Clinical Study Report (Synopse ICH E3)

Study Title:	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	
Study Acronym	NIC-PD	
Study Sponsor-ID	KKS-135	
EudraCT No.	2010-020299-42	
CSR Version	V02F	
CSR Date	03-MAR-2020	
	Date	**Signature**
Sponsor Carmen Schade-Brittinger	03.03.2020	C. Schade-Brittinger
Project-Management Kerstin Balthasar	03.03.2020	K. Balthasar
Review Sylvia Reinecker	03.03.2020	
Author Dr. Eckhard Bergmann	03.03.2020	

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Clinical Study Report (Synopse ICH E3)

1 Name of Sponsor/Company

Philipps-University Marburg
Biegenstraße 10
35037 Marburg

2 Name of Finished Product

Nicotinell®/24-Stunden-Pflaster

(Novartis) 7 mg/24 Stunden und 14mg/24 Stunden
(Zulassungsnummer 65054.00.00 und 65055.00.00)

3 Name of Active Substance

S(-)-nicotine

4 Individual Study Table: Referring to Part of the Dossier (Volume, Page)

N. A.

5 Title of Study

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; ***V03F, 31-OCT-2011***

Datum der BOB Genehmigung:	***10-JUN-2011***	
BOB Vorlagen Nummer	***4037278***	
Ggf. Daten von Genehmigungen nachträglicher Änderungen nach § 10 Abs. 1 GCP-V		
Prüfplan V02F dated 01.08.2011	*genehmigt am:*	*05.10.2011*
Prüfplan V03F dated 31.10.2011	*genehmigt am:*	*13.02.2012*
Anzeige Studienende (§13 (8) GCP-V)	*am:*	*15.02.2017*
Datum Zustimmung der Ethikkommission	***30-AUG-2011***	
Aktenzeichen der zuständigen EK: Kommission für Ethik in der ärztlichen Forschung des FB Humanmedizin der Philipps-Universität Marburg	***56/11 A-ff***	
Ggf. Daten von Genehmigungen nachträglicher Änderungen nach § 10 Abs. 1 GCP-V		
Prüfplan V02F dated 01.08.2011, Patienteninformation V02F dated 04.07.2011	*genehmigt am*	*30.08.2011*
Prüfplan V03F dated 31.10.2011	*genehmigt am*	*30.01.2012*
Patienteninformation V03F vom 21.02.2012	*genehmigt am*	*05.03.2012*
Patienteninformation V04F vom 05.12.2013 (und Zusatz-Patienteninformation für bereits eingeschlossene Patienten)	*genehmigt am*	*13.02.2014*
Anzeige Studienende (§13 (8) GCP-V)	*am*	*15.02.2017*

Description of Amendmends:

Amendment 1/ *Prüfplan V02F dated 01.08.2011 with changes due to Ethic review (deficiency letter of ethical review by EC Marburg dated 31.05.2011)*
Revision of the exclusion criteria with regard to the summary of product characteristics and to the Ethics Committee's recommendations as well as adaptions corresponding to patient information version V02F dated 04.07.2011 with regard to the summary of product characteristics.

Amendment 2/ *Prüfplan V03F dated 31.10.2011 with changes due to ethical review in U.S. Change of Coordinating Investigator for U.S.A., addition of a new exclusion criterion due to ethical review (IRB Rochester): "patients under treatment with dihydropyridines"*

Amendment 3 – only to EC - / Patient Information Version V03F dated 21.02.2012
Formatting changes and change of section (page 4 of 16) on possible reimbursement travel costs (formerly not possible) and section 7(page of 16) on reimbursement.

Amendment 4 – only to EC - / Patient Information Version V04F dated 06.12.2013
Section on new information on SUSARs were added (page 8), as well as a separate patient information was created to inform patients already included on new information on SUSARs (Syncope and instable angina pectoris).

6 Investigators

Please refer to section 7 of this report.

7 Study centre(s)

-Study centres in Germany[1]

Recruiting sites: Principal Investigator listed at the end of study						
Title	**Given name of Principal Investigator**	**Family name of Principal Investigator**	**Hospital**	**Department**	**Post-code**	**City**
Prof. Dr. med.	Wolfgang	**Oertel**	Universitätsklinikum Giessen u. Marburg GmbH, Standort Marburg	Klinik für Neurologie	D-35043	Marburg
Prof. Dr. med.	Claudia	**Trenkwalder**	Paracelsus-Elena-Klinik Kassel	-	D-34128	Kassel
Dr. med.	Rommi	**Born**	Klinikum Hanau gGmbH	Klinik für Neurologie	D-63450	Hanau
Dr. med.	Moritz	**Brandt**	Universitätsklinikum Carl Gustav Carus	Klinik und Poliklinik für Neurologie	D-01307	Dresden
Dr. med.	Kathrin	**Brockmann**	Universitätsklinikum Tübingen	Zentrum für Neurologie, Abt. Neurodegeneration	D-72076	Tübingen
Dr. med.	Axel	**Lipp**	Charité Campus Virchow Klinikum	Klinik und Poliklinik für Neurologie	D-13353	Berlin
Prof. Dr. med.	Per	**Odin**	Klinikum Bremerhaven	Neurologische Klinik	D-27574	Bremerhaven

[1] PI Change in Marburg (Vote 30.01.2012), in Hanau (Vote 23.10.2015), in Dresden (Vote 13.10.2015), in Freiburg (Votum 27.08.2013),and in Tübingen (Vote 17.06.2016)

Prof. Dr. med.	Alfons	**Schnitzler**	Universitätsklinikum Düsseldorf	Klinik für Neurologie	D-40225	Düsseldorf
Prof. Dr. med.	Jan	**Kassubek**	Universitätsklinikum Ulm	Abteilung Neurologie	D-89091	Ulm
Prof. Dr. med.	Joseph	**Claßen**	Universitätsklinikum Leipzig	Klinik und Poliklinik für Neurologie	D-04103	Leipzig
Prof. Dr. med.	Ulrich	**Dillmann**	Universitätsklinikum des Saarlandes	Neurologische Klinik	D-66421	Homburg/Saar
Prof. Dr. med.	Günter	**Höglinger**	Deutsches Zentrum für Neurodegenerative Erkrankungen e.V. (DZNE)	Abt. für Translationale Neurodegeneration	D-81377	München
Dr. med.	Michel	**Rijntjes**	Neurologische Universitätsklinik Freiburg	Neurozentrum	D-79106	Freiburg
Prof. Dr. med.	Andreas	**Kupsch**	Otto-von-Guericke-Universität Magdeburg	Universitätsklinik für Neurologie	D-39120	Magdeburg
Not recruiting sites:						
Prof. Dr. med.	Günther	**Deuschl**	Universitätsklinikum Schleswig-Holstein, Standort Kiel	Klinik für Neurologie	D-24105	Kiel

-Study centres in USA
The Parkinson's Institute, CA 94085 Sunnyvale
University of Pensylvania, Penn Neurological Institute, PA 19107 Philadelphia
University of South Florida, PD and Movement Disorders CTR., FL 33613 Tampa
University of Kansas Medical Center, Department of Neurology Medical Center, KS 66160-7314 Kansas City
Vanderbild University Medical Center, A-1103 MCN, TN 37232 Nashville
University of Southern Carolina, Med. Dept of Neurology, CA 90033 Los Angeles
Feinstein Institute for Medical Research, North Shore-JIL Health System, NY 11030 Manhasset
University of Vermont, Department of Neurology, VT 05405 Burlington
Pacific Health Research & Education Institute, VA Pacific Island Health Care System, HI 96819 Honolulu
Struthers Parkinson's Center, MN 55427 Golden Valley

8 Publication (reference)

Not applicable.

9 Studied period (years): date of first enrolment, date of last completed

Date of first enrolment: 17.10.2012
Date of last completed: 15.09.2016

10 Phase of development

Phase II

11 Objectives

Primary objective:

- To demonstrate that transdermal nicotine treatment retards 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).

Secondary objectives:

- To demonstrate the effect of nicotine on total (part I, II, III) UPDRS score between baseline and after 52 weeks (12 months) of treatment.
- to evaluate the effect on quality of life (Parkinson's Disease Questionnaire, PDQ-8),
- to evaluate the effect on cognitive function (measured by SCOPA-COG (SCales for Outcomes of PArkinson's disease-COGnition)),
- to evaluate the effect on mood (measured by the Beck Depression Inventory, BDI-II),
- to evaluate the effect on sleep (measured by the Parkinson’s disease Sleep Scale, PDSS),
- to determine and to compare the time to initiation of a symptomatic treatment (if deemed necessary),
- to determine the total UPDRS score at the time of initiation of a dopaminergic treatment (if applicable),
- to evaluate tolerability and safety,
- to evaluate the incidence of adverse events.

12 Methodology

The NIC-PD study is a multi-national, multi-center,randomized, placebo-controlled, double-blind prospective phase II study to assess the disease-modifying potential of transdermal nicotine treatment compared to placebo in drug-naïve, early-phase Parkinson´s disease patients over a treatment period of 12 months.

The following table shows the schedule of activities during the trial:

	Scre e-ning	**Treatment with study medication**															**…**						**No study medication**					
			Titration ↑ (see table 3)								**Maintenance**					**Wash-out** (in case of withdrawal symptoms refer to table 5) **Titration** ↓ (see table 4)						**Run out**					
	Week - 0	**BL**	**1-4**	d1/ W5	**5-8**	d1/ W9	**9-12**	d1/ W13	**13-16**	d1/ W17	**17-28**	d1/ W29	**29-40**	d1/ W41	**41-52**	d1/ W53	**53**	d1/ W54	**54**	d1/ W55	**55**	d1/ W56	d1/ W57	**57, 58**	d1/ W59	**59, 60**	d1/ W61
Visit (±7 days for each visit)	**V0**	**V1**		**(T)**		**V2**		**(T)**		**V3**		**V4**		**V5**		**V6**		**(T)**		**(T)**		**(T)**	**V7**		**V8**		**V9**
			7mg		**14mg**		**21mg**		**28mg**								**21mg**		**14mg**		**7 mg**	**0mg**					
Written informed consent	X																											
Check Incl. / Excl. Criteria	X	X																										
Pregnancy test in women with childbearing potential		X																										
Demography & Medical History	X																											
Adverse Event Reporting			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Suicidal Risk Assessment (CSSRS)	X	X[I]														X												X
Physical Examination	X	X[I]		X[II]		X		X[II]		X		X		X		X		X[II]		X[II]		X[II]	X		X			X
Vital Signs	X	X[I]		X[II]		X		X[II]		X		X		X		X		X[II]		X[II]		X[II]	X		X			X
UPDRS (I-III) incl. Hoehn &Yahr[III]	X	X[I]										X		X		X							X		X			X
SCOPA-COG		X										X				X							X					X
PDQ-8		X										X				X							X					X
Beck Depression Inventory		X										X				X							X					X
PD Sleep Scale (PDSS)		X										X				X							X					X
Neurological Examination	X	X[I]										X				X												X

Mini Mental State Examination (MMSE)		X										X				X											X
Randomization		X																									
Medication Compliance Check (drug accountability, review drug compliance diary)		X				X				X		X		X		X							X				X

Unscheduled visits: Please perform activities according to visit V3; case of premature end/withdrawal: please perform activities according to visit V9.

[I]) Information at baseline on current medical conditions, physical & neurological examination as well as vital signs and H&Y are only necessary if results from screening are older than 28 days

[II]) These visits will be performed via telephone (T). Medical condition and adverse events should be asked and documented. Other (physical & neurological examination, vital signs) are optional in case it should be necessary - after telephone contact - to see the subject in-house, when these investigations should be done and documented as unscheduled visit.

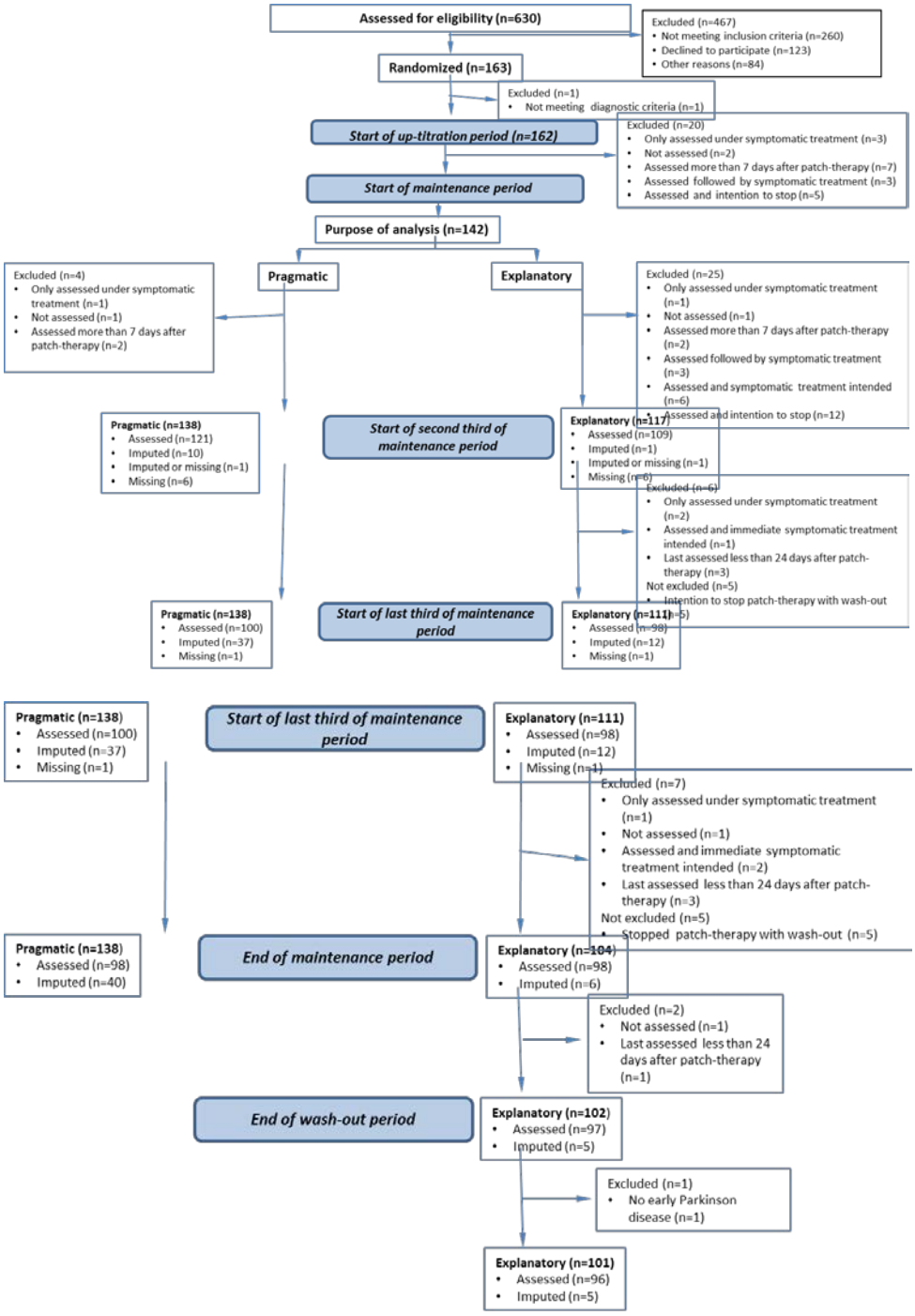
[III]) The UPDRS assessment including H&Y staging should be done by a separate trained UPDRS rater.

13 Number of patients (planned and analysed)

Planned number of patients: 160/138

Analyzed number of patients: 163

- Flow-chart of <u>assessed</u> and <u>analyzed</u> patients:



14 Diagnosis and main criteria for inclusion

Diagnosis:
-Diagnosis of Parkinson Disease according to the UK Brain Bank Diagnostic Criteria

Main inclusion criteria:
- Early PD subjects within 18 months of diagnosis
- Hoehn and Yahr stage ≤ 2
- Patients not receiving or needing dopamine agonist or levodopa therapy presently or for the next year

15 Test product, dose and mode of administration, batch number

1. Charge:
Nicotinell 14mg/24hrs Batch number: 473200
Nicotinell 14mg/24hrs Placebo Batch number: 473400
Nicotinell 7mg/24hrs Batch number: 473500
Nicotinell 7mg/24hrs Placebo Batch number: 473600

2. Charge:
Nicotinell 14mg/24hrs Batch number: 494400
Nicotinell 14mg/24hrs Placebo Batch number: 495300
Nicotinell 7mg/24hrs Batch number: 494500
Nicotinell 7mg/24hrs Placebo Batch number: 495200

3. Charge:
Nicotinell 14mg/24hrs Batch number: 509600
Nicotinell 14mg/24hrs Placebo Batch number: 516700
Nicotinell 7mg/24hrs Batch number: 510100
Nicotinell 7mg/24hrs Placebo Batch number: 510300

16 Duration of treatment

52 weeks treatment plus 3 weeks down-titration

17 Reference therapy, dose and mode of administration, batch number

Placebo-patch, transdermal; batch numbers:
See section 16

18 Criteria for evaluation:

Efficacy:

- 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).
- change in PDQ-8, SCOPA-COG, BDI-II, and PDSS between baseline and 52 weeks as well as 60 weeks respectively, (52 weeks treatment plus 8 weeks wash-out).
- time to initiation of a symptomatic treatment
- slope of the curves for the total UPDRS score in active- and placebo-treated subjects

Safety:

- analysis of frequency of adverse events

19 Statistical methods

Efficacy / test accuracy:
Difference in the distribution of the change in total UPDRS scores (part I-III) between nicotine and placebo treated subjects.
Description of the primary efficacy / test accuracy analysis and population:
Two-sided stratified Mann-Whitney-Wilcoxon-test at a significance level of 0.05 for testing differences between treatment groups in the intent-to-treat-population.
Stratification:
Factors for stratification are the pretreatment with MAO-B inhibitor treatment at inclusion (yes / no) as well as the country (US/GER) which form together 4 strata.
Safety:
Descriptive analysis of AEs, SAEs and SUSAR.
Secondary endpoints:
Descriptive and explorative analysis.

20 Summary - Conclusions:

In summary – in contrast to the working hypothesis – nicotine is not effective in slowing down the progression of PD but it rather the study shows rather an opposite effect.

Efficacy Results:

Difference between the nicotine arm and the placebo arm:
Explanatory: Changes in scores between baseline and 60 weeks
Pragmatic: Changes in scores between baseline and 52 weeks

Explanatory:

-UPDRS I-III
Means: in patients treated with placebo (N=54) 3.50 versus 6.02 in patients treated with nicotine (N=47).
Difference (Hodges-Lehmann estimate with 95% confidence interval): -3 [-6; 0], p=0.0560, a quantitative interaction with MAO-B is possible

-PDQ8
Means: in patients treated with placebo (N=54) 1.40 versus 0.65 in patients treated with nicotine (N=46).
Difference (Hodges-Lehmann estimate with 95% confidence interval): 0 [-1; 1], however an interaction with MAO-B is possible

-SCOPA-COG
Means: in patients treated with placebo (N=53) 3.27 versus 4.26 in patients treated with nicotine (N=45).
Difference (Hodges-Lehmann estimate with 95% confidence interval): -1 [-2; 1]

-PDSS
Means: in patients treated with placebo (N=52) 0.72 versus -0.09 in patients treated with nicotine (N=46).
Difference (Hodges-Lehmann estimate with 95% confidence interval): 1 [-1; 4], however an interaction with MAO-B is possible

-BDI-II
Means: in patients treated with placebo (N=54) 0.67 versus 1.18 in patients treated with nicotine (N=46).
Difference (Hodges-Lehmann estimate with 95% confidence interval): -1 [-3.12; 1], however an interaction with MAO-B is possible

Pragmatic:

-UPDRS I-III
Means: in patients treated with placebo (N=74) 5.40 versus 9.12 in patients treated with nicotine (N=64).
Difference (Hodges-Lehmann estimate with 95% confidence interval): -4 [-7; -1, p=0.0100], a quantitative interaction with MAO-B is possible

-PDQ8
Means: in patients treated with placebo (N=74) 2.02 versus 1.53 in patients treated with nicotine (N=64).
Difference (Hodges-Lehmann estimate with 95% confidence interval): 0.28 [-0.24; 1.04], however an interaction with MAO-B is possible

-SCOPA-COG
Means: in patients treated with placebo (N=73) 1.86 versus 1.99 in patients treated with nicotine (N=61).
Difference (Hodges-Lehmann estimate with 95% confidence interval): -0.11 [-1.79; 1]

-PDSS
Means: in patients treated with placebo (N=71) 1.29 versus 3.17 in patients treated with nicotine (N=64).
Difference (Hodges-Lehmann estimate with 95% confidence interval): -1.55 [-3.29; 0.19], however a quantitative interaction with MAO-B is possible

-BDI-II
Means: in patients treated with placebo (N=74) 1.61 versus 3.57 in patients treated with nicotine (N=64).
Difference (Hodges-Lehmann estimate with 95% confidence interval): -1 [-3; 0.88], however an interaction with MAO-B is possible

Time to initiation of a symptomatic treatment
-Nicotine (24 events) relative to placebo (23 events) (hazard ratio estimate with 95% confidence interval): 1.34 [0.74; 2.40]

Slope of the curves for the total UPDRS score in active- and placebo-treated subjects
-Analysis of slope of the curves is not available yet.

Safety Results:

Serious Adverse Events (SAE)

- In 20 subjects 21 SAEs have been observed and are documented
  - 3 SAEs reported in US (in N=60 subjects)
  - 18 SAEs reported in Germany (N=102 subjects)
- N=5 subjects or 3.09 % of the study population (N=162) had 5 SAEs with relation to study medication
- N=16 or 76,19 % of the SAEs were reported in 16 subjects as not related to study medication and are reported in the appendix, overall 21 SAEs were reported

Preferred Term (MedDRA)	Germany		USA		Total	
	Frequency[1]	Percent[2]	Frequency[1]	Percent[2]	Frequency[1]	Percent[3]
	N=102		N=60		N=162	
Angina unstable	1	0.98	0	0	1	0.62
Anxiety	1	0.98	0	0	1	0.62
Depression	1	0.98	0	0	1	0.62
Diplopia	1	0.98	0	0	1	0.62
Syncope	1	0.98	0	0	1	0.62

[1] Number of subjects with an event related to the study medication

[2] Percentage refers to each population of country (GE N=102, US N=60)

[3] Percentage refers to total study population (N=162)

Adverse Events (AE)

- In 151 subjects 716 AEs (SAEs are included in this number) have been observed and are documented
  - 275 AEs reported in US (in N=60 subjects)
  - 441 AEs reported in Germany (in N=102 subjects)
- N=127 subjects or 78.4% of the study population (N=162) had 327 AEs with relation to study medication
- N=389 or 54.33% of the AEs were reported as not related to study medication and are reported in the appendix, overall 716 AEs were reported

Preferred Term (MedDRA)	Germany		USA		Total	
	Frequency[1]	Percent[2]	Frequency[1]	Percent[2]	Frequency[1]	Percent[3]
	N=102		N=60		N=162	
Application site erythema	14	13.73	22	36.67	36	22.22
Dizziness	10	9.80	11	18.33	21	12.96
Headache	11	10.78	10	16.67	21	12.96
Erythema	12	11.76	5	8.33	17	10.49
Application site pruritus	6	5.88	9	15.00	15	9.26
Skin reaction	8	7.84	4	6.67	12	7.41
Nausea	6	5.88	5	8.33	11	6.79
Application site irritation	4	3.92	5	8.33	9	5.56
Pruritus	6	5.88	3	5.00	9	5.56
Dermatitis allergic	7	6.86	0	0.00	7	4.32
Insomnia	3	2.94	4	6.67	7	4.32
Rash	4	3.92	2	3.33	6	3.70
Abnormal dreams	3	2.94	2	3.33	5	3.09
Application site rash	2	1.96	3	5.00	5	3.09
Application site reaction	3	2.94	2	3.33	5	3.09
Fatigue	3	2.94	2	3.33	5	3.09
Hypertension	5	4.90	0	0.00	5	3.09
Dermatitis contact	4	3.92	0	0.00	4	2.47
Blood pressure increased	2	1.96	1	1.67	3	1.85
Depression	2	1.96	1	1.67	3	1.85
Dry mouth	1	0.98	2	3.33	3	1.85
Feeling jittery	0	0.00	3	5.00	3	1.85
Hot flush	1	0.98	2	3.33	3	1.85
Myalgia	2	1.96	1	1.67	3	1.85
Tremor	1	0.98	2	3.33	3	1.85

Preferred Term (MedDRA)	Germany		USA		Total	
	Frequency[1]	Percent[2]	Frequency[1]	Percent[2]	Frequency[1]	Percent[3]
	N=102		N=60		N=162	
Arthralgia	2	1.96	0	0.00	2	1.23
Asthenia	1	0.98	1	1.67	2	1.23
Chest discomfort	2	1.96	0	0.00	2	1.23
Chest pain	2	1.96	0	0.00	2	1.23
Cold sweat	2	1.96	0	0.00	2	1.23
Constipation	1	0.98	1	1.67	2	1.23
Diplopia	2	1.96	0	0.00	2	1.23
Dysaesthesia	2	1.96	0	0.00	2	1.23
Dysgeusia	1	0.98	1	1.67	2	1.23
Hyperhidrosis	2	1.96	0	0.00	2	1.23
Influenza like illness	0	0.00	2	3.33	2	1.23
Initial insomnia	2	1.96	0	0.00	2	1.23
Lethargy	0	0.00	2	3.33	2	1.23
Nervousness	2	1.96	0	0.00	2	1.23
Orthostatic intolerance	2	1.96	0	0.00	2	1.23
Palpitations	2	1.96	0	0.00	2	1.23
Paraesthesia	1	0.98	1	1.67	2	1.23
Restlessness	2	1.96	0	0.00	2	1.23
Retching	1	0.98	1	1.67	2	1.23
Skin irritation	1	0.98	1	1.67	2	1.23
Skin odour abnormal	2	1.96	0	0.00	2	1.23
Sleep disorder	2	1.96	0	0.00	2	1.23
Vertigo	2	1.96	0	0.00	2	1.23
Vomiting	2	1.96	0	0.00	2	1.23
Acne	1	0.98	0	0.00	1	0.62
Agitation	0	0.00	1	1.67	1	0.62
Alopecia	1	0.98	0	0.00	1	0.62
Angina unstable	1	0.98	0	0.00	1	0.62
Anxiety	1	0.98	0	0.00	1	0.62
Aphasia	0	0.00	1	1.67	1	0.62
Application site dermatitis	1	0.98	0	0.00	1	0.62
Application site erosion	0	0.00	1	1.67	1	0.62
Application site hypersensitivity	1	0.98	0	0.00	1	0.62
Axillary pain	1	0.98	0	0.00	1	0.62
Back pain	1	0.98	0	0.00	1	0.62
Blood pressure fluctuation	1	0.98	0	0.00	1	0.62

Preferred Term (MedDRA)	Germany		USA		Total	
	Frequency[1]	Percent[2]	Frequency[1]	Percent[2]	Frequency[1]	Percent[3]
	N=102		N=60		N=162	
Body temperature increased	1	0.98	0	0.00	1	0.62
Breath sounds	1	0.98	0	0.00	1	0.62
Cardiovascular disorder	1	0.98	0	0.00	1	0.62
Circadian rhythm sleep disorder	1	0.98	0	0.00	1	0.62
Confusional state	0	0.00	1	1.67	1	0.62
Cytomegalovirus infection	1	0.98	0	0.00	1	0.62
Depressive symptom	0	0.00	1	1.67	1	0.62
Diarrhoea	0	0.00	1	1.67	1	0.62
Disturbance in attention	1	0.98	0	0.00	1	0.62
Dizziness exertional	0	0.00	1	1.67	1	0.62
Dizziness postural	1	0.98	0	0.00	1	0.62
Dry eye	0	0.00	1	1.67	1	0.62
Eczema	1	0.98	0	0.00	1	0.62
Energy increased	0	0.00	1	1.67	1	0.62
Erectile dysfunction	1	0.98	0	0.00	1	0.62
Extrasystoles	1	0.98	0	0.00	1	0.62
Feeling cold	1	0.98	0	0.00	1	0.62
Flushing	1	0.98	0	0.00	1	0.62
Gait disturbance	1	0.98	0	0.00	1	0.62
Gastritis	1	0.98	0	0.00	1	0.62
Gastrointestinal disorder	1	0.98	0	0.00	1	0.62
Hair growth abnormal	1	0.98	0	0.00	1	0.62
Heart rate increased	0	0.00	1	1.67	1	0.62
Hyperaesthesia	1	0.98	0	0.00	1	0.62
Hypersensitivity	1	0.98	0	0.00	1	0.62
Injection site reaction	1	0.98	0	0.00	1	0.62
Loss of libido	1	0.98	0	0.00	1	0.62
Middle insomnia	0	0.00	1	1.67	1	0.62
Motor dysfunction	1	0.98	0	0.00	1	0.62
Muscle contractions involuntary	1	0.98	0	0.00	1	0.62
Muscle spasms	1	0.98	0	0.00	1	0.62
Musculoskeletal pain	1	0.98	0	0.00	1	0.62
Nasopharyngitis	0	0.00	1	1.67	1	0.62
Oedema	1	0.98	0	0.00	1	0.62
Pain in extremity	1	0.98	0	0.00	1	0.62

Preferred Term (MedDRA)	Germany		USA		Total	
	Frequency[1]	Percent[2]	Frequency[1]	Percent[2]	Frequency[1]	Percent[3]
	N=102		N=60		N=162	
Parkinson's disease	0	0.00	1	1.67	1	0.62
Pollakiuria	0	0.00	1	1.67	1	0.62
Poor quality sleep	1	0.98	0	0.00	1	0.62
Rhinorrhoea	0	0.00	1	1.67	1	0.62
Salivary hypersecretion	1	0.98	0	0.00	1	0.62
Sedation	1	0.98	0	0.00	1	0.62
Sinus congestion	0	0.00	1	1.67	1	0.62
Spinal pain	1	0.98	0	0.00	1	0.62
Syncope	1	0.98	0	0.00	1	0.62
Tinnitus	1	0.98	0	0.00	1	0.62
Weight decreased	1	0.98	0	0.00	1	0.62

[1] Number of subjects with an event related to the study medication

[2] Percentage refers to each population of country (GER: N=102, US: N=60)

[3] Percentage refers to total study population (N=162)

AEs of special interest (with relation or unrelated)

- In 97 subjects N=135 AEs of special interest (which is 18.85% of all AEs) have been observed and are documented
  - 56 AEs reported in US (in N=40 subjects, 24.69% of subjects)
  - 79 AEs reported in Germany (in N=57 subjects, 35.19% of subjects)

Preferred Term (MedDRA)	Germany		USA		Total	
	Frequency[1]	Percent[2]	Frequency[1]	Percent[2]	Frequency[1]	Percent[3]
	N=102		N=60		N=162	
Application site erythema	14	13.73	22	36.67	36	22.22
Erythema	13	12.75	5	8.33	18	11.11
Application site pruritus	6	5.88	8	13.33	14	8.64
Skin reaction	8	7.84	4	6.67	12	7.41
Application site irritation	4	3.92	5	8.33	9	5.56
Rash	6	5.88	2	3.33	8	4.94
Dermatitis allergic	7	6.86	0	0.00	7	4.32
Pruritus	5[4]	4.90	2[4]	3.33	7	4.32
Application site rash	2	1.96	3	5.00	5	3.09
Application site reaction	3	2.94	2	3.33	5	3.09
Dermatitis contact	4	3.92	0	0.00	4	2.47
Skin irritation	1	0.98	1	1.67	2	1.23
Application site dermatitis	1	0.98	0	0.00	1	0.62
Application site erosion	0	0.00	1	1.67	1	0.62
Application site hypersensitivity	1	0.98	0	0.00	1	0.62
Dermatitis atopic	1	0.98	0	0.00	1	0.62
Eczema	0	0.00	1	1.67	1	0.62
Hypersensitivity	1	0.98	0	0.00	1	0.62
Injection site reaction	1	0.98	0	0.00	1	0.62
Rash generalised	1	0.98	0	0.00	1	0.62

[1] Number of subjects having AE of special interest

[2] Percentage refers to each population of country (GER: N=102, US: N=60)

[3] Percentage refers to total study population (N=162)

[4] Compared to table 6.1 two events 'Pruritus' (one in every country) was dropped by Safety Management and not considered as AEs of special interest. From the AE description there is no indication that the patch is responsible for these events.

Frequency of SAEs unrelated to study medication

- N=16 subjects or 9.88 % of study population (N=162) had 16 SAEs not related to study medication

Preferred Term (MedDRA)	Germany		USA		Total	
	Frequency[1]	Percent[2]	Frequency[1]	Percent[2]	Frequency[1]	Percent[3]
	N=102		N=60		N=162	
Angina unstable	1	0.98	0	0.00	1	0.62
Appendicitis	1	0.98	0	0.00	1	0.62
Bladder mass	1	0.98	0	0.00	1	0.62
Cervical spinal stenosis	1	0.98	0	0.00	1	0.62
Facial paresis	1	0.98	0	0.00	1	0.62
Knee arthroplasty	0	0.00	1	1.67	1	0.62
Motor dysfunction	1	0.98	0	0.00	1	0.62
Obstructive uropathy	1	0.98	0	0.00	1	0.62
Orthostatic intolerance	1	0.98	0	0.00	1	0.62
Pituitary tumour removal	0	0.00	1	1.67	1	0.62
Post procedural infection	0	0.00	1	1.67	1	0.62
Pulmonary embolism	1	0.98	0	0.00	1	0.62
Transient ischaemic attack	1	0.98	0	0.00	1	0.62
Uterine haemorrhage	1	0.98	0	0.00	1	0.62
Varicose vein operation	1	0.98	0	0.00	1	0.62
Waldenstrom's macroglobulinaemia recurrent	1	0.98	0	0.00	1	0.62

[1] Number of subjects with an event unrelated to the study medication

[2] Percentage refers to each population of country (GE N=102, US N=60)

[3] Percentage refers to total study population (N=162)

Conclusion:

We did not observe a clinically meaningful positive effect of nicotine, neither in the primary endpoint nor in any major secondary efficacy endpoint. In particular, we failed to demonstrate a benefit of nicotine compared with placebo. In the explanatory data set the primary endpoint clearly and beyond doubt shows, that nicotine therapy does not slow down the progression of Parkinson disease in de novo PD patients who either received no additional PD therapy or who in addition were under therapy with an MAO-B-inhibitor.
In fact the data suggest that the treatment with nicotine patch may even be harmful, as the difference between placebo and nicotine therapy in respect to the primary endpoint nearly meets with p= 0.056 the predefined statistical significance value of 0.05 in favor of placebo.
This strong trend is not only seen in the analysis of the explanatory, but is strongly supported by the pragmatic data set. The analysis of the pragmatic primary endpoint assesses the observed negative trend statistically with a p value of 0.01.
When stratifying for with pretreatment/cotreatment with MAO-B-inhibitor against without pretreatment/cotreatment with MAO-B-inhibitor the data indicate a somehow protective effect of a MAO-B-inhibitor on the negative effect of nicotine in the primary endpoint analysis.

In respect to safety and tolerability of the tested compound, it should be pointed out, that the relative high number of adverse events in the nicotine group due to skin reactions was unexpected.

In summary – in contrast to the working hypothesis – nicotine is not effective in slowing down the progression of PD but the study shows rather an opposite effect.

21 Date of report

03-MAR-2020