



## Clinical trial results:

### Nabilone for non-motor symptoms in Parkinson's disease: A Randomized Placebo-controlled, double-blind, parallel-group, enriched enrollment randomized withdrawal Study

#### Summary

EudraCT number	2017-000192-86
Trial protocol	AT
Global end of trial date	15 July 2019

#### Results information

Result version number	v1 (current)
This version publication date	29 July 2020
First version publication date	29 July 2020
Summary attachment (see zip file)	SmPC Nabilone (141013_Canemes_SPC_AT.pdf) Clinical Study Protocol 1.4 (Clinical_Study_Protocol_Nabilone_Version_1.4_signed.pdf) Complete list of AEs (Complete_list_AEs_original.xlsx) Data Safety Monitoring Board Meeting (Data_Safety_Board_Meeting.pdf) IMPD_Nabilone (IMPD_NABC_SwissCo_170615_final.pdf) IMPD_Placebo (IMPD_NABC_SwissCo_170712_final.pdf) Individual Patient Demographics (Individual_Patient_Demographics.pdf) List of patient identifiers (List_of_patients_identifier.pdf) Protocol Deviation Log (Protocol_Deviation_Log.pdf) Final report (Final report.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	NMSNabStudy
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##### Additional study identifiers

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

Notes:

##### Sponsors

Sponsor organisation name	Medical University of Innsbruck
Sponsor organisation address	Anichstraße 35, Innsbruck, Austria, 6020
Public contact	Clinical Trial Center Neurology, Medizinische Universität Innsbruck, Universitätsklinik für Neurologie, +43 51250425810, raphaela.stolz@tirol-kliniken.at
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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 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 July 2019
Global end of trial reached?	Yes
Global end of trial date	15 July 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary efficacy objective of this study is to demonstrate the efficacy of nabilone concerning non-motor symptoms of patients with Parkinson's disease, based on the change from baseline to Week 4/Termination visit in the MDS-UPDRS Part I.

Protection of trial subjects:

For all work involving data collection or management of subjects, the study centre adhered to the law as laid down in the European Regulation (EU) 2016/679 as well as to the national data protection law.

Safety Assessments

Tolerability was described through the: Number of subjects (%) who discontinue the study and the number of subjects (%) who discontinue the study due to AE

Safety Measures included the following: AEs, SAEs, SUSARs, Clinical and laboratory assessment, Vital signs including performance of active orthostatism (measurement of heart rate and blood pressure after 10 minutes of quiet rest in the supine position and at 1, 2, 3, 5, and 10 minutes of active standing), ECG results, Patient's Compliance, Prior and Concomitant Medication Use, Hallucination item (1.2), OH item (1.12), and Day-time sleepiness item (1.8) of the MDS-UPDRS, C-SSRS

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 October 2017
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	Austria: 47
Worldwide total number of subjects	47
EEA total number of subjects	47

Notes:

<b>Subjects enrolled per age group</b>	
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)	18
From 65 to 84 years	29
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patient recruitment was started in October 2017 and ended in July 2019. The first patient was included in December 2017.

### Pre-assignment

Screening details:

Forty-eight participants were screened. There was one screening failure due to the use of prohibited concomitant medication. During open-label titration (phase 1) nine patients were either non-responder as defined per protocol (n=5, 10.42%) or discontinued (1 drop-out, 3 due to AEs). Thirty-eight patients entered phase 2 and were randomised 1:1.

### Period 1

Period 1 title	Phase 1 of the trial = open-label
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Arm title	Nabilone
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Arm description:

Phase 1 of the trial was open-label (OL) and nabilone, manufactured by AOP Orphan Pharmaceuticals AG (Vienna, Austria), was given orally daily starting with a dose of 0.25 milligrams (mg, one capsule) in the evening after the baseline visit. It was titrated in 0.25 mg-increments every one to four days after consultation with the study team during regular telephone calls. Dose adjustments were performed until patients met the responder criterion defined as a patient-based rating of their NMS as "much improved" (CGI-I Rating Scale: 2) or "very much improved" (CGI-I Rating Scale: 1) on the 7-point CGI-I Scale. Patients failing to meet this response criterion at the maximum daily dose of 2 mg or patients with intolerable side effects believed to be related to the study drug were discontinued.

Arm type	Experimental
Investigational medicinal product name	Nabilone
Investigational medicinal product code	verum
Other name	Canemes
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

nabilone, manufactured by AOP Orphan Pharmaceuticals AG (Vienna, Austria), was given orally daily. dose specified during phase 1 of the trial

Number of subjects in period 1	Nabilone
Started	47
Completed	38
Not completed	9
Consent withdrawn by subject	1
Adverse event, non-fatal	3
Lack of efficacy	5

## Period 2

Period 2 title	Phase 2 of the trial - double-blind
Is this the baseline period?	Yes <sup>[1]</sup>
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

### Blinding implementation details:

Treatment responders were randomly assigned (1:1) to either nabilone in their individual optimal dose or placebo (corn starch) of matching colour and shape and supplied in identical packaging. Randomisation was performed with a computer-generated randomisation schedule provided by the Department of Medical Statistics of the MUI. Respective medication boxes with either verum or placebo were labelled consecutively (1-48) according to the randomisation list to ensure concealment.

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Nabilone

### Arm description:

Treatment Arm

Arm type	Active comparator
Investigational medicinal product name	Nabilone
Investigational medicinal product code	verum
Other name	Canemes
Pharmaceutical forms	Capsule
Routes of administration	Oral use

### Dosage and administration details:

nabilone, manufactured by AOP Orphan Pharmaceuticals AG (Vienna, Austria), was given orally daily. dose specified during phase 1 of the trial

<b>Arm title</b>	Placebo
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### Arm description:

matching placebo

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

### Dosage and administration details:

matching placebo, taken orally daily

### Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Primary Endpoint is based on period 2 of the trial, therefore baseline values refer to the randomisation visit.

Number of subjects in period 2 <sup>[2]</sup>	Nabilone	Placebo
Started	19	19
Completed	19	19

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Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Primary Endpoint is based on period 2 of the trial, therefore baseline values refer to the randomisation visit.

## Baseline characteristics

### Reporting groups

Reporting group title	Nabilone
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Reporting group description:
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Treatment Arm
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Reporting group title	Placebo
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Reporting group description:
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matching placebo
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Reporting group values	Nabilone	Placebo	Total
Number of subjects	19	19	38
Age categorical			
Units: Subjects			
Adults (18-64 years)	7	9	16
From 65-84 years	12	10	22
85 years and over	0	0	0
Not recorded	0	0	0
Gender categorical			
Units: Subjects			
Female	9	5	14
Male	10	14	24

## End points

### End points reporting groups

Reporting group title	Nabilone
Reporting group description:	
Phase 1 of the trial was open-label (OL) and nabilone, manufactured by AOP Orphan Pharmaceuticals AG (Vienna, Austria), was given orally daily starting with a dose of 0.25 milligrams (mg, one capsule) in the evening after the baseline visit. It was titrated in 0.25 mg-increments every one to four days after consultation with the study team during regular telephone calls. Dose adjustments were performed until patients met the responder criterion defined as a patient-based rating of their NMS as "much improved" (CGI-I Rating Scale: 2) or "very much improved" (CGI-I Rating Scale: 1) on the 7-point CGI-I Scale. Patients failing to meet this response criterion at the maximum daily dose of 2 mg or patients with intolerable side effects believed to be related to the study drug were discontinued.	
Reporting group title	Nabilone
Reporting group description:	
Treatment Arm	
Reporting group title	Placebo
Reporting group description:	
matching placebo	

### Primary: change of the MDS-UPDRS Part 1

End point title	change of the MDS-UPDRS Part 1
End point description:	
The primary endpoint of the study was the change from randomisation to week four visit in the Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part I (non-motor Experiences of daily living) score.	
End point type	Primary
End point timeframe:	
The mean durations of phase 2 (i.e. double-blind, withdrawal phase) was 28.37 days $\pm$ 3.23 (median 28.00 days).	

End point values	Nabilone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: points				
arithmetic mean (confidence interval 95%)	1 (-0.16 to 2.16)	2.63 (1.53 to 3.74)		

### Statistical analyses

Statistical analysis title	Primary endpoint analysis
Statistical analysis description:	
The primary, secondary, and exploratory endpoints of this study were analysed separately for the nabilone and the placebo group using a Wilcoxon matched-pairs test for within-group comparison (with correction for multiple comparisons with a factor of two) and a Mann-Whitney U test for between-group comparisons. For all analyses, statistical significance was set at a two-sided 5% level.	
Comparison groups	Placebo v Nabilone



Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	$\leq 0.05$
Method	Wilcoxon (Mann-Whitney)

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Safety and tolerability summaries were based on the safety set which includes all patients receiving at least one dose of study medication during both trial phases. Reporting for Phase 2 (28.37 days  $\pm$  3.23).

Adverse event reporting additional description:

Tolerability: n of subjects (%) who discontinue the study and n of subjects (%) who discontinue the study due to AEs

Safety Measures: AEs, SAEs, SUSARs, Clinical and laboratory assessment, Vital signs +performance of active orthostatism, ECG results, Patient's Compliance, Prior and Concomitant Medication Use, C-SSRS, items of the MDS-UPDRS

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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### Reporting groups

Reporting group title	Nabilone
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Reporting group description:

Treatment Arm

Reporting group title	Placebo
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Reporting group description:

matching placebo

Serious adverse events	Nabilone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Nabilone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 19 (21.05%)	7 / 19 (36.84%)	
Nervous system disorders			
Insomnia			
subjects affected / exposed	2 / 19 (10.53%)	2 / 19 (10.53%)	
occurrences (all)	2	2	
Fall			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	1 / 19 (5.26%) 1	
Syncope subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	2 / 19 (10.53%) 2	
Musculoskeletal and connective tissue disorders Pain subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	2 / 19 (10.53%) 2	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	3 / 19 (15.79%) 3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2018	26th January, 2018: Amendment 1: Primary reason for the amendment: Eye-tracking was added as an exploratory endpoint. A change in the list of prohibited medication was made. Protocol Version 1.3
13 July 2018	13th July, 2018: Amendment 2: Primary reason for the amendment: The protocol was adapted to reflect changes in EU data protection regulations. Protocol Version 1.4

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported