Clinical trial results:
A randomized multi-centre double-blind placebo controlled trial to demonstrate the efficacy and safety of nabiximols in the treatment of adults with chronic tic disorders (CANNA-TICS)

Summary

EudraCT number	2016-000564-42
Trial protocol	DE
Global end of trial date	20 November 2020

Results information

Result version number	v1 (current)
This version publication date	31 December 2023
First version publication date	31 December 2023

Trial information

Trial identification

Sponsor protocol code	CANNA-TICS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03087201
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hannover Medical School
Sponsor organisation address	Carl-Neuberg-Str. 1, Hannover, Germany, 30625
Public contact	Zentrum für Klinische Forschung (ZKS), Hannover Medical School, EudraCT@mh-hannover.de
Scientific contact	Zentrum für Klinische Forschung (ZKS), Hannover Medical School, EudraCT@mh-hannover.de

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 November 2020
Global end of trial reached?	Yes
Global end of trial date	20 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that treatment with the cannabis extract nabiximols is superior to placebo in reducing tics and comorbidities in patients with Tourette syndrome and chronic tic disorders

Protection of trial subjects:

The clinical trial was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and with the standards of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). A continuous risk assessment was performed during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 97
Worldwide total number of subjects	97
EEA total number of subjects	97

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	97
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

98 adult patients with chronic tic disorders (Tourette Syndrom (TS) or other chronic tic disorders) were recruited across 6 centers throughout Germany

Pre-assignment

Screening details:

Eligibility will be determined based upon the inclusion and exclusion criteria

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Nabiximol arm

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Nabiximol
Investigational medicinal product code	
Other name	Sativex
Pharmaceutical forms	Sublingual spray
Routes of administration	Sublingual use

Dosage and administration details:

1-12 puffs/day; 1 puff = 100 µl spray = 2.7 mg THC and 2.5 mg cannabidiol (CBD)), oromucosal spray. Nabiximols (Sativex®) is a plant extract from Cannabis sativa L. It is a sublingually administered oromucosal spray that contains THC and CBD at about a 1:1 ratio.

Arm title	Placebo arm

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Sativex placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual spray
Routes of administration	Subgingival use

Dosage and administration details:

Placebo (1-12 puffs/day; 1 puff = 100 µl spray), oromucosal spray.

Number of subjects in period 1	Nabiximol arm	Placebo arm
Started	64	33
Completed	48	24
Not completed	16	9
Consent withdrawn by subject	6	2
Physician decision	1	1
other reasons	2	1
Adverse event, non-fatal	5	1
patient was deblinded during study	2	-
deblinded patient	-	3
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Nabiximol arm
Reporting group description: -	
Reporting group title	Placebo arm
Reporting group description: -	

Reporting group values	Nabiximol arm	Placebo arm	Total
Number of subjects	64	33	97
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	64	33	97
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	15	9	24
Male	49	24	73

End points

End points reporting groups	
Reporting group title	Nabiximol arm
Reporting group description: -	
Reporting group title	Placebo arm
Reporting group description: -	

Primary: primary response >25% in YGTSS-TTS	
End point title	primary response >25% in YGTSS-TTS
End point description:	
Response to treatment according to YGTSS-TTS, defined as a reduction in YGTSS-TTS of at least 25% (compared to baseline) after 9 weeks of stable treatment.	
End point type	Primary
End point timeframe:	
9 weeks of stable treatment	

End point values	Nabiximol arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	33		
Units: subjects	14	3		

Statistical analyses

Statistical analysis title	Primary response > 25%
Statistical analysis description:	
Primary response > 25% (as determined in blind review) ITT	
Comparison groups	Placebo arm v Nabiximol arm
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0755
Method	Mantel-Haenszel
Parameter estimate	Mantel-Haenszel estimate
Point estimate	-0.1278
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2688
upper limit	0.0131

Primary: Primary response > 30%	
End point title	Primary response > 30%
End point description:	
Response to treatment according to YGTSS-TTS, defined as a reduction in YGTSS-TTS of at least 25% (compared to baseline) after 9 weeks of stable treatment.	
End point type	Primary
End point timeframe:	
9 weeks of stable treatment	

End point values	Nabiximol arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	33		
Units: subjects	8	1		

Statistical analyses

Statistical analysis title	Primary response > 30%
Comparison groups	Nabiximol arm v Placebo arm
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0633
Method	Mantel-Haenszel
Parameter estimate	Mantel-Haenszel estimate
Point estimate	-0.0947
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1946
upper limit	0.0052

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event documentation period for this trial begins upon first administration of the IMP(s) and ends with the last follow-up visit.

Adverse event reporting additional description:

Numbers in the non-serious adverse events section reflect all adverse events occurring during the study (non-serious and serious).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Placebo

Reporting group description: -

Reporting group title	Nabiximols

Reporting group description: -

Serious adverse events	Placebo	Nabiximols	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 33 (3.03%)	1 / 64 (1.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Social circumstances			
Pregnancy Of Partner			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Tic			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	Nabiximols	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 33 (78.79%)	61 / 64 (95.31%)	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 33 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	3	
Hypertension			
subjects affected / exposed	1 / 33 (3.03%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Surgical and medical procedures			
Dental implantation			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Nasal septal operation			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Sluggishness			
subjects affected / exposed	0 / 33 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	3	
Application site dryness			
subjects affected / exposed	3 / 33 (9.09%)	12 / 64 (18.75%)	
occurrences (all)	3	12	
Application site dysaesthesia			
subjects affected / exposed	1 / 33 (3.03%)	2 / 64 (3.13%)	
occurrences (all)	2	2	
Application site hypoaesthesia			
subjects affected / exposed	2 / 33 (6.06%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Application site irritation			
subjects affected / exposed	3 / 33 (9.09%)	5 / 64 (7.81%)	
occurrences (all)	3	5	
Application site pain			

subjects affected / exposed	2 / 33 (6.06%)	3 / 64 (4.69%)	
occurrences (all)	2	3	
Application site paraesthesia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Asthenia			
subjects affected / exposed	1 / 33 (3.03%)	8 / 64 (12.50%)	
occurrences (all)	1	11	
Chest pain			
subjects affected / exposed	0 / 33 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Condition aggravated			
subjects affected / exposed	0 / 33 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	3	
Crying			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Facial pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	8 / 33 (24.24%)	19 / 64 (29.69%)	
occurrences (all)	12	20	
Feeling abnormal			
subjects affected / exposed	1 / 33 (3.03%)	26 / 64 (40.63%)	
occurrences (all)	1	35	
Feeling cold			
subjects affected / exposed	0 / 33 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Feeling drunk			
subjects affected / exposed	0 / 33 (0.00%)	4 / 64 (6.25%)	
occurrences (all)	0	4	
Feeling hot			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	2	
Feeling jittery			

subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Feeling of relaxation			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Glassy eyes			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Hunger			
subjects affected / exposed	0 / 33 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Influenza like illness			
subjects affected / exposed	4 / 33 (12.12%)	4 / 64 (6.25%)	
occurrences (all)	4	4	
Malaise			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Pre-existing condition improved			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Sense of oppression			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Application site discomfort			
subjects affected / exposed	0 / 33 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	3	
Social circumstances			
Pregnancy of partner			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Sexual dysfunction			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Tonsillar inflammation			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	2	
Pneumonitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Psychiatric disorders			
Panic disorder			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Panic attack			
subjects affected / exposed	1 / 33 (3.03%)	4 / 64 (6.25%)	
occurrences (all)	2	4	
Nervousness			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Mood swings			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Aggression			
subjects affected / exposed	0 / 33 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Agitation			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Apathy			

subjects affected / exposed	0 / 33 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Confusional state			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Daydreaming			
subjects affected / exposed	0 / 33 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Depressed mood			
subjects affected / exposed	0 / 33 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	3	
Depression			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Dysphemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Euphoric mood			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Fear of disease			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Impulsive behaviour			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Indifference			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Initial insomnia			
subjects affected / exposed	1 / 33 (3.03%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Insomnia			
subjects affected / exposed	1 / 33 (3.03%)	1 / 64 (1.56%)	
occurrences (all)	1	2	
Irritability			

subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Libido decreased			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Libido increased			
subjects affected / exposed	0 / 33 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Middle insomnia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Mood altered			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Thought blocking			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Stress			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Restlessness			
subjects affected / exposed	2 / 33 (6.06%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Psychomotor retardation			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Time perception altered			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

Animal bite			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Muscle strain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Road traffic accident			
subjects affected / exposed	1 / 33 (3.03%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Congenital, familial and genetic disorders			
Tourette's disorder			
subjects affected / exposed	4 / 33 (12.12%)	4 / 64 (6.25%)	
occurrences (all)	5	6	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 33 (0.00%)	5 / 64 (7.81%)	
occurrences (all)	0	5	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	2 / 33 (6.06%)	2 / 64 (3.13%)	
occurrences (all)	4	3	
Taste disorder			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Sensory disturbance			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 33 (3.03%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Muscle contractions involuntary			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	

Migraine			
subjects affected / exposed	1 / 33 (3.03%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Memory impairment			
subjects affected / exposed	0 / 33 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	3	
Loss of consciousness			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	7 / 33 (21.21%)	9 / 64 (14.06%)	
occurrences (all)	9	10	
Disturbance in attention			
subjects affected / exposed	2 / 33 (6.06%)	6 / 64 (9.38%)	
occurrences (all)	3	6	
Head discomfort			
subjects affected / exposed	1 / 33 (3.03%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Fumbling			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	11 / 33 (33.33%)	23 / 64 (35.94%)	
occurrences (all)	12	33	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Ocular hyperaemia			
subjects affected / exposed	0 / 33 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	3	
Visual impairment			

subjects affected / exposed	0 / 33 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Vision blurred			
subjects affected / exposed	0 / 33 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	4	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	3 / 33 (9.09%)	5 / 64 (7.81%)	
occurrences (all)	4	5	
Toothache			
subjects affected / exposed	2 / 33 (6.06%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Frequent bowel movements			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Faeces soft			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Eructation			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 33 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	4	
Defaecation urgency			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	

Aphthous ulcer			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Abnormal faeces			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Abdominal pain lower			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	1 / 33 (3.03%)	2 / 64 (3.13%)	
occurrences (all)	1	2	
Abdominal distension			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Bladder irritation			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 64 (0.00%)	
occurrences (all)	3	0	
Back pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Fibromyalgia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	2	

Muscle spasms			
subjects affected / exposed	1 / 33 (3.03%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Muscle twitching			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Nuchal rigidity			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Pain in jaw			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Abscess			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 33 (3.03%)	3 / 64 (4.69%)	
occurrences (all)	1	3	
Gastrointestinal infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	4 / 33 (12.12%)	9 / 64 (14.06%)	
occurrences (all)	5	10	
Oral herpes			

subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)	2 / 64 (3.13%)	
occurrences (all)	1	2	
Upper respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 33 (3.03%)	2 / 64 (3.13%)	
occurrences (all)	1	2	
Feeding intolerance			
subjects affected / exposed	0 / 33 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Food craving			
subjects affected / exposed	0 / 33 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	3	
Increased appetite			
subjects affected / exposed	2 / 33 (6.06%)	3 / 64 (4.69%)	
occurrences (all)	2	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2017	Revision of study protocol: i.a. implementation of the study part `fitness to drive`
22 November 2017	Application for resumption of recruitment after temporary halt
19 March 2019	Revision of study protocol: i.a. alteration in manufacturing chain, extension duration of recruitment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 June 2018	due to defective label	08 August 2018

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36878177

http://www.ncbi.nlm.nih.gov/pubmed/36213751

http://www.ncbi.nlm.nih.gov/pubmed/33594741

http://www.ncbi.nlm.nih.gov/pubmed/33324255