Clinical trial results:
A randomized, placebo-controlled, double-blind, multi-center trial to assess the disease-modifying potential of transdermal nicotine in early Parkinson's disease in Germany and the USA (NIC-PD)

Summary

EudraCT number	2010-020299-42
Trial protocol	DE
Global end of trial date	15 February 2017

Results information

Result version number	v1 (current)
This version publication date	23 March 2022
First version publication date	23 March 2022
Summary attachment (see zip file)	E3-Synopse_NIC-PD_V02F (E3-Synopse_NIC-PD_V02F_2020-03-03 - signed_.pdf)

Trial information

Trial identification

Sponsor protocol code	KKS-135

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01560754
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Philipps-Universität Marburg
Sponsor organisation address	Biegenstr. 10, Marburg, Germany, 35037
Public contact	KKS Marburg, Koordinierungszentrum für Klinische Studien, info@kks.uni-marburg.de
Scientific contact	KKS Marburg, Koordinierungszentrum für Klinische Studien, info@kks.uni-marburg.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 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 February 2017
Global end of trial reached?	Yes
Global end of trial date	15 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study assessed the disease-modifying potential of transdermal nicotine treatment compared to placebo in early Parkinson’s disease (PD) patients over a treatment period of 12 months treatment plus 2 months wash-out: The primary endpoint reflecting the explanatory character of the trial was calculated as the difference between the nicotine arm and the placebo arm in the change in total UPDRS I-III score between baseline and 14 months (12 months treatment plus 2 months wash-out). The difference between the nicotine arm and the placebo arm in the change in total UPDRS I-III score between baseline and 12 months became a variant of the primary endpoint for pragmatic interpretation which is subordinated in this phase II trial.

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 102
Country: Number of subjects enrolled	United States: 60
Worldwide total number of subjects	162
EEA total number of subjects	102

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	65
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited between period - between 17Oct2012 and 09Jul2015 with "last patient out" on 15Sept2016 with 163 subjects were randomized (61 at US centers, 102 at German centers) over a 33 months period. The progress through the phases of the trial is presented in the style of a CONSORT.

Pre-assignment

Screening details:

Wash-out: The primary endpoint is calculated as the difference between the nicotine arm and the placebo arm in the change in total
UPDRS I-III score between baseline and 60 weeks (14 months) (52 weeks treatment plus 8 weeks wash-out).

Period 1

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

Blinding implementation details:

Patches, identical in size, shape and colour

Arms

Are arms mutually exclusive?	Yes
Arm title	Transdermal nicotine patch

Arm description:

Transdermal nicotine patches (7 to 28 mg/day)

Arm type	Experimental
Investigational medicinal product name	NICOTINE
Investigational medicinal product code	N07B A01
Other name	SUB14645MIG
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

52 weeks treatment (7 to 28 mg/day) plus 3 weeks down-titration

Arm title	Placebo patch

Arm description:

Transdermal patches, identical in size, shape and colour

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

52 weeks treatment (7 to 28 mg/day) plus 3 weeks down-titration

Number of subjects in period 1	Transdermal nicotine patch	Placebo patch
Started	79	83
Completed	66	76
Not completed	13	7
end of study therapy	7	1
no valid assessment	6	6

Baseline characteristics

Reporting groups	
Reporting group title	Transdermal nicotine patch
Reporting group description:	
Transdermal nicotine patches (7 to 28 mg/day)	
Reporting group title	Placebo patch
Reporting group description:	
Transdermal patches, identical in size, shape and colour	

Reporting group values	Transdermal nicotine patch	Placebo patch	Total
Number of subjects	79	83	162
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
geometric mean	61	61	
standard deviation	± 9.5	± 10.3	-
Gender categorical			
Units: Subjects			
Female	28	23	51
Male	51	60	111

End points

End points reporting groups

Reporting group title	Transdermal nicotine patch
Reporting group description: Transdermal nicotine patches (7 to 28 mg/day)	
Reporting group title	Placebo patch
Reporting group description: Transdermal patches, identical in size, shape and colour	

Primary: Mean worsening of total UPDRS I-III score after 60 weeks (between baseline and 14 months; 12 months treatment plus 2 months wash-out)

End point title	Mean worsening of total UPDRS I-III score after 60 weeks (between baseline and 14 months; 12 months treatment plus 2 months wash-out)
End point description: To demonstrate that transdermal nicotine treatment retrads disease progression as measured by change in total (part I,II, III) UPDRS score between baseline and after 52 weeks of study treatment plus two more months wash out (60 weeks)	
End point type	Primary
End point timeframe: Baseline (T0), after 28 weeks (V6), after 40 weeks (V7), after 52 weeks (V8), after 55 weeks (V9), after 57 weeks (V10), after 60 weeks (V11)	

End point values	Transdermal nicotine patch	Placebo patch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	54		
Units: Number				
number (not applicable)	6.02	3.5		

Statistical analyses

Statistical analysis title	Stratified two-sided Mann-Whitney-Wilcoxon-test
Comparison groups	Transdermal nicotine patch v Placebo patch
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.056
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-3

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-6
upper limit	0
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events reporting period is defined from the time the informed consent is signed, up to and including 30 days following last administration of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Transdermal nicotine patch

Reporting group description:

Transdermal nicotine patches (7 to 28 mg/day)

Reporting group title	Placebo patch

Reporting group description:

Transdermal patches, identical in size, shape and colour

Serious adverse events	Transdermal nicotine patch	Placebo patch	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 79 (17.72%)	7 / 83 (8.43%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Catheterisation cardiac			
subjects affected / exposed	0 / 79 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 79 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	2 / 79 (2.53%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 79 (2.53%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cancer surgery			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour removal			
subjects affected / exposed	0 / 79 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Motor dysfunction			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinsonism			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic intolerance			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Waldenstrom's macroglobulinaemia recurrent			
subjects affected / exposed	0 / 79 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 79 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			

subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 79 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder mass			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 79 (1.27%)	0 / 83 (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	Transdermal nicotine patch	Placebo patch	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 79 (77.22%)	69 / 83 (83.13%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 79 (1.27%)	4 / 83 (4.82%)	
occurrences (all)	1	4	
Investigations			
Weight decreased			
subjects affected / exposed	4 / 79 (5.06%)	0 / 83 (0.00%)	
occurrences (all)	4	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 79 (3.80%)	5 / 83 (6.02%)	
occurrences (all)	3	5	
Cardiac disorders			
Dizziness			
subjects affected / exposed	18 / 79 (22.78%)	12 / 83 (14.46%)	
occurrences (all)	28	14	
Nervous system disorders			
Motor dysfunction			
subjects affected / exposed	1 / 79 (1.27%)	4 / 83 (4.82%)	
occurrences (all)	2	4	
Headache			
subjects affected / exposed	17 / 79 (21.52%)	15 / 83 (18.07%)	
occurrences (all)	23	23	
Tremor			
subjects affected / exposed	7 / 79 (8.86%)	6 / 83 (7.23%)	
occurrences (all)	9	6	
Abnormal dreams			
subjects affected / exposed	4 / 79 (5.06%)	1 / 83 (1.20%)	
occurrences (all)	6	2	
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	22 / 79 (27.85%)	14 / 83 (16.87%)	
occurrences (all)	29	19	
Application site pruritus			

subjects affected / exposed	8 / 79 (10.13%)	7 / 83 (8.43%)	
occurrences (all)	9	7	
Application site reaction			
subjects affected / exposed	1 / 79 (1.27%)	4 / 83 (4.82%)	
occurrences (all)	1	4	
Fatigue			
subjects affected / exposed	7 / 79 (8.86%)	2 / 83 (2.41%)	
occurrences (all)	10	3	
Application site irritation			
subjects affected / exposed	7 / 79 (8.86%)	2 / 83 (2.41%)	
occurrences (all)	7	2	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 79 (5.06%)	1 / 83 (1.20%)	
occurrences (all)	5	2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	10 / 79 (12.66%)	4 / 83 (4.82%)	
occurrences (all)	17	5	
Constipation			
subjects affected / exposed	5 / 79 (6.33%)	2 / 83 (2.41%)	
occurrences (all)	10	2	
Vomiting			
subjects affected / exposed	4 / 79 (5.06%)	1 / 83 (1.20%)	
occurrences (all)	5	2	
Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis			
subjects affected / exposed	13 / 79 (16.46%)	18 / 83 (21.69%)	
occurrences (all)	16	22	
Upper respiratory tract infection			
subjects affected / exposed	2 / 79 (2.53%)	4 / 83 (4.82%)	
occurrences (all)	2	5	
Bronchitis			
subjects affected / exposed	1 / 79 (1.27%)	4 / 83 (4.82%)	
occurrences (all)	1	4	
Skin and subcutaneous tissue disorders			

Erythema			
subjects affected / exposed	12 / 79 (15.19%)	6 / 83 (7.23%)	
occurrences (all)	13	12	
Skin reaction			
subjects affected / exposed	6 / 79 (7.59%)	6 / 83 (7.23%)	
occurrences (all)	10	7	
Rash			
subjects affected / exposed	4 / 79 (5.06%)	4 / 83 (4.82%)	
occurrences (all)	5	4	
Pruritus			
subjects affected / exposed	6 / 79 (7.59%)	3 / 83 (3.61%)	
occurrences (all)	7	3	
Dermatitis allergic			
subjects affected / exposed	6 / 79 (7.59%)	2 / 83 (2.41%)	
occurrences (all)	6	3	
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 79 (2.53%)	6 / 83 (7.23%)	
occurrences (all)	2	6	
Insomnia			
subjects affected / exposed	6 / 79 (7.59%)	6 / 83 (7.23%)	
occurrences (all)	6	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 79 (2.53%)	10 / 83 (12.05%)	
occurrences (all)	2	11	
Musculoskeletal pain			
subjects affected / exposed	3 / 79 (3.80%)	6 / 83 (7.23%)	
occurrences (all)	3	7	
Pain in extremity			
subjects affected / exposed	1 / 79 (1.27%)	7 / 83 (8.43%)	
occurrences (all)	1	7	
Muscle spasms			
subjects affected / exposed	1 / 79 (1.27%)	4 / 83 (4.82%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported