Clinical trial results:
Nabilone for non-motor symptoms in Parkinson's disease: An open-label study to evaluate long-term safety and efficacy

Summary

EudraCT number	2017-004253-16
Trial protocol	AT
Global end of trial date	31 January 2020

Results information

Result version number	v1 (current)
This version publication date	10 February 2021
First version publication date	10 February 2021
Summary attachment (see zip file)	Adverse event Log (Adverse_event_Log.xlsx) IMPD Nabilone (IMPD_NABC_SwissCo_170615_final.pdf) Data Safety Board Meeting (Data_Safety_Board_Meeting.pdf) Demographics of Individual Patients (Demographics of Individual Patients.pdf) SAE Form_002 (SAE Meldeformular_BASG_FU_002.docx.pdf) SAE Form_003 (SAE Meldeformular_BASG_FU_003.pdf) SAE Form_004 (SAE_Meldeformular_BASG_FU4_004.pdf) SAE Form_006 (SAE_Meldeformular_FU_BASG_006.pdf) Clinical study protocol V1.3 (Clinical Study Protocol__Version_1.3.pdf) Final report (Final report long.pdf)

Trial information

Trial identification

Sponsor protocol code	NMSNab2study

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03773796
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Innsbruck, Department of Neurology
Sponsor organisation address	Anichstraße 35, Innsbruck, Austria, 6020
Public contact	Clinical Trial Center Neurology, Medical University of Innsbruck, Department of Neurology, 6801449268 51250425810, klaus.seppi@tirol-kliniken.at
Scientific contact	Clinical Trial Center Neurology, Medical University of Innsbruck, Department of Neurology, 6801449268 51250425810, klaus.seppi@tirol-kliniken.at

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	23 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2020
Global end of trial reached?	Yes
Global end of trial date	31 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate long-term safety and tolerability of nabilone in PD patients.

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. Permission for the conduct of the trial was received from the ethics committee (IEC) of the Medical University of Innsbruck (MUI) on February 07th, 2018 (reference number: 1214/2017) and the Austrian regulatory authorities approved the study on the 13th of April 2018. One substantial amendment with changes in prohibited concomitant medication, study team members, and to conform to the EU Data Protection Law 2018 have been approved by the EC of the MUI and non-prohibited by the regulatory authorities. Two amendments for changes in study team members were approved by the EC of the MUI. Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (IEC MUI, reference number 1214/2017 and the national regulatory authorities) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As the trials primary endpoint was safety, (serious) adverse events, reasons for discontinuation of the study, clinical examination, vital signs, compliance, and suicidality were documented and/or closely monitored.

Background therapy:

All Anti-PD Medications were allowed in this study. The addition of any new anti-PD medication or other prescribed / non-prescribed drugs were allowed during the study as well as changes to frequency or intervals between doses. All non-pharmacological therapies (e.g., physical therapy, exercise, yoga) the patient wanted to perform to improve his/her Parkinson symptoms were allowed to be continued during participation in the study. During the trial, such non-pharmacological therapies were allowed to be started as well. The concomitant non-pharmacological therapies should have been kept on the same level during the study.

Evidence for comparator:

-

Actual start date of recruitment	10 August 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	Austria: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	8
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty-two patients participated in the NMS-Nab2 study between August 10, 2018, and January 31, 2020 (last patient last visit). There was no screening failure. Up-titration was started in all patients. One patient was a non-responder and therefore discontinued before V 1. Two patients were drop-outs (reasons: AE, own will).

Pre-assignment

Screening details:

All 38 patients that finished the double-blind phase of the preceding NMS-Nab study were assessed for eligibility. Reasons for declined partic. in NMS-Nab2: satisfaction with symptomatic control (4), planned surgery (2), wish for modification of PD treatment regime (4), cannabinoid treatment outside of study (2), scheduling difficulties (3), other

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

no blinding, open-label study

Arms

Arm title	Nabilone

Arm description:

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 screening 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 titration phase of the trial

Number of subjects in period 1	Nabilone
Started	22
Completed	19
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	1

Lack of efficacy	1

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	8	8	
From 65-84 years	14	14	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	66.50		
standard deviation	± 6.75	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	10	10	
Disease duration Units: years			
arithmetic mean	9.02		
standard deviation	± 5.91	-	

Subject analysis sets

Subject analysis set title	Full data set
Subject analysis set type	Per protocol

Subject analysis set description:

Safety and tolerability summaries were based on a safety set which included all patients receiving at least one dose of study medication and completing at least V 1. Additionally, summaries of baseline and demographic data were produced out of the safety set. The efficacy analyses for the secondary endpoints included all screened subjects with at least one Visit after screening.

Reporting group values	Full data set		
Number of subjects	21		
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)	7		
From 65-84 years	14		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	67.23		
standard deviation	±		
Gender categorical			
Units: Subjects			
Female	11		
Male	10		
Disease duration			
Units: years			
arithmetic mean	9.30		
standard deviation	± 6.04		

End points

End points reporting groups

Reporting group title	Nabilone

Reporting group description:

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 screening 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.

Subject analysis set title	Full data set
Subject analysis set type	Per protocol

Subject analysis set description:

Safety and tolerability summaries were based on a safety set which included all patients receiving at least one dose of study medication and completing at least V 1. Additionally, summaries of baseline and demographic data were produced out of the safety set. The efficacy analyses for the secondary endpoints included all screened subjects with at least one Visit after screening.

Primary: primary endpoint

End point title	primary endpoint[1]

End point description:

The primary endpoint of the study was safety (see AE page). On parameter assessed in this category was the C-SSRS describing suicidality. No patient experienced suicidality, therefore the count is 0.

End point type	Primary

End point timeframe:

V 1 to V 3, 6 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoint was safety. Please refer to the Adverse event - section.

End point values	Full data set			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: yes or no	0			

Statistical analyses

No statistical analyses for this end point

Secondary: change of the different MDS-UPDRDS Parts

End point title	change of the different MDS-UPDRDS Parts

End point description:

The secondary efficacy criteria were measured as the change in the different clinical scales and questionnaires regarding motor symptoms and different domains of non-motor symptoms in Parkinson´s Disease between V 1 and V 3.

End point type	Secondary

End point timeframe:
V 1 to V 3, 6 months

End point values	Nabilone			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: points				
arithmetic mean (standard deviation)				
Part 1	1.58 (± 13.87)			
Part 2	-0.58 (± 3.49)			
Part 3	-1.89 (± 6.88)			
Part 4	-0.16 (± 2.14)			
Motor Sum Score	-2.47 (± 7.88)			
Sum Score Part 1 - 3	-0.89 (± 14.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: change in other secondary endpoints

End point title	change in other secondary endpoints

End point description:

End point type	Secondary

End point timeframe:
V 1 to V 3, 6 months

End point values	Nabilone			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: points				
arithmetic mean (standard deviation)				
Hoehn and Yahr	-0.16 (± 0.38)			
CGI-I	-1.16 (± 1.30)			
NMSS Total Score	-4.84 (± 18.08)			
KPPS Total Score	-6.84 (± 15.12)			
HADS-A	-0.16 (± 1.50)			
HADS-D	1 (± 2.08)			
PDQ-8 SI	-2.96 (± 9.11)			
ESS	0.11 (± 2.75)			
FSS	4.26 (± 10.08)			

QUIP-RS	0.11 (± 1.41)			

Statistical analyses

No statistical analyses for this end point

Secondary: change in scores for cognition

End point title	change in scores for cognition

End point description:

End point type	Secondary

End point timeframe:

variable, scores at the screening visit of the preceeding NMS-Nab1 study were compared to V 3 of this study

End point values	Nabilone			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: points				
arithmetic mean (standard deviation)				
MMSE	0.42 (± 1.84)			
MoCA	-0.11 (± 1.94)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

V 1 to V 3 = 6 months

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Nabilone

Reporting group description:

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 screening 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.

Serious adverse events	Nabilone		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 22 (18.18%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal cancer			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
worsening of Parkinson´s disease symptoms			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting	Additional description: medication-induced		

subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion	Additional description: herniated disc in the segment 4/5		
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Nabilone		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 22 (95.45%)		
Nervous system disorders			
Disturbance in attention	Additional description: concentration difficulties		
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Fall			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Hypoesthesia (face)	Additional description: transient numbness of the face		
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
worsening of Parkinson´s Disease symptoms			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Osteoarthropathy			

subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Infections and infestations Respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 4 / 22 (18.18%) 4 2 / 22 (9.09%) 2		
Metabolism and nutrition disorders Osteopenia subjects affected / exposed occurrences (all)	 2 / 22 (9.09%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2018	(Substantial) Amendment 1: Primary reason for the amendment: The protocol was adapted to reflect changes in EU data protection regulations. A change in the list of prohibited medication was made. Changes in study team members were added. Protocol Version 1.1 Approved by the EC: 25th August 2018 Non-prohibition by the regulatory authorities: 6th September 2018

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported