SUPPLEMENTARY MATERIAL

Continuous Subcutaneous Foslevodopa/Foscarbidopa in Parkinson's Disease: Safety and Efficacy Results From a 12-Month, Single-Arm, Open-Label, Phase 3 Study

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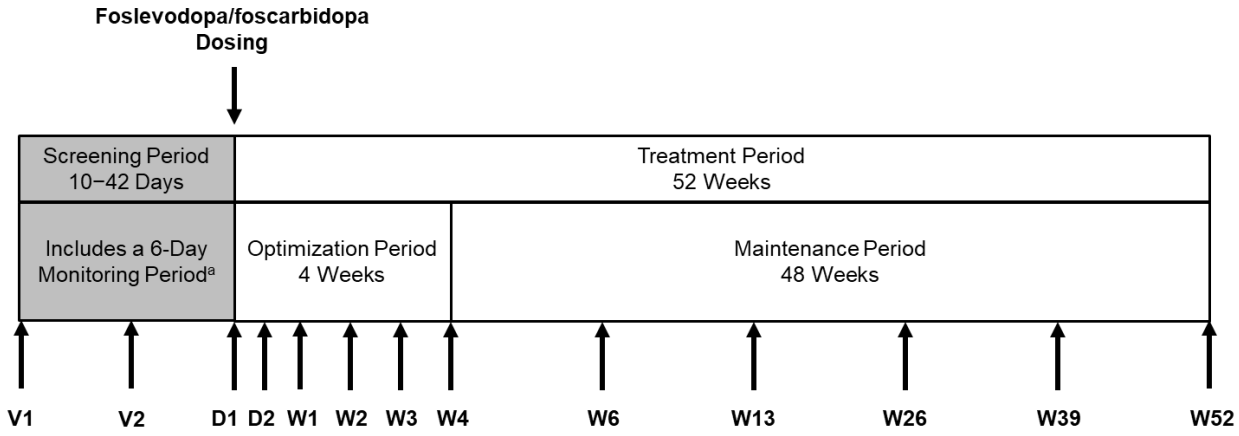

Fig. S1 Study design
D day, *PD* Parkinson's disease, *V* visit, *W* week
[a]The 6-day monitoring period can occur at any time during the screening period. During the monitoring period, PD diaries are collected for a minimum of two consecutive days

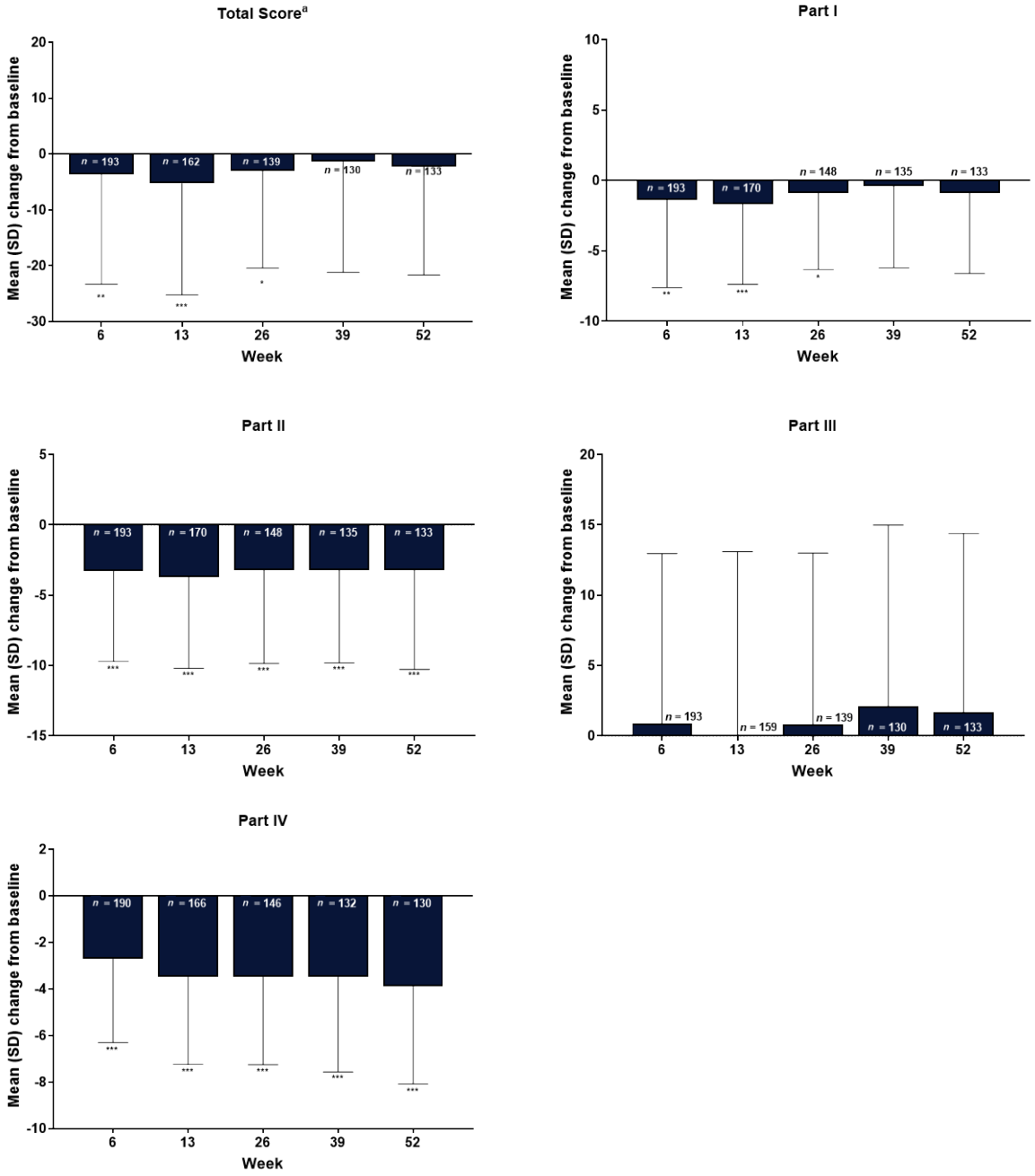

Fig. S2 Change from baseline in MDS-UPDRS (full analysis set)
MDS-UPDRS Movement Disorder Society Unified Parkinson's Disease Rating Scale, SD standard deviation
[a]Total score of parts I−III
MDS-UPDRS was measured in the "On" state at each study visit
***$p \leq 0.001$, **$p < 0.01$, *$p < 0.05$, calculated using a two-sided paired-sample *t* test

Table S1 LD equivalent dose range

Medication	**Conversion factors to calculate LED**
Controlled-release LD (e.g., Sinemet® CR, Madopar® CR)	Multiply daily dose by 0.75
Extended-release LD (Rytary®), mg	Multiply total daily dose by:
0–855	0.42
856–1755	0.48
1756–2340	0.56
2341 or above	0.67
COMT inhibitors such as entacapone (e.g., Comtan® or Stalevo®) or tolcapone (e.g., Tasmar®)	Multiply all LEDs calculated from LD-containing medications by 1.33

COMT catechol-O-methyltransferase, *CR* controlled release, *LD* levodopa, *LED* levodopa equivalent dose

Table S2 Suggested foslevodopa/foscarbidopa starting infusion rates

LED from all oral LD-containing medications taken over a waking time of 16 hours (mg)	Suggested foslevodopa/foscarbidopa starting infusion rate (mL/h)[a]	Approximate corresponding hourly LD amount (mg/h)[b]
< 500	0.17	29
500–599	0.17–0.20	30–34
600–699	0.20–0.24	34–41
700–799	0.24–0.27	41–46
800–899	0.27–0.30	46–51
900–999	0.30–0.34	51–58
1000–1099	0.34–0.37	58–63
1100–1199	0.37–0.40	63–68
1200–1299	0.40–0.44	68–75
1300–1399	0.44–0.47	75–80
1400–1499	0.47–0.51	80–87
1500–1599	0.51–0.54	87–92
1600–1699	0.54–0.57	92–97
1700–1799	0.57–0.61	97–104
1800–1899	0.61–0.64	104–109
1900–1999	0.64–0.68	109–116
> 2000	0.70	119

LD levodopa, *LED* levodopa equivalent dose
[a]The suggested infusion rates are calculated for the mid-point of the interval to which they refer
[b]Based on the foslevodopa/foscarbidopa concentration of LD phosphate 240 mg/mL and molecular weight conversion factor 100 mg LD = 141 mg LD phosphate

Table S3 Allowed concomitant medications and prohibited medications

Allowed concomitant medications	Prohibited medications
Non-ergolinic dopamine agonists (pramipexole, ropinirole, rotigotine)	Apomorphine[a,b]
Selective MAO-B inhibitors (e.g., rasagiline, selegiline)	Dopamine-depleting agents (such as, but not limited to, reserpine, tetrabenazine, amphetamines)
Amantadine (IR and ER formulations)	MAO-A inhibitors and other non-selective MAO inhibitors
Safinamide	Ergot dopamine agonists (lisuride, bromocriptine, cabergoline, etc.)
Zonisamide[c]	Dopamine antagonist or partial agonist, first-generation antipsychotics, antiemetic medications, and second-generation antipsychotic with higher dopamine receptors interaction (such as, but not limited to, fluphenazine, loxapine, perphenazine, thiothixene, haloperidol, metoclopramide, aripiprazole, asenapine, risperidone, paliperidone, perospiron)
Istradefylline[c,d]	Oral and/or inhaled medications containing levodopa[a,e]
	COMT inhibitors (such as entacapone, tolcapone, opicapone)[a]

CD carbidopa, *COMT* catechol-O-methyltransferase, *DDCI* DOPA decarboxylase inhibitor, *ER* extended release, *IR* immediate release, *LD* levodopa, *MAO* monoamine oxidase

[a]Allowed during the screening period; must be discontinued for at least 12 hours before commending foslevodopa/foscarbidopa and is prohibited for the duration of the treatment period

[b]Apomorphine for continuous subcutaneous delivery (approved in Europe) must be discontinued 30 days before commencing foslevodopa/foscarbidopa

[c]Approved in Japan

[d]Approved in the United States

[e]LD+DDCI IR or levodopa inhalation powder is allowed in case of serious medical need such as in the case of pump malfunction. LD/CD IR was also used as a loading dose with foslevodopa/foscarbidopa initiation

Table S4 Foslevodopa/foscarbidopa drug exposure (safety analysis set)

Treatment duration, days	**Total** ***N*** **= 244**
1–7	7 (2.9)
8–14	10 (4.1)
15–21	13 (5.3)
22–28	8 (3.3)
29–42	11 (4.5)
43–91	18 (7.4)
92–182	26 (10.7)
183–273	10 (4.1)
≥ 274	141 (57.8)
Study drug exposure, mean (SD), days	242.9 (152.3)

SD standard deviation
Data are presented as *n* (%) unless otherwise noted

Table S5 Mean LD equivalent daily (24-hour) dose from foslevodopa/foscarbidopa (safety analysis set)

Week	*n*	Mean (SD) total dose[a]
1	220	1621.9 (657.3)
2	220	1723.4 (660.7)
3	200	1762.8 (669.5)
4	192	1817.3 (686.9)
6	183	1832.3 (689.7)
13	172	1842.5 (716.9)
26	155	1802.2 (724.7)
39	137	1811.5 (713.8)
52	124	1859.8 (717.3)

LD levodopa, *SD* standard deviation

[a]Includes continuous infusion and bolus doses

Table S6 Use of concomitant PD medications

		Number of classes of concomitant PD medication[a], *n* (%)	
Study week	**Patients receiving no concomitant PD medication, *n* (%)**	**1**	**≥ 2**
1 (*n* = 244)	53 (21.7)	87 (35.7)	104 (42.6)
2 (*n* = 237)	58 (24.5)	89 (37.6)	90 (38.0)
3 (*n* = 227)	62 (27.3)	86 (37.9)	79 (34.8)
4 (*n* = 214)	60 (28.0)	79 (36.9)	75 (35.0)
Maintenance period (week 5−52)[b] *n* = 206	55 (26.7)	79 (38.3)	72 (35.0)

COMT catechol-O-methyltransferase, *LD* levodopa, *PD* Parkinson's disease

[a]Does not include LD or COMT inhibitors; per protocol, oral LD was only permitted as loading dose, rescue therapy, or temporary dose interruption, and COMT inhibitors were not permitted during the treatment period. Includes all other PD medications permitted in the study

[b]Includes all patients with concomitant medications recorded for week 5 or later

Table S7 Infusion site irritation (safety analysis set)

Irritation grade assessed by Infusion Site Evaluation Scale, n (%)	**Total *N* = 244**
Patients with ≥ 1 observation of numeric grade ≥ 5	59 (24.2)
Patients with ≥ 1 observation of letter grade ≥ D	39 (16.0)
Patients with ≥ 1 observation of numeric grade ≥ 5 or letter grade ≥ D	72 (29.5)
Patients with ≥ 1 observation of numeric grade ≥ 5 and letter grade ≥ D	25 (10.2)

Infusion site irritation was assessed by investigators on a 7-point numeric scale. Notable skin reactions were defined a priori as having numeric grade ≥ 5 or letter grade ≥ D. Numeric grade 5 = erythema, edema, and papules, grade 6 = vesicular eruption, and grade 7 = strong reaction spreading beyond the test site. Letter grade D = glazing with peeling and cracking, grade E = glazing with fissures, grade F = film of dried serous exudates covering all or portion of the patch site, and grade G = small petechial erosions and/or scabs

Table S8 Adverse events of special interest (safety analysis set)

Safety events, *n* (%)	**Total *N* = 244**
Infusion site reactions	200 (82.0)
Infusion site–related infections	86 (35.2)
Falls and associated injuries	74 (30.3)
Hallucinations/psychosis	61 (25.0)
Weight loss	27 (11.1)
Somnolence	12 (4.9)
Polyneuropathy (narrow SMQ)	8 (3.3)

SMQ Standardized Medical Dictionary for Regulatory Activities query
Preferred terms classified using the Medical Dictionary for Regulatory Activities, version 24.0

Table S9 Overview of interim study results

Safety events (safety analysis set), *n* (%)	**Interim analysis[a] 1 *N* = 223**	**Interim analysis[a] 2 *N* = 244**	**Interim analysis[a] 3 *N* = 244**
AEs	206 (92.4)	230 (94.3)	230 (94.3)
AEs considered associated with study drug	201 (90.1)	224 (91.8)	224 (91.8)
Severe AEs	56 (25.1)	62 (25.4)	63 (25.8)
SAEs	53 (23.8)	61 (25.0)	63 (25.8)
AEs leading to discontinuation of study drug	54 (24.2)	62 (25.4)	63 (25.8)
Deaths[b]	3 (1.3)	3 (1.2)	3 (1.2)
AEs occurring in > 10% of patients in the third interim analysis			
Infusion site erythema	113 (50.7)	125 (51.2)	126 (51.6)
Infusion site nodule	61 (27.4)	68 (27.9)	69 (28.3)
Infusion site cellulitis	53 (23.8)	56 (23.0)	56 (23.0)
Infusion site edema	45 (20.2)	47 (19.3)	47 (19.3)
Hallucination	37 (16.6)	41 (16.8)	42 (17.2)
Fall	34 (15.2)	39 (16.0)	40 (16.4)
Infusion site pain	33 (14.8)	38 (15.6)	38 (15.6)
Infusion site reaction	31 (13.9)	31 (12.7)	30 (12.3)
Anxiety	24 (10.8)	28 (11.5)	29 (11.9)
Infusion site abscess	19 (8.5)	26 (10.7)	27 (11.1)
Dizziness	24 (10.8)	25 (10.2)	25 (10.2)
Efficacy endpoints (full analysis set), mean (SD) change from baseline at week 52			
Daily “Off” time, h	−3.5 (2.9)*** *n* = 63	−3.4 (3.1)*** *n* = 96	−3.4 (3.1)*** *n* = 104
Daily “On” time without dyskinesia, h	3.7 (4.6)*** *n* = 63	3.8 (4.3)*** *n* = 96	3.8 (4.2)*** *n* = 104
Daily “On” time with non-troublesome dyskinesia, h	−0.04 (3.9) *n* = 63	−0.2 (3.4) *n* = 96	−0.3 (3.4) *n* = 104
Daily “On” time with troublesome dyskinesia, h	−0.2 (1.6) *n* = 63	−0.2 (1.5) *n* = 96	−0.1 (2.0) *n* = 104
Daily “On” time without troublesome dyskinesia, h	3.7 (2.8)*** *n* = 63	3.6 (3.0)*** *n* = 96	3.5 (3.1)*** *n* = 104
MDS-UPDRS total score[c]	−3.5 (20.6) *n* = 75	−1.9 (19.7) *n* = 108	−1.9 (19.6) *n* = 120
Part I	−0.5 (6.0) *n* = 75	−0.6 (5.9) *n* = 108	−0.8 (5.9) *n* = 120
Part II	−3.8 (7.7)*** *n* = 75	−2.8 (7.4)*** *n* = 108	−3.0 (7.2)*** *n* = 120
Part III	0.8 (13.5) *n* = 75	1.5 (12.8) *n* = 108	1.8 (12.9) *n* = 120
Part IV	−4.5 (3.7)*** *n* = 75	−3.9 (4.5)*** *n* = 108	−3.8 (4.3)*** *n* = 120
PDSS-2 total score	−7.1 (9.4)***	−6.8 (10.6)***	−7.1 (10.6)***

PDQ-39 summary index	*n* = 74 −5.8 (13.0)***	*n* = 106 −5.7 (13.2)***	*n* = 118 −6.8 (13.6)***
EQ-5D-5L summary index[d]	*n* = 74 0.078 (0.2032)**	*n* = 107 0.089 (0.2175)***	*n* = 119 0.092 (0.2139)***
EQ-5D-5L VAS	*n* = 69 10.3 (23.7)***	*n* = 100 12.5 (25.0)***	*n* = 111 13.0 (24.7)***
	n = 69	*n* = 100	*n* = 111

AE adverse event, *EQ-5D-5L* EuroQol 5-dimensions questionnaire, *h* hours, *MDS-UPDRS* Movement Disorder Society Unified Parkinson's Disease Rating Scale, *PDQ-39* 39-item Parkinson's Disease Questionnaire, *PDSS-2* Parkinson's Disease Sleep Scale-2, *SAE* serious adverse event, *SD* standard deviation, *VAS* visual analog scale

[a]Each interim analysis was conducted prior to the final analysis

[b]There were a total of 5 deaths; two were non-treatment emergent

[c]Total score of parts I−III

[d]Based on the USA index value, which ranges from a worst score of –0.109 to a best score of 1

***$p \leq 0.001$, **$p < 0.01$, calculated using a two-sided paired-sample *t* test

Preferred terms classified using the Medical Dictionary for Regulatory Activities, version 24.0

Table S10 Change from baseline to week 52 in sleep, QoL, and HRQoL (full analysis set)

Assessment	Mean (SD) change
PDSS-2	*n* = 131
Total score	−7.5 (10.8)***
Motor symptoms at night	−2.3 (4.8)***
PD symptoms at night	−2.3 (4.3)***
Disturbed sleep score	−2.9 (4.6)***
PDQ-39	*n* = 132
Summary index	−7.2 (13.7)***
Mobility	−10.9 (20.8)***
Activities of daily living	−10.9 (21.1)***
Emotional well-being	−3.1 (19.8)
Stigma	−8.1 (22.6)***
Social support[a]	0.9 (18.2)
Cognition	−2.6 (18.2)
Communication	−1.9 (21.5)
Bodily discomfort	−11.8 (22.7)***
EQ-5D-5L	*n* = 122
VAS	14.1 (24.7)***
Summary index[b]	0.097 (0.2134)***

EQ-5D-5L EuroQol 5-dimensions questionnaire, *HRQoL* health-related quality of life, *PD* Parkinson's disease, *PDQ-39* 39-item Parkinson's Disease Questionnaire, *PDSS-2* Parkinson's Disease Sleep Scale-2, *QoL* quality of life, *SD* standard deviation, *VAS* visual analog scale

***$p \leq 0.001$, calculated using a two-sided paired-sample *t* test

[a]$n = 114$

[b]Based on the USA index value, which ranges from a worst score of –0.109 to a best score of 1

Supplementary Appendix IEC/IRB Approvals

Name of IEC/IRBs	Country
Alfred Health Ethics Committee	Australia
Research and Ethics Office Concord Repatriation General Hospital	Australia
St Vincent's Hospital Melbourne HREC	Australia
CEM CHC Groupe Santé – Clinique du Montlégia	Belgium
Commissie Medische Ethiek	Belgium
Commissie voor Ethiek AZ Sint-Jan Brugge-Oostende AV	Belgium
Ethische Commissie Onderzoek UZ/KU Leuven	Belgium
Conjoint Health Research Ethics Board	Canada
De Videnskabsetiske Komiteer for Region Hovedstaden	Denmark
Ethik-Kommission an der Universitaet Ulm	Germany
Ethikkommission der Fakultaet fuer Medizin der TU Muenchen	Germany
Ethik-Kommission der Landesaerztekammer Brandenburg	Germany
Comitato Etico IRCCS Sicilia - CENTRO NEUROLESI BONINO PULEJO	Italy
Comitato Etico per la Sperimentazione Clinica della Provincia di Padova	Italy
Istituto Neurologico Carlo Besta	Italy
IRB of National Hospital Organization Utano National Hospital	Japan
Juntendo University Hospital Institutional Review Board	Japan
National Center of Neurology and Psychiatry Institutional Review Board	Japan
National Hospital Organization Asahikawa Medical Center Institutional Review Board	Japan
Osaka University Hospital Institutional Review Board	Japan
Medical Ethical Review Committee Erasmus MC	Netherlands
METC Erasmus MC	Netherlands
Ethics Council at the Ministry of Healthcare of the Russian Federation	Russia
Expert Ethics Committee at City Clinical Hospital #40	Russia
First Pavlov State Medical University of Saint Petersburg	Russia
CEIm Provincial de Sevilla	Spain
Etikprovningsmyndigheten	Sweden
London - Fulham Research Ethics Committee	United Kingdom
NRES Committee London - Fulham	United Kingdom
Advarra	United States
Greenville Health Systems	United States
Human Research Protection Office Washington University St. Louis	United States
Indiana University Institutional Review Board, c/o Office of Research Compliance	United States
Legacy Health Institutional Review Board	United States
Quorum Institutional Review Board[a]	United States
University of Kansas Medical Center IRB	United States
University of Kentucky Institutional Review Board	United States
University of Missouri-Columbia Health Services	United States
Western Institutional Review Board	United States

IEC, independent ethics committee, IRB, institutional review board.
[a]Quorum was acquired by Advarra effective February 28, 2019