577-586. doi:10.1002/jts.20243
- Bremner, J. D., Southwick, S. M., Darnell, A., & Charney, D. S. (1996). Chronic PTSD in Vietnam combat veterans: Course of illness and substance abuse. *American Journal of Psychiatry*, 153(3), 369-375.
- Brownlow, J. A., Harb, G. C., & Ross, R. J. (2015). Treatment of Sleep Disturbances in Post-Traumatic Stress Disorder: A Review of the Literature. *Curr Psychiatry Rep*, 17(6), 41. doi:10.1007/s11920-015-0587-8
- Cameron, C., Watson, D., & Robinson, J. (2014). Use of a Synthetic Cannabinoid in a Correctional Population for Posttraumatic Stress Disorder-Related Insomnia and Nightmares, Chronic Pain, Harm Reduction, and Other Indications A Retrospective Evaluation. *Journal of Clinical Psychopharmacology*, 34(5), 559-564. doi:10.1097/Jcp.0000000000000180
- Cukor, J., Olden, M., Lee, F., & Difede, J. (2010). Evidence-based treatments for PTSD, new directions, and special challenges. *Ann N Y Acad Sci*, 1208, 82-89. doi:10.1111/j.1749-6632.2010.05793.x
- Fraser, G. A. (2009). The Use of a Synthetic Cannabinoid in the Management of Treatment-Resistant Nightmares in Posttraumatic Stress Disorder (PTSD). *Cns Neuroscience & Therapeutics*, 15(1), 84-88. doi:10.1111/j.1755-5949.2008.00071.x
- Hauschke, D., Steinijans, V., & Pigeot, I. (2007). Bioequivalence studies in drug development: meth-ods and applications (Vol. 60). John Wiley & Sons.
- Jetly, R., Heber, A., Fraser, G., & Boisvert, D. (2015). The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. *Psychoneuroendocrinology*, 51, 585-588. doi:10.1016/j.psyneuen.2014.11.002
- Monson, E., Caron, J., McCloskey, K., & Brunet, A. (2017). Longitudinal analysis of quality of life across the trauma spectrum. *Psychol Trauma*, 9(5), 605-612. doi:10.1037/tra0000254
- Pietrzak, R. H., Goldstein, R. B., Southwick, S. M., & Grant, B. F. (2011a). Medical comorbidity of full and partial posttraumatic stress disorder in US adults: results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychosom Med*, 73(8), 697-707. doi:10.1097/PSY.0b013e3182303775
- Pietrzak, R. H., Goldstein, R. B., Southwick, S. M., & Grant, B. F. (2011b). Prevalence and Axis I comorbidity of full and partial posttraumatic stress disorder in the United States: results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *J Anxiety Disord*, 25(3), 456-465. doi:10.1016/j.janxdis.2010.11.010
- Pocock S. Group sequential methods in the design and analysis of clinical trials. *Biometrika*. 1977;64(2):191-9.
- Raskind, M. A., Peskind, E. R., Hoff, D. J., Hart, K. L., Holmes, H. A., Warren, D., . . . McFall, M. E. (2007). A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry*, 61(8), 928-934. doi:10.1016/j.biopsych.2006.06.032

- Roitman, P., Mechoulam, R., Cooper-Kazaz, R., & Shalev, A. (2014). Preliminary, open-label, pilot study of add-on oral Delta9-tetrahydrocannabinol in chronic post-traumatic stress disorder. *Clin Drug Investig*, 34(8), 587-591. doi:10.1007/s40261-014-0212-3
- Sareen, J., Afifi, T. O., McMillan, K. A., & Asmundson, G. J. (2011). Relationship between household income and mental disorders: findings from a population-based longitudinal study. *Arch Gen Psychiatry*, 68(4), 419-427. doi:10.1001/archgenpsychiatry.2011.15
- Shalev, A., Liberzon, I., & Marmar, C. (2017). Post-Traumatic Stress Disorder. *N Engl J Med*, 376(25), 2459-2469. doi:10.1056/NEJMra1612499
- Van Buuren, S. (2012). Flexible imputation of missing data. CRC press.
- Wilkinson, S. T., Radhakrishnan, R., & D'Souza, D. C. (2016). A Systematic Review of the Evidence for Medical Marijuana in Psychiatric Indications. *J Clin Psychiatry*, 77(8), 1050-1064. doi:10.4088/JCP.15r10036
- World Health Organization (2004). Mortality and Burden of Disease Estimates for WHO Member States: Persons, all ages (2004). (xls). Retrieved 2009-11-12.

17 Appendices

17.1 Appendix 1 Responsibilities and participating organizations

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“Treating Nightmares in Posttraumatic Stress Disorder with Dronabinol: A Randomized Controlled Study (THC PTSD-trial)”

Protocol code number: THC-PTSD
EudraCT-Number: 2019-002211-25

Protocol

Version 4.0 / 28.06.2024

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- Confidential -

The information contained in this protocol has to be kept strictly confidential. Therefore the protocol is only provided to Investigators in confidence for review, to study staff, Independent Ethics Committee/Institutional Review Board, regulatory authorities and CROs (or CTO) and for obtaining written informed consent from patients.

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Abbreviations

ADL	Activities of daily living
ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	Analysis of Covariance
BSL-23	Borderline Symptom List 23
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
CAPS-IV B2	Clinician-Administered PTSD Scale for DSM-IV score for Item B2
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CTFG	Clinical Trial Facilitation Group
CTQ	Childhood Trauma Questionnaire
DALY	disability-adjusted life year
DSM-5	Diagnostic and Statistical Manual of Mental Disorders DSM-5
eCRF	electronic Case Report Form
ECG	Electrocardiogram
EWR	Europäischer Wirtschaftsraum
EQ-5D	Health Related Quality of Life
FPI	Last Patent out
GCP	Good Clinical Practice
ICH	International Conference of Harmonisation
IEC	Ethic Committee
IMP	Investigational Medicinal Product
ITT	Intent to treat Population
ITI	International Trauma Interview
ITQ	International Trauma Questionnaire
KKS	Koordinierungszentrum für Klinische Studien
LPO	Last Patient out
MADRS	Montgomery-Åsberg Depression Rating Scale
MWC	Marijuana Withdrawal Checklist
PCL-5	PTSD Checklist for DSM-5
PGIC	Patient Global Impression of Change
PPP	Per protocol population
PSQI-	Pittsburgh Sleep Quality Index
PSQI-A	Pittsburgh Sleep Quality Index-Addendum for PTSD
PTSD	Posttraumatic Stress Disorder
SAE	Serious Adverse Event
SCID-5	Structured Clinical Interview for DSM-5
SDV	Source Data Verification
SOFAS	Social and Occupational Functioning Assessment Scale
SSL	Secure Socket Layer
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
WHO	World Health Organization
WOCBP	women of childbearing potential

1 Synopsis

Study title	Treating Nightmares in Posttraumatic Stress Disorder with Dronabinol: A Randomized Controlled Study (THC-PTSD-trial)
EudraCT Number	2019-002211-25
Study design	Multi-centric, double-blind, randomized, placebo-controlled, parallel group, interventional exploratory phase II trial
Medical Condition	Posttraumatic Stress Disorder
Sponsor	Charité – Universitätsmedizin Berlin Charitéplatz 1, D-10117 Berlin
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Hypothesis	Dronabinol (2.5-15 mg) improves nightmares in patients with PTSD to a greater extent than placebo as measured by the CAPS-IV B2 score (intensity and frequency of nightmares) after 10 weeks of treatment in a parallel group design.
Rationale	No pharmacological agent has been approved to treat nightmares associated with PTSD in Europe. First empirical evidence shows that nightmares, other PTSD related sleep symptoms, hyperarousal, and other PTSD symptoms can be treated with dronabinol. This randomized controlled trial will test the hypothesis that oral dronabinol improves nightmares (primary outcome), other PTSD symptoms and psychopathology (secondary outcomes) to a greater extent than placebo over a ten week intervention phase in a parallel group design.
Primary objective	To examine whether oral dronabinol (2.5 to 15 mg) reduces nightmares to a greater extent than placebo in patients with posttraumatic stress disorder
Primary endpoint	Primary efficacy endpoint: Frequency and intensity of nightmares, measured with the Clinician-Administered PTSD Scale-IV (CAPS-IV) B2 score for the last week, range 0–8, directly after last intervention (10 weeks, Visit 8). A lower score indicates less frequent and/or intense nightmares.

Secondary objectives	Secondary objectives of the study are to examine the efficacy of oral dronabinol in reducing other PTSD-specific symptoms, general sleep parameters and depressive symptoms in patients with posttraumatic stress disorder
Key secondary endpoint(s)	1. Change from baseline of the frequency and intensity of nightmares, measured with the Clinician-Administered PTSD Scale-IV (CAPS-IV) B2 score for the last week, range 0–8, at Visit 3 – Visit 7 2. Change from baseline of the CAPS-5 total score (overall PTSD symptoms, last week) at Visit 6 and Visit 8 3. Change from baseline of the Pittsburgh Sleep Quality Index-Addendum for PTSD (PSQI-A) (PTSD related sleep symptoms) at Visit 6 and Visit 8 4. Change from baseline of the Montgomery-Åsberg Depression Rating Scale (MADRS, depressive symptoms) at Visit 6 and Visit 8 5. Weekly mean of change from baseline of the patients daily total sleep time (in minutes), sleep onset latency at night (in minutes), recuperation of night sleep (5-point Likert scale, 1 = very much; 5 = not at all), and time awake at night (in minutes), number of nightmares last night (0, 1, 3, 4 or more) and intensity of nightmares (5-point Likert scale, 0 = not at all; 5 = extreme) assessed with sleep diaries during Visit 2 – Visit 8 6. Change from baseline of PTSD symptoms assessed with the PTSD Checklist for DSM-5 (PCL-5) at Visit 6 and Visit 8 7. Change from baseline of the Borderline Symptom List 23 (BSL-23) score at Visit 6 and Visit 8 8. Change from baseline of the Health-Related Quality of Life (EQ-5D) score at Visit 6 and Visit 8 9. Overall patients status measured by the Patient Global Impression of Change (PGIC) at Visit 6 and Visit 8 10. Change from baseline of the Social and Occupational Functioning Assessment Scale (SOFAS) at Visit 6 and Visit 8 11. Change from baseline of the Pittsburgh Sleep Quality Index (PSQI) at Visit 6 and Visit 8 12. Change from baseline of symptoms of PTSD and complex PTSD according to ICD-11 assessed with the International Trauma Questionnaire (ITQ) at Visit 6 and Visit 8 13. Change from baseline of THC withdraw symptoms assessed with the Marijuana Withdrawal Checklist (MWC) at Visit 6, Visit 8, and Visit 9 14. Responder analysis: proportion of patients showing improvement in nightmares (change from baseline) defined as decrease of CAPS-IV B2 $\geq 50\%$ assessed at the end of treatment (Visit 8) 15. Remitter analysis: proportion of patients showing full remission of nightmares defined as CAPS-IV B2 = 0, assessed at the end of treatment (Visit 8)

Inclusion criteria	1. Diagnosis of posttraumatic stress disorder (PTSD) according to DSM-5 with a 20 item CAPS-5 total score ≥ 26 2. At least two nightmares a week, an intensity score ≥ 2, with a CAPS-IV B2 (frequency and intensity for the last week) score ≥ 5 3. Men and women between 18 and 65 years of age 4. Written informed consent 5. The patient has the capacity to give consent (He/she is able to understand the nature and anticipated effects/side effects of the proposed medical intervention) 6. The patient is not breastfeeding 7. Women of child-bearing potential must have a negative urine or serum pregnancy test 8. All participants must use highly effective contraception 9. The patient received stable pharmacological medication for at least 4 weeks prior to study entry (any changes in medication dose or frequency of therapy must be answered with no)
Exclusion criteria	1. Lifetime cannabis use disorder 2. Current substance/alcohol use disorder (≤ 3 months); 3. Acute suicidality; 4. Psychotic disorder; 5. Bipolar disorder; 6. Current anorexia nervosa; 7. Current major depressive episodes and a MADRS score > 29; 8. Dementia; 9. Trauma-focused psychotherapy four weeks before the trial 10. Initiation of sleep medication 4 weeks prior screening or initiation of alpha adrenergic agents 4 weeks prior to screening 11. Acute or unstable medical illness. 12. Epilepsy 13. Relevant heart diseases 14. Known HIV- and/or active Hepatitis-B- or Hepatitis-C-infection 15. Current or past malignant illness 16. The patient is unwilling to consent to saving, processing and propagation of pseudonymized medical data for study reasons 17. Patients, who may be dependent on the sponsor, the investigator or the trial sites, have to be excluded from the trial 18. The patient is legally detained in an official institution 19. The patient does have a known allergy or contraindication against Dronabinol 20. The patient does have clinically significant abnormalities in 12-lead ECG 21. The patient does have clinically significant laboratory abnormalities 22. The patient did participate in other interventional trials during the 3 months before and at the time of this trial

Visit and documentation schedule	Eligible patients will be screened up to 10 days prior to randomization. After baseline assessment, patients will be randomized and receive either 2.5 mg oral dronabinol (oily solution) per day before bedtime or undistinguishable placebo (cannabis aroma). Oral dronabinol will be titrated with the goal of complete elimination of trauma nightmares to up to 15 mg/day in first four weeks. Until week 4 one visit per week will take place. Dose increase in steps of 2.5 mg every 3-4th day according to effect (complete elimination of nightmares) and side effect over the first 4 weeks (titration period). If side effects occur (ADRs), dose will be decreased to the lower prior dose (in steps of 2.5 mg) until next trial visit. The intervention phase will be 10 weeks, i.e., 4 weeks titration phase and 6 weeks maintenance phase, when dronabinol dose (or placebo) will be kept stable. Beside assessment of primary and secondary endpoints, adverse events will be monitored. There will be a post-trial follow-up visit at week 12. See also Table 1 ("Outline of trial visits") at the end of the synopsis.
Safety Assessment	Assessment of blood pressure and heart rate at every visit. Assessment of laboratory parameters - safety laboratory - at screening and end of trial (visit 8 in week 10); physical examination at screening and end of trial; ECG at screening, end of trial and in case of significant abnormal ECG findings at visit 8 (week 10) a further ECG at follow-up (visit 9, week 12). Urinary pregnancy test (women only) at screening, baseline, visit 3 (week 2), visit 5 (week 4), visit 6 (week 6), visit 7 (week 8), and visit 8 (week 10). Standard procedures for reporting of adverse events will be used. Adverse events will be assessed at every visit starting at visit 1.
Safety and Discontinuation Criteria	<u>The following events must cause premature termination of the individual subject:</u> • Unblinding in case of a medical emergency • The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study • Pregnancy • Consent withdrawn by patient • CTCAE catalogue (Common Terminology Criteria for Adverse Events, Version 5.0) score > 3 • Complete missing of two consecutive visits <u>Premature termination of the clinical trial:</u> • Unjustifiable risk and negative risk-benefit analysis (decision taken by the sponsor) • New scientific evidence provided during the study that could affect the patient's safety (benefit-risk analysis no longer positive) • Decision of the sponsor, the coordinating investigator, by request of an authority or because of withdrawal of a positive vote by a responsible ethics committee.

	<u>Sponsor may terminate the trial at an individual study centre, if:</u> • the investigator no longer considers the risk-benefit ratio to be reasonable, • the centre's recruitment rate is too low, • the drop-out rate is unusually high, or • the investigator does not comply with the protocol or other regulations with the necessary care.		
Study medication	BX-1 is an oily solution containing 25 mg/ml dronabinol.		
Placebo/ Reference Medication	Oily Placebo Solution (cannabis aroma)		
Pharmacological-toxicological evaluation	Dronabinol is in medical use for several years in Germany. A number of clinical trials proved tolerability, safety and low incidence of side effects.		
Trial Duration	Start of the trial	01.09.2020	
	Start of recruitment	01.10.2020	
	Planned end of recruitment	01.11.2024	
	End of trial	30.01.2025	
	Duration of the trial	52 months	
	Duration of individual participation	3 months	
	If any, duration of sub study	3 months	
Duration of Intervention per Patient	10 weeks (4 weeks titration, 6 weeks observation)		
Follow- up per Patient	2 weeks		
Total number of patients	to be assessed for eligibility (n = 450) To be enrolled into trial (n = 176) To be analyzed (n = 158 in full analysis set, excluding patients that are randomized but never received study medication, n = 18, ≈10%)		
Statistical analysis	<u>Primary analysis:</u> Confirmatory analysis will be conducted based on the full analysis set consisting of all randomized patients which received the study medication at least once. The aim is to show that scores at 10 weeks are lower in the intervention group (I) than the control group (C). An ANCOVA model including the baseline score, will be applied (Hauschke et al. 2007). The global two-sided significance level will be 0.05. Missing values will be replaced using multiple imputation (van Buuren 2012). <u>Secondary analyses:</u> Descriptive methods will be used to analyze secondary outcomes, including appropriate summary measures of the empirical distribution as well as 95% confidence intervals and descriptive two-sided p-values. Safety analysis will include calculation		

	of frequencies and rates of adverse and serious adverse events. Additionally, sensitivity will analyzed in different populations (per-protocol population, patients with complete cases). Further statistical methods will be used to assess data quality. All analyses will be done using validated statistical software.
Participating Organization	• please refer to appendix 1
Funding	Bionorica SE, Kerschensteinerstrasse 11-15, 92318 Neumarkt (Bionorica provides the IMP and financial resources as funding)

Table 1: Outline of trial visits

Assessments	SC	BL Visit 1 W 0	Visit 2 W 1	Visit 3 W 2	Visit 4 W 3	Visit 5 W 4	Visit 6 W 6	Visit 7 W 8	Visit 8 W 10	FU Visit 9 W 12
Screening and consent										
Inclusion/exclusion criteria	X									
Informed consent	X									
Physical examination ¹	X								X	
Prior and concomitant medication and non-drug therapy	X	X	X	X	X	X	X	X	X	X
Medical history	X									
IMP dispersion		X	X	X	X	X	X	X		
IMP return			X	X	X	X	X	X	X	
Safety										
Blood test ²	X								X	
Cannabis test	X									
Pregnancy test	X	X		X		X	X	X	X	
ECG	X								X	(X) ³
Blood pressure, pulse	X	X	X	X	X	X	X	X	X	X
Weight	X	X					X		X	X
Adverse event recording		X	X	X	X	X	X	X	X	X
Effectiveness										
primary										
CAPS-IV B2									X	
secondary										
CAPS-IV B2	X	X	X	X	X	X	X	X		
CAPS-5	X ^a	X ^b					X ^b		X ^b	
PSQI-A		X					X		X	
MADRS	X	X				X			X	
Sleep diary		X	X	X	X	X	X	X	X	
PCL-5		X					X		X	
BSL-23		X					X		X	
EQ-5D		X					X		X	
PGIC							X		X	
SOFAS		X					X		X	
PSQI		X					X		X	
ITQ		X					X		X	
MWC		X					X		X	X
others										
Demographics	X									
CTQ	X									
MINI-5	X									
ITI	X									

Note: SC = screening, W. = week +/- 3 days, BL = baseline and randomization, FU = post-trial follow-up, CAPS-IV B2 = B2 score of the Clinician-Administered PTSD Scale for DSM-IV (frequency and intensity of nightmares), CAPS-5 = Clinician-Administered PTSD Scale for DSM-5 (a = last month version, b = last week version), PSQI-A = Pittsburgh Sleep Quality Index-Addendum for PTSD, MADRS = Montgomery-Åsberg Depression Rating Scale, PCL-5 = PTSD Checklist for DSM-5, BSL-23 = Borderline Symptom List 23, EQ-5D = Health-Related Quality of Life, PGIC = Patient Global Impression of Change, SOFAS = Social and Occupational Functioning Assessment Scale, PSQI = Pittsburgh Sleep Quality Index, ITQ = international trauma questionnaire, MWC = Marijuana Withdrawal Checklist, CTQ = Childhood trauma questionnaire, MINI-5 = The Mini International Neuropsychiatric Interview for DSM-5, ITI = International Trauma Interview. 1 Physical examination includes height and weight of the patient and the skin, abdomen, respiratory system, head and extremities will be examined, 2: blood test s include haematology (erythrocytes, haemoglobin, haematocrit, platelets, leukocytes (including neutrophils, eosinophils, basophils, lymphocytes, monocytes) and serum chemistry (sodium, potassium, chloride, calcium, creatinine, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, aspartate aminotransferase, bilirubin, lipase, thyroid stimulating hormone), 3. In case of significant abnormal ECG findings at the visit 8 (week 10), a further ECG will be recorded at the follow-up visit.

2 Introduction

2.1 Introduction and background

PTSD is associated with serious disability, medical illness, and a severely impaired quality of life (Monson, Caron, McCloskey, & Brunet, 2017; Shalev, Liberzon, & Marmar, 2017). The WHO has reported an overall disability-adjusted life year (DALY) rate per 100,000 inhabitants of Germany of 54 for PTSD; 80 in women, 28 in men (WHO 2004). PTSD places a high socioeconomic burden on patients with marked reductions in household income (Sareen, Afifi, McMillan, & Asmundson, 2011). More than 50% of PTSD patients suffer from comorbid mood, anxiety, and substance-use disorders (Pietrzak, Goldstein, Southwick, & Grant, 2011b). Various medical comorbidities are very common in PTSD patients with cardiovascular diseases among the most prevalent (Pietrzak, Goldstein, Southwick, & Grant, 2011a). Distressing nightmares are an independent risk factor for comorbidity and severity in PTSD patients. Nightmares also contribute to alcohol and substance abuse, suicidal ideation, and even completed suicide (Raskind et al., 2007). Further, distress related to insomnia is one of the most common residual symptoms after specific psychotherapy for PTSD (Larsen *et al.*, 2018). Only SSRIs (in Germany paroxetine) are currently approved as pharmacological treatment for PTSD with low response and remission rates (Cukor, Olden, Lee, & Difede, 2010). Further, there is no evidence that SSRIs can treat nightmares in PTSD (Brownlow, Harb, & Ross, 2015). Accumulating clinical data indicate that cannabinoid agonists (e.g., dronabinol) can improve nightmare symptomatology and overall PTSD symptoms in patients with PTSD (Wilkinson, Radhakrishnan, & D'Souza, 2016). First, many patients with PTSD cite motives of self-medication for continued use of cannabis due to its ability to promote relaxation and sleep, and reduce anxiety symptoms and hyperarousal (Betthausen, Pilz, & Vollmer, 2015; Bonn-Miller, Vujanovic, Feldner, Bernstein, & Zvolensky, 2007; Bremner, Southwick, Darnell, & Charney, 1996). Second, an uncontrolled open-label study of nabilone (0.5-6mg/day) at bedtime reduced nightmares in patients with PTSD, 34 out of 47 patients exhibiting either total cessation or significant reduction in nightmares (Fraser, 2009). Third, a retrospective chart review showed that nabilone (mean dose 4 mg/day) treatment was associated with a significant improvement in sleep and a reduction in nightmares (severity and frequency) as well as a general reduction in PTSD symptom severity (Cameron, Watson, & Robinson, 2014). Fourth, an open label, uncontrolled pilot study examined the impact of adding 5 mg of $\Delta(9)$ -THC twice a day as add-on treatment onto existing medications in PTSD patients and found that THC consumption specifically improved sleep quality, reduced nightmares, and reduced symptoms of hyperarousal (Roitman, Mechoulam, Cooper-Kazaz, & Shalev, 2014). Fifth, a small, randomized, double-blind, placebo controlled crossover study assessed nabilone (3 mg daily) and found significant reduction in severity and frequency of nightmares, and increased general well-being (Jetly, Heber, Fraser, & Boisvert, 2015). Further, no negative results of cannabinoid-agonists in PTSD treatments are published to date.

Currently are three ongoing randomized clinical trials of THC treatment in patients with PTSD registered at clinicaltrials.gov (NCT02759185, NCT02517424, NCT03251326). None of these studies is in direct concurrence with the current trial proposal.

2.2 Rationale

No pharmacological agent has been approved to treat nightmares associated with PTSD in Europe. First empirical evidence shows that nightmares, other PTSD related sleep symptoms, hyperarousal, and other PTSD symptoms can be treated with dronabinol (see background

information). This randomized controlled exploratory phase II trial will test the hypothesis that oral dronabinol improves nightmares (primary outcome) and other PTSD symptoms (secondary outcomes) to a greater extent than placebo over a ten week intervention phase in a parallel group design.

3 Study objectives

3.1 Primary endpoint

Primary objective of the study is to examine the efficacy of oral dronabinol over placebo in reducing nightmares in patients with posttraumatic stress disorder.

Primary efficacy endpoint: Frequency and intensity of nightmares, measured with the Clinician-Administered PTSD Scale (CAPS-IV) B2 score for the last week, range 0–8 (Blake et al., 1995) directly after last intervention (10 weeks).

3.2 Secondary endpoints

Secondary objectives of the study are to examine the efficacy of oral dronabinol in reducing disorder-specific symptoms in patients with posttraumatic stress disorder, and to examine the efficacy of oral dronabinol in reducing sleep disturbance in patients with posttraumatic stress disorder.

Secondary endpoints:

1. Change from baseline of the frequency and intensity of nightmares, measured with the Clinician-Administered PTSD Scale-IV (CAPS-IV) B2 score for the last week, range 0–8, at Visit 3 – Visit 7
2. Change from baseline of the CAPS-5 total score (overall PTSD symptoms, last week) at Visit 6 and Visit 8
3. Change from baseline of the Pittsburgh Sleep Quality Index-Addendum for PTSD (PSQI-A) (PTSD related sleep symptoms) at Visit 6 and Visit 8
4. Change from baseline of the Montgomery-Åsberg Depression Rating Scale (MADRS, depressive symptoms) at Visit 6 and Visit 8
5. Weekly change from baseline of the patients daily total sleep time (in minutes), sleep onset latency at night (in minutes), recuperation of night sleep (5-point Likert scale, 1 = very much; 5 = not at all), and time awake at night (in minutes), number of nightmares last night (0, 1, 3, 4 or more) and intensity of nightmares (5-point Likert scale, 0 = not at all; 5 = extreme) assessed with sleep diaries during Visit 2 – Visit 8
6. Change from baseline of PTSD symptoms assessed with the PTSD Checklist for DSM-5 (PCL-5) at Visit 6 and Visit 8
7. Change from baseline of the Borderline Symptom List 23 (BSL-23) score at Visit 6 and Visit 8
8. Change from baseline of the Health-Related Quality of Life (EQ-5D) score at Visit 6 and Visit 8
9. Overall patients status measured by the Patient Global Impression of Change (PGIC) at Visit 6 and Visit 8
10. Change from baseline of the Social and Occupational Functioning Assessment Scale (SOFAS) at Visit 6 and Visit 8
11. Change from baseline of the Pittsburgh Sleep Quality Index (PSQI) at Visit 6 and Visit 8
12. Change from baseline of symptoms of PTSD and complex PTSD according to ICD-11 assessed with the International Trauma Questionnaire (ITQ) at Visit 6 and Visit 8

13. Change from baseline of THC withdraw symptoms assessed with the Marijuana Withdrawal Checklist (MWC) at Visit 6, Visit 8, and Visit 9
14. Responder analysis: proportion of patients showing improvement in nightmares (change from baseline) defined as decrease of CAPS-IV B2 $\geq 50\%$ assessed at the end of treatment (Visit 8)
15. Remitter analysis: proportion of patients showing full remission of nightmares defined as CAPS-IV B2 = 0, assessed at the end of treatment (Visit 8)

Descriptive methods (see above) will be used to analyze secondary outcomes, including appropriate summary measures of the empirical distribution as well as 95% confidence intervals and descriptive two-sided p-values. Safety analysis will include calculation of frequencies and rates of adverse and serious adverse events. Additionally, sensitivity will be analyzed in different populations (per-protocol population, patients with complete cases). Further statistical methods will be used to assess data quality. All analyses will be done using validated statistical software.

3.3 Study design

The study is a multi-centric, double-blind, randomized, placebo-controlled, parallel group interventional exploratory phase II trial.

3.4 Timetable

Start of the trial	01.09.2020
Start of recruitment	01.10.2020
Planned end of recruitment	01.11.2024
End of trial	30.01.2025
Duration of the trial	52 months
Duration of individual participation	3 months
If any, duration of sub study	3 months

4 Study population

176 patients will be enrolled (sample size estimation, see chapter 14.1). There will be no specific gender distribution as no gender specific differences concerning efficacy and safety of the investigational product are expected (see GCP-V § 7 (2) No. 12).

4.1 Inclusion criteria

Obligatory inclusion criteria:

1. Diagnosis of posttraumatic stress disorder (PTSD) according to DSM-5 with a 20 item CAPS-5 total score ≥ 26
2. At least two nightmares a week, an intensity score ≥ 2 , with a CAPS-IV B2 (frequency and intensity for the last week) score ≥ 5
3. Men and women between 18 and 65 years of age
4. Written informed consent
5. The patient has the capacity to give consent (He/she is able to understand the nature and anticipated effects/side effects of the proposed medical intervention)
6. The patient is not breastfeeding
7. Women of child-bearing potential must have a negative urine or serum pregnancy test
8. All participants must use highly effective contraception
9. The patient received stable pharmacological medication for at least 4 weeks prior to study entry (any changes in medication dose or frequency of therapy must be answered with no)

4.2 Exclusion criteria

The following exclusion criteria are obligatory.

1. Lifetime cannabis use disorder
2. Current substance/alcohol use disorder (≤ 3 months);
3. Acute suicidality;
4. Psychotic disorder;
5. Bipolar disorder;
6. Current anorexia nervosa;
7. Current major depressive episodes and a MADRS score > 29 ;
8. Dementia;
9. Trauma-focused psychotherapy four weeks before the trial
10. Initiation of sleep medication 4 weeks prior screening or initiation of alpha adrenergic agents 4 weeks prior to screening
11. Acute or unstable medical illness
12. Epilepsy
13. Relevant heart diseases
14. Known HIV- and/or active Hepatitis-B- or Hepatitis-C-infection
15. current or past malignant illness

16. The patient is unwilling to consent to saving, processing and propagation of pseudonymized medical data for study reasons
17. Patients, who may be dependent on the sponsor, the investigator or the trial sites, have to be excluded from the trial
18. The patient is legally detained in an official institution
19. The patient does have a known allergy or contraindication against Dronabinol
20. The patient does have clinically significant abnormalities in 12-lead ECG
21. The patient does have clinically significant laboratory abnormalities
22. The patient did participate in other interventional trials during the 3 months before and at the time of this trial

4.3 Contraception and WOCBP

Study participants with reproductive capacity (both: male and female) have to use highly effective methods of contraception according to the guideline of the Clinical Trial Facilitation Group (CTFG) (Sep 2014):

- Highly effective contraception for both male and female subjects throughout the study and for at least 30 days after the last IMP treatment
 - A female subject is eligible to enter the study if she is:
 - Not pregnant or nursing
 - Of non-childbearing potential (i.e., post-menopausal defined as having been amenorrheic for at least 1 year prior to screening, or has had bilateral oophorectomy or complete hysterectomy)
- Women of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test prior to drug administration and be using a highly effective means of contraception during study participation and until 1 month after the last dose of study drug. Highly effective contraception methods (that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:
- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
 - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal or transdermal.
 - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable or implantable.
 - Intrauterine device (IUD).
 - Intrauterine hormone-releasing system (IUS).
 - Bilateral tubal occlusion.
 - Vasectomised partner (provided that the partner is the sole sexual partner of the female trial participant and that the vasectomized partner has received medical assessment of the surgical success).
 - .

Definition of Women of childbearing potential (WOCBP):

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.

According to the recommendations of the CTFG, the use of condoms is regarded as a contraceptive method in male study participants.

5 Plan for medical treatment

5.1 Description of study medication / investigational medicinal product

BX-1 is an oily solution containing 25 mg/ml dronabinol. Dronabinol ((-)-trans- Δ^9 -Tetrahydrocannabinol, Δ^9 -THC) is the major psychoactive constituent of Cannabis sativa L.. Dronabinol is a clear to amber resin. It is highly lipid soluble. Dronabinol is thermolabile, photolabile and susceptible to oxidation.

Adverse drug reactions and restrictions, contra-indications, drug interactions

Expected adverse reactions are: anxiety/restlessness, depression, euphoria, sleep disorder, thinking abnormal, dizziness, headache, disturbance in attention, memory impairment, speech difficulties, tremor, vertigo, tachycardia, hypertension, hypotonia, dry nose, dyspnea, tiredness, asthenia/muscular weakness, feeling abnormal, nausea, constipation, diarrhoea, abdominal pain upper, dry mouth, flatulence, vomiting, hypoaesthesia oral, increased appetite, loss of appetite, sweating, local hypersensitivity reactions, pressure behind the eyes, dry eye, abnormal sensation in eye. In case of occurrence of intolerable side effects dosages should be adjusted.

In case of overdose of BX-1 the patient must be closely monitored. Overdose treatment should be based on symptomatic treatment of adverse reactions. A potentially serious overdose of BX-1, if recent, should be treated with gut decontamination. In unconscious patients with a secure airway, activated carbon should be administered via a nasogastric tube (30 to 100 g for adults). A saline laxative or sorbitol may be added to the first dose of activated carbon. Patients who show depressive, hallucinatory or psychotic reactions must be placed in a quiet room and calmed by persuasion. Benzodiazepines (1 to 2.5 mg lorazepam p.o.) can be used to treat extreme agitation. Hypotension usually responds to the Trendelenburg position and i.v. fluid. Vasopressors are rarely necessary. Tachycardia can be treated with beta blockers. Due to the initial half-life time of dronabinol and its active metabolite, it is expected that the effect of BX-1 is significantly reduced after 8 hrs. BX-1 should be administered with caution to patients with mania, depression or schizophrenia, heart diseases, history of seizure-related diseases and history of substance abuse. If seizures are occurring, treatment with BX-1 should be immediately discontinued. There might be additional or synergistic effects in patients treated concomitantly with sedative, hypnotic or other psychoactive medicinal products on central nervous system adverse reactions.

The probability of occurrence of withdrawal symptoms after discontinuation of BX-1 in the allowed dosage as well as the development of tolerance and dependence is quite low in the allowed dosages. Furthermore, it is not expected that BX-1 is abused after chronic intake if the patient has no history of drug abuse. Nevertheless, if there is suspicion of such symptoms the patient must be closely monitored and if deemed necessary the treatment should be discontinued. Non-clinical studies showed that dronabinol has no mutagenic, genotoxic, carcinogen, and teratogenic effect. Nevertheless, in animals it negatively affected fertility and caused embryo- and/or fetal toxicity. Therefore, BX-1 should not be administered to pregnant or breastfeeding women.

Patients should be warned not to drive or engage in activities requiring unimpaired judgement and coordination until it is established that they are able to tolerate the drug and to perform such tasks safely. Alcohol may interact with dronabinol, particularly in affecting coordination, concentration and ability to respond quickly.

Please refer also to Table 9: Reported adverse reactions in Bionorica sponsored clinical trials (IB of BX-1, Ed.3.0, 27.Sep 20189), Section 7 “Risk-benefit-assessment” of this Protocol.

Rational for selection of doses

The detailed dosage schedule is described in section 5.1.3.

Due to the experience in previous trials with cannabis based medicine in healthy individuals and clinical groups, including patients with PTSD, the daily dose was determined between 2.5 mg per day to 15 mg per day (single administration) with an increase in dose by 2.5 mg every third/fourth day (see Investigators Brochure, Edition Number Final 3.0, Date of release: 27SEP2019, page 30ff, 6. Effects in Humans). The Investigators Brochure recommends 30 mg dronabinol per day as maximal dose. As single dosing will be applied in this study the maximal daily dose of dronabinol has been restricted to 15 mg which also corresponds to our clinical experience. Effects of THC on nightmares in PTSD have been found in an open label pilot study with 10 mg per day of THC (5 mg twice a day), starting with 5 mg per day (2.5 mg twice a day) (Roitman et al., 2014). However, pharmacokinetic parameters of dronabinol show high intra-individual variability. To determine the optimal individual dose with respect to efficacy (decrease of intensity and frequency of nightmares) and side effects, up-titration in steps of 2.5 mg dronabinol per day will be performed with an increase every third/fourth day. Alternating increase every third and every fourth day has been chosen to take into account that the clinical visits will be take place every seventh day (once a week) in the up-titration period (first four weeks of treatment, Visit 1 to Visit 5). Comparable titration schemas have been used in previous and ongoing trials with dronabinol in other indications (e.g., NCT03756974) and correspond to our clinical experience.

5.1.3

Treatment schedule

The trial comprises 2 phases: screening period of up to 10 days (Visit 0 to Visit 1) and intervention period of 10 weeks, i.e., titration period of 4 weeks (Visit 1 to Visit 5) and maintenance period of 6 weeks (Visit 5 to Visit 8). This is followed by a safety follow-up period of 2 weeks (Visit 8 to Visit 9).

Trial design

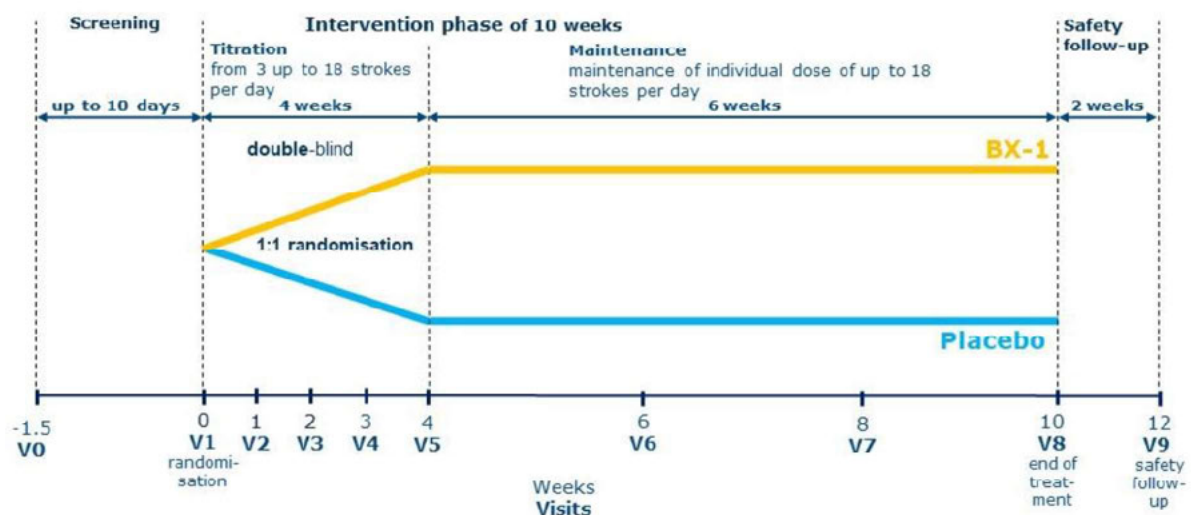


Figure 1: treatment schedule

Screening period

Eligible patients will be screened up to 10 days prior to randomization. No treatment during the screening period is administered.

Titration period

At baseline (Visit 1), patients will be randomised in 1:1 ratio to one of the 2 treatment groups (BX-1 or placebo). The titration period lasts 4 weeks and is performed double-blinded, neither the patient nor the investigator/sponsor knows the identity of the IMP.

All patients start with 3 strokes per day (corresponding to 2.5 mg THC in the active treatment group) and keep the dosage constant for 4 days. On the following day (day 5) an increase with additional 3 strokes (corresponding to 5 mg THC in the active treatment group) should be done. This should be repeated on day 8, day 12, day 15 and day 19 until the maximum dosage of 18 strokes per day (corresponding to 15 mg THC in the active treatment group) is reached. Day of up-titration differs between 3 and 4 days due to the weekly visits during up-titration. See also Figure 2 for a titration schedule.

day of titration period	1	2	3	4	5	6	7	8	9	10	11	12	13	14
No. of strokes/night	3	3	3	3	6	6	6	9	9	9	9	12	12	12
IMP per day [mg THC]	2.5	2.5	2.5	2.5	5	5	5	7.5	7.5	7.5	7.5	10	10	10

day of titration period	15	16	17	18	19	20	21	22	23	24	25	26	27	28
No. of strokes/night	15	15	15	15	18	18	18	18	18	18	18	18	18	18
IMP per day [mg THC]	12.5	12.5	12.5	12.5	15	15	15	15	15	15	15	15	15	15

Figure 2: Titration schedule

However, 18 strokes as the maximal number of strokes per day is **not the treatment goal** of this trial. Patients should not be instructed to reach the maximum dosage, but **the optimal dosage**. The optimal dose is reached if nightmares are completely eliminated. It should therefore be noted, that the instructions above are only a suggested titration scheme. Only the starting dose of 3 strokes at night is fixed. Uptitration should only be based on tolerability and stopped if intolerable side effects appear. In case that nightmares reappear during titration phase, uptitration has to be continued.

In case of intolerable side effect, the increase of doses can be interrupted, delayed or the dose may be decreased in steps of 3 strokes per day until side effects are on an acceptable level. Further increases in steps of 3 strokes per day are allowed if study medication is well tolerated again and if the desired effect is not reached. These cycles might be repeated within the titration period until the optimal dose is obtained. If the optimal dosage is reached it should be continued until the end of the titration period.

It should be noted, however, that the appearance of an adverse event does not necessarily qualify for a down-titration as not all adverse events are an intolerable side effect at the same time. It is in the responsibility of the investigator to define an intolerable side effect together with the patient. A close interaction between investigator and patient has to be established in order to define the individual optimal daily dosage.

Maintenance and treatment period

The individually established daily dosage, i.e. the daily dosage established at day 28, should be maintained throughout the 6 weeks double-blinded maintenance and treatment period.

Safety follow-up period

No treatment during the 2 week lasting safety follow-up period is administered.

Instructions for application:

The solution is taken as follows: IMP has to be placed on a spoon and taken without any additional fluid. To place the oily drops of IMP on the spoon the bottle has to be placed head first and the pump-fed needs to be pressed strongly. The IMP is for oral application only, NOT nasal application! Before first use of the bottle, the pump-fed needs to be pressed several times until the first drop flows. The first drop needs to be discarded. The patients will receive an intake instruction and the correct use will be demonstrated with help of a demo-kit.

Storage requirements and administration (distribution and return of study drug)

5.1.4
IMP has to be stored between 15 and 25°C in the folding box separately from normal practice stocks of marketed drugs or any other IMPs, in a safe (250 kg of weight) with restricted access. The applicable regulatory requirements for controlled drugs have to be considered.

The temperature has to be controlled using calibrated thermometers for this specific trial or by another temperature control system approved by the sponsor in advance. The minimum and maximum temperature of the respective storage condition must be recorded at site on a daily basis (working days). Site staff has to reset daily the minimum temperature as well as the maximum temperature. Temperature of IMP storage must be documented at least until last patient of the site has finished Visit 8.

IMP shipments will be performed under controlled conditions (between 15 and 25°C) by using an electronic temperature data logger. The whole IMP return process will be managed by the pharmacy (Myonex GmbH) until receipt and reconciliation of IMP at the depot.

5.1.5

Treatment compliance

Compliance will be checked for each patient at Visits 2-8 by weighing the bottles when returned by the patient with a calibrated balance. The weight of each bottle is to be documented as source data in the eCRFs. Based on a mean weight for full bottles the system calculates the medication intake. In order to have the correct calculation it must be marked if the cap is on the bottle or not.

The compliance of the patient will be calculated for each visit and for the complete trial. Patients are non-compliant for the complete trial if less than 80% or more than 120% of the individually established dosage (Visit 5) was taken.

If IMP was lost or broken an intake has to be assumed. Therefore, the patient should be asked if the IMP was full, partially used or empty when broken or lost. If the IMP was full it is assumed that there was no intake, if the IMP was empty it is assumed that complete IMP was taken. If the IMP was partially used it is assumed that half was taken (125 mg dronabinol).

5.2 Placebo / reference medication

There is no discernible difference between BX-1 and the corresponding placebo with regard to colour, taste, and appearance, thus ensuring the trials double-blind character. However, batch-specific variations of odour and colour may occur. In addition, all medications for the double-blind period will be labelled with a common batch number.

Trial treatments are double-blinded. The medication list and the randomisation list are stored at the pharmacy (Myonex GmbH) and the allocation to treatment groups will be managed by the pharmacy (Myonex GmbH) and will not be known to the investigator or any other person involved in the conduct of the trial until completion of the trial, except in case of an emergency (see 5.5).

5.3 Concomitant medication / concomitant therapy

In general, concomitant medications and non-drug therapies should be kept to a minimum during the trial and if any is necessary a stable dose should be taken. If the administration of any concomitant treatment becomes necessary, it must be reported in the patient's medical file and the eCRF.

All previous medications taken within 4 weeks or other (non-trauma focused) therapies applied within two-weeks before the start of the trial (screening) must also be documented in the medical file and eCRF. All medications or other therapies being taken by the patient on entry to the trial or at any time during the trial in addition to the IMP are regarded as concomitant treatments and must be documented in the patient's medical file and the eCRF. Concomitant therapy with any medication not listed under "not permitted concomitant pharmacotherapy" is allowed. Trauma-focused psychotherapy is not allowed 4 weeks prior to the trial (screening) and during the entire trial.

Treatments specified here are only allowed if stable in the defined timeframe prior to the trial and unaltered during the trial.

Pharmacotherapy

All psychotropic medication needs to be stable at least 4 weeks prior to the start of the study (screening) and has to remain stable until visit 8 (end of study) All other non-psychiatric medication has to be stable at least 4 weeks prior to screening and during the entire trial with some exceptions. Medications for minor transient non-psychiatric medical conditions (e.g., common cold and menstrual cramps) such as NSAIDs are allowed. Pharmacotherapy with alpha-2-agonists, alpha-1-antagonists will not be allowed (see 'not permitted concomitant pharmacotherapy'). Trauma-focused psychotherapy is not allowed 4 weeks prior to screening and during the trial. Non-trauma-focused psychotherapy is allowed during the trial in stable doses. All clinical exacerbation requiring prescription of other psychotropic drugs will be considered a serious adverse event (SAE).

Not permitted concomitant pharmacotherapy

The following concomitant therapy that interferes with the treatment evaluation of the Investigational Medicinal Product (IMP) is not permitted:

(1) Cannabis-based medicine

Dronabinol or other cannabis-based medicine is not permitted during the trial or within 3 months prior to screening. The intake of such medication has to be clarified with the patient in an interview. In addition, drug abuse screening test is performed. The investigator may not apply such medication during the course of the trial and has to inform the patient that it is not allowed during the trial.

(2) Cannabis herb

Consumption of cannabis herb/marijuana is not permitted during the trial or within 3 months prior to screening. The consumption has to be clarified with the patient in an interview. In addition, drug screening test is performed at screening. The investigator should inform the patient that the consumption is not allowed during the trial.

(3) Sleep medication

Sleep medication that has been initiated 4 or more weeks before screening can be continued at stable dose during the trial.

Initiation of sleep medication 4 weeks prior screening and during the trial is not allowed. I.e., initiation of all benzodiazepines, non-benzodiazepines and other sleep medication are not allowed 4 weeks prior to screening and during the trial.

As examples the following active ingredients (not trade names) are considered as non-benzodiazepines and other sleep medication. Please note that this list is not extensive:

- All benzodiazepines
- Non-benzodiazepines: zaleplon, zolpidem, zopiclon,
- Other sleep medication: Chloralhydrate, Melatonin, Antihistaminergic agents (diphenhydramine, doxylamine, promethazine), mirtazapine, trazodone, trimipramine, doxepin, pipamperon, melperon)

(4) Alpha adrenergic agents (where some evidence of effect on nightmares in PTSD patients has been shown)

Alpha adrenergic agents that has been initiated 4 or more weeks before screening can be continued at stable dose during the trial.

Initiation of alpha adrenergic agents 4 weeks prior screening and during the trial is not allowed.

As examples the following active ingredients (not trade names) are considered as alpha or beta adrenergic agents. Please note that this list is not extensive:

- Doxazosin, prazosin, terazosin, clonidine

Psychotherapy

Non-trauma-focused psychotherapy is allowed if initiated 2 weeks prior to screening and at stable dose during the trial. Psychotherapy frequency has to be documented in the medical file and eCRF.

Trauma-focused psychotherapy is not allowed 4 weeks prior to the trial (screening) and during the entire trial.

5.4 Blinding procedures and emergency envelopes

Treatment is blinded by use of a matching placebo. The Sponsor, study personnel, and subjects will be blinded to treatment until the database is locked. Emergency envelopes will be provided by the pharmacy and will be stored in the trial sites. These emergency envelopes could then be used by investigators in case of emergencies.

5.5 Procedures in case of emergency and unblinding

In the case of an emergency, access to the study treatment code for an individual subject will be possible at the trial sites. Emergency envelopes will be stored at the trial sites.

Every trial patient will receive a patient ID card where the address and telephone number of the responsible investigator in case of emergency and the complete address of the trial site will be indicated. The patient ID card contains information that the patient is participating in a clinical trial involving exposure to BX-1 with dronabinol as the active ingredient or corresponding placebo.

A patient's investigational product assignment can be unblinded by a study center when knowledge of the investigational product assignment is essential for the care of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. The Sponsor may unblind a subject's investigational product assignment for safety reporting as required by regulatory authorities.

Whenever the treatment assignment of a subject is unblinded, the reason, the date and time of the unblinding must be included in source documentation. The name of the individual who broke the blind must be included in the site's source documentation as well.

The decision about necessity of unblinding lies in the responsibility of the investigator or the authorised person. However, the investigator should promptly document and explain to the sponsor any premature unblinding.

6 Study procedures

6.1 Recruitment / screening procedures

Patient's will be recruited via the in- and outpatients center at the recruiting centers. Flyer, advertising the study, will be distributed at other treatment centers and private practice for psychiatry and psychotherapy.

A recruitment period of 21 months is planned

Eligible patients will be screened up to 10 days prior to randomization.

The following will be collected at screening:

- Signed informed consent form
- Review of study eligibility (inclusion and exclusion criteria)
- Physical examination
- Blood pressure, pulse, weight
- Prior and concomitant medication and non-drug therapy
- Medical history
- Blood test
- Urinary or serum cannabis test
- Pregnancy test
- ECG
- Blood pressure, pulse
- CAPS-IV B2score
- CAPS-5
- MADRS
- Demographics
- CTQ
- MINI-5
- ITI

6.2 Methods of obtaining informed consent

Every study site will assess patients for eligibility to enroll into the study. Before enrolment, every patient will receive full oral and written information about the nature, purpose, expected advantages and possible risks of the trial. The patient will agree to participate in the trial by signing the informed consent form. Patients must be given an opportunity to enquire about details of the study. After a sufficient period of time for the individual's consideration and decision, comprehension and consent shall be documented on the consent form by the dated signature of the patient and the Investigator. If a patient is able to consent but cannot sign himself/herself, oral information and written consent need to be testified and signed by a witness.

The subject must read, sign, and date the informed consent form before entering in the trial, takes study treatment or undergoes any study-specific procedures. The entry into this trial is defined as the patient's signature of the consent. The final versions of patient information and consent will be presented to the Ethics Committee. Both the patient information and the patient consent form are produced in duplicate. One of each form for the Investigator, a

duplicate will be handed to the patient. Twice the patient informed consent form are signed. One of each form is for the patient file, another will be handed to the patient. Patients will not have any disadvantage by not participating in the study. Patients have the right to withdraw from the study at any time for any reason after giving informed consent.

6.3 Methods of avoiding simultaneous enrolment in other trials

Those patients recruited in the present study could not be recruited in other clinical interventional trials. They will not receive any other investigational drug. The investigator will register in the medical records of the patient that he/she has been included in a clinical trial and the expected duration of it. Patients are informed that they may not enter into other interventional trials. A patient study card will be given to each patients informing about the participation in this trial.

6.4 Enrolment and randomisation (assignment of study medication)

Patients, who meet all inclusion criteria and who have given their written informed consent will be randomised for study treatment in one of the two study arms. The patients receive a 5-digit randomization number (= subject ID). The study medication is provided by the pharmacy with kit numbers. The pharmacy allocates the kit-numbers (study medication) to the patients on the basis of a randomisation plan. Patient data will be captured in the medical files (source data) and are consecutively transferred pseudonymized to the eCRF.

6.5 Clinical examinations and trial-related deviations from clinical practice

6.5.1

Screening

The following examinations will be performed at screening: evaluation of inclusion/exclusion Criteria, Informed consent, Physical examination, blood pressure, pulse, weight, assessment of prior and concomitant medication and non-drug therapy, assessment of medical history, blood test, urinary or serum cannabis test, urinary or serum pregnancy test, ECG recording, blood pressure and pulse measurement, assessment of CAPS-IV B2, CAPS-5, MADRS, Demographics, CTQ, MINI-5, and ITI.

Examinations during trial

At baseline, assessment includes prior and concomitant medication and non-drug therapy, blood test (see 6.5.5 Laboratory assessments), urinary or serum cannabis test, urinary or serum pregnancy test, ECG, blood pressure and pulse, weight, adverse event recording, CAPS-IV B2, CAPS-5, PSQI-A, MADRS, Sleep diary, PCL-5, BSL-23, EQ-5D, PGIC, SOFAS, PSQI, ITQ, MWC. Further assessments during the trial will be performed at visit 2 (week 1), visit 3 (week 2), visit 4 (week 3), visit 5 (week 4), visit 6 (week 6), visit 7 (week 7), and the final examination (visit 8 in week 10). At visit 2 (week 1), visit 3 (week 2), visit 4 (week 3), visit 5 (week 4), and visit 7 (week 7), concomitant medication and non-drug therapy, blood pressure and pulse, Adverse event recording, CAPS-IV B2 Sleep diary will be assessed.

At visit 6 (week 6), concomitant medication and non-drug therapy, blood pressure and pulse, weight, adverse event recording, CAPS-IV B2, PSQI-A, Sleep diary, CAPS-5, PCL-5, BSL-23, EQ-5D, PGIC, SOFAS, PSQI, ITQ, and MWC will be assessed.

Table 1: Outline of trial visits

Assessments	SC	BL Visit 1 W 0	Visit 2 W 1	Visit 3 W 2	Visit 4 W 3	Visit 5 W 4	Visit 6 W 6	Visit 7 W 8	Visit 8 W 10	FU Visit 9 W 12
Screening and consent										
Inclusion/exclusion criteria	X									
Informed consent	X									
Physical examination ¹	X								X	
Prior and concomitant medication and non-drug therapy	X	X	X	X	X	X	X	X	X	X
Medical history	X									
IMP dispersion		X	X	X	X	X	X	X		
IMP return			X	X	X	X	X	X	X	
Safety										
Blood test ²	X								X	
Cannabis test	X									
Pregnancy test	X	X		X		X	X	X	X	
ECG	X								X	(X) ³
Blood pressure, pulse	X	X	X	X	X	X	X	X	X	X
Weight	X	X					X		X	X
Adverse event recording		X	X	X	X	X	X	X	X	X
Effectiveness										
primary										
CAPS-IV B2									X	
secondary										
CAPS-IV B2	X	X	X	X	X	X	X	X		
CAPS-5	X ^a	X ^b					X ^b		X ^b	
PSQI-A		X					X		X	
MADRS	X	X				X			X	
Sleep diary		X	X	X	X	X	X	X	X	
PCL-5		X					X		X	
BSL-23		X					X		X	
EQ-5D		X					X		X	
PGIC							X		X	
SOFAS		X					X		X	
PSQI		X					X		X	
ITQ		X					X		X	
MWC		X					X		X	X
others										
Demographics	X									
CTQ	X									
MINI-5	X									
ITI	X									

Note: SC = screening, W. = week +/- 3 days, BL = baseline and randomization, FU = post-trial follow-up, CAPS-IV B2 = B2 score of the Clinician-Administered PTSD Scale for DSM-IV (frequency and intensity of nightmares), CAPS-5 = Clinician-Administered PTSD Scale for DSM-5 (a = last month version, b = last week version), PSQI-A = Pittsburgh Sleep Quality Index-Addendum for PTSD, MADRS = Montgomery-Åsberg Depression Rating Scale, PCL-5 = PTSD Checklist for DSM-5, BSL-23 = Borderline Symptom List 23, EQ-5D = Health-Related Quality of Life, PGIC = Patient Global Impression of Change, SOFAS = Social and Occupational Functioning Assessment Scale, PSQI = Pittsburgh Sleep Quality Index, ITQ = international trauma questionnaire, MWC = Marijuana Withdrawal Checklist, CTQ = Childhood trauma questionnaire, MINI-5 = The Mini International Neuropsychiatric Interview for DSM-5, ITI = International Trauma Interview. 1 Physical examination includes height and weight of the patient and the skin, abdomen, respiratory system, head and extremities will be examined, 2: blood tests include hematology (erythrocytes, haemoglobin, haematocrit, platelets, leukocytes (including neutrophils, eosinophils, basophils, lymphocytes, monocytes) and serum chemistry (sodium, potassium, chloride, calcium, creatinine, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, aspartate aminotransferase, bilirubin, lipase, thyroid stimulating hormone), 3. In case of significant abnormal ECG findings at the visit 8 (week 10), a further ECG will be recorded at the follow-up visit.

Final examination

The final examination will be performed at visit 8 (week 10) and include a physical examination, concomitant medication and non-drug therapy recording, IMP return, blood tests, urinary or serum pregnancy tests, ECG, measurement of blood pressure and pulse, weight, adverse event recording, assessment of CAPS-IV B2, PSQI-A, MADRS, sleep diary, PCL-

5, BSL-23, EQ-5D, PGIC, SOFAS, PSQI, ITQ, MWC. Further, number of remitters (defined as CAPS-IV B2 = 0) and responders (defined as decrease of CAPS-IV B2 $\geq 50\%$) from baseline to week 10 will be determined.

Follow-up examination

A follow-up visit will take place at Visit 9 (W12) and include blood pressure, pulse, and weight assessment, adverse event recording, and concomitant medication and non-drug therapy. In case of significant abnormal ECG findings at visit 8 (week 10), a further ECG will be recorded at the follow-up visit.

Laboratory assessments

Laboratory assessments of blood parameters will be performed at screening and at Visit 8 (w10). Blood tests include haematology (erythrocytes, haemoglobin, haematocrit, platelets, leukocytes (including neutrophils, eosinophils, basophils, lymphocytes, monocytes) and serum chemistry (sodium, potassium, chloride, calcium, creatinine, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, aspartate aminotransferase, bilirubin, lipase, thyroid stimulating hormone).

6.6 Individual trial duration

After screening (10 days maximum), patients will be randomized and allocated to IMP or placebo. The individual patient will be treated for 10 weeks and a follow-up visit will take place after 2 weeks.

7 Risk-benefit-assessment

Risks, adverse reactions, stresses, advantages and disadvantages for the participants

In general, dronabinol is well tolerated, but the patient's individual maximum dosage is limited by adverse reactions. Expected adverse reactions are listed in the table below.

System Organ Class	Adverse Reactions	Frequency
Psychiatric disorders	Anxiety/restlessness, depression, euphoria, sleep disorder	Common
	Thinking abnormal	Uncommon
Nervous system disorders	Dizziness, headache, disturbance in attention, memory impairment, speech difficulties	Common
	Tremor	Uncommon
Ear and labyrinth disorders	Vertigo	Common
Cardiac disorders	Tachycardia	Uncommon
Vascular disorders	Hypertension, hypotonia	Uncommon
Respiratory, thoracic and mediastinal disorders	Dry nose	Common
	Dyspnoea	Uncommon
General disorders and administration site conditions	Tiredness	Very common
	Asthenia/muscular weakness, feeling abnormal	Common
Gastrointestinal disorders	Nausea, constipation, diarrhoea, abdominal pain upper, dry mouth	Common
	Flatulence, vomiting, hypoaesthesia oral	Uncommon
Metabolism and nutrition disorders	Increased appetite, loss of appetite	Common
Skin and subcutaneous tissue disorders	Sweating, local hypersensitivity reactions	Common
Eye disorders	Pressure behind the eyes	Common
	Dry eye, abnormal sensation in eye	Uncommon

Table 2: Reported adverse reactions in Bionorica sponsored clinical trials

(IB of BX-1, Ed.3.0, 27.Sep 2019; please refer to table 9 of the IB)

The following frequency categories are used for the evaluation of these adverse reactions:

Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$)

Due to the known effects of dronabinol, BX-1 should be administered with caution to patients with mania, depression or schizophrenia, heart diseases, history of seizure-related diseases and history of substance abuse. There might be additional or synergistic effects on central nervous system adverse reactions in patients treated concomitantly with sedative, hypnotic or other psychoactive medicinal products. BX-1 is not intended for the use in pregnant or breastfeeding women.

In order to minimize the risk for patients, patient groups with a significant risk are excluded from trial participation.

In addition to the risks related to the investigational medicinal product, there is a trial procedure related risk. Blood sampling might be painful, or the patients might temporarily become dizzy. Patients may also experience intermittent complaints like re-bleeding or puncture site bruises, blood clot (thrombus) in the punctured vessel (rarely), puncture site infections (rarely) or mechanical nerve damage (very rarely). After initial irritation, vein puncturing for blood sampling is usually painless and hardly noticeable.

The total volume of blood sampling during the entire clinical trial will be approximately 18 ml within approximately 14 weeks and is far below the volume of a normal blood donation. However, in single cases it might be necessary to repeat single blood sampling, e.g. an additional sample has to be taken due to re-measurements of clinical laboratory samples or due to bad vein conditions and a new sample must be taken from another vein, etc. Thus, the total blood volume may deviate in single cases by a small amount. No safety related risk is expected from this blood sampling.

In case of emergency, standard emergency procedures will be employed. The responsible investigator is to be consulted and informed immediately. He/she will provide all the necessary emergency equipment and specially trained staff to handle emergency events during this clinical trial. All cases of emergency have to be immediately reported as required to the sponsor comprising legal stipulations.

Benefits

There is no current approved medication to treat nightmares in patients with PTSD. Distressing nightmares are an independent risk factor for comorbidity and severity in PTSD patients. Nightmares also contribute to alcohol and substance abuse, suicidal ideation, and even suicide (Raskind et al., 2007). There is initial evidence for dronabinol either in combination with other active ingredients or as the sole active ingredient having a clinically relevant effect on nightmares in patients with nightmares and PTSD (Roitman et al., 2014; Wilkinson et al., 2016). For example, an open label, uncontrolled pilot study examined the impact of adding 5 mg of $\Delta(9)$ -THC twice a day as add-on treatment onto existing medications in PTSD patients and found that THC consumption specifically improved sleep quality, reduced nightmares, and reduced symptoms of hyperarousal (Roitman et al., 2014). Further, no negative results of cannabinoid-agonists in PTSD treatments are published to date.

Conclusion

Based on available literature data and trial conceptual design a positive benefit-risk balance is expected for BX-1 in this trial.

A Data and Safety Monitoring Board (DSMB) will be in place to monitor potential safety findings during the conduct of the trial.

8 Termination and subsequent treatment

8.1 Premature termination of the individual participant

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled. Withdrawal from the study will not jeopardize their future medical care or relationship with the investigator. Subjects will be asked to specify the reason for their termination, but have the right not to answer.

The investigator may decide to withdraw a subject from the study at any time with reasonable rationale. The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the study until completion of the study.

The reason for withdrawal of a patient should be recorded, if possible, in the eCRF and in the subject's records (Withdrawal of Consent Form).

A subject who withdraws Informed Consent before randomization or who develops a condition infringing with selection criteria before randomization is defined as a screening failure. No follow-up of screening failures will be performed.

The following events must cause premature termination of the individual subject:

- Unblinding in case of a medical emergency
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study
- Pregnancy
- Consent withdrawn by patient
- Events with a score > 3 according to the CTCAE catalogue (Common Terminology Criteria for Adverse Events, Version 5.0)
- Complete missing of two consecutive visits

8.2 Premature termination of the clinical study

The following events must cause premature termination of the clinical trial:

- Unjustifiable risk and negative risk-benefit analysis (decision taken by the sponsor)
- New scientific evidence provided during the study that could affect the patient's safety (benefit-risk analysis no longer positive)
- Decision of the Sponsor or the Competent Authority that the study should be discontinued or because of withdrawal of a positive vote by a responsible ethics committee.

Sponsor may terminate the trial at an individual study centre, if

- the investigator no longer considers the risk-benefit ratio to be reasonable,
- the centre's recruitment rate is too low,
- the drop-out rate is unusually high, or
- the investigator does not comply with the protocol or other regulations with the necessary care.

8.3 Follow-up and continuing treatment after regular / premature termination

After the end of the trial, the patients will be treated according to local standard practice. No further post-trial therapy will be offered by the sponsor.

In the case of premature termination, the reason for withdrawal must be entered on the appropriate case report form (CRF) page and must be followed for safety and efficacy until 8 days (five times half-life of 36 h) after discontinuation.

9 Adverse events

9.1 Definitions (according to guideline 2001/20/EG)

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE could be diseases, signs or symptoms which occur or worsen after enrolment of the patient in the clinical trial.

Serious Adverse Event (SAE)

A 'serious adverse event or serious adverse reaction' is any untoward medical occurrence or effect that at any dose

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- or is a congenital anomaly or birth defect;
- other medically important event (as described in 9.3.1)

Adverse Reactions

Adverse reactions are all untoward and unintended responses to an investigational medicinal product related to any dose administered.

Suspected Unexpected Serious Adverse Reactions (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is any suspected adverse reaction related to the study treatment that is both serious and unexpected.

"Unexpected" means that the nature and severity of the adverse reaction are not consistent with the information about the study medication in question set out in the reference safety information.

The evaluation of expectedness will be done by the sponsor.

9.2 Treatment of (S)AEs

All AEs should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization or any other medically required intervention.

9.3 Assessment of SAEs

As far as possible, each AE should be evaluated to determine:

1. the severity grade (CTCAE v5.0)
2. its relationship to the study drug (assessment of causality)
3. its duration (start and end dates or if continuing at final exam)

4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this AE; hospitalization)
5. whether it constitutes a serious adverse event (SAE)

Assessment of Seriousness

Seriousness shall be determined according to the definition above.

Furthermore medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room, or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug addiction or drug abuse.

Assessment of intensity

CTCAE grading:

9.3.2

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

9.3.3

Assessment of causality

Causal relationship between the occurrence of an AE and the administration of the IMP as assessed by the investigator according to the available data:

Related: There is a reasonable causal relationship, which means that there is evidence to suggest a causal relationship. The adverse event could medically (pharmacologically/clinically) be attributed to the investigational product under trial in this protocol.

Not related: There is no reasonable causal relationship, which means that there is no evidence to suggest a causal relationship. The adverse event could not medically (pharmacologically/clinically) be attributed to the investigational product under trial in this protocol.

9.4 Documentation of AEs and SAEs

All Serious Adverse Events (SAEs) and all Adverse Events (AEs) need to be documented, no matter if the Investigator suspects a causal connection to the investigational product or not. The documentation needs to include the type of event, start, duration, severity and causality, outcome, action taken.

Related signs, symptoms and laboratory changes should be summarized to a specific disease. The event will be recorded in the CRF SAEs need to be documented on a separate SAE form.

Out of normal range laboratory data need to be analysed concerning their clinical relevance by the Investigator – and if relevant documented as an AE itself. CTCAE criteria will be applied to laboratory values.

All adverse events need to be followed until they subside or stabilize.

The Sponsor will carefully document all SAEs reported by the Investigator. His documentation will be sent to the relevant regulatory authorities and to relevant authorities of other European member states and other contracting states of the EWR agreement, if the study is run in their territory and if they so request.

9.5 Reporting of SAEs

To ensure patient safety all SAEs occurring after the patient has provided informed consent must be reported, regardless of causality, by the local investigator to the Sponsor within 24 hours of learning its occurrence. The local Investigator is responsible for reporting all adverse events reported by the participant or detected by the study staff without delay and within 24 hours to the Sponsor's designee (CTO Charité, Pharmacovigilance Department). It has to be documented on the appropriate pages of the case report form (CRF).

The Investigator will report any Serious Adverse Event promptly after becoming aware to the Sponsor's designee (CTO Charité, Pharmacovigilance Department) and will afterwards send an extended written record.

This announcement will be done via fax or email to:

Pharmacovigilance, CTO Charité

Fax: +49 (0)30 – 450 7554 489

Email: pv-cto @charite.de

9.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor's designee (CTO Charité) will report all suspicious cases of Suspected Unexpected Serious Adverse Reactions (SUSARs) which had been occurred in one of clinical trials conducted by the same sponsor with the same drug substance/IMP to the relevant Ethics Committee, the relevant regulatory authorities and to relevant regulatory authorities of other European member states and other contracting states of the EWR agreement, if the study is run in their territory immediately, at the latest 15 days after it becomes known. He will also inform all Investigators involved in the trial.

In case of a fatal or life threatening SUSAR the Sponsor will report all information relevant for judging the event immediately, at the latest 7 days after the event becomes known to the relevant Ethics Committee, the relevant regulatory authorities and to relevant regulatory authorities of other European member states and other contracting states of the EWR agreement, if the study is run in their territory as well as to all Investigators involved in the trial. After a further 8 days all further relevant information must be available.

9.7 Other safety issues requiring expedited reporting

The Sponsor's designee will immediately, at the latest 15 days after it becomes known report all circumstances that require a revision of the risk-benefit analysis to the relevant Ethics Committee, the relevant regulatory authorities and to relevant regulatory authorities of other European member states and other contracting states of the EWR agreement, if the study is run in their territory. This especially includes:

- Singular cases of expected severe adverse events with an unexpected outcome.
- Increased incidence of expected severe adverse events that are judged as being clinically relevant.
- SUSARs which occur after termination of the clinical trial (up to 8 days (five times half-life of 36 h) after termination or exclusion)
- Events related to study procedures or development of the study medication, which could affect a subject's safety.

All person-related data will always be transmitted pseudonymised. Before reporting a SUSAR the subject will be unblinded.

9.8 Follow-up of adverse events

Once an AE is detected, it should be followed until its resolution or stabilisation, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study, the interventions required to treat it and the outcome.

Follow-up information is sent to the same address to which the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

For a follow-up report to the authorities, the investigator may be required to collect further information for a detailed description and a final evaluation of the case, including copies of hospital reports, autopsy reports, or other relevant documents.

9.9 Pregnancy

The investigator will collect pregnancy information on any female patient, or female partner of male patient who becomes pregnant while participating in this clinical trial. The investigator will further ask for written consent to collect information on pregnancy of partners of any male patients, that are currently enrolled in the study. The investigator will record pregnancy information on the Pregnancy report form - occurrence on the SAE form (under other medically important condition) and submit it to the sponsor immediately (i.e. within 24 hours after acknowledgment of a patient's pregnancy). The receipt of reports concerning pregnancy will be confirmed immediately, but not later than three (3) working days after the receipt. Without confirmation after three working days, the investigator has to transmit the report again on the following working day and will be followed up.

Any patient who becomes pregnant while participating in the trial should discontinue treatment immediately and will be withdrawn from the trial.

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Generally, follow-up will be no longer than 3 months following the estimated delivery date. Any follow-up information will be sent to the sponsor immediately (i.e. within 24 hours after acknowledgment).

Newly diagnosed pregnancy in a clinical trial patient is not considered to be an AE or SAE unless meeting seriousness criteria, or it is suspected that the IMP interacted with a contraceptive method and led to pregnancy.

Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Furthermore, any SAE occurring as in association with a pregnancy (in cases where the pregnancy occurred after the end of the trial participation of the patient) brought to the investigator's attention after the patient has completed the trial and considered by the investigator as reasonably related to the IMP must be promptly reported to the sponsor.

9.10 Contact for reporting

Name	Pharmacovigilance, CTO-Charité
Study centre	Charité – Universitätsmedizin Berlin, Campus Charité Mitte
Address	Charitéplatz 1, 10117 Berlin
Fax:	+49-(0)30-450 7554 489
E-Mail:	pv-cto@charite.de

9.11 Annual Safety Reporting

Once a year throughout the clinical trial, the sponsor will provide the Member States in whose territory the clinical trial is being conducted and the relevant Ethics Committees with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.' For the format reference is made to the guideline ICH Topic E2F — Development Safety Update Report ('DSUR', hereinafter 'note for guidance ICH E2F').

9.12 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be constituted to protect the safety of study participants. A DSMB is a group of external independent experts assessing the progress, safety data, and, if needed, critical efficacy endpoints of clinical study.

The DSMB will receive blinded CRF data in the form of tables and listings (prepared by an independent statistician) and adjudicate on patient status changes and dosing decisions. Where appropriate, the DSMB may receive unblinded data (on a patient level or treatment group level) that should be reviewed in a closed session.

The data should include, but is not limited to, demographics, patient enrolment, baseline characteristics, (S)AE data (by seriousness, intensity, causality, expectedness), laboratory data, dose adjustments, protocol adherence, and patient withdrawals.

The Sponsor will establish a Charter document explaining the working procedures for the DSMB.

10 Documentation

10.1 Case Report Forms (CRF)

Data collected on each subject will be captured in the medical files (source data) and are consecutively recorded in the eCRF (electronically).

10.2 Investigator Site File (ISF)

All essential documents will be kept in the Investigator Site File which will be stored at the study site in accordance with ICH GCP chapter 8.

10.3 Drug accountability / flow of study medication

IMP will be provided by Bionorica SE via the pharmacy “Myonex GmbH”. Labelling and secondary packaging for use in a clinical trial will be performed by the pharmacy “Myonex GmbH” under the responsibility of Bionorica SE.”. The pharmacy “Myonex GmbH” will provide study medication to the study centers. Emergency envelopes will also be sent to the study centers by the pharmacy “Myonex GmbH”. The study centers will provide study medication to the participants. IMP will be weighed after return of IMP at the study centers with an analytical balance. After return of study medication to the study centers IMP will be sent to the “Myonex GmbH”. Discreation of IMP will be performed at “Myonex GmbH”.

11 Quality management

11.1 Control of trial progress and data quality

Monitoring, Data Quality Assurance

The trial site will be monitored by CTOCharité to ensure the quality of the data collected. The objectives of the monitoring procedures are to ensure that the trial subject's safety and rights as a study participant are respected, that accurate, valid and complete data are collected, and that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation.

All investigators agree that the monitor regularly visits the trial site and assure that the monitor will receive appropriate support in his activities at the trial site.

The declaration of informed consent includes a statement to the effect that the monitor has the right – while observing the provisions of data protection legislation – to compare the case report forms (eCRFs) with the trial subject's medical records (doctor's notes, ECGs, laboratory printouts etc.). The investigator will secure access for the monitor to all necessary documentation for trial-related monitoring. The aims of the monitoring visits are as follows:

- To check the declarations of informed consent.
- To monitor trial subject safety (occurrence and documentation/reporting of AEs and SAEs).
- To check the completeness and accuracy of entries on the eCRF.
- To validate the entries on the eCRF against those in the source documents (source data verification, SDV).
- To evaluate the progress of the trial.
- To evaluate compliance with the trial protocol.
- To assess whether the trial is being performed according to GCP at the trial site.
- To discuss with the investigator aspects of trial conduct and any deficiencies found.

A monitoring visit report is prepared for each visit describing the progress of the clinical trial and any problems (e.g. refusal to give access to documentation).

Audits / inspections

Authorised representatives of the Sponsor, a regulatory authority, or an Independent Ethics Committee (IEC) may visit the centre to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements.

12 Data entry und data management

All patient related data will be recorded under a pseudonym. Every patient will receive a patient number / pseudonym which will be unique for this individual patient. The Investigator will compile a confidential list, which relates these patient numbers to the patient's full name. This list will only be accessible to the study team and the monitor. Original patient files may be viewed by monitors, auditors and inspectors.

12.1 Data collection/Case Report Form (CRF)

All data will be recorded in an electronic Case Report Form. The study software used is SecuTrial.

All data will be recorded online/offline and will be transmitted directly to the database of the study centre. Data will be transferred between the workstation computer at the study site and the study server via a secure connection (secure socket layer /SSL) so that the data cannot be manipulated.

All patient data will be saved under a pseudonym. The study software will automatically generate a pseudonym for every new patient/the pseudonym for new patients can be typed into the study software. A document for clear patient allocation will be printed and must be kept in a safe place.

12.2 Source Data and Patient Files

The information in original documents and records (e. g. patient files, laboratory notes) are defined as Source Data and will be reviewed by the Monitor for Source Data Verification. All patient data, including the weight of the bottles for documentation of treatment compliance, will be captured in the medical files (source data) and are consecutively transferred pseudonymized to the eCRF.

12.3 Data processing

The study centre / Sponsor / biometrical centre will file all data electronically. To verify accuracy of the data, range, validity and consistency checks will be performed. Implausible or missing data can be corrected or added after consulting the Investigator. Documentation for these corrections will be stored with the CRFs.

All validated data will be stored in a database Oracle.

After termination of the study and after all entries have been completed, the database will be closed for further entries. This process will be documented.

The analysis will be performed using the following commercial software SAS.

The DSMB will be constituted to protect the safety of study participants and be responsible for making recommendations regarding any potential problems during the conduct of the study. It will assess the progress, safety data, and, if needed, critical efficacy endpoints of clinical study.

12.4 Generation of pseudonym

First, the patients will receive a screening number. With enrolment into the study, patients receive randomization numbers (subject IDs), which consist of a number for the study centers and a sequential number. The pseudonym for new patients can be typed into the study software. A document for clear patient allocation will be printed and must be kept in a safe place at the trial site.

13 Statistical Analysis

13.1 Sample size estimation

The sample size calculation is based on the primary endpoint “Clinician-Administered PTSD Scale-IV (CAPS-IV) B2 score at 10 weeks” in the ITT population including all randomized patients who received the study medication at least once. The aim is to show a lower average score at 10 weeks in the intervention group (I) than in the control group (C). Sample size calculation will be based on a two-sided, two-sample t-test. Adjustment for baseline scores in an ANCOVA model which is applied for the primary efficacy analysis will increase the power compared with a two-sample t-test, which ignores the influence of different baseline values. Therefore, this strategy for sample size calculation is a conservative procedure. In a recent random-effects meta-analysis of four RCTs investigating the effect of prazosin on PTSD nightmares, a combined standardized mean difference (Cohen’s d) of 0.5 (95% CI = 0.03–0.96) was observed (Augedal, Hansen, Kronhaug, Harvey, & Pallesen, 2013). We conservatively assume a standardized effect which is a little smaller and given by 0.45. This assumed effect can be considered as clinically relevant because distressing nightmares are an independent risk factor for comorbidity and severity in PTSD patients. Nightmares also contribute to alcohol and substance abuse, suicidal ideation, and even completed suicide (Raskind et al., 2007). As studies assessing minimal clinically important difference (MCID) for reduction of nightmares in PTSD are currently missing, clinical significance cannot be used to calculate sample size. The required sample size to detect this effect of 0.45 with a power of 0.8 is 158 (79 per group) calculated with nQuery Version 8.2.1.0. We conservatively assume that there will be no more than 10% of patients who are randomized but never get the study medication. Therefore the total number of patients to be recruited is 176 ($158/176=0.9$) or 88 per group.

13.2 Randomisation

Patients will be randomized at baseline in a 1:1 allocation using block randomization with fixed block lengths stratified by study center. Randomization will be performed by the pharmacy (Myonex GmbH).

13.3 Statistical analysis

Hypotheses

The null hypothesis states that the score at 10 weeks is higher on average in the intervention group (I) than the control group (C) whereas the alternative hypothesis states that the score at 10 weeks is lower on average in the intervention group (I) than the control group (C).

Definition of population for analysis

Confirmatory analysis will be conducted based on full analysis set.

Definition of the full analysis set: The full-analysis set consists of all randomized patients which received the study medication at least once. Patients are analysed as randomized. This is the population as close as possible to the intention-to-treat population. Exclusion of patients who never received the study medication is explicitly stated as an option in the ICH E) Guideline.

Definition of the per protocol set: The per-protocol population includes all patients without major protocol violations, to be defined in the statistical analysis plan which must be finalized before data base closure.

Definition of the safety set: The safety set as the basis for all safety analyses corresponds to the full analysis set.

We assume that 15% of patients who are randomized and received the study medication at least once will not finish the study as planned (non-completers). Non-complete cases will be subject to missing value imputation as specified below. Non-completers will not reduce the sample size of the primary analysis.

Sensitivity analyses will be conducted based on the per-protocol population including all patients without major protocol violations, to be defined in the statistical analysis plan which must be finalized before data base closure.

13.3.3 Analysis of primary and secondary endpoints

Primary analysis: The aim is to show that the score at 10 weeks is lower in the intervention group (I) than the control group (C). An ANCOVA model including the baseline score and adjusted for study center, will be applied for primary analysis. The global two-sided significance level will be 0.05.

Missing values for the analysis of the primary endpoint will be imputed as follows: If the follow-up assessment at 10 weeks is missing but the patient has at least one follow-up assessment after baseline, last observation carried forward will be used for missing value imputation. If the baseline visit is missing but follow-up assessments are available, the baseline value will be imputed using multiple imputation (van Buuren 2012).

Secondary analyses: Descriptive methods will be used to analyse secondary outcomes, including appropriate summary measures of the empirical distribution as well as 95% confidence intervals and descriptive two-sided p-values. For analyses the secondary endpoints considering the primary score at different follow-up times, the same imputation mechanisms as specified above will be applied. For all other secondary endpoints no imputation is planned. Additionally, sensitivity of the primary analysis will be analysed in different populations to assess the impact of the analysis population and of the imputation method (comparison to per-protocol population, patients with complete cases). All analyses will be done using validated statistical software.

Analysis of safety

Safety analysis will include (if appropriate) calculation of frequencies and rates of adverse and serious adverse events, adverse drug reaction and serious adverse drug reaction, laboratory parameters, vital signs, physical examinations, and ECGs.

Interim analyses and endpoints for premature study termination

We use the conditional rejection principle for the interim analysis (IA) in order to account for the initially unplanned analysis. The overall one-sided alpha will be 0.025 (which is equivalent to the initially planned two-sided alpha of 0.05 but a two sided calculation is not possible due to the non-binding futility boundary).

The IA will be done after 79/176 (44.9%) patients are enrolled (79 is half of the needed analyzable patients (158) since currently there are no non-starters - the initial reason for an increased recruitment number).

For the boundaries we choose alpha_1 equal to 0.0008213 which is according to an alpha spending scheme (O'Brien Fleming) with 2 looks and a non-binding futility alpha_0 of 0.5 (indicating efficacy in the wrong direction)

If the interim analysis indicates continuation, a sample size recalculation will be done using the previously assumed effect size of $d = 0.45$. If the recalculated sample size exceeds an additional number of 80 patients beyond the initially planned 176 patients, a conditional power calculation for a design with $n = 256$ ($176+80$) will be done. If the conditional power is less than 50%, the trial will also be stopped due to futility. Adverse Events and Serious Adverse Events are analysed in summary. Details can be found in the statistical analyses plan.

14 Reporting

14.1 Statistical report

The statistical analysis and composition of a biometrical report will be performed by Univ.-Prof. Dr. Frank Konietzke in cooperation with the Sponsor and the Principal Investigator. All data in this report is confidential.

14.2 Final report

After completion of the biometric evaluation, the sponsor will prepare a study report. The report will include all trial results, irrespective of whether favourable or not. Within 12 months after the end of the trial, the sponsor will submit a summary of the final report to the ethics committee and to the competent federal authorities. The summary will be prepared in the format provided for report synopses by the ICH Guideline E3, "Guidance on Structure and Content of Clinical Study Reports".

14.3 Publication (policy)

The study results will be published irrespective of the study outcome.

15 Ethical, legal and regulatory aspects

15.1 ICH-GCP-guidelines

This trial will be conducted in accordance with the current ICH-GCP-guidelines. Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

15.2 Legal requirements of the study

- Approval of Ethics Committee (according to AMG § 42 (1) and GCP-V § 7)
- Approval of competent authority (according to AMG § 42 (2) and GCP-V § 7)
- Approval of the competent authority (Bundesopiumstelle) (according to BtMG § 3)
- Notification to regional authorities (according to AMG § 67)
- Informed Consent
- Insurance
- Data privacy and confidentiality

Approval of Ethics Committee

^{15.2.1} Study protocol, patient information and consent form will be presented to the relevant Ethics Committee for survey. According to AMG § 42 (1) and GCP-V § 7 the study will only start after ethics approval has been granted. The Ethics Committee will immediately be informed (by the Sponsor) of all changes to the protocol (according to GCP-V § 10) and of all events that could affect a patients safety. The Ethics Committee will also be informed of all suspected SUSARs and of regular or premature termination of the study.

The Investigators have to register with the Ethics Committee (enter proof of qualification) before they enrol any patients.

Approval of competent authority

According to AMG § 42 (2), GCP-V § 7 and BtMG § 3 the trial will be submitted to the relevant federal authorities (BfArM, "Fachregistratur Klinische Prüfung" and "Bundesopiumstelle") for approval. The trial will only start after approval has been granted.

15.2.4 Notification to regional authorities

According to AMG § 67 and GCP-V § 12 Abs. 1-3 the trial will be submitted to the relevant state authorities. The Sponsor and all Investigators will be reported by full name.

Patient information and informed consent

Patient Information

Before enrolment every patient will receive full oral and written information about the nature, purpose, expected advantages and possible risks of the trial. (see 6.2).

Consent to participation in the trial:

The patient will agree to participation in the trial by signing the informed consent form. Patients must be given an opportunity to enquire about details of the study. After a sufficient period of time for the individual's consideration and decision, comprehension and consent

shall be documented on the consent form by the dated signature of the patient and the Investigator/ treating doctor. If a patient is able to consent but cannot sign himself/herself, oral information and written consent need to be testified and signed by a witness.

Adults who cannot give their consent must be represented by a legal carer.

Design and language will be adjusted to the study site's needs. The final versions of patient information and consent will be presented to the Ethics Committee. Both the patient information and the patient consent form are prepared in duplicate. One of each form for the Investigator, a duplicate will be handed to the patient.

Patient insurance

For participating patients, an insurance (gem. AMG § 40 Absatz 1 Satz 3 Nr. 8) has been established. The insurance (HDI Global SE, Am Schönenkamp 45, 40599 Düsseldorf), policy number 4312562503674 will cover for incidents from the commencement of the study. The insurance is limited to a maximum of 500.000 Euro per patient.

Data Privacy and confidentiality

The participants' data will be saved in a pseudonymous form, which will neither contain initials nor full date of birth. All regulative requirements applying to data protection will be met. Re-identification of a participant subject's name is possible from the patient identification log, which is kept in a locked research office at the Trial site where access is only possible by the principal Investigator or persons authorised by the principal Investigator.

Patients will be informed that their disease-related data will be saved for scientific purpose (Publication, etc.) using a pseudonym. Consenting patients have got the right to be informed about the data recorded. Patients will also be informed that their pseudonymised data will be forwarded to the 'Bundesoberbehörde' (BfArM) and to the Ethics Committee responsible, in accordance with legal notification obligation for drug safety. Patients, who disagree with this process of data transfer, are not allowed to participate in this study.

15.3 Archiving of data / access to records

Originals of all study-related report forms will be stored in the study headquarters at the trial site for at least 10 years after completion of the trial (GCP-V § 13(10)).

The Investigator / principle Investigator stores all administrative documents (correspondence with the Ethics Committee, the Supervising Authority, trial centre, study site), patient identification log, the signed patient consent forms, copies of the data documentation form and common study documentation (protocol, amendments) for the duration mentioned above. Original data of study patients (medical records) will be stored for at least 10 years.

A list allowing patient identification will be kept for 15 years (directive 2001/83/EG).

15.4 Financing

The trial is funded by **Bionorica SE**, Kerschensteinerstrasse 11-15, 92318 Neumarkt. Bionorica provides the IMP and financial resources as funding.

16 References

- Augedal, A. W., Hansen, K. S., Kronhaug, C. R., Harvey, A. G., & Pallesen, S. (2013). Randomized controlled trials of psychological and pharmacological treatments for nightmares: a meta-analysis. *Sleep Med Rev*, 17(2), 143-152. doi:10.1016/j.smrv.2012.06.001
- Betthausen, K., Pilz, J., & Vollmer, L. E. (2015). Use and effects of cannabinoids in military veterans with posttraumatic stress disorder. *Am J Health Syst Pharm*, 72(15), 1279-1284. doi:10.2146/ajhp140523
- Bonn-Miller, M. O., Vujanovic, A. A., Feldner, M. T., Bernstein, A., & Zvolensky, M. J. (2007). Posttraumatic stress symptom severity predicts marijuana use coping motives among traumatic event-exposed marijuana users. *Journal of Traumatic Stress*, 20(4), 577-586. doi:10.1002/jts.20243
- Bremner, J. D., Southwick, S. M., Darnell, A., & Charney, D. S. (1996). Chronic PTSD in Vietnam combat veterans: Course of illness and substance abuse. *American Journal of Psychiatry*, 153(3), 369-375.
- Brownlow, J. A., Harb, G. C., & Ross, R. J. (2015). Treatment of Sleep Disturbances in Post-Traumatic Stress Disorder: A Review of the Literature. *Curr Psychiatry Rep*, 17(6), 41. doi:10.1007/s11920-015-0587-8
- Cameron, C., Watson, D., & Robinson, J. (2014). Use of a Synthetic Cannabinoid in a Correctional Population for Posttraumatic Stress Disorder-Related Insomnia and Nightmares, Chronic Pain, Harm Reduction, and Other Indications A Retrospective Evaluation. *Journal of Clinical Psychopharmacology*, 34(5), 559-564. doi:10.1097/Jcp.0000000000000180
- Cukor, J., Olden, M., Lee, F., & Difede, J. (2010). Evidence-based treatments for PTSD, new directions, and special challenges. *Ann N Y Acad Sci*, 1208, 82-89. doi:10.1111/j.1749-6632.2010.05793.x
- Fraser, G. A. (2009). The Use of a Synthetic Cannabinoid in the Management of Treatment-Resistant Nightmares in Posttraumatic Stress Disorder (PTSD). *Cns Neuroscience & Therapeutics*, 15(1), 84-88. doi:10.1111/j.1755-5949.2008.00071.x
- Hauschke, D., Steinijans, V., & Pigeot, I. (2007). Bioequivalence studies in drug development: meth-ods and applications (Vol. 60). John Wiley & Sons.
- Jetly, R., Heber, A., Fraser, G., & Boisvert, D. (2015). The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. *Psychoneuroendocrinology*, 51, 585-588. doi:10.1016/j.psyneuen.2014.11.002
- Monson, E., Caron, J., McCloskey, K., & Brunet, A. (2017). Longitudinal analysis of quality of life across the trauma spectrum. *Psychol Trauma*, 9(5), 605-612. doi:10.1037/tra0000254
- Pietrzak, R. H., Goldstein, R. B., Southwick, S. M., & Grant, B. F. (2011a). Medical comorbidity of full and partial posttraumatic stress disorder in US adults: results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychosom Med*, 73(8), 697-707. doi:10.1097/PSY.0b013e3182303775
- Pietrzak, R. H., Goldstein, R. B., Southwick, S. M., & Grant, B. F. (2011b). Prevalence and Axis I comorbidity of full and partial posttraumatic stress disorder in the United States: results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *J Anxiety Disord*, 25(3), 456-465. doi:10.1016/j.janxdis.2010.11.010
- Pocock S. Group sequential methods in the design and analysis of clinical trials. *Biometrika*. 1977;64(2):191-9.
- Raskind, M. A., Peskind, E. R., Hoff, D. J., Hart, K. L., Holmes, H. A., Warren, D., . . . McFall, M. E. (2007). A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry*, 61(8), 928-934. doi:10.1016/j.biopsych.2006.06.032

- Roitman, P., Mechoulam, R., Cooper-Kazaz, R., & Shalev, A. (2014). Preliminary, open-label, pilot study of add-on oral Delta9-tetrahydrocannabinol in chronic post-traumatic stress disorder. *Clin Drug Investig*, 34(8), 587-591. doi:10.1007/s40261-014-0212-3
- Sareen, J., Afifi, T. O., McMillan, K. A., & Asmundson, G. J. (2011). Relationship between household income and mental disorders: findings from a population-based longitudinal study. *Arch Gen Psychiatry*, 68(4), 419-427. doi:10.1001/archgenpsychiatry.2011.15
- Shalev, A., Liberzon, I., & Marmar, C. (2017). Post-Traumatic Stress Disorder. *N Engl J Med*, 376(25), 2459-2469. doi:10.1056/NEJMra1612499
- Van Buuren, S. (2012). Flexible imputation of missing data. CRC press.
- Wilkinson, S. T., Radhakrishnan, R., & D'Souza, D. C. (2016). A Systematic Review of the Evidence for Medical Marijuana in Psychiatric Indications. *J Clin Psychiatry*, 77(8), 1050-1064. doi:10.4088/JCP.15r10036
- World Health Organization (2004). Mortality and Burden of Disease Estimates for WHO Member States: Persons, all ages (2004). (xls). Retrieved 2009-11-12.

17 Appendices

17.1 Appendix 1 Responsibilities and participating organizations

Sponsor	Charité – Universitätsmedizin Berlin Charitéplatz 1, D-10117 Berlin
Coordinating Investigator (LKP)/ Representative of the Sponsor	Prof. Dr. Stefan Röpke Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin, Klinik für Psychiatrie und Psychotherapie Hindenburgdamm 30, 12203 Berlin phone: +49-(0)30 450-517545 fax: +49-(0)30 450-517942 email: stefan.roepke@charite.de
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Trial Statistician	Univ.-Prof. Dr. Frank Konietschke Charité – Universitätsmedizin Berlin, Campus Mitte Institute of Biometry and Clinical Epidemiology Charitéplatz 1, 10117 Berlin phone: +49-(0)30 450-562161 email: frank.konietschke@charite.de
IMP	manufacturing, labelling, final releasing manufacturer: Bionorica SE Kerschensteinerstr. 11-15 92318 Neumarkt in der Oberpfalz
IMP	randomisation list, emergency envelopes, shipment: Myonex GmbH, Salzufer 13/14, 10587 Berlin Tel.: 030/31983-2211 e-mail: ct.de@myonex.com
CRO	regulatory affairs, monitoring, datamanagement, pharmacovigilance Clinical Trial Organization (CTO /) Charité – Universitätsmedizin Berlin, Campus Charité Mitte Charitéplatz 1, 10117 Berlin Tel.: 49 40 450 553 016 Fax: 49 30 450 553 937

Summary of Main Protocol Amendments

Date of Substantial Amendment*	Protocol Version/ Date	Summary of Changes
03 Nov 2021	Version 1.4/ 04 May 2020	An updated version of the IMPD was submitted. Minor editorial changes from protocol v1.3 to v1.4 were made: A missing checkbox in Table 1 (AE documentation at visit 1) Discrepancies between the protocol and the participant information were corrected. Several details were further specified.
12 Aug 2022	Version 2.0/ 01 Aug 2022	Incorporation of an interim analysis based on new evidence indicating a lack of treatment effect of THC. This information can be used for further DSMB issues. Extended duration of the trial due to covid-19 pandemic Minor corrections
24 Oct 2023	Version 3.0/ 16 Oct 2023	Manufacturer responsible for labeling and secondary packaging was changed.
12 Aug 2024	Version 4.0/ 28 Jun 2024	Study duration revised: recruitment start updated to 01 Oct 2020; projected study end set to 30 Jan 2025 Minor corrections regarding pregnancy follow-up procedures added

* Date of Submission

Treating Nightmares in Posttraumatic Stress Disorder with Dronabinol: A Randomized Controlled Study (THC PTSD-trial)

THC-PTSD

Statistical Analysis Plan for final analysis

Version 1.0 of 2.07. 2025

Investigational medicinal product: Dronabinol
Comparator: Oily Placebo Solution (cannabis aroma)
Indication: Posttraumatic Stress Disorder
Sponsor: Charité – Universitätsmedizin Berlin
Financial support: Bionorica SE
Protocol registry identification: THC-PTSD
Development phase: Phase II
EudraCT-Number: 2019-002211-25
Protocol version: 4.0 from June 28th 2024

Approved by

Prof. Dr. Stefan Röpke,
Principal Investigator

Berlin, 2 July 2025

Place and date

M. Sc. Robert Röhle,
Statistician

Place and date

**Stefan
Röpke**

Signature

Robert Röhle

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Version	Relevant changes from previous version
1.0	Initial draft

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Abbreviations

Abbreviation	Term
AE	Adverse event
BL	Baseline
CAPS	Clinician-Administered PTSD Scale
FAS	Full analysis set
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MADRS	Montgomery-Åsberg Depression Rating Scale
MCID	Minimal clinically important difference
MMRM	Mixed model for repeated measures
PPS	Per-Protocol set
PTSD	Posttraumatic stress disorder
SAE	Serious adverse event
SAP	Statistical Analysis plan
TEAE	Treatment-emergent adverse events

1 Purpose of this document

In this document, the final analysis including statistical methods for the THC-PTSD trial is described. The content is based on the study protocol version 4.0, dated June 28th 2024, on the SAP for the interim analysis version 0.3, dated March 3rd 2023 and on and on documentation provided in the ethics application for a separate follow-up study (local ethics committee Charité – Universitätsmedizin Berlin, EA1/339/24).

The reporting of the statistical data will be performed in compliance with the following guidance:

- ICH E3 Structure and content of clinical study reports - Scientific guideline, Current step 5 version, dated July 1st 1996
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-3-structure-and-content-clinical-study-reports-step-5_en.pdf
- ICH E9 statistical principles for clinical trials - Scientific guideline, current step 5 version, dated September 1st 1998
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf

2 Background

2.1 Trial objective

Primary objective of the study is to examine the efficacy of oral dronabinol over placebo in reducing nightmares in patients with posttraumatic stress disorder.

Secondary objectives of the study are to examine the efficacy of oral dronabinol in reducing disorder-specific symptoms in patients with posttraumatic stress disorder, and to examine the efficacy of oral dronabinol in reducing sleep disturbance in patients with posttraumatic stress disorder.

2.2 Trial design

The study is a multi-centric, double blind, randomized, placebo-controlled, parallel group interventional exploratory phase II trial.

2.2.1 Study plan

The study plan including all visits is shown in Table 1.

In addition to the assessments listed in Table 1, additional data were collected at the follow-up visit (Visit 9) as part of a sub-study. Specifically, CAPS-IV B2, PSQI-A, PSQI, and PCL-5 were assessed at this visit. Participation in the sub-study was voluntary, and not all participants of the main study took part.

Furthermore, an additional assessment as part of a separate follow-up study was implemented after study completion but prior to database lock and unblinding, asking participants to indicate whether they believed they had received THC or placebo.

2.2.2 Treatments

Description of study medication / investigational medicinal product

BX-1 is an oily solution containing 25 mg/ml dronabinol. Dronabinol ((-)-trans- Δ^9 -Tetra-hydro-cannabinol, Δ^9 -THC) is the major psychoactive constituent of Cannabis sativa L. Dronabinol is a clear to amber resin. It is highly lipid soluble. Dronabinol is thermolabile, photolabile and susceptible to oxidation.

Placebo / reference medication

There is no discernible difference between BX-1 and the corresponding placebo with regard to colour, taste, and appearance, thus ensuring the trials double-blind character. However,

batch-specific variations of odour and colour may occur. In addition, all medications for the double-blind period will be labelled with a common batch number.

Trial treatments are double-blinded. The medication list and the randomisation list are stored at the pharmacy (Myonex GmbH) and the allocation to treatment groups will be managed by the pharmacy (Myonex GmbH) and will not be known to the investigator or any other person involved in the conduct of the trial until completion of the trial, except in case of an emergency.

2.2.3 Blinding / Unblinding

Treatment is blinded by use of a matching placebo. The Sponsor, study personnel, and subjects will be blinded to treatment until the database is locked. Emergency envelopes will be provided by the pharmacy and will be stored in the trial sites. These emergency envelopes could then be used by investigators in case of emergencies.

Table 1: Outline of trial visits

Assessments	SC	BL Visit 1 W 0	Visit 2 W 1	Visit 3 W 2	Visit 4 W 3	Visit 5 W 4	Visit 6 W 6	Visit 7 W 8	Visit 8 W 10	FU Visit 9 W 12
Screening and consent										
Inclusion/exclusion criteria	X									
Informed consent	X									
Physical examination ¹	X								X	
Prior and concomitant medication and non-drug therapy	X	X	X	X	X	X	X	X	X	X
Medical history	X									
IMP dispersion		X	X	X	X	X	X	X		
IMP return			X	X	X	X	X	X	X	
Safety										
Blood test ²	X								X	
Cannabis test	X									
Pregnancy test	X	X		X		X	X	X	X	
ECG	X								X	(X) ³
Blood pressure, pulse	X	X	X	X	X	X	X	X	X	X
Weight	X	X					X		X	X
Adverse event recording		X	X	X	X	X	X	X	X	X
Effectiveness										
Primary										
CAPS-IV B2									X	
Secondary										
CAPS-IV B2	X	X	X	X	X	X	X	X		
CAPS-5	X ^a	X ^b					X ^b		X ^b	
PSQI-A		X					X		X	
MADRS	X	X				X			X	
Sleep diary		X	X	X	X	X	X	X	X	
PCL-5		X					X		X	
BSL-23		X					X		X	
EQ-5D		X					X		X	
PGIC							X		X	
SOFAS		X					X		X	
PSQI		X					X		X	
ITQ		X					X		X	
MWC		X					X		X	X
Others										
Demographics	X									
CTQ	X									
MINI-5	X									
ITI	X									

Note: SC = screening, W. = week +/- 3 days, BL = baseline and randomization, FU = post-trial follow-up, CAPS-IV B2 = B2 score of the Clinician-Administered PTSD Scale for DSM-IV (frequency and intensity of nightmares), CAPS-5 = Clinician-Administered PTSD Scale for DSM-5 (a = last month version, b = last week version), PSQI-A = Pittsburgh Sleep Quality Index-Addendum for PTSD, MADRS = Montgomery-Åsberg Depression Rating Scale, PCL-5 = PTSD Checklist for DSM-5, BSL-23 = Borderline Symptom List 23, EQ-5D = Health-Related Quality of Life, PGIC = Patient Global Impression of Change, SOFAS = Social and Occupational Functioning Assessment Scale, PSQI = Pittsburgh Sleep Quality Index, ITQ = international trauma questionnaire, MWC = Marijuana Withdrawal Checklist, CTQ = Childhood trauma questionnaire, MINI-5 = The Mini International Neuropsychiatric Interview for DSM-5, ITI = International Trauma Interview. 1 Physical examination includes height and weight of the patient and the skin, abdomen, respiratory system, head and extremities will be examined, 2: blood test s include haematology (erythrocytes, haemoglobin, haematocrit, platelets, leukocytes (including neutrophils, eosinophils, basophils, lymphocytes, monocytes) and serum chemistry (sodium, potassium, chloride, calcium, creatinine, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, aspartate aminotransferase, bilirubin, lipase, thyroid stimulating hormone), 3. In case of significant abnormal ECG findings at the visit 8 (week 10), a further ECG will be recorded at the follow-up visit.

2.2.4 Inclusion criteria

- Diagnosis of posttraumatic stress disorder (PTSD) according to DSM-5 with a 20 item CAPS-5 total score ≥ 26
- At least two nightmares a week, an intensity score ≥ 2 , with a CAPS-IV B2 (frequency and intensity for the last week) score ≥ 5
- Men and women between 18 and 65 years of age
- Written informed consent
- The patient has the capacity to give consent (He/she is able to understand the nature and anticipated effects/side effects of the proposed medical intervention)
- The patient is not breastfeeding
- Women of child-bearing potential must have a negative urine or serum pregnancy test
- All participants must use highly effective contraception
- The patient received stable pharmacological medication for at least 4 weeks prior to study entry (any changes in medication dose or frequency of therapy must be answered with no)

2.2.5 Exclusion criteria

- Lifetime cannabis use disorder
- Current substance/alcohol use disorder (≤ 3 months)
- Acute suicidality
- Psychotic disorder
- Bipolar disorder
- Current anorexia nervosa
- Current major depressive episodes and a MADRS score > 29
- Dementia
- Trauma-focused psychotherapy four weeks before the trial
- Initiation of sleep medication 4 weeks prior screening or initiation of alpha adrenergic agents 4 weeks prior to screening
- Acute or unstable medical illness
- Epilepsy
- Relevant heart diseases
- Known HIV- and/or active Hepatitis-B- or Hepatitis-C-infection
- Current or past malignant illness
- The patient is unwilling to consent to saving, processing and propagation of pseudonymized medical data for study reasons
- Patients, who may be dependent on the sponsor, the investigator or the trial sites, have to be excluded from the trial
- The patient is legally detained in an official institution
- The patient does have a known allergy or contraindication against Dronabinol
- The patient does have clinically significant abnormalities in 12-lead ECG
- The patient does have clinically significant laboratory abnormalities
- The patient did participate in other interventional trials during the 3 months before and at the time of this trial

2.2.6 Randomisation

Patients are randomized at baseline in a 1:1 allocation using block randomization with fixed block lengths stratified by study centre.

2.2.7 Sample size

The initial sample size calculation was based on the primary endpoint “Clinician-Administered PTSD Scale-IV (CAPS-IV) B2 score at 10 weeks” in the full-analysis set (FAS) including all randomized patients who received the study medication at least once. The aim was to show a lower average score at 10 weeks in the intervention group (I) than in the control group (C). Sample size calculation was based on a two-sided, two-sample t-test. Adjustment for baseline scores in an analysis of covariance model, which is applied for the primary efficacy analysis, will increase the power compared with a two-sample t-test, which ignores the influence of different baseline values. Therefore, this strategy for sample size calculation was a conservative procedure. In a random-effects meta-analysis of four randomized controlled clinical trials investigating the effect of prazosin on PTSD nightmares, a combined standardized mean difference (Cohen’s d) of 0.5 (95% CI = 0.03–0.96) was found [1]. We conservatively assumed a standardized effect which was a little smaller and given by 0.45. This assumed effect can be considered as clinically relevant because distressing nightmares are an independent risk factor for comorbidity and severity in PTSD patients. Nightmares also contribute to alcohol and substance abuse, suicidal ideation, and even completed suicide. As studies assessing minimal clinically important difference for reduction of nightmares in PTSD are currently missing, clinical significance cannot be used to calculate sample size.

The required sample size to detect this effect of 0.45 with a power of 0.8 was 158 (79 per group) calculated with nQuery Version 8.2.1.0. We conservatively assumed that there will be no more than 10% of patients who are randomized but never get the study medication. Therefore, the total number of patients to be recruited was 176 ($158/0.9 = 176$) or 88 per group.

Based on new external evidence [2] that emerged during the course of the study, the sponsor decided to perform an interim analysis that was not prespecified in the initial protocol. The initial sample size calculation was influenced by the interim analysis as follows (see also SAP for the interim analysis): The conditional rejection principle was used for the interim analysis. The overall one-sided alpha was set to 0.025 (which is equivalent to the initially planned two-sided alpha of 0.05 but a two-sided calculation was not possible due to the non-binding futility boundary). The interim analysis was done after 94 of the initially planned 176 patients (53.4%) finished visit 8. For the boundaries we chose a one-sided alpha_1 equal to 0.002162 which is corresponding to an alpha spending scheme (O’Brien Fleming) with 2 looks and a non-binding futility alpha_0 of 0.5 (indicating efficacy in the wrong direction). The interim analysis indicated continuation of the study. The two-sided alpha for the final analysis will be calculated based on the actual sample size when recruitment is final (= n_final) and the alpha spent at the interim analyses to account for under- or overrecruitment as suggested by the developers of the R package rpact used for calculation of the interim analysis [3]:

```
design_thc_ptsd_2 <- getDesignInverseNormal(typeOfDesign = "asUser",
kMax = 2, alpha = 0.025, beta = 0.2, sided = 1, informationRates =
c(94/n_final, 1), futilityBounds = 0, bindingFutility = FALSE,
userAlphaSpending = c(0.002162, 0.025))
alpha_final <- 2*design_thc_ptsd_2$stageLevels[2]
```

3 Analysis sets

3.1 Definitions

The FAS consists of all randomized patients, which received the study medication at least once. Patients are analysed as randomized. This is the population as close as possible to the

intention-to-treat (ITT) population. Exclusion of patients who never received the study medication or who provided no data on efficacy post baseline is explicitly stated as an option in the ICH E9 Guideline.

The Per-Protocol set (PPS) consists of all randomized patients without major protocol violations. Major protocol violations for this study include

- Intake > 120% of recommended amount of study drug (dronabinol or placebo)
- Intake < 80% of recommended amount of study drug (dronabinol or placebo)
- Termination of study drug intake prior to 10 week visit

Further, individual violations as identified in the blinded data review may lead to exclusion from the PPS

The safety set consists of all randomized patients, which received the study medication at least once.

3.2 Application

The primary and the secondary analyses will be performed in the FAS set. As a sensitivity analysis, the primary analysis will be repeated in the PPS. Safety analyses will be performed in the safety set.

4 Trial centres

The study was conducted in 4 centres (two in Berlin, one in Hamburg, and one in Mannheim) in Germany.

5 Analysis variables

5.1 Demography and baseline characteristics

- Age [years]
- Age group [<55 ; ≥ 55]
- Sex (assigned at birth; female, male)
- Weight [kg], mean (SD)
- BMI [kg/m^2], mean (SD)
- Highest Educational Level (School and Vocational Training)
- Marital Status
 - Single/widowed/divorced vs. partnered
- Co-Morbid Mental Disorder
 - Major Depressive Disorder (Current vs Lifetime (lifetime = current + past or recurrent))
 - Alcohol abuse in past 12 months
 - Other substance abuse than alcohol in past 12 months
- Current ongoing Psychotherapy
- Medication (document = THC_Prior_Medication_ATC_Coding)
 - Current Antidepressant use (ATC = N06)
 - Current Antipsychotics (ATC = N05)
 - Current Sleep-promoting Medication
 - Sedating Antidepressants (ATC = N06 + sedating)
 - Sedating Antipsychotics (ATC = N05AH, N05AD)
 - Sedating Antihistaminic (ATC = R06 + sedating)
 - Other (sedating)
- LEC (multiple selections possible)

- Index Traumatic Event (as indexed in CAPS-5, criterion A)

5.2 Primary variable

Frequency and intensity of nightmares, measured with the Clinician-Administered PTSD Scale (CAPS-IV) B2 score for the last week, range 0–8 [4] directly after last intervention (10 weeks – visit 8).

Due to the short-lived effect of the drug, we will further investigate the CAPS-IV B2 score at the last visit on study medication. This is either after the last intervention (10 weeks) for study completers or throughout the trial if study drug is discontinued.

5.3 Secondary variables

5.3.1 Key secondary efficacy variables

- Change from baseline of the CAPS-5 total score (overall PTSD symptoms, last week) at Visit 8
- Change from baseline of the Montgomery-Åsberg Depression Rating Scale (MADRS, depressive symptoms) at Visit 8
- Overall patient's status measured by the Patient Global Impression of Change (PGIC) at Visit 8

5.3.2 Further secondary efficacy variables

- Change from baseline of the frequency and intensity of nightmares, measured with the Clinician-Administered PTSD Scale-IV (CAPS-IV) B2 score for the last week, range 0–8, at Visits 2 to 7
- Change from baseline of the CAPS-5 total score (overall PTSD symptoms, last week) at Visit 6
- Change from baseline of the Montgomery-Åsberg Depression Rating Scale (MADRS, depressive symptoms) at Visit 5
- Overall patient's status measured by the Patient Global Impression of Change (PGIC) at Visit 6
- Change from baseline of the Pittsburgh Sleep Quality Index- Addendum for PTSD (PSQI-A) (PTSD related sleep symptoms) at Visit 6 and Visit 8
- Change from baseline of PTSD symptoms assessed with the PTSD Checklist for DSM-5 (PCL-5) at Visit 6 and Visit 8
- Change from baseline of the Health-Related Quality of Life (EQ-5D) score at Visit 6 and Visit 8
- Change from baseline of the Social and Occupational Functioning Assessment Scale (SO-FAS) at Visit 6 and Visit 8
- Weekly mean of change from baseline of the patients
 - daily total sleep time (in minutes),
 - sleep onset latency at night (in minutes),
 - recuperation of night sleep (5-point Likert scale, 1 = very much; 5 = not at all),
 - and time awake at night (in minutes),
 - number of nightmares last night (0, 1, 3, 4 or more) and
 - intensity of nightmares (5-point Likert scale, 0 = not at all; 5 = extreme) assessed with sleep diaries during Visit 2 – Visit 8
- Change from baseline of the Borderline Symptom List 23 (BSL-23) score at Visit 6 and Visit 8
- Change from baseline of the Pittsburgh Sleep Quality Index (PSQI) at Visit 6 and Visit 8

- Change from baseline of symptoms of PTSD and complex PTSD according to ICD-11 assessed with the International Trauma Questionnaire (ITQ) at Visit 6 and Visit 8
- Change from baseline of THC withdraw symptoms assessed with the Marijuana Withdrawal Checklist (MWC) at Visit 6, Visit 8, and Visit 9
- Responder analysis: proportion of patients showing improvement in nightmares (change from baseline) defined as decrease of CAPS-IV B2 $\geq 50\%$ assessed at the end of treatment (week 10 - Visit 8) and at the last visit under study medication
- Remitter analysis: proportion of patients showing full remission of nightmares defined as CAPS-IV B2 = 0, assessed at the end of treatment (week 10 - Visit 8) and at the last visit under study medication

5.3.3 Safety/Tolerability

- Adverse events
- Serious adverse events

5.3.4 Laboratory Parameters

Laboratory assessments of blood parameters will be performed at screening and at Week 10 (Visit 8). These include:

- Haematology: Erythrocytes, Haemoglobin, Haematocrit, Platelets, Leukocytes (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes)
- Serum Chemistry: Sodium, Potassium, Chloride, Calcium, Creatinine, Alanine Aminotransferase, Alkaline Phosphatase, Gamma Glutamyl Transferase, Aspartate Aminotransferase, Bilirubin, Lipase, Thyroid Stimulating Hormone

5.3.5 Follow-Up-Visit

- MWC and change from baseline and from Visit 8 to Visit 9
- CAPS-IV B2 and change from baseline and from Visit 8 to Visit 9
- PSQI-A and change from baseline and from Visit 8 to Visit 9
- PSQI and change from baseline and from Visit 8 to Visit 9
- PCL-5 and change from baseline and from Visit 8 to Visit 9
- Status of guessing treatment allocation

6 Handling of missing values and outliers

6.1 Missing values

Missing values for the analysis of the primary endpoint will be imputed using reference based multiple imputation. The underlying strategy will be "Jump to Reference", treating missing values as if respective patients had switched to the control group at the time missing (adjusted for included covariates). A required assumption is that there is no intermittent missing, meaning that these patients have no later non-missing values. We will include CAPS-IV B2 score at the visits and demographics as well as adjusting variables for the primary analyses within the imputation. We decide for 20 imputation sets for the analysis. For key secondary endpoints, a similar approach will be chosen.

The R package `rbmi` will be used for imputations using the following code:

```
rbmi_vars = rbmi::set_vars(outcome = "caps_4", visit = "time",
  subjid = "mnpaid", group = "trt_group",
  covariates = c("age", "gender", "trt_group*time"),
  strategy = "strategy")
rbmi_method = rbmi::method_bayes(n_samples = 20,
  control = rbmi::control_bayes(warmup = 200, thin = 5))
```

```
set.seed(314159265)
drawObj = rbmi::draws(data = data_to_imp3, data_ice = dat_ice,
vars = rbmi_vars, method = rbmi_method, quiet = T)
imputeObj = rbmi::impute(drawObj, references =
c("Control" = "Control", "Intervention" = "Control"))
```

6.2 Outliers

Prior to data analysis, distributions of the primary and key secondary endpoints will be inspected visually using boxplots, histograms and q-q-plots. Extreme values will be checked for wrong entries and decision on handling the values will be made individually in the blind data review process. No predefined rule for outlier detection will be applied since all endpoints resemble standardized questionnaires with a fixed range of values.

7 Statistical analyses / methods

7.1 General Remarks

Descriptive analyses for continuous variables include number of available data including percentage, mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum. For categorical variables, it includes number of available data including percentage, absolute and relative frequency. In general, results will be shown for the whole cohort and per treatment group.

7.2 Subject disposition

Subject disposition will be shown descriptively (see Appendix 11.1) and in a flow chart as suggested by CONSORT [5].

7.3 Demography and baseline characteristics

Demographic and baseline variables will be analysed descriptively.

7.4 Prior or concomitant medication and diseases

Prior or concomitant medication and diseases will be analysed descriptively.

7.5 Exposition to treatment/Compliance

Exposition to treatment will be measured by percentage of intake of recommended study drug. From Week 4 (Visit 5) on, the set dose should be taken daily until Week 10 (Visit 8). From these values the total amount of recommended study drug intake will be calculated by multiplying the days from Visit 5 to Visit 8 with the daily dose. The actual amount of intake measured by weighing bottles, bottle count and manual documentation will be divided by the total amount of recommended study drug intake. In case of insufficient documentation regarding the intake of study drug from Visit 5 to Visit 8 the overall treatment compliance (Visit 1 to Visit 8) is calculated including recommended amount of study drug intake and actual amount of intake of the titration phase Visit 1 to Visit 5.

7.6 Primary analysis

The primary analysis will be done using a mixed model for repeated measurements (MMRM) with an unstructured variance-covariance matrix. The model will include the change of the CAPS IV B2 score from BL as dependent variable and the BL CAPS IV B2, the centre, the treatment group, the visit, the treatment-by-visit interaction, and BL CAPS IV B2-by-visit interaction as fixed, independent variables.

The least square mean difference between interventions at Week 10 will be calculated including a two-sided 95% confidence interval and will be used for the primary analysis of the primary

endpoint. A two-sided p-value of ≤ 0.0486 will be considered as statistically significant; the adjusted significance level was derived based on Section 2.2.7 with a final sample size of 176 patients. Should the final sample size be different, the cut-off for significance will be determined accordingly as stated in on Section 2.2.7.

The following code demonstrates the calculation in R using the packages `mmrm` and `emmeans` and is based on recommendations for the use as given in the documentation [6]:

```
fit_primary <- mmrm(
  formula = caps_bl_visit ~ caps_4.v1_w0*time + mnpctrname +
    trt_group * time + us(time | mnpaid),
  data = data_thc_prim_analysis_long,
  control = mmrm_control(method = "Kenward-Roger"))
summary(fit_primary)

lsmeans_by_visit_primary <- emmeans(fit_primary, ~ trt_group | time)
lsmeans_by_visit_primary
pairs(lsmeans_by_visit_primary, reverse = TRUE)
confint(pairs(lsmeans_by_visit_primary, reverse = TRUE))
```

In case of a significant result from the interim analysis, the study will be declared as successful. The primary analysis will still be carried out as described above for all available data, but would have only supporting character; formal hypothesis testing for the primary endpoint would be based on the interim analysis. The effect estimate of the MMRM as described before including a two-sided 95% confidence interval will be reported for both, the interim analysis and the final analysis. The analogous model for the change from BL to last CAPS IV B2 under medication as dependent variable will be calculated as part of the sensitivity analysis. Furthermore, the analysis will be repeated in the per-protocol population.

7.7 Secondary analyses

7.7.1 Efficacy

For the key secondary endpoints including CAPS-5 and MADRS an analogous model as for the primary endpoint will be calculated and the results will be presented in an analogous fashion. The PGIC values at visit 8 will be dichotomized (at least some improvement vs. no improvement or worse) and a logistic regression model will be used for analysis. Treatment group and centre will be used as independent variables and the coefficient for treatment is the parameter of interest. Further, odds ratios and 95% confidence intervals will be calculated.

Results (i.e. least square means or regression coefficient) from these analyses of the key secondary endpoints will be analysed using the Hochberg procedure (global alpha 0.05) if the primary analysis was significant.

Analyses of key secondary endpoints at the additional visits (visit 5 or visit 6) will be analysed analogously to the analysis stated for the key secondary endpoints (visit 8, see before).

Further continuous secondary endpoints will be analysed analogously to the primary endpoint and results will be presented in an analogous fashion.

Response and remission at each visit will be analysed using a logistic regression model where treatment group and centre will be used as independent variables. Secondary endpoint from the sleep diaries will be analysed descriptively.

Results from further secondary efficacy analyses are to be interpreted in an exploratory manner.

7.7.2 Safety/Tolerability

7.7.2.1 Adverse events

Adverse events will be listed per patient. The number of Adverse events (AE) and serious adverse events (SAE), number of AES and SAE that led to permanent discontinuation of study drug are shown descriptively. The number of AEs and SAEs in each severity and relationship to treatment category will also be shown. The same will be done for the number of patients with AEs and SAEs. See Appendix 11.1 for further details.

7.7.2.2 Laboratory parameters

The parameters will be analysed descriptively using summary measures, both for the full cohort at BL as well as the treatments group separately for each visit. The analysis includes the measures for the respective time point and the difference to BL for each time point.

7.7.2.3 Follow-Up Assessments

Additional parameters for the FU-visit part will be analysed descriptively.

Further, to check the blinding of the patients and anticipation of treatment allocation, a chi-squares test will be carried out between both treatment groups and Cohen's kappa will be calculated including the patients' guesses and the true allocation.

7.8 Planned subgroup analyses

The following subgroups will be considered in the analysis:

- Age,
- Sex (assigned at birth),
- Severity at BL ($\leq$ median of BL CAPS-5 total score vs. $>$ median of BL CAPS-5 total score),
- Comorbidities:
 - Complex PTSD
 - Comorbid Depression (Current depression yes vs. no)
 - Borderline personality disorder

Subgroups analysis for the primary endpoint will be done by adding a main effect and a subgroup by treatment interaction effect to the model for the primary analysis.

7.9 Interim analysis

The details of the interim analysis are described in the Statistical Analysis Plan for interim analysis version 0.3, dated March 3rd 2023. The conditional rejection principle was used for the interim analysis in order to account for the unplanned analysis. The overall one-sided alpha was 0.025 (which was equivalent to the initially planned two-sided alpha of 0.05 but a two-sided calculation was not possible due to the non-binding futility boundary).

The IA was done after 94/176 (53.4%) patients finished visit 8.

For the boundaries we chose α_1 equal to 0.002162 which is according to an alpha spending scheme (O'Brien Fleming) with 2 looks and a non-binding futility α_0 of 0.5 (indicating efficacy in the wrong direction).

For the effect size, the following formula given in Nakagawa and Cuthill [7] was used:

$$d = t \cdot \sqrt{(n_1 + n_2) / (n_1 \cdot n_2 \cdot df)},$$

where d is the equivalent of Cohen's d for an adjusted regression coefficient, t is the t-test statistic from the adjusted regression coefficient, n_1 and n_2 are the sample sizes for the treatment and the control group, and df is the number of degrees of freedom from the adjusted regression model. The adjusted regression model included the CAPS IV at week 10 as de-

pendent variable and the baseline CAPS IV, the centre and the treatment group as independent variables. The t statistic from the regression coefficient for the treatment group was used for the calculation of d.

The analogous regression model for the last CAPS IV B2 under medication as dependent variable was be calculated as part of the sensitivity analysis.

8 Deviations from the protocol

The Study Protocol states that “Last Observation Carried Forward” should be used to impute missing data. We consider the approach mentioned herein of reference based multiple imputation superior to this method, resulting in a better sensitivity analysis.

Further, we used an MMRM and least square means instead of calculating Cohen’s d since the mentioned effect estimate resembled the research question more appropriately.

Key secondary endpoints were identified during the study and integrated in the testing procedure using a combination of hierarchical testing and the Bonferroni-Holm method. This was done to acknowledge the additional importance of these key secondary endpoints for the patients and to make claims about them.

Due to the corona pandemic some face-to-face visits were switched to telephone visits, therefore some bottles of study drug have not been weighed from visit to visit as initially intended. In the case of missing information for the calculation of treatment compliance according to the protocol from visit 5 to visit 8, treatment compliance was calculated over the entire period of the study (visit 1 to visit 8) instead if sufficient information was available.

9 Software

For the analysis the software R (version 4.1.2 or newer) [8] will be used. Within this software, the packages rbmi version 1.4.1 (or higher) [9], mmrm version 0.2.2 (or higher) [10], rpact version 3.3.2 (or higher) [11] and emmeans version 1.8.4-1 (or higher) [12] will be used.

10 References

1. Augedal, A.W., et al., *Randomized controlled trials of psychological and pharmacological treatments for nightmares: a meta-analysis*. *Sleep Med Rev*, 2013. **17**(2): p. 143–52.
2. Bonn-Miller, M.O., et al., *The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: A randomized cross-over clinical trial*. *PLoS One*, 2021. **16**(3): p. e0246990.
3. Wolbers, M., G. Wassmer, and F. Pahlke. *An Example to Illustrate Boundary Re-Calculations during the Trial with rpact*. 2025 04.06.2025]; Available from: https://www.rpact.org/vignettes/planning/rpact_boundary_update_example/.
4. Blake, D.D., et al., *The development of a Clinician-Administered PTSD Scale*. *J Trauma Stress*, 1995. **8**(1): p. 75–90.
5. Hopewell, S., et al., *CONSORT 2025 statement: updated guideline for reporting randomised trials*. *BMJ*, 2025. **389**: p. e081123.
6. Sabanes Bove, D., et al. *Package Introduction*. 2025 04.06.2025]; Available from: <https://openpharma.github.io/mmrm/main/articles/introduction.html>.
7. Nakagawa, S. and I.C. Cuthill, *Effect size, confidence interval and statistical significance: a practical guide for biologists*. *Biological Reviews*, 2007. **82**(4): p. 591–605.
8. Team, R.C., *A language and environment for statistical computing*. *R Foundation for Statistical Computing*. 2021.
9. Gower-Page, C. and A. Noci, *rbmi: Reference Based Multiple Imputation*. 2022.
10. Sabanes Bove, D., et al., *mmrm: Mixed Models for Repeated Measures*. 2022.
11. Wassmer, G. and F. Pahlke, *rpact: Confirmatory Adaptive Clinical Trial Design and Analysis*. 2022.
12. Lenth, R.V., *emmeans: Estimated Marginal Means, aka Least-Squares Means*. 2023.

11 Appendices

11.1 Planned tables sample

Subject disposition

Table A1: Patient disposition

Category	Control Arm (N =) n (%)	Intervention Arm (N =) n (%)	Overall (N =) n (%)
Patients screened			
Patients who failed screening			
Patients randomized			
Patients randomized but not treated			
Patients Treated			
Patients completed the study (Week 12)			
Patients Discontinued/Withdrawn from study			
Reason for Discontinued/Withdrawn:			
No reasons available			
Screening failure due to unfulfilled criteria			
Unblinding			
Consent withdrawal			
Investigator/Sponsor decision			
Serious adverse events, with a CTCAE grade > 3			
Loss of contact to patient			
Severe aberration from the study protocol			
Subsequent occurrence of exclusion criteria (e.g., pregnancy) after enrolment			
Death			
Other			

N = Number of patients in group; n = number of patients in each category; % = (n/N)*100

Table A2: Number of patients in analysis sets

Category	Control Arm (N =) n (%)	Intervention Arm (N =) n (%)	Overall (N =) n (%)
Full Analysis Set (FAS)			
Per Protocol Analysis Set (PPS)			
Safety Analysis Set (SAF)			

N = Number of patients in group; n = number of patients in each category; % = (n/N)*100

Primary analysis

Table A3: Least square means difference for the primary endpoint between control and intervention (FAS + PPS)

Contrast	Estimate	Standard Error	df	T value ratio	p value	95% Confidence interval
Intervention – control (FAS)						
Intervention – control (PPS)						

Df = degrees of freedom

Safety

Table A4: Overview Summary of Treatment-emergent adverse events (TEAE) – number of patients with events (Safety Analysis Set)

Category	Control Arm (N =) n (%)	Intervention Arm (N =) n (%)	Overall (N =) n (%)
Any TEAE			
TEAE Intensity			
Mild			
Moderate			
Severe			
Life-threatening consequences			
Death related to AE			
TEAE Relationship			
Sure			
Probable			
Possible			
Unlikely			
Not Related			
Cannot be evaluated			
TEAE Leading to Drug Discontinuation			
Any Serious TEAE			

N = Number of patients in group; n = number of patients in each category; % = (n/N)*100

Table A5: Overview Summary of Treatment-emergent adverse events (TEAE) – number of events (Safety Analysis Set)

Category	Control Arm (N =) #E	Intervention Arm (N =) #E	Overall (N =) #E
Any TEAE			
TEAE Intensity			
Mild			
Moderate			
Severe			
TEAE Relationship			
Sure			
Probable			
Possible			
Unlikely			
Not Related			
Cannot be evaluated			
TEAE Leading to Drug Discontinuation			
Any Serious TEAE			

N = Number of patients in group; #E = number of events

Table A6: Treatment-emergent adverse events (TEAE) by System Organ Class and AE Term - number of patients with events (Safety Analysis Set)

Category	Control Arm (N =) n (%)	Intervention Arm (N =) n (%)	Overall (N =) n (%)
System Organ Class B1			
Any Event			
AE Term A1			
AE Term A2			
.....			
System Organ Class B2			
Any Event			
AE Term C1			
AE Term C2			
.....			
System Organ Class B3			
Any Event			
AE Term D1			
AE Term D2			
...			

N = Number of patients in group; n = number of patients in each category; % = (n/N)*100

Table A7: Treatment-emergent adverse events (TEAE) by System Organ Class and AE Term - number of events (Safety Analysis Set)

Category	Control Arm (N =) #E	Intervention Arm (N =) #E	Overall (N =) #E
System Organ Class B1			
Any Event			
AE Term A1			
AE Term A2			
.....			
System Organ Class B2			
Any Event			
AE Term C1			
AE Term C2			
.....			
System Organ Class B3			
Any Event			
AE Term D1			
AE Term D2			
...			

N = Number of patients in group; #E = number of events

Table A8: Treatment-emergent adverse events (TEAE) by System Organ Class, AE Term and Severity - number of patients with events (Safety Analysis Set)

Category	Severity	Control Arm (N =) n (%)	Intervention Arm (N =) n (%)	Overall (N =) n (%)
System Organ Class B1	Mild			
	Moderate			
	Severe			
AE Term A1	Mild			
	Moderate			
	Severe			
AE Term A2	Mild			
	Moderate			
	Severe			

N = Number of patients in group; n = number of patients in each category; % = (n/N)*100

Table A9: Treatment-emergent adverse events (TEAE) by System Organ Class, AE Term and Severity - number of events (Safety Analysis Set)

Category	Severity	Control Arm (N =) #E	Intervention Arm (N =) #E	Overall (N =) #E
System Organ Class B1	Mild			
	Moderate			
	Severe			
AE Term A1	Mild			
	Moderate			
	Severe			
AE Term A2	Mild			
	Moderate			
	Severe			

N = Number of patients in group; #E = number of events

Table A10: Treatment-emergent adverse events (TEAE) by System Organ Class, AE Term and relationship - number of patients with events (Safety Analysis Set)

Category	Relationship	Control Arm (N =) n (%)	Intervention Arm (N =) n (%)	Overall (N =) n (%)
System Organ Class B1	Sure			
	Probable			
	Possible			
	Unlikely			
	Not Related			
	Cannot be evaluated			
AE Term A1	Sure			
	Probable			
	Possible			
	Unlikely			
	Not Related			
	Cannot be evaluated			
AE Term A2	Sure			
	Probable			
	Possible			
	Unlikely			
	Not Related			
	Cannot be evaluated			

N = Number of patients in group; n = number of patients in each category; % = (n/N)*100

Table A11: Treatment-emergent adverse events (TEAE) by System Organ Class, AE Term and relationship - number of events (Safety Analysis Set)

Category	Relationship	Control Arm (N =) #E	Intervention Arm (N =) #E	Overall (N =) #E
System Organ Class B1	Sure			
	Probable			
	Possible			
	Unlikely			
	Not Related			
	Cannot be evaluated			
AE Term A1	Sure			
	Probable			
	Possible			
	Unlikely			
	Not Related			
	Cannot be evaluated			
AE Term A2	Sure			
	Probable			
	Possible			
	Unlikely			
	Not Related			
	Cannot be evaluated			

N = Number of patients in group; #E = number of events

Table A12: SAE by System Organ Class and AE Term - number of patients with events (Safety Analysis Set)

Category	Control Arm (N =) n (%)	Intervention Arm (N =) n (%)	Overall (N =) n (%)
System Organ Class B1			
Any Event			
AE Term A1			
AE Term A2			
.....			
System Organ Class B2			
Any Event			
AE Term C1			
AE Term C2			
.....			
System Organ Class B3			
Any Event			
AE Term D1			
AE Term D2			
...			

N = Number of patients in group; n = number of patients in each category; % = $(n/N) \times 100$

Table A13: SAE by System Organ Class and AE Term - number of events (Safety Analysis Set)

Category	Control Arm (N =) #E	Intervention Arm (N =) #E	Overall (N =) #E
System Organ Class B1			
Any Event			
AE Term A1			
AE Term A2			
.....			
System Organ Class B2			
Any Event			
AE Term C1			
AE Term C2			
.....			
System Organ Class B3			
Any Event			
AE Term D1			
AE Term D2			
...			

N = Number of patients in group; #E = number of events

Descriptive results

Table A14: Table for descriptive summary (for FAS + PPS)

Category	Level	Control Arm (N =) n (%)	Intervention Arm (N =) n (%)	Overall (N =) n (%)
Continuous endpoint	n (%)			
	Mean (SD)			
	Median (IQR)			
	Range			
Categorical endpoint	n (%)			
	Category 1			
	Category 2			
	...			

N = Number of patients in group; n = number of patients in each category; % = $(n/N) \cdot 100$

Treating Nightmares in Posttraumatic Stress Disorder with Dronabinol: A Randomized Controlled Study (THC PTSD-trial)

THC-PTSD

Statistical Analysis Plan for interim analysis

Version 0.3 of March 3rd 2023

Investigational medicinal product: Dronabinol
Comparator: Oily Placebo Solution (cannabis aroma)
Indication: Posttraumatic Stress Disorder
Sponsor: Charité – Universitätsmedizin Berlin
Financial support: Bionorica SE
Protocol registry identification: THC-PTSD
Development phase: Phase II
EudraCT-Number: 2019-002211-25
Protocol version: Version 2.0 / 01.08.2022

Approved by

Prof. Dr. Stefan Röpke, Principal Investigator

**Stefan
Roepke**

Place and date

Signature

Digital unterschrieben
von Stefan Roepke
Datum: 2023.03.21
16:12:16 +01'00'

Robert Röhle, Statistician

Robert Roehle

Place and date

Signature

Digital unterschrieben von Robert Roehle
Datum: 2023.03.23 17:11:36 +01'00'

Version	Relevant changes from previous version
0.1	Initial draft
0.2	Addition of demography and baseline variables, secondary endpoints for interim analysis, adverse events, correction of trial visits
0.3	Inclusion of imputation method for primary endpoint Addition of sensitivity analysis for the primary endpoint

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Abbreviations

Abbreviation	Term
SAP	Statistical Analysis plan
PTSD	Posttraumatic stress disorder
CAPS	Clinician-Administered PTSD Scale
MADRS	Montgomery-Åsberg Depression Rating Scale
MCID	Minimal clinically important difference
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
AE	Adverse event
SAE	Serious adverse event

1 Purpose of this document

In this document, the unplanned interim analysis for the THC-PTSD trial is described. The Statistical analysis plan (SAP) for the final analysis will be provided in a different document.

2 Background

2.1 Trial objective

Primary objective of the study is to examine the efficacy of oral dronabinol over placebo in reducing nightmares in patients with posttraumatic stress disorder.

Secondary objectives of the study are to examine the efficacy of oral dronabinol in reducing disorder-specific symptoms in patients with posttraumatic stress disorder, and to examine the efficacy of oral dronabinol in reducing sleep disturbance in patients with posttraumatic stress disorder.

2.2 Trial design

The study is a multi-centric, double blind, randomized, placebo-controlled, parallel group interventional exploratory phase II trial.

2.2.1 Study plan

The study plan including all visits is shown in Table 1.

2.2.2 Treatments

Description of study medication / investigational medicinal product

BX-1 is an oily solution containing 25 mg/ml dronabinol. Dronabinol ((-)-trans- Δ^9 -Tetra-hydro-cannabinol, Δ^9 -THC) is the major psychoactive constituent of Cannabis sativa L.. Dronabinol is a clear to amber resin. It is highly lipid soluble. Dronabinol is thermolabile, photolabile and susceptible to oxidation.

Placebo / reference medication

There is no discernible difference between BX-1 and the corresponding placebo with regard to colour, taste, and appearance, thus ensuring the trials double-blind character. However, batch-specific variations of odour and colour may occur. In addition, all medications for the double-blind period will be labelled with a common batch number.

Trial treatments are double-blinded. The medication list and the randomisation list are stored at the pharmacy (St-Hubertus Apotheke) and the allocation to treatment groups will be managed by the pharmacy (St-Hubertus Apotheke) and will not be known to the investigator or any other person involved in the conduct of the trial until completion of the trial, except in case of an emergency (see 5.5).

2.2.3 Blinding

Treatment is blinded by use of a matching placebo. The Sponsor, study personnel, and subjects will be blinded to treatment until the database is locked. Emergency envelopes will be provided by the pharmacy and will be stored in the trial sites. These emergency envelopes could then be used by investigators in case of emergencies.

Table 1: Outline of trial visits

Assessments	SC	BL Visit 1 W 0	Visit 2 W 1	Visit 3 W 2	Visit 4 W 3	Visit 5 W 4	Visit 6 W 6	Visit 7 W 8	Visit 8 W 10	FU Visit 9 W 12
Screening and consent										
Inclusion/exclusion criteria	X									
Informed consent	X									
Physical examination ¹	X								X	
Prior and concomitant medication and non-drug therapy	X	X	X	X	X	X	X	X	X	X
Medical history	X									
IMP dispersion		X	X	X	X	X	X	X		
IMP return			X	X	X	X	X	X	X	
Safety										
Blood test ²	X								X	
Cannabis test	X									
Pregnancy test	X	X		X		X	X	X	X	
ECG	X								X	(X) ³
Blood pressure, pulse	X	X	X	X	X	X	X	X	X	X
Weight	X	X					X		X	X
Adverse event recording		X	X	X	X	X	X	X	X	X
Effectiveness										
Primary										
CAPS-IV B2									X	
Secondary										
CAPS-IV B2	X	X	X	X	X	X	X	X		
CAPS-5	X ^a	X ^b					X ^b		X ^b	
PSQI-A		X					X		X	
MADRS	X	X				X			X	
Sleep diary		X	X	X	X	X	X	X	X	
PCL-5		X					X		X	
BSL-23		X					X		X	
EQ-5D		X					X		X	
PGIC							X		X	
SOFAS		X					X		X	
PSQI		X					X		X	
ITQ		X					X		X	
MWC		X					X		X	X
Others										
Demographics	X									
CTQ	X									
MINI-5	X									
ITI	X									

Note: SC = screening, W. = week +/- 3 days, BL = baseline and randomization, FU = post-trial follow-up, CAPS-IV B2 = B2 score of the Clinician-Administered PTSD Scale for DSM-IV (frequency and intensity of nightmares), CAPS-5 = Clinician-Administered PTSD Scale for DSM-5 (a = last month version, b = last week version), PSQI-A = Pittsburgh Sleep Quality Index-Addendum for PTSD, MADRS = Montgomery-Åsberg Depression Rating Scale, PCL-5 = PTSD Checklist for DSM-5, BSL-23 = Borderline Symptom List 23, EQ-5D = Health-Related Quality of Life, PGIC = Patient Global Impression of Change, SOFAS = Social and Occupational Functioning Assessment Scale, PSQI = Pittsburgh Sleep Quality Index, ITQ = international trauma questionnaire, MWC = Marijuana Withdrawal Checklist, CTQ = Childhood trauma questionnaire, MINI-5 = The Mini International Neuropsychiatric Interview for DSM-5, ITI = International Trauma Interview. 1 Physical examination includes height and weight of the patient and the skin, abdomen, respiratory system, head and extremities will be examined, 2: blood test s include haematology (erythrocytes, haemoglobin, haematocrit, platelets, leukocytes (including neutrophils, eosinophils, basophils, lymphocytes, monocytes) and serum chemistry (sodium, potassium, chloride, calcium, creatinine, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, aspartate aminotransferase, bilirubin, lipase, thyroid stimulating hormone), 3. In case of significant abnormal ECG findings at the visit 8 (week 10), a further ECG will be recorded at the follow-up visit.

2.2.4 Inclusion criteria

- Diagnosis of posttraumatic stress disorder (PTSD) according to DSM-5 with a 20 item CAPS-5 total score ≥ 26
- At least two nightmares a week, an intensity score ≥ 2 , with a CAPS-IV B2 (frequency and intensity for the last week) score ≥ 5
- Men and women between 18 and 65 years of age
- Written informed consent
- The patient has the capacity to give consent (He/she is able to understand the nature and anticipated effects/side effects of the proposed medical intervention)
- The patient is not breastfeeding
- Women of child-bearing potential must have a negative urine or serum pregnancy test
- All participants must use highly effective contraception
- The patient received stable pharmacological medication for at least 4 weeks prior to study entry (any changes in medication dose or frequency of therapy must be answered with no)

2.2.5 Exclusion criteria

- Lifetime cannabis use disorder
- Current substance/alcohol use disorder (≤ 3 months);
- Acute suicidality;
- Psychotic disorder;
- Bipolar disorder;
- Current anorexia nervosa;
- Current major depressive episodes and a MADRS score > 29 ;
- Dementia;
- Trauma-focused psychotherapy four weeks before the trial
- Initiation of sleep medication 4 weeks prior screening or initiation of alpha adrenergic agents 4 weeks prior to screening
- Acute or unstable medical illness
- Epilepsy
- Relevant heart diseases
- Known HIV- and/or active Hepatitis-B- or Hepatitis-C-infection
- current or past malignant illness
- The patient is unwilling to consent to saving, processing and propagation of pseudonymized medical data for study reasons
- Patients, who may be dependent on the sponsor, the investigator or the trial sites, have to be excluded from the trial
- The patient is legally detained in an official institution
- The patient does have a known allergy or contraindication against Dronabinol
- The patient does have clinically significant abnormalities in 12-lead ECG
- The patient does have clinically significant laboratory abnormalities
- The patient did participate in other interventional trials during the 3 months before and at the time of this trial

2.2.6 Randomization

Patients will be randomized at baseline in a 1:1 allocation using block randomization with fixed block lengths stratified by study center.

2.2.7 Sample size

The sample size calculation is based on the primary endpoint “Clinician-Administered PTSD Scale-IV (CAPS-IV) B2 score at 10 weeks” in the ITT population including all randomized patients who received the study medication at least once. The aim is to show a lower average score at 10 weeks in the intervention group (I) than in the control group (C). Sample size calculation will be based on a two-sided, two-sample t-test. Adjustment for baseline scores in an ANCOVA model which is applied for the primary efficacy analysis will increase the power compared with a two-sample t-test, which ignores the influence of different baseline values. Therefore, this strategy for sample size calculation is a conservative procedure. In a recent random-effects meta-analysis of four RCTs investigating the effect of prazosin on PTSD nightmares, a combined standardized mean difference (Cohen’s d) of 0.5 (95% CI = 0.03–0.96) was observed (Augedal, Hansen, Kronhaug, Harvey, & Pallesen, 2013). We conservatively assume a standardized effect which is a little smaller and given by 0.45. This assumed effect can be considered as clinically relevant because distressing nightmares are an independent risk factor for comorbidity and severity in PTSD patients. Nightmares also contribute to alcohol and substance abuse, suicidal ideation, and even completed suicide (Raskind et al., 2007). As studies assessing minimal clinically important difference (MCID) for reduction of nightmares in PTSD are currently missing, clinical significance cannot be used to calculate sample size.

The required sample size to detect this effect of 0.45 with a power of 0.8 is 158 (79 per group) calculated with nQuery Version 8.2.1.0. We conservatively assume that there will be no more than 10% of patients who are randomized but never get the study medication. Therefore the total number of patients to be recruited is 176 ($158/0.9 = 176$) or 88 per group.

3 Analysis sets

3.1 Definitions

The full-analysis set consists of all randomized patients, which received the study medication at least once. Patients are analysed as randomized. This is the population as close as possible to the intention-to-treat population. Exclusion of patients who never received the study medication is explicitly stated as an option in the ICH E9 Guideline.

The safety set as the basis for all safety analyses corresponds to the full analysis set.

3.2 Application

The interim analysis will be done in the full-analysis set.

4 Trial centres

The study so far was conducted in 3 centers (two in Berlin and one in Mannheim) in Germany.

5 Analysis variables for the interim analysis

5.1 Demography and baseline characteristics

- Age [years]
- Gender
- CAPS IV B2 score at screening

5.2 Primary variable

Frequency and intensity of nightmares, measured with the Clinician-Administered PTSD Scale (CAPS-IV) B2 score for the last week, range 0–8 (Blake et al., 1995) directly after last intervention (10 weeks).

Due to the very short-lived effect of the drug, we will further investigate the CAPS-IV B2 score at the last visit under medication. This is either after the last intervention (10 weeks) for study completers or throughout the trial if the patient stopped taking medication. If the stop occurs in the dosing phase, the last visit before the stop will be taken as the measure.

5.3 Secondary variables

- Change from baseline of the CAPS-5 total score (overall PTSD symptoms, last week) at Visit 6 and Visit 8

6 Handling of missing values and outliers

6.1 Missing values

Missing values for the analysis of the primary endpoint will be imputed as follows: If the follow-up assessment at 10 weeks is missing but the patient has at least one follow-up assessment after baseline, last observation carried forward will be used for missing value imputation. If no value post-baseline is available, the patient will be excluded from the analysis.

If the baseline visit is missing but follow-up assessments are available, the baseline value will be imputed using multiple imputation.

6.2 Outliers

No outlier detection will be done in the interim analysis.

7 Statistical analyses / methods

7.1 General remarks

Descriptive analyses for continuous variables includes number of available data including percentage, mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum. For categorical variables, it includes number of available data including percentage, absolute and relative frequency. In general, results will be shown for the whole cohort and per treatment group.

7.2 Demography and baseline characteristics

Demographic and baseline variables will be analysed descriptively.

7.3 Primary analysis

We use the conditional rejection principle for the interim analysis in order to account for the unplanned analysis.

The overall one-sided alpha will be 0.025 (which is equivalent to the initially planned two-sided alpha of 0.05 but a two sided calculation is not possible due to the non-binding futility boundary).

The IA will be done after 79/176 (44.9%) patients finished visit 8 (79 is half of the needed analyzable patients (158) since currently there are no non-starters - the initial reason for an increased recruitment number)

For the boundaries we choose α_1 equal to 0.0008213 which is according to an alpha spending scheme (O'Brien Fleming) with 2 looks and a non-binding futility α_0 of 0.5 (indicating efficacy in the wrong direction).

For the effect size, the following formula given in Nakagawa and Cuthill will be used:

$$d = t \cdot \sqrt{(n_1 + n_2) / (n_1 \cdot n_2 \cdot df)},$$

where d is the equivalent of Cohen's d for an adjusted regression coefficient, t is the t -test statistic from the adjusted regression coefficient, n_1 and n_2 are the sample sizes for the treatment and the control group, and df is the number of degrees of freedom from the adjusted regression model. The adjusted regression model will include the CAPS IV at week 10 as dependent variable and the baseline CAPS IV, the center and the treatment group as independent variables. The t statistic from the regression coefficient for the treatment group will be used for the calculation of d .

If the interim analysis indicates continuation, a sample size recalculation will be done using the previously assumed effect size of Cohen's $d = 0.45$. If the recalculated sample size exceeds an additional number of 80 patients beyond the initially planned 176 patients, a conditional power calculation for a design with $n = 256$ ($176+80$) will be done.

If the conditional power is less than 50%, the trial will also be stopped due to futility.

The analogous regression model for the last CAPS IV B2 under medication as dependent variable will be calculated as part of the sensitivity analysis.

7.4 Secondary analyses

7.4.1 Secondary endpoints

The CAPS IV B2 at baseline and the differences from baseline to visits 6 and from baseline to visit 8 will be shown descriptively.

7.4.2 Adverse events

Adverse events will be listed per patient. The number of Adverse events (AE) and serious adverse events (SAE), number of AEs and SAE that led to discontinuation and shown descriptively. The number of AEs and SAEs in each severity and relationship to treatment category will also be shown. The same will be done for the number of patients with AEs and SAEs.

8 Software

For the analysis the software R (version 4.1.2 or newer) will be used.

9 References

Nakagawa, S. and Cuthill, I.C. (2007), Effect size, confidence interval and statistical significance: a practical guide for biologists. *Biological Reviews*, 82: 591-605. <https://doi.org/10.1111/j.1469-185X.2007.00027.x>