Supplementary information

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Period of recruitment and follow up
Patients were recruited and followed between the 17 August 2009 and the 22 March 2011. See Supplementary table 3 for details.

Criteria for discontinuation of the study
Subjects were free to discontinue their participation in the study at any time. A subject's participation in the study might be discontinued at any time at the discretion of the investigator. Dosing for any individual subject wil be stopped if the subject experiences a possibly drug-related SAE or a possibly drug-related significant non-serious adverse event, which in the opinion of the study physician, principal investigator or sponsor's medical representative, warrants discontinuation for that subject's well being.
A subject's participation will also be discontinued if any of the following applies:

- Subject's general condition in the opinion of the investigator contraindicates continuing the study
- Subject refuses to cooperate
- Development of intracranial bleeding that is assessed as related to the study drug
- Development of intracranial or spinal tumor
- Development of increased intracranial pressure requiring active intervention

Criteria for dose escalation
Dosing in the second and third dose groups was not initiated until the DSMB has given their approval to proceed after reviewing the data for AE, ECG's, vital signs, clinical laboratory tests, and withdrawals collected during the dosing periods and one additional week in the previous group.
Progression to a higher dose level was stopped if one or more subjects experience a possibly, probably or definitely drug-related SAE or medically significant event that, in the opinion of the principal investigator or sponsor's medical representative, warrants discontinuation of the dose increments.

Stopping criteria
If any of the following events occured in a subject receiving active PDGF-BB, dosing with active PDGF-BB/placebo was to be be stopped in all subjects until the relationship to the study drug has been fully evaluated.

- Intracranial bleeding that is assessed as related to the study drug. Bleeding related to the catheter implantation is not considered a stopping criterion.
- Development of intracranial tumor or spinal tumor

Supplementary Table 1: Inclusion Criteria

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1. Male or female.
2. Diagnosis of idiopathic PD of moderate severity (modified Hoehn & Yahr Stage IIb-III).
3. Effect duration of oral L-dopa dose intake < 4 hours.
4. Dopaminergic responsiveness with at least 33% decrease in the UPDRS Part III score
5. Disease duration at least 5 years.
6. Age 30 to 75 years
7. Stable anti-Parkinson treatment for at least 3 months.
8. Ophthalmologic examination with normal findings regarding vascular structure and function.
9. Magnetic resonance imaging examination of the brain and cervical spinal cord within three months before anticipated implantation of the device with no findings of tumors or potential sources of pathological bleedings, or abnormality that could interfere with the assessments of safety or efficacy or would, in the judgment of the investigator, represent a surgical risk to the patient.

Supplementary Table 2: Exclusion criteria

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1. Atypical forms of PD including repeated head trauma, drug- or toxin-induced PD, and other neurological conditions including multiple system atrophy, progressive supranuclear palsy, Wilson's disease, Huntington's disease, PKAN/Hallervorden- Spatz syndrome, Alzheimer's disease, Creutzfeldt-Jakob disease, olivopontocerebellar atrophy, and post-traumatic encephalopathy
2. Concurrent dementia with a score of 20 or lower on the MMSE rating scale
3. Concurrent clinically significant depression with a score of 16 or higher on the MADRS rating scale, equivalent to moderate or severe depression
4. Exposure to neuroleptic drugs blocking dopamine receptors within 6 months
5. History of structural brain disease including tumors and hyperplasia
6. History of increased intracranial pressure
7. Prior surgical procedures or implantation of device for the treatment of PD
8. Prior exposure to any formulation of PDGF-BB (including topical)
9. Uncontrolled hypertension with blood pressure >160 mmHg systolic or >90 mmHg diastolic
10. Any disorder that precluded a surgical procedure (***e.g.***, signs of sepsis or inadequately treated infection), altered wound healing (***e.g.***, including bleeding disorders), or rendered chronic ICV delivery or device implants medically unsuitable
11. Presence of risk for increased or uncontrolled bleeding and/or risk of bleeding that was not managed optimally. Physicians were specifically to investigate anatomical factors at or near the implant site (***e.g.***, vascular abnormalities, neoplasms, or other abnormalities), underlying disorders of the coagulation cascade, platelet function, or platelet count (***e.g.***, hemophilia, Von Willebrand's disease, liver disease, or other medical conditions), and the administration of any anti-platelet or anticoagulant medication (***e.g.***, aspirin, Plavix, non-steroidal anti-inflammatory drugs) in the pre- or perioperative period. Any of those conditions or drugs could place a patient at an increased risk for intraoperative or postoperative bleeding.

12. Presence of an implanted shunt for the drainage of CSF or an implanted central nervous system catheter
13. Presence of cardiac pacemakers, spinal cord stimulators, implantable programmable intraspinal drug pumps, or any other device that may interfere or interact with the programmer.
14. Clinically significant abnormalities in hematology or clinical chemistry parameters as assessed by the Investigator
15. Ongoing medical condition that according to the Investigator would interfere with the conduct and assessments in the study. Examples were medical disability (***e.g***., severe degenerative arthritis, compromised nutritional state and peripheral neuropathy) that would interfere with the assessment of safety and efficacy of IMP or device performance, or would compromise the ability of the patient to undergo study procedures (***e.g***., MRI or PET), or to give informed consent
16. Participation in another clinical trial with an investigational drug or device within 3 months prior to the Screening visit
17. Breast feeding

Supplementary Table 3: Detailed investigational schedule

Visit	Screening	Post-inclusion	1	2	3	4
Study day	-42	Before -14	-14	1-20	50+/-2	85+/-5
Informed consent	X					
Eligibility criteria	X					
Medical/surgical history & demographics	X					
Physical examination	X			X [a]		**X**
Body weight	X			X [b]	X	**X**
Vital signs	X			X [b]		**X**
Body temp (oral)				X [b]		
12-lead ECG	X			X [b]	X	**X**
Clinical chemistry/hematology/coagulation	X			X [c]	X	**X**
Modified Hoehn and Yahr rating	X					**X**
Dopaminergic responsiveness	X					**X**
UPDRS including videotaping	X			X [c]		**X**
MMSE	X					**X**
MADRS	X					**X**
Quality of life (EQ-5D scale)	X					**X**
MRI or computed tomography (CT)	X		X [d]	X [c]		**X**
X-ray			X			
Funduscopy	X			X [b]		**X**
Visual acuity and perimetry	X			X [e]		
PET scan		X				**X**
Lumbar puncture [f]		X		X [g]		**X**
Device implantation, general anesthesia			X [h]			
Drug/placebo infusion				X [i]		
Saline infusion			→		→	
AE recording		X	X	X	X	**X**
Concomitant medication recording [j]	**X**	**X**	**X**	**X**	**X**	**X**

[a] Before start of infusion, at the change to saline on Day 13, and on Day 20

[b] *Before start of infusion and every morning Day 2-20*

[c] *Before start of infusion and on Day 18 or 19*

[d] *The day before implantation and immediately after implantation*

[e] *Day 5, 9, 13 and 17. A deviation by +/-1 day for each investigational day was allowe*

[f] *CSF sampling for determination of PDGF antibodies, albumin and bilirubin*

[g] *Day 13*

[h] *Post-operative surveillance in hospital for 2 days*

[i] *Infusion of drug/placebo Day 1-13 and thereafter change to saline*

[j] *All treatments for PD within 3 months before screening were also recorded.*

Supplementary Table 4

Change in [^{11}C]PE2I DAT-binding in the right and left caudate over 4 months by PDGF-BB dose and baseline binding value as predicted by a regression model. Various other nigrostriatal regions are displayed in Table 5 and Supplementary table 5 and 6.

Region	Dose **µg/day**	Baseline value	Change	95% C.I.
Right Caudate N.S.	0	0.5	0.075117	-0.72, 0.87
		1	0.021597	-0.65, 0.70
		1.5	-0.031	-0.60, 0.53
	0.2	0.5	0.092	-0.69, 0.88
		1	0.038	-0.62, 0.70
		1.5	-0.014	-0.56, 0.53
	1.5	0.5	0.20	-0.54, 0.95
		1	0.15	-0.46, 0.77
		1.5	0.098	-0.40, 0.60
	5	0.5	0.50	-0.46, 1.5
		1	0.45	-0.43, 1.3
		1.5	0.40	-0.40, 1.2
Left Caudate N.S.	0	0.5	0.35	-0.46, 1.2
		1	0.24	-0.45, 0.93
		1.5	0.13	-0.45, 0.71
	0.2	0.5	0.37	-0.42, 1.2
		1	0.26	-0.41, 0.94
		1.5	0.15	-0.41, 0.71
	1.5	0.5	0.53	-0.19, 1.3
		1	0.42	-0.17, 1.0
		1.5	0.31	-0.18, 0.80
	5	0.5	0.96	0.039, 1.9
		1	0.85	-0.0033, 1.7
		1.5	0.73	-0.067, 1.5

Supplementary Table 5
Change in [^{11}C]PE2I DAT-binding in the right and left ventral striatum over 4 months by PDGF-BB dose and baseline binding value as predicted by a regression model. Various other nigrostriatal regions are displayed in Table 5 and Supplementary table 4 and 6.

Region	Dose **µg/day**	Baseline value	Change	95% C.I.
Right Vent. Striatum N.S.	0	0.5	0.28	-0.65, 1.2
		1	0.15	-0.63, 0.94
		1.5	0.033	-0.61, 0.69
	0.2	0.5	0.32	-0.61, 1.3
		1	0.20	-0.58, 0.98
		1.5	0.075	-0.57, 0.71
	1.5	0.5	0.59	-0.39, 1.6
		1	0.47	-0.35, 1.3
		1.5	0.34	-0.32, 1.0
	5	0.5	1.3	-0.11, 2.7
		1	1.2	-0.098, 2.5
		1.5	1.1	-0.099, 2.2
Left Vent. Striatum N.S.	0	0.5	0.0063	-0.99, 1.0
		1	-0.051	-0.85, 0.75
		1.5	-0.11	-0.73, 0.51
	0.2	0.5	0.042	-0.96, 1.0
		1	-0.015	-0.82, 0.79
		1.5	-0.073	-0.70, 0.55
	1.5	0.5	0.27	-0.83, 1.4
		1	0.22	-0.68, 1.1
		1.5	0.16	-0.54, 0.86
	5	0.5	0.90	-0.74, 2.6
		1	0.84	-0.61, 2.3
		1.5	0.79	-0.49, 2.1

Supplementary Table 6
Change in [^{11}C]PE2I DAT-binding in the right and left Substantia nigra over 4 months by PDGF-BB dose and baseline binding value as predicted by a regression model. Various other nigrostriatal regions are displayed in Table 5 and Supplementary table 4 and 5.

Region	Dose µg/day	Baseline value	Change	95% C.I.
Right Sub. Nigra N.S.	0	0.5	-0.11	-0.24, 0.025
		1	-0.26	-0.44, -0.088
		1.5	-0.42	-0.76, -0.092
	0.2	0.5	-0.093	-0.22, 0.034
		1	-0.25	-0.42, -0.080
		1.5	-0.41	-0.74, -0.083
	1.5	0.5	-0.011	-0.13, 0.11
		1	-0.16	-0.32, -0.019
		1.5	-0.32	-0.63, -0.021
	5	0.5	0.21	-0.037, 0.46
		1	0.05	-0.18, 0.29
		1.5	-0.11	-0.44, 0.23
Left Sub. Nigra N.S.	0	0.5	-0.078	-0.22, 0.064
		1	-0.23	-0.41, -0.048
		1.5	-0.39	-0.74, -0.036
	0.2	0.5	-0.066	-0.20, 0.071
		1	-0.22	-0.40, -0.041
		1.5	-0.37	-0.72, -0.026
	1.5	0.5	0.013	-0.11, 0.14
		1	-0.14	-0.31, 0.025
		1.5	-0.30	-0.63, 0.044
	5	0.5	0.22	-0.021, 0.47
		1	0.07	-0.19, 0.33
		1.5	-0.084	-0.47, 0.31

Supplementary Table 7
[^{11}C]PE2I DAT-binding in various nigrostriatal regions at baseline and after treatment in the different treatment cohorts expressed as raw binding values. Note that the time interval between PET-scans and the baseline values varied between different individuals why changes in [^{11}C]PE2I DAT-binding are better expressed using a regressing model that takes the time between scans, baseline binding potential and dose PDGF-BB into account as predictive factors as presented in Table 5 and Supplementary table 4, 5 and 6.

Dose µg/day	**Region**	**Scan 1**	**Scan2**	**Region**	**Scan 1**	**Scan 2**
placebo	Right putamen	0.97	0.85	Left putamen	0.58	0.64
		1.04	0.89		0.96	1.06
		0.53	0.36		0.71	0.38
	Right caudate	2.37	2.79	Left caudate	2.04	2.34
		3.45	3.21		3.62	3.67
		1.03	0.74		1.50	1.20
	Right ventral Striatum	2.41	2.87	Left ventral Striatum	1.83	2.14
		2.62	2.72		2.34	2.54
		1.16	1.11		1.73	1.49
	Right Substantia Nigra	0.52	0.53	Left Substantia Nigra	0.44	0.48
		0.51	0.50		0.60	0.56
		0.53	0.40		0.72	0.48
0.2	Right putamen	1.56	1.14	Left putamen	1.58	1.29
		0.59	0.71		0.50	0.62
		1.07	0.85		0.95	0.63
	Right caudate	4.27	3.7	Left caudate	5.50	4.21
		2.47	2.75		1.58	1.73
		2.85	2.15		2.60	2.36
	Right ventral Striatum	2.55	1.93	Left ventral Striatum	2.67	2.15
		2.79	3.14		1.92	2.02
		3.61	3.13		3.61	3.20
	Right Substantia Nigra	0.81	0.35	Left Substantia Nigra	0.91	0.54
		0.54	0.45		0.34	0.35
		0.55	0.56		0.60	0.54
1.5	Right putamen	0.48	0.38	Left putamen	0.79	0.58
		0.88	0.77		0.81	1.03
		1.78	1.51		1.14	0.94
	Right caudate	1.77	1.89	Left caudate	2.30	2.54
		2.10	2.45		2.48	3.28
		4.99	4.48		3.98	3.21
	Right ventral Striatum	1.88	1.60	Left ventral Striatum	2.40	2.15
		2.52	1.82		2.40	2.33
		5.49	4.44		4.13	3.30

	Right Substantia Nigra	0.44	0.09	Left Substantia Nigra	0.39	0.24
		0.60	0.61		0.78	0.92
		1.48	1.21		1.28	1.05
5	Right putamen	0.99	0.97	Left putamen	1.07	1.31
		0.55	0.64		0.55	0.53
		1.47	1.60		1.52	1.53
	Right caudate	2.60	2.87	Left caudate	2.99	3.22
		1.45	0.99		1.46	1.37
		3.04	3.68		3.22	3.82
	Right ventral Striatum	3.14	3.02	Left ventral Striatum	3.11	2.98
		1.20	1.37		1.58	1.31
		3.76	5.07		4.29	5.64
	Right Substantia Nigra	0.49	0.52	Left Substantia Nigra	0.53	0.83
		0.49	0.40		0.41	0.47
		0.85	1.02		0.78	0.90