Clinical trial results:
Prednisolone addition for atients with recent onset psychotic disorder: the role of immune-modulating strategies in the treatment of psychosis.

Summary

EudraCT number	2014-000520-14
Trial protocol	NL BE
Global end of trial date	16 May 2019

Results information

Result version number	v1 (current)
This version publication date	03 December 2021
First version publication date	03 December 2021

Trial information

Trial identification

Sponsor protocol code	NL46653

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02949232
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UMC Utrecht
Sponsor organisation address	Heidelberglaan 100, Utrecht, Netherlands,
Public contact	i.winter@umcutrecht.nl, University Medical Center Utrecht, i.winter@umcutrecht.nl
Scientific contact	i.winter@umcutrecht.nl, University Medical Center Utrecht, i.winter@umcutrecht.nl

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	16 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 May 2019
Global end of trial reached?	Yes
Global end of trial date	16 May 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Different lines of evidence now suggest that low grade inflammation in the central lines of the central nervous system is involved in the pathogenesis of schizophrenia. Such inflammation could cause increased gray matter loss and consequently contribute to more severe negative and cognitive symptoms. We propose to investigate the effect of administering prednisolone (a broad-acting, potent immune suppressive agent) versus placebo, on psychotic symptoms, in addition to standard antipsychotic medication in patients with early stage schizophrenia or related disorders. This may revent neuronal damage caused by low-grade inflammatory rocesses in the brain. It is expected that symptom severity will be improved with prednisolone use.

Protection of trial subjects:

Several events that may jeopardize the patient's health will prompt clinicians to end the study and start tapering the patient off the study medication immediately in line with the treatment guidelines for Inflammatory Bowel Diseases (2008) These events include the patient developing:
- a blood glucose exceeding 7,0 mmol/L, In case a non-fasting glucose level was determined: a blood glucose level exceeding 11 mmol/L
- suicidal ideations assessed by the CDSS, the following cut-off are applicable based on item 8: Suicidal ideations within the CDSS; Score of 0: no action (no suicidal ideation), Score of 1: consult with clinician (passive suicidal ideation), Score of 2/3: potential cause to stop study medication treatment – consult with clinician (active suicidal ideation).
- the PANSS positive subscores which increase by 10 or more points without a clear reason (i.e. medication non-adherence)
- the PANSS item G6 exceeding a score of 4
- the need for coercive treatment
- pregnancy
- oral systematic infectious disease.

Laboratory assessments were conducted several times during this study. The lab results were checked by the study physician. Addiontally, each visit the adverse events and the concomitant medication were checked by the study physician.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety, Scientific research
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 19
Country: Number of subjects enrolled	Belgium: 23

Worldwide total number of subjects	42
EEA total number of subjects	42

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)	42
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited between 01 July 2014 and 01 February 2019. In total 246 potential candidates were approached for this study of which 68 patients signed informed consent and were screened for eligibility.

Pre-assignment

Screening details:

Eligible patients were aged 18-70, diagnosed with schizophrenia, schizophreniform disorder, schizoaffective disorder or psychosis NOS no longer than 7 years ago, treated with a stable dose of antipsychotic medication for at least three weeks and a minimum PANSS total score of 60. Patients were excluded when their BMI exceeded 30.

Period 1

Period 1 title	Assignment and baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Carer, Assessor

Blinding implementation details:

Randomization was performed centrally at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands. A web-based application was used and stratification was applied for sex. Blockrandomisation was performed for sexe and different centers and countries. . Trial treatment randomization codes were not available to the study staff.

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline: Prednisolone

Arm description:

Prednisolone was initiated during the first week at 40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks; in the second week, patients will use 25 mg/day, in the third week 20 mg/day is used etc. In the last week the patients will only take prednisolone on day 1-3 and day 5 and 7.

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

Dosage and administration details:

40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks.

Arm title	Baseline: Placebo

Arm description:

Matching placebo 40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks. After six weeks the placebo was completely discontinued.

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

Dosage and administration details:

40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks.

Number of subjects in period 1	Baseline: Prednisolone	Baseline: Placebo
Started	21	21
Completed	21	21

Period 2

Period 2 title	End of treatment - 6 weeks treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	End of treatment: Prednisolone

Arm description:

Prednisolone was initiated during the first week at 40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks; in the second week, patients will use 25 mg/day, in the third week 20 mg/day is used etc. In the last week the patients will only take prednisolone on day 1-3 and day 5 and 7. At this visit, prednisolone was completely discontinued.

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

Dosage and administration details:

Subjects will ingest the products in the form of identical tablets. In the current study, the following titration schedule will be employed (in line with the treatment guidelines for Inflammatory Bowel Diseases (2008)) which should minimize the occurrence of any side effects and withdrawal symptoms.

1. week 1: day 1-3: 40 mg/day, divided over two intakes; day 4-7: 30 mg/day, divided over two intakes
2. week 2: 25 mg/day, divided over two intakes
3. week 3: 20 mg/day, divided over two intakes
4. week 4: 15 mg/day, divided over two intakes
5. week 5: 10 mg/day, intake once daily
6. week 6: day 1-3: 5 mg/day, intake once daily; day 4-7: on day 5 and 7, 5 mg/day, intake once

daily, on day 4 and 6 no tablets
After week 6, prednisolone will be discontinued. These dosages are within the registered therapeutic dose range for prednisolone, which varies from 10 to 120mg/daily depending on disease severity.

Arm title	End of treatment : Placebo

Arm description:

Participants will receive placebo capsules entirely matching prednisolone. At this visit the study medication was completely discontinued.

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

Dosage and administration details:

Subjects will ingest the products in the form of identical tablets. In the current study, the following titration schedule will be employed (in line with the treatment guidelines for Inflammatory Bowel Diseases (2008)) which should minimize the occurrence of any side effects and withdrawal symptoms.

1. week 1:
day 1-3: 40 mg/day, divided over two intakes
day 4-7: 30 mg/day, divided over two intakes
2. week 2:
25 mg/day, divided over two intakes
3. week 3:
20 mg/day, divided over two intakes
4. week 4:
15 mg/day, divided over two intakes
5. week 5:
10 mg/day, intake once daily
6. week 6:
day 1-3: 5 mg/day, intake once daily
day 4-7: on day 5 and 7, 5 mg/day, intake once daily, on day 4 and 6 no tablets.

Number of subjects in period 2	End of treatment: Prednisolone	End of treatment : Placebo
Started	21	21
Completed	19	20
Not completed	2	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	-	1
Lost to follow-up	1	-

Period 3

Period 3 title	16-weeks follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Prednisolone

Arm description: -

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

Dosage and administration details:

In the follow-up phase study medication was not used. However, patients, investigators, assessors and monitors were still blinded for the treatment arm.

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks. Study medication was already discontinued.

Number of subjects in period 3	Prednisolone	Placebo
Started	19	20
Completed	9	7
Not completed	10	13
Visit not conducted.	8	9
Lost to follow-up	2	4

Period 4

Period 4 title	26 weeks follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	26 weeks follow-up: Prednisolone

Arm description:

Patients were not using prednisolone as this was discontinued at week 6.

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

Dosage and administration details:

40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks. Study medication was discontinued. Patients were not using study medication at this visit.

Arm title	26 weeks follow-up: Placebo

Arm description:

Patients were not using placebo anymore, as study medication was discontinued at week 6.

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

Dosage and administration details:

40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks. Study medication was discontinued at this visit.

Number of subjects in period 4	26 weeks follow-up: Prednisolone	26 weeks follow-up: Placebo
Started	9	7
Completed	16	10
Not completed	1	6
Patient missed visit	1	-
Patients missed visit	-	5
Lost to follow-up	-	1
Joined	8	9
Visit 16 was not conducted	8	9

Period 5	
Period 5 title	52 weeks follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	52 weeks follow-up: Prednisolone

Arm description:

Prednisolone study medication was discontinued.

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

Dosage and administration details:

40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks. STudy medication was not used at this visit.

Arm title	52 weeks follow-up: placebo

Arm description:

Placebo study medication was discontinued.

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

Dosage and administration details:

: 40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks. Study medication was already discontinued.

Number of subjects in period 5	52 weeks follow-up: Prednisolone	52 weeks follow-up: placebo
Started	16	10
Completed	12	13
Not completed	5	2
Lost to follow-up	5	2
Joined	1	5
Patient skipped 26 weeks visit	1	5

Baseline characteristics

Reporting groups	
Reporting group title	Baseline: Prednisolone
Reporting group description:	
Prednisolone was initiated during the first week at 40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks; in the second week, patients will use 25 mg/day, in the third week 20 mg/day is used etc. In the last week the patients will only take prednisolone on day 1-3 and day 5 and 7.	
Reporting group title	Baseline: Placebo
Reporting group description:	
Matching placebo 40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks. After six weeks the placebo was completely discontinued.	

Reporting group values	Baseline: Prednisolone	Baseline: Placebo	Total
Number of subjects	21	21	42
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)	21	21	42
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	32.24	28.0	
standard deviation	± 10.60	± 7.11	-
Gender categorical Units: Subjects			
Female	2	5	7
Male	19	16	35
PANSS total Units: PANSS score			
arithmetic mean	81.23	75.24	
standard deviation	± 13.23	± 10.54	-
PANSS positive Units: PANSS score			
arithmetic mean	20.52	17.95	
standard deviation	± 5.48	± 3.47	-
PANSS negative Units: PANSS score			
arithmetic mean	20.90	19.38	
standard deviation	± 6.32	± 4.49	-
PANSS general			

Units: PANSS score			
arithmetic mean	39.81	37.9	
standard deviation	± 8.23	± 7.46	-
GAF score			
Units: GAF score			
arithmetic mean	41.57	50.48	
standard deviation	± 15.47	± 16.38	-
CDS score			
Units: CDS score			
arithmetic mean	5.38	4.09	
standard deviation	± 4.71	± 3.52	-

Subject analysis sets

Subject analysis set title	Intention to treat sample
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Of the patients who signed IC and passed the screening assessments, only those patients are included in the main analyses who have received the study medication.

Reporting group values	Intention to treat sample		
Number of subjects	42		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	42		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	30.12		
standard deviation	± 9.168		
Gender categorical			
Units: Subjects			
Female			
Male			
PANSS total			
Units: PANSS score			
arithmetic mean	78.23		
standard deviation	± 12.25		
PANSS positive			
Units: PANSS score			
arithmetic mean	19.24		
standard deviation	± 4.72		
PANSS negative			

Units: PANSS score			
arithmetic mean	20.14		
standard deviation	± 5.47		
PANSS general			
Units: PANSS score			
arithmetic mean	38.86		
standard deviation	± 7.82		
GAF score			
Units: GAF score			
arithmetic mean	46.2		
standard deviation	± 16.7		
CDS score			
Units: CDS score			
arithmetic mean	4.74		
standard deviation	± 4.16		

End points

End points reporting groups

Reporting group title	Baseline: Prednisolone

Reporting group description:

Prednisolone was initiated during the first week at 40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks; in the second week, patients will use 25 mg/day, in the third week 20 mg/day is used etc. In the last week the patients will only take prednisolone on day 1-3 and day 5 and 7.

Reporting group title	Baseline: Placebo

Reporting group description:

Matching placebo 40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks. After six weeks the placebo was completely discontinued.

Reporting group title	End of treatment: Prednisolone

Reporting group description:

Prednisolone was initiated during the first week at 40mg/day for 3 days and 30mg/day for 4 days, followed by a decrease of 5mg/day per week during the remaining 5 weeks; in the second week, patients will use 25 mg/day, in the third week 20 mg/day is used etc. In the last week the patients will only take prednisolone on day 1-3 and day 5 and 7. At this visit, prednisolone was completely discontinued.

Reporting group title	End of treatment : Placebo

Reporting group description:

Participants will receive placebo capsules entirely matching prednisolone. At this visit the study medication was completely discontinued.

Reporting group title	Prednisolone

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Reporting group title	26 weeks follow-up: Prednisolone

Reporting group description:

Patients were not using prednisolone as this was discontinued at week 6.

Reporting group title	26 weeks follow-up: Placebo

Reporting group description:

Patients were not using placebo anymore, as study medication was discontinued at week 6.

Reporting group title	52 weeks follow-up: Prednisolone

Reporting group description:

Prednisolone study medication was discontinued.

Reporting group title	52 weeks follow-up: placebo

Reporting group description:

Placebo study medication was discontinued.

Subject analysis set title	Intention to treat sample
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Of the patients who signed IC and passed the screening assessments, only those patients are included in the main analyses who have received the study medication.

Primary: End of treatment

End point title	End of treatment

End point description:

End point type	Primary

End point timeframe:

The end of the six weeks treatment period.

End point values	End of treatment: Prednisolone	End of treatment : Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: PANSS total				
arithmetic mean (standard deviation)	64.18 (± 16.51)	57.73 (± 10.16)		

Statistical analyses

Statistical analysis title	Treatment effect

Statistical analysis description:

The analysis for the primary outcome was performed with a mixed model. Three nested mixed models were fitted to test the effects of the interaction between treatment and time (number of weeks after baseline) and of treatment as main effect respectively. These effects were tested using the Likelihood ratio test (LRT) by subtracting the −2 log Likelihoods from models with and without the relevant effect, which has a $\chi 2$ distribution. The modelsincluded time (categorical) and PANSS total baseline.

Comparison groups	End of treatment: Prednisolone v End of treatment : Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.96
Method	Mixed models analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events were reported until the end of the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Prednisolone

Reporting group description:

Treatment of six weeks prednisolone

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Prednisolone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 21 (9.52%)	5 / 21 (23.81%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Psychiatric disorders			
Psychotic exacerbation			
subjects affected / exposed	2 / 21 (9.52%)	5 / 21 (23.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug use disorder			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour			

subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Prednisolone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 21 (80.95%)	17 / 21 (80.95%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 21 (4.76%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	0 / 21 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Increased appetite			
subjects affected / exposed	7 / 21 (33.33%)	4 / 21 (19.05%)	
occurrences (all)	7	4	
Fatigue			
subjects affected / exposed	3 / 21 (14.29%)	1 / 21 (4.76%)	
occurrences (all)	3	1	
Decreased appetite			
subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Ankle edema			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Spots before eyes			

subjects affected / exposed	1 / 21 (4.76%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Stomach ache			
subjects affected / exposed	3 / 21 (14.29%)	1 / 21 (4.76%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	2 / 21 (9.52%)	2 / 21 (9.52%)	
occurrences (all)	2	2	
Abdominal discomfort			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
obstipation			
subjects affected / exposed	1 / 21 (4.76%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Heartburn			
subjects affected / exposed	0 / 21 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Dry mouth			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Saliva increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	

Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Swelling face			
subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Dry skin			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Skin red			
subjects affected / exposed	1 / 21 (4.76%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Skin lesion			
subjects affected / exposed	0 / 21 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Hirsutism			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Pimple			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Sweating			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depressive symptom			
subjects affected / exposed	3 / 21 (14.29%)	1 / 21 (4.76%)	
occurrences (all)	3	1	
Mood altered			
subjects affected / exposed	2 / 21 (9.52%)	4 / 21 (19.05%)	
occurrences (all)	2	4	
Insomnia			
subjects affected / exposed	2 / 21 (9.52%)	2 / 21 (9.52%)	
occurrences (all)	2	2	

Aggression			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	1 / 21 (4.76%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Mood elevated			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Restlessness			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Sleep excessive			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Suicidal ideation			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Tobacco abuse			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Euphoric mood			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Psychotic exacerbation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	2 / 21 (9.52%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Leg pain			

subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Cramp in hand			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Delayed healing of wound			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Muscle weakness			
subjects affected / exposed	0 / 21 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Pain in thumb			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Muscle stiffness			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	1 / 21 (4.76%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Polydipsia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2016	Change in eligibility criteria due to recruitment barrier o Inclusion criteria CRP ≥3.9 was deleted as inclusion criterion Duration of illness no longer than 5 years ago was changed into no longer than 7 years ago o Exclusion criteria BMI >27.5 was changed into BMI >30.0
19 October 2016	- PBMC analysis was deleted from the study protocol as this analysis could not be performed by the majority of the participating centers. - Change in blood volume withdrawn for laboratory assessment - Change in Serious Adverse Event reporting were implemented; hospitalization due to psychiatric exacerbation is reported only in the annual line listings, due to the high frequency of occurrence at this stage of the illness and the fact that immediate reporting does not have added value. - Addition of a new participating center
26 January 2017	- Addition of extra visit; 16 weeks after baseline - Recruitment extension - Change in laboratory assessment
15 May 2019	- Reduction of participant sample and prematurely termination of the trial

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported