Supplementary Material

Safety, Pharmacokinetics, and Pharmacodynamics of Oral Venglustat in Patients with Parkinson's Disease and a GBA Mutation: Results from Part 1 of the Randomized, Double-Blinded, Placebo-Controlled MOVES-PD Trial

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Supplementary Table 1. List of common GBA mutations screened to determine MOVES-PD enrolment eligibility[a]

Category	Allele name[b]	cDNA nucleotide substitution	Amino acid substitution
Severe *GBA* mutations	**Frameshift**		
	72delC	72delC	p.Leu25SerfsX66
	84GG	84dupG	p.Leu29AlafsX18
	119delC	119delC	Not determined
	122CC	122insC	p.Arg41ProfsX6
	148-149insGTAT	148-149insGTAT	p.Tyr50CysfsX15
	203Cdel	203delC	p.Pro68ArgfsX23
	329–333del CAGAA	329–333del CAGAA	Not determined
	330delA	330delA	p.Glu111AsnfsX7
	413delC	413delC	p.Pro138LeufsX62
	493insA	493insA	Not determined
	500insT	500insT	p.Ser168LeufsX12
	532delC	532delC	Not determined
	534delT	534delT	p.Asp179MetfsX21
	595–596delCT	595_596delCT	p.Leu199AspfsX62
	p.V214Stop	741delC	p.Trp248GlyfsX6
	898delG	898delG	p.Ala300ProfsX4
	914Cdel	914delC	p.Pro305LeufsX31
	953delT	953delT	p.Leu318ProfsX18
	p.Tyr343Stop	1029delT	p.Tyr343X
	1093–1094insG	1093dupG	p.Glu365GlyfsX71
	1098insA	1098dupA	p.His367ThrfsX69
	1122–1123insTG	1121_1122dupTG	p.Leu375CysfsX20
	1147delG	1147delG	Not determined
	1214delGC	1214_1215delGC	p.Ser405AsnfsX30
	1263–1317del	1263–1317del	Not determined
	1284delA	1284delA	p.GlyAspfsX15
	1326insT	1326dupT	p.Val443CysfsX26
	1447–1466del20,insTG	1447_1466delinsTG	p.Leu483_Met489delinsTrp
	Substitutions		
	p.W(-4)Stop	108G>A	p.Trp36X
	p.C16S	164G > C	p.Cys55Ser
	p.E41K	238G>A	p.Glu80Lys
	p.R47Stop	256C>T	p.Arg86X
	p.Q73Stop	334C>T	p.Gln112X
	p.K74Stop	337A>T	p.Lys113X
	p.S107L	437C > T	p.Ser146Leu
	p.I119T	473T > C	Ile158Thr
	p.R120W	475C>T	p.Arg159Trp
	p.R120Q	476G > A	p.Arg159Gln
	p.R131C	508C > T	p.Arg170Cys
	p.R131L	509G > T	p.Arg170Leu
	p.Y135Stop	522T>A	p.Tyr174X
	p.K157Q	586A>C	p.Lys196Gln
	p.K157N	588G>T	p.Lys196Asn
	p.R163Stop	604C>T	p.Arg202X
	p.Q169Stop	622C>T	p.Gln208X
	p.S173Stop	635C>G	p.Ser212X
	p.P178S	649C > T	p.Pro217Ser

	p.W179Stop	653G>A	p.Trp218X
	p.P182L	662C > T	p.Pro221Leu
	p.A190T	685G>A	p.Ala229Thr
	p.A190E	686C>A	p.Ala229Glu
	p.G193W	694G>T	p.Gly232Trp
	p.G195W	700G>T	p.Gly234Trp
	p.G195E	701G>A	p.Gly234Glu
	p.L197F	706C>T	p.Leu236Phe
	p.K198E	709A>G	p.Lys237Glu
	p.G202R	721G > A	p.Gly241Arg
	p.F213I	754T > A	pPhe252Ile
	p.T231R	809C>G	p.Thr270Arg
	p.E233Stop	814G>T	p.Glu272X
	p.S237P	826T>C	p.Ser276Pro
	p.L240P	836T>C	p.Leu279Pro
	841-842insTGA	839_841dupTGA	p.Leu280_Ser281insMet
	p.F251L	870C>A	p.Phe290Leu
	p.H255Q	882T>G	p.His294Gln
	p.R257Stop	886C>T	p.Arg296X
	p.R257Q	887G > A	p.Arg296Gln
	p.P266L	914C>T	Pro305Leu
	p.R285H	971G > A	p.Arg324His
	p.Y304C	1028A>G	p.Tyr343Cys
	p.Y304Stop	1029T>G	p.Tyr343X
	p.H311R	1049A>G	His350Arg
	p.G325R	1090G > A	p.Gly364Arg
	p.A341T	1138G>A	p.Ala380Thr
	p.C342G	1141T>G	p.Cys381Gly
	p.C342Y	1142G>A	p.Cys381Tyr
	p.Q350Stop	1165C>T	p.Gln389X
	p.R353G	1174C>G	p.Arg392Gly
	p.G355D	1181G>A	p.Gly394Asp
	p.R359Stop	1192C>T	p.Arg398X
	p.S364R	1207A>C	p.Ser403Arg
	p.W378Stop	1250G>A	p.Trp417X
	p.D380A	1256A>C	p.Asp419Ala
	p.L385P	1271T>C	p.Leu424Pro
	p.E388Stop	1279G>T	p.Glu427X
	p.G389E	1283G>A	p.Gly428Glu
	p.G390R	1285G>A	p.Gly429Arg
	p.N392I	1292A>T	p.Asn431Ile
	p.V394L	1297G > T	p.Val433Leu
	p.V398L	1309G>C	p.Val437Leu
	p.V398F	1309G>T	p.Val437Phe
	p.D399N	1312G>A	p.Asp438Asn
	p.I402F	1321A>T	p.Ile441Phe
	p.D409H	1342G > C	p.Asp448His
	p.D409V	1343A>T	p.Asp448Val
	p.Q414Stop	1357C>T	p.Gln453X
	p.Q414R	1358A>G	p.Gln453Arg
	p.P415R	1361C>G	p.Pro454Arg
	p.K425E	1390A>G	p.Lys464Glu
	p.L444P	1448T>C	p.Leu483Pro

	p.L444R	1448T>G	p.Leu483Arg
	p.A456P	1483G > C	p.Ala495Pro
	p.N462K	1503C>G	p.Asn501Lys
	p.R463C	1504C > T	p.Arg502Cys
	p.R463Q	1505G>A	p.Arg502Gln
	p.T491I	1589C > T	p.Thr530Ile
	Splice variants		
	(-203)a>g + IVS4-2a>g	(-203a>g; 455-2a>g)	Not determined
	IVS2+1g>a	115+1g>a	Not determined
	IVS2+1g>t	115+1g>t	Not determined
	IVS5+1g>t	588+1g>t	Not determined
	IVS10+2t>a	1505+2t>a	Not determined
	IVS10(+2)	1505+2t>g	Not determined
Other *GBA* mutations	p.V15L	160G>T	p.Val54Leu
	222-224delTAC	222_224del TAC	p.Thr75del
	p.F37V	226T>G	p.Phe76Val
	p.T43I	245C>T	p.Thr82Ile
	p.G46E	254G > A	p.Gly85Glu
	p.R48W	259C > T	p.Arg87Trp
	p.L66P	314T>C	p.Leu105Pro
	p.K79N	354G>C	p.Lys118Asn
	p.A90T	385G>A	p.Ala129Thr
	p.N117D	466A > G	p.Asn156Asp
	p.P122S	481C>T	p.Pro161Ser
	p.M123V	484A > G	p.Met162Val
	p.D127V	497A>T	p.Asp166Val
	p.T134I	518C>T	p.Thr173Ile
	p.D140H	535G > C	p.Asp179His
	p.P159T	592C > A	Pro198Thr
	p.P159L	593C > T	Pro198Leu
	p.R170C	625C>T	p.Arg209Cys
	p.R170P	626G>C	p.Arg209Pro
	p.W184R	667T>C	p.Trp223Arg
	p.N188R	680_681 delinsGG	p.Asn227Arg
	p.N188S	680A > G	p.Asn227Ser
	p.G189V	683G > T	p.Gly228Val
	p.F216Y	764T>A	p.Phe255Tyr
	p.A232G	812C>G	p.Ala271Gly
	p.P266R	914C > G	p.Pro305Arg
	p.S271G	928A>G	p.Ser310Gly
	p.S271N	929G>A	p.Ser310Asn
	p.P289L	983C>T	p.Pro328Leu
	p.W312C	1053G>T	p.Trp351Cys
	p.T323I	1085C>T	p.Thr362Ile
	p.C342R	1141T>C	p.Cys381Arg
	p.V352L	1171G>C	p.Val391Leu
	p.R359Q	1193G>A	p.Arg398Gln
	p.S364T	1208G>C	p.Ser403Thr
	p.S364N	1208G>A	p.Ser403Asn
	p.S366G	1213A>G	p.Ser405Gly
	p.N370S	1226A > G	p.Asn409Ser
	p.L371V	1228C>G	p.Leu410Val
	p.V375L	1240G>T	p.Val414Leu

	p.V375G	1241T>G	p.Val414Gly
	p.G377S	1246G > A	p.Gly416Ser
	p.G377C	1246G>T	p.Gly416Cys
	p.W378G	1249T>G	p.Trp417Gly
	p.R395C	1300C>T	p.Arg434Cys
	p.N396T	1304A>C	p.Asn435Thr
	p.F397S	1307T>C	p.Phe436Ser
	p.P401L	1319C>T	p.Pro440Leu
	p.I402T	1322T>C	p.Ile441Thr
	p.D409G	1343A>G	p.Asp448Gly
	p.K413Q	1354A>C	p.Lys452Gln
	p.R433G	1414A>G	p.Arg472Gly
	p.R496C	1603C>T	p.Arg535Cys
	p.R496H	1604G>A	p.Arg535His
Sequence variants for which history of RBD or co-occurrence of any mutation on the list are required	p.E326K	1093G>A	p.Glu365Lys
	p.T369M	1223C>T	p.Thr408Met

[a]Consult was required to determine eligibility for participants with *GBA* mutations not present in this list. [b]Historical allele name omitting the first 39 amino acids.

cDNA, complementary DNA; *GBA*, glucocerebrosidase (glucosylceramidase beta) gene; RBD, rapid eye movement sleep behavior disorder.

Supplementary Table 2. List of inclusion and exclusion criteria for enrolment in MOVES-PD

Inclusion criteria	Male or female participants with a diagnosis of PD (with at least two of the following signs: resting tremor, postural instability, akinesia/hypokinesia, and muscle rigidity) and who are heterozygous carriers of a *GBA* mutation[a,b] OR Participants carrying known sequence variants associated with *GBA*-PD (p.E326K [p.Glu365Lys]),[a,b] in addition to having a diagnosis of PD (with at least two of the following signs: resting tremor, postural instability, akinesia/hypokinesia, or muscle rigidity), must also have a diagnosis of RBD confirmed by historically documented polysomnography or by RBD screening questionnaire Age ≥18 years to 80 years, inclusive, at the time of signing the informed consent (for Japanese participants only: aged 20–80 years, inclusive, at the time of signing the informed consent) Symptoms of PD for ≥2 years Hoehn and Yahr stage of ≤2 for PD at baseline; for participants on a stable dose of PD medication, this should be done in the ON state If on levodopa or any other PD medication (such as a dopamine agonist), the medication regimen must be stable for ≥30 days (≥60 days for rasagiline) prior to randomization The participant is cooperative, able to ingest oral medication, and able to complete all aspects of the study and capable of doing so alone, according to the investigator's judgment The participant is willing to abstain from consumption of grapefruit, grapefruit juice, and/or grapefruit-containing products for 72 h prior to administration of the first dose of venglustat and for the duration of the entire treatment period (Part 1 and Part 2) The participant is able to provide a signed written informed consent
Exclusion criteria	Parkinsonism due to drug(s) and/or toxin(s) Participants carrying the *LRRK2* p.G2019S (p.Gly2019Ser) mutation Participants with GD as defined by clinical signs and symptoms (i.e., hepatosplenomegaly, cytopenia, skeletal disease) and/or marked deficiency of GCase activity compatible with GD MoCA score of <20 Participants who have past surgical history of deep brain stimulation Participants who have a baseline MRI without contrast showing a structural abnormality that is a possible etiology of PD-related signs and symptoms Any medical disorders and/or clinically relevant findings in the physical examination, medical history, or laboratory assessments that, in the opinion of the investigator, could interfere with study-related procedures (e.g., heart failure, hypokalemia, etc.). This includes condition(s) that precludes the safe performance of routine LP, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia Current participation in another investigational interventional study Current treatment with anticoagulants (e.g., coumadin, heparin) that might preclude safe completion of the LP An investigational medicinal product, including ambroxol, within 3 months or 5 half-lives, whichever is longer, before study inclusion Presence of severe depression as measured by BDI-II >28 and/or a history of a major affective disorder within 1 year of screening examination A history of drug and/or alcohol abuse within the past year prior to the first screening visit A known hypersensitivity to DAT scan (either the active substance of ioflupane I-123 or to any of the excipients) The participant is sexually active and is not willing to use two forms of birth control during the study and up to 90 days after the day of last dose Women of childbearing potential not protected by two highly effective methods of birth control and/or who are unwilling or unable to be tested for pregnancy for up to 45 days after the day of last dose Male participants must use two forms of birth control during the study and refrain from donating sperm up to 90 days after the day of last dose. If the participant has a female partner of childbearing potential, the participant must wear a condom and female partner must use at least one highly effective method of birth control The participant is scheduled for inpatient hospitalization including elective surgery during the study The participant, in the opinion of the investigator, is unable to adhere to the requirements of the study. This includes any participant who, in the judgment of the investigator, is likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development Any country-related specific regulation that would prevent the subject from entering the study Any participant who is the investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study Know hypersensitivity to venglustat or any component of the excipients Use of any medication specifically used for treating memory dysfunction, such as, but not limited to, cholinesterase inhibitors or memantine within 30 days or 5 half-lives prior to randomization, whichever is longer The use of concomitant medications that prolong the time from ECG Q wave to the end of the T wave or corrected T wave corresponding to electrical systole (QT/QTc interval) Liver enzymes (ALT/AST) or total bilirubin >2 times the ULN at the time of screening. Participants with Gilbert's disease are excluded only from Part 1 participation

	Renal insufficiency as defined by creatinine >1.5 times ULN at the screening visit The participant has a documented diagnosis, as per local regulations, of any of the following infections: hepatitis B, hepatitis C, human immunodeficiency virus 1 or 2 The participant has received strong or moderate inducers or inhibitors of CYP3A4 within 30 days or 5 half-lives, prior to randomization, whichever is longer The participant has, according to World Health Organization Grading, a cortical cataract > one-quarter of the lens circumference (Grade cortical cataract-2) or a posterior subcapsular cataract >2 mm (Grade posterior subcapsular cataract-2). Participants with nuclear cataracts will not be excluded The participant is currently receiving potentially cataractogenic medications, including a chronic regimen (more frequently than every 2 weeks) of any dose or route of corticosteroids or any medication that may cause cataract or worsen the vision of participants with cataract (e.g., glaucoma medications) according to the prescribing information If female, pregnant (defined as positive β-HCG blood test) or lactating or breast-feeding A marked baseline prolongation of QT/QTc interval on screening ECG (such as a QTc interval >450 ms in male subjects and >470 ms in female subjects)

[a]List of most common *GBA* mutations screened, including the p.E326K (p.Glu365Lys) variant, is shown in Supplementary Table 1. [b]A consult was required to determine enrolment eligibility for participants with *GBA* mutations not listed in Supplementary Table 1. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BDI-II, Beck Depression Inventory (second edition); CYP3A4, cytochrome P450 3A4; DAT, dopamine transporter; ECG, electrocardiogram; *GBA*, glucocerebrosidase (glucosylceramidase beta) gene; GCase, glucocerebrosidase; GD, Gaucher disease; β-HCG, beta-human chorionic gonadotropin; LP, lumbar puncture; *LRRK2*, leucine-rich repeat kinase 2 gene; MAOB, monoamine oxidase type B; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; QTc, corrected QT interval; RBD, rapid eye movement sleep behavior disorder; ULN, upper limit of normal.

Supplementary Table 3. Post hoc analysis of data from pooled Japanese and non-Japanese participants in Part 1 of the MOVES-PD trial

	Pooled Japanese and non-Japanese participants (N=29)			
	Placebo (n=7)	Venglustat		
		Low (n=7)	Mid (n=8)	High (n=7)
Baseline characteristics				
Age, y, mean (SD)	52.6 (8.7)	57.9 (5.6)	59.4 (6.1)	56.4 (12.0)
Sex, n (%)				
Male	6 (85.7)	3 (42.9)	6 (75.0)	5 (71.4)
Female	1 (14.3)	4 (57.1)	2 (25.0)	2 (28.6)
Race, n (%)				
White	4 (57.1)	4 (57.1)	5 (62.5)	4 (57.1)
Asian	3 (42.9)	3 (42.9)	3 (37.5)	3 (42.9)
Time since symptoms onset, y				
Mean (SD)	4.9 (2.5)	7.8 (4.2)	6.6 (2.3)	7.7 (5.9)
Median (min, max)	5.0 (2, 9)	6.6 (2, 14)	5.8 (5, 10)	5.0 (2, 18)
Time since diagnosis, y				
Mean (SD)	2.9 (2.4)	6.3 (4.5)	4.7 (2.0)	6.9 (6.2)
Median (min, max)	1.9 (0, 7)	5.9 (0, 14)	4.2 (3, 9)	3.5 (2, 18)
Predominant symptoms at onset, n (%)				
Rigidity/bradykinesia	3 (42.9)	1 (14.3)	6 (75.0)	3 (42.9)
Tremor	4 (57.1)	6 (85.7)	2 (25.0)	4 (57.1)
Family history of PD, n (%)				
Yes	2 (28.6)	4 (57.1)	2 (25.0)	2 (28.6)
No	5 (71.4)	3 (42.9)	6 (75.0)	5 (71.4)
MoCA total score, mean (SD)	27.0 (3.8)	25.4 (4.0)	25.6 (2.8)	28.3 (2.5)
MDS-UPDRS part II + part III score,[a,b] mean (SD)	36.0 (17.4)	58.0 (16.1)	45.8 (18.4)	40.9 (17.4)
MDS-UPDRS part II score,[a] mean (SD)	6.1 (3.8)	13.9 (7.6)	10.1 (6.8)	11.3 (7.4)
MDS-UPDRS part III score,[b] mean (SD)	29.9 (14.7)	44.1 (11.6)	35.6 (13.8)	29.6 (11.9)
Any *GBA* mutation, n (%)	7 (100)	7 (100)	8 (100)	7 (100)
Any severe[c] *GBA* mutation, n (%)	5 (71.4)	4 (57.1)	4 (50.0)	4 (57.1)
p.L444P (p.Leu483Pro)	3 (42.9)	3 (42.9)	0	3 (42.9)
p.84GG (p.Leu29AlafsX18)	1 (14.3)	1 (14.3)	1 (12.5)	0
p.A456P (p.Ala495Pro)[d]	1 (14.3)	1 (14.3)	0	1 (14.3)
p.R120W (p.Arg159Trp)	1 (14.3)	0	1 (12.5)	1 (14.3)
p.D409H (p.Asp448His)	0	0	1 (12.5)	0
p.G193W (p.Gly232Trp)	0	0	1 (12.5)	0
Any other[e] *GBA* mutation, n (%)	2 (28.6)	3 (42.9)	4 (50.0)	3 (42.9)
p.N370S (p.Asn409Ser)	1 (14.3)	0	3 (37.5)	3 (42.9)
p.E326K (p.Glu365Lys)	1 (14.3)	1 (14.3)	1 (12.5)	0
p.R496C (p.Arg535Cys)	0	2 (28.6)	0	0
Participants with AEs by MedDRA Primary System Organ Class throughout Part 1 of MOVES-PD,[f] n (%)				
Any AE	6 (85.7)	7 (100)	7 (87.5)	6 (85.7)
Ear and labyrinth disorders	0	1 (14.3)	0	1 (14.3)
Eye disorders	0	3 (42.9)	2 (25.0)	0
Gastrointestinal disorders	2 (28.6)	5 (71.4)	2 (25.0)	1 (14.3)
General disorders and administration site conditions	0	0	1 (12.5)	1 (14.3)
Infections and infestations	1 (14.3)	2 (28.6)	0	2 (28.6)
Injury, poisoning, and procedural complications	0	1 (14.3)	2 (25.0)	3 (42.9)
Investigations	1 (14.3)	0	1 (12.5)	0

Musculoskeletal and connective tissue disorders	0	2 (28.6)	1 (12.5)	0
Nervous system disorders	3 (42.9)	2 (28.6)	1 (12.5)	0
Psychiatric disorders	0	4 (57.1)	5 (62.5)	2 (28.6)
Renal and urinary disorders	1 (14.3)	0	0	2 (28.6)
Respiratory, thoracic, and mediastinal disorders	0	0	0	1 (14.3)
Skin and subcutaneous tissue disorders	0	0	1 (12.5)	1 (14.3)
Vascular disorders	0	0	0	1 (14.3)
AEs leading to treatment discontinuation[g,h]	0	1 (14.3)	0	1 (14.3)
Confusional state	0	1 (14.3)	0	0
Panic attack	0	0	0	1 (14.3)
Pharmacokinetic parameters				
Plasma pharmacokinetic parameters at week 4[i]				
C_{max}, ng/mL, mean (SD)	-	47.9 (9·66)	80.0 (17.5)	139 (14.7)
Geometric mean (CV%)	-	46.9 (20.2)	78.3 (21.8)	139 (10.6)
t_{max}, h, median (range)	-	4.33 (1.00–24.00)	2.84 (1.92–8.03)	2.10 (1.93–3.98)
$AUC_{0–24}$, ng•h/mL, mean (SD)	-	839 (178)[j]	1560 (317)	2720 (447)[k]
Geometric mean (CV%)	-	825 (21.2)	1540 (20.2)	2690 (16.4)
CL_{SS}/F, mL/h, mean (SD)	-	4930 (944)[j]	5280 (979)	5660 (1070)[k]
Geometric mean (CV%)	-	4850 (19.2)	5200 (18.5)	5580 (18.9)
CSF pharmacokinetic concentrations at week 4 (2–4 h post dose)				
CSF concentration, ng/mL, mean (CV%)	-	1.98 (9.6)[l]	3.74 (36.6)[l]	8.02 (30.0)[m]
Pharmacodynamics				
Pharmacodynamic biomarkers in plasma				
Plasma GL-1 at baseline, µg/mL, mean (SD)	5.5 (1.2)	5.5 (1.0)	5.2 (0.7)	5.6 (1.2)
Plasma GL-1 at week 4, µg/mL, mean (SD)	5.6 (0.8)	2.1 (0.6)	1.5 (0.2)	1.2 (0.3)
Percent change in plasma GL-1 from baseline at week 4, mean (SD)	3.7 (13.2)	-62.1 (8.3)	-70.9 (3.7)	-78.4 (2.2)
Pharmacodynamic biomarkers in CSF				
CSF GL-1 at baseline, ng/mL, mean (SD)	7.5 (3.5)	6.2 (2.5)	9.8 (8.0)	8.2 (4.6)
CSF GL-1 at week 4, ng/mL, mean (SD)	7.7 (2.5)	4.1 (1.8)	3.9 (3.1)	2.2 (1.3)
Percent change in CSF GL-1 from baseline at week 4, mean (SD)	6.9 (15.1)	-32.8 (28.2)	-61.4 (12.9)	-73.2 (6.9)

[a]Part II (motor experiences of daily living [13 items]) [1,2]. [b]Part III (motor examination [33 items]) [1,2]. [c]Severe *GBA* mutations are categorized as those that cause GD types 2 and 3 [3]. [d]All participants with p.A456P (p.Ala495Pro) mutations also had p.L444P (p.Leu483Pro) mutations and were determined not to have GD (based on similar GCase enzymatic activity in these patients to heterozygous individuals, suggesting these 2 mutations were present in the same allele). [e]Other, nonsevere *GBA* mutations included mild *GBA* mutations that have been associated with GD type 1 [3], and the p.E326K (p.Glu365Lys) variant (no participant carried the p.T369M [p.Thr408Met] variant). [f]Includes AEs that occurred during the treatment-emergent period (defined as the period from first intake of treatment to last intake of treatment, with an additional 6-week post-treatment period). [g]Presented by MedDRA Preferred Terms. [h]Both patients discontinued the study after week 4 since venglustat initiation. [i]Plasma samples were collected at 1 h predose and 1, 2, 4, 8, and 24 h post dose. [j]n=5. [k]n=6. [l]n=6; one participant in low-dose group and two participants in mid-dose group were not included in the CSF pharmacokinetic analysis because week 4 CSF sample was collected before dose instead of at the protocol-specified postdose time. [m]n=6; week 4 CSF sample was not collected for one participant. AE, adverse event; $AUC_{0–24}$, area under the plasma concentration versus time curve from 0 to 24 h; CL_{SS}/F, total systemic clearance at steady state; C_{max}, maximum observed concentration; CSF, cerebrospinal fluid; CV%, coefficient of variation; *GBA*, glucocerebrosidase (glucosylceramidase beta) gene; GL-1, glucosylceramide; max=maximum; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MedDRA, Medical Dictionary for Regulatory Activities min, minimum; MoCA, Montreal Cognitive Assessment; NA, not applicable; PD, Parkinson's disease; t_{max}, time to maximum concentration.

Supplementary Table 4. List of concomitant symptomatic PD medications

	Japanese (n=12)	Non-Japanese (n=17)
Any concomitant symptomatic PD medication,[a] n (%)	12 (100)	15 (88.2)
Levodopa and levodopa derivatives	12 (100)	12 (70.6)
Dopamine agonists	9 (75.0)	11 (64.7)
MOAB inhibitors	1 (8.3)	11 (64.7)
Tertiary amines	2 (16.7)	4 (23.5)
Other dopaminergic agents	1 (8.3)	3 (17.6)
Adamantane derivatives	5 (41.7)	1 (5.9)

[a]Medication can be counted in more than one therapeutic class, and an individual participant can receive more than one concomitant symptomatic PD medication. MOAB, monoamine oxidase B; PD, Parkinson's disease

Supplementary Table 5. Psychiatric disorders in Part 1 participants of the MOVES-PD trial[a]

Japanese (n=12)				
		Venglustat		
	Placebo (n=3)	Low (n=3)	Mid (n=3)	High (n=3)
Psychiatric disorders, n (%)[b]	0	1 (33.3)	2 (66.7)	0
Delirium	0	0	1 (33.3)	0
Hallucination	0	0	1 (33.3)	0
Insomnia	0	1 (33.3)	0	0
Non-Japanese (n=17)				
		Venglustat		
	Placebo (n=4)	Low (n=4)	Mid (n=5)	High (n=4)
Psychiatric disorders, n (%)[b]	0	3 (75.0)	3 (60.0)	2 (50.0)
Anxiety	0	0	0	2 (50.0)
Depressed mood	0	1 (25.0)	1 (20.0)	0
Hallucination (visual)	0	0	2 (40.0)	0
Confusional state	0	1 (25.0)	0	0
Depression	0	1 (25.0)	0	0
Panic attack	0	0	0	1 (25.0)

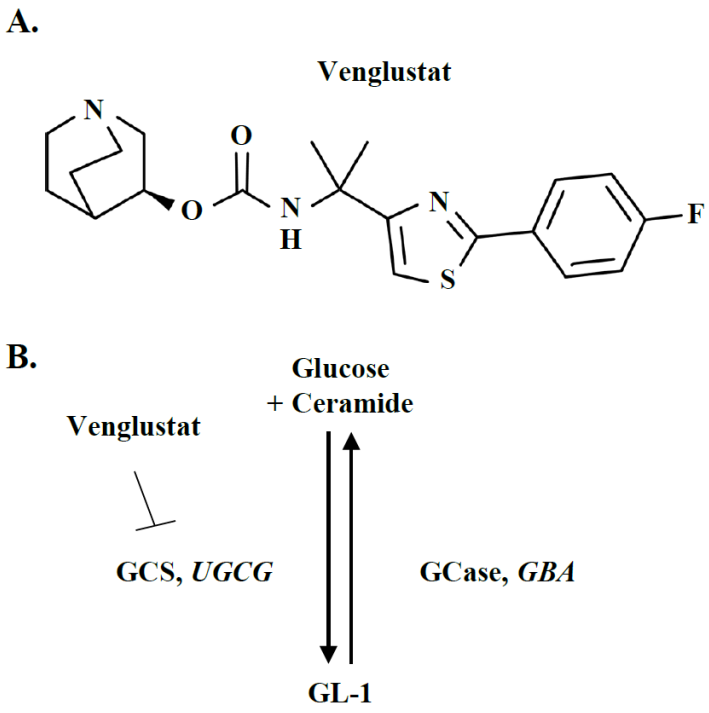
[a]Adverse events presented by MedDRA Preferred Terms. MedDRA, Medical Dictionary for Regulatory Activities.

Supplementary Table 6. Plasma pharmacokinetic parameters of venglustat following dose on day 1[a]

	Japanese (n=9)			Non-Japanese (n=13)		
	Venglustat			Venglustat		
	Low (n=3)	Mid (n=3)	High (n=3)	Low (n=4)	Mid (n=5)	High (n=4)
C_{max}, ng/mL, mean (SD)	21.8 (2.44)	31.3 (10.5)	54.1 (11.7)	13.8 (2.27)	26.3 (12.3)	47.4 (6.03)
Geometric mean (CV%)	21.7 (11.2)	29.9 (33.6)	53.3 (21.6)	13.6 (16.5)	23.8 (46.7)	47.1 (12.7)
t_{max}, h, median (range)	4.33 (4.00–7.17)	4.02 (2.08–7.00)	4.10 (4.00–7.17)	4.07 (1.00–8.00)	4.17 (2.00–8.00)	3.94 (2.25–7.00)
$AUC_{0–24}$, ng•h/mL, mean (SD)	393 (52.8)	623 (211)	990 (203)	255 (59.6)	457 (186)	873 (108)
Geometric mean (CV%)	390 (13.4)	596 (33.9)	977 (20.5)	249 (23.4)	422 (40.8)	868 (12.4)
$AUC_{0–48}$, ng•h/mL, mean (SD)	661 (47.4)	1130 (431)	1590 (312)	431 (111)	776 (269)	1450 (127)
Geometric mean (CV%)	660 (7.2)	1070 (38.3)	1570 (19.6)	419 (25.7)	735 (34.6)	1440 (8.8)

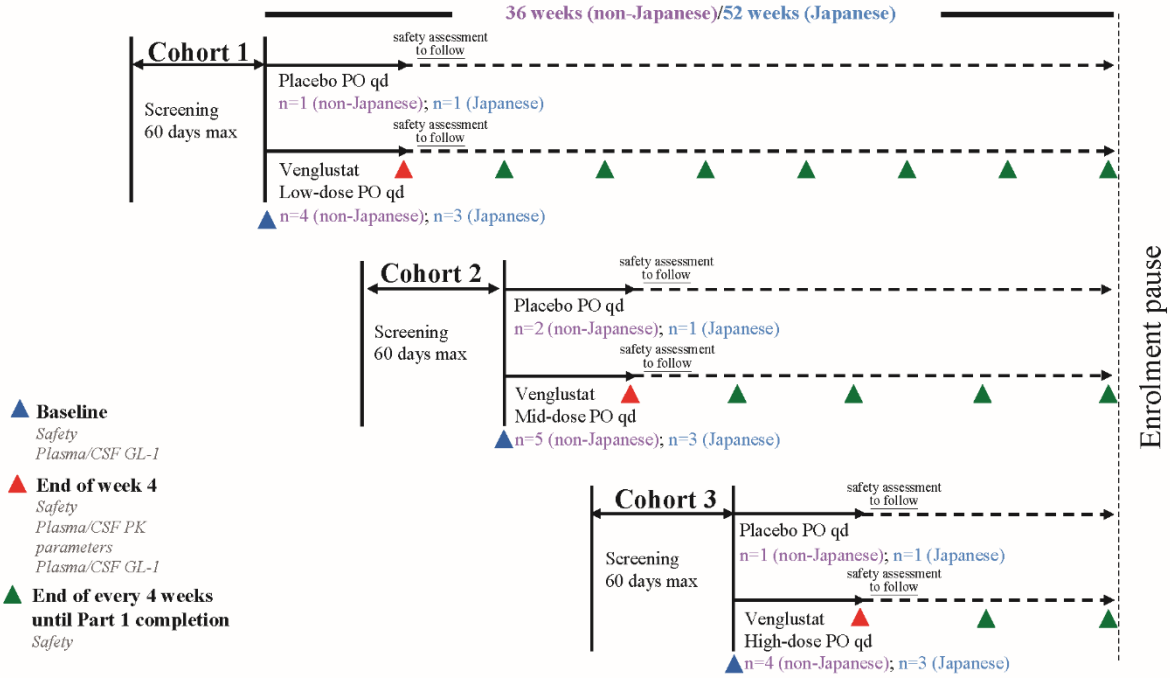
[a]Plasma samples were collected at predose and 1, 2, 4, 8, 24, 48 h post dose. $AUC_{0–24}$, area under the plasma concentration versus time curve from 0 to 24 h; $AUC_{0–48}$, area under the plasma concentration versus time curve from 0 to 48 h; C_{max}, maximum observed concentration; CV%, coefficient of variation; t_{max}, time to maximum concentration.

Supplementary Figure 1. Structure and mechanism of action of venglustat, a GCS inhibitor



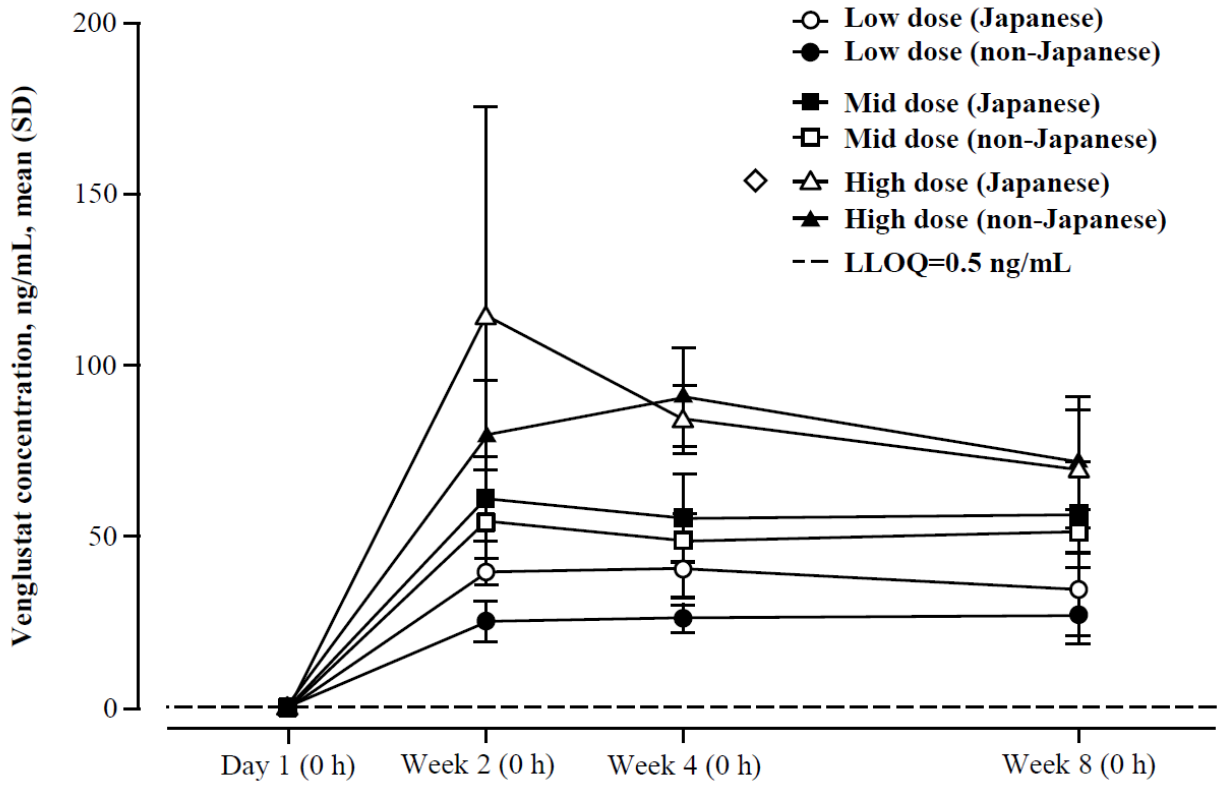
(A) Venglustat structure. (B) Schematic of GCS inhibition by venglustat. *GBA*, glucocerebrosidase (glucosylceramidase beta) gene; GCase, glucocerebrosidase; GCS, glucosylceramide synthase; GL-1, glucosylceramide; *UGCG*, UDP-glucose ceramide glucosyltransferase gene.

Supplementary Figure 2. MOVES-PD Part 1 study design



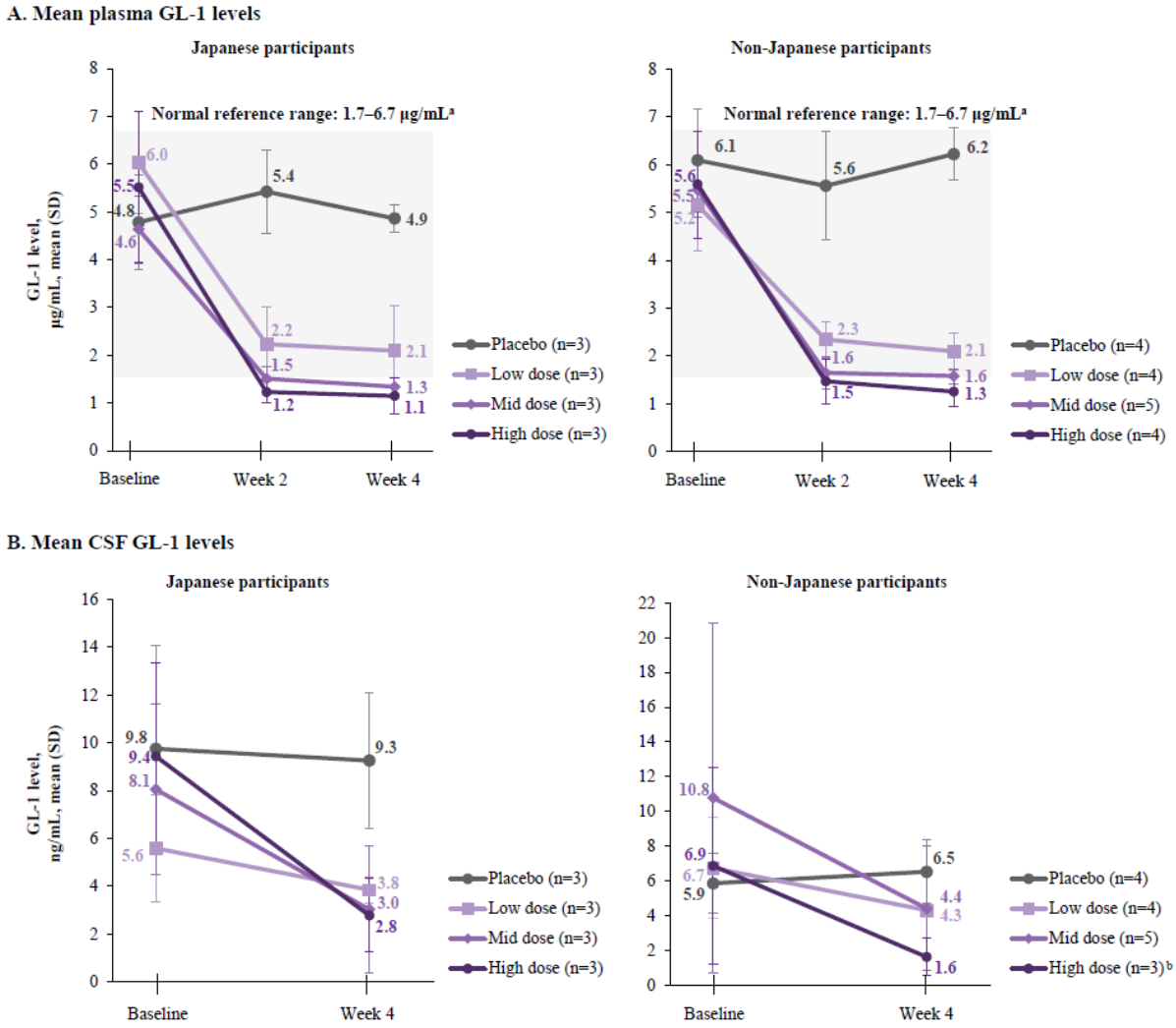
Part 1 of MOVES-PD was a placebo-controlled, double-blinded dose-escalation study of three different venglustat doses using a sequential cohort design. Venglustat dose was escalated in sequential cohorts; only when safety and tolerability were demonstrated after data review when all participants completed the first 4-week course of therapy, escalation to the next higher level in the next cohort could occur. All participants were followed every 4 weeks for a maximum of 36 weeks (up to 52 weeks for Japanese participants). Primary endpoint was evaluation of safety and tolerability, with assessments recorded at days 1, 2, and 3 and weeks 2 and 4 post dose, and then every 4 weeks, up to 36 weeks for non-Japanese participants and 52 weeks for Japanese participants. Secondary endpoint was venglustat pharmacokinetics in plasma and CSF at the end of week 4. Exploratory endpoint was venglustat pharmacodynamics as assessed by GL-1 levels in plasma and CSF samples collected at baseline and end of week 4 (plasma GL-1 levels were also assessed at end of week 2). Additional exploratory analyses assessed the effect of venglustat on selected scales and questionnaires, including MDS-UPDRS (parts II and III) scores through week 8. [a]Part II (motor experiences of daily living [13 items]) and part III (motor examination [33 items]) [1,2]. [b]Maximum duration of follow-up for the first of sequential non-Japanese groups randomized to low-dose venglustat or placebo. [c]Maximum duration of follow-up for the first of sequential Japanese groups randomized to low-dose venglustat or placebo. AE, adverse event; CSF, cerebrospinal fluid; GL-1, glucosylceramide; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PK, pharmacokinetics.

Supplementary Figure 3. Venglustat trough plasma concentrations



C_{trough} over 8 weeks in Japanese and non-Japanese participants who received venglustat (low, mid, or high dose) in Part 1 of the MOVES-PD trial. C_{trough}, plasma concentration observed just before treatment administration during repeated dosing; LLOQ, lower limit of quantification.

Supplementary Figure 4. Plasma and CSF GL-1 levels after venglustat treatment



Mean GL-1 levels at baseline, week 2, and week 4 in plasma (A) and at baseline and week 4 in CSF (B) in Japanese and non-Japanese participants who received placebo or venglustat (low, mid, or high dose) in Part 1 of the MOVES-PD trial. [a]As reported previously [4]. [b]Week 4 CSF sample was not collected for one participant from the non-Japanese population. CSF, cerebrospinal fluid; GL-1, glucosylceramide.

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[1] Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, Stern MB, Tilley BC, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, Van Hilten JJ, LaPelle N (2007) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): process, format, and clinimetric testing plan. *Mov Disord* **22**, 41-47.

[2] Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N, Movement Disorder Society UPDRS Revision Task Force (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* **23**, 2129-2170.

[3] Gan-Or Z, Amshalom I, Kilarski LL, Bar-Shira A, Gana-Weisz M, Mirelman A, Marder K, Bressman S, Giladi N, Orr-Urtreger A (2015) Differential effects of severe vs mild *GBA* mutations on Parkinson disease. *Neurology* **84**, 880-887.

[4] Zheng K, Ji A, Chung LL, Culm-Merdek K, Liu H, Richards S, Sung C (2016) Enhancement of human plasma glucosylceramide assay sensitivity using delipidized plasma. *Mol Genet Metab Rep* **8,** 77-79.

CONSORT 2010 checklist of information to include when reporting a randomized trial*

Section/topic	Item No.	Checklist item	Reported on page No.
Title and abstract			
	1a	Identification as a randomized trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4,5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5,6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5,6
Participants	4a	Eligibility criteria for participants	5,6, Supplementary material (5,6)
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6,7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7,8,9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	7
Randomization:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomization; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			

Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	10, Table 2 (24,25), Fig. 1 (28)
	13b	For each group, losses and exclusions after randomization, together with reasons	10, Table 2 (24,25), Fig. 1 (28)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1 (21)
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10, Table 2 (24,25), Fig. 1 (28), Fig. 2 (29), Supplementary Figure 2 [13])
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10,11,12, Table 2 (24,25), Table 3 (26), Fig. 2 (29)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10, Table 2 (24,25)
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	12,13,14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12,13,14
Other information			
Registration	23	Registration number and name of trial registry	7
Protocol	24	Where the full trial protocol can be accessed, if available	17
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	9,15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacologic treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.