

Research Report

Cost-Effectiveness and Cost-Utility of Early Levodopa in Parkinson's Disease

Constant V.M. Verschuur^{a,*}, Sven R. Suwijn^a, Rob J. de Haan^b, Judith A. Boel^b, Bart Post^c, Bas R. Bloem^c, Johannes J. van Hilten^d, Teus van Laar^e, Gerrit Tissingh^f, Alexander Munts^g, Marcel G.W. Dijkgraaf^{b,1} and Rob M.A. de Bie^{a,1}

^a*Department of Neurology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands*

^b*Department of Epidemiology and Data Science, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands*

^c*Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, The Netherlands*

^d*Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands*

^e*Department of Neurology, University Medical Center Groningen, Groningen, The Netherlands*

^f*Department of Neurology, Zuyderland Medical Center, Heerlen, The Netherlands*

^g*Department of Neurology, Excellent Klinieken, Dordrecht, The Netherlands*

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Abstract.

Background: In the Levodopa in EARly Parkinson's disease (LEAP) study, 445 patients were randomized to levodopa/carbidopa 100/25 mg three times per day for 80 weeks (early-start) or placebo for 40 weeks followed by levodopa/carbidopa 100/25 mg three times per day for 40 weeks (delayed-start).

Objective: This paper reports the results of the economic evaluation performed alongside the LEAP-study.

Methods: Early-start treatment was evaluated versus delayed-start treatment, in which the cost-effectiveness analysis (CEA) and the cost-utility analysis (CUA) were performed from the societal perspective, including health care costs among providers, non-reimbursable out-of-pocket expenses of patients, employer costs of sick leave, and lowered productivity while at work. The outcome measure for the CEA was the extra cost per unit decrease on the Unified Parkinson's Disease Rating Scale 80 weeks after baseline. The outcome measure for the CUA was the extra costs per additional quality adjusted life year (QALY) during follow-up.

Results: 212 patients in the early-start and 219 patients in the delayed-start group reported use of health care resources. With savings of €59 per patient (BCa 95% CI: -829, 788) in the early-start compared to the delayed-start group, societal costs were balanced. The early-start group showed a mean of 1.30 QALYs (BCa 95% CI: 1.26, 1.33) versus 1.30 QALYs (BCa 95% CI: 1.27, 1.33) for the delayed-start group. Because of this negligible difference, incremental cost-effectiveness and cost-utility ratios were not calculated.

Conclusion: From an economic point of view, this study suggests that early treatment with levodopa is not more expensive than delayed treatment with levodopa.

Keywords: Parkinson's disease, levodopa, cost analysis

*Correspondence to: Constant V.M. Verschuur, MD, Amsterdam University Medical Centers, University of Amsterdam, Department of Neurology, Amsterdam Neuroscience,

Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel.: +31 20 5669111; E-mail: c.v.verschuur@amsterdamumc.nl.

¹Shared senior authorship.

INTRODUCTION

In the randomized delayed-start Levodopa in Early Parkinson's disease (LEAP) study, levodopa/carbidopa 100/25 mg three times per day had a beneficial effect on symptoms in early Parkinson's disease (PD) without a disease-modifying impact in the follow-up period of 80 weeks [1]. Considering the absence of a difference in side effects at the end of the follow-up period and the low costs of levodopa, these results leave room for answering the question whether the start of treatment with levodopa in early PD may be cost-effective. If so, this would be an argument in favor of starting levodopa early after the diagnose has been made.

This paper reports the results of the economic evaluation that was performed alongside the LEAP-study. The cost-effectiveness (CEA) and cost-utility (CUA) analyses can be used in support of health care policy stakeholders to set treatment priorities, respectively to allocate scarce resources to distinct disease populations, diagnostic and interventional strategies, and health care sectors.

METHODS

General design

To separate possible disease-modifying effects from the direct symptomatic effect of levodopa, a multi-center, randomized delayed-start, double-blind placebo-controlled trial design was used. Patients with early PD whose functional health did not yet warrant initiation of PD-medication were randomized to either 80 weeks of treatment with levodopa/carbidopa 100/25 mg three times per day (early-start group) or to 40 weeks placebo followed by levodopa/carbidopa 100/25 mg three times per day for 40 weeks (delayed-start group). A total of eight study-visits were performed. To be able to detect a minimal clinically important difference of four points on the Unified Parkinson's Disease Rating Scale (UPDRS) [2] at 80 weeks, 446 patients needed to be included [3]. This prospective study was approved by the Amsterdam University Medical Centers Institutional Ethics Committee under number 2011.057.

Early levodopa treatment was economically evaluated versus delayed-start levodopa as the current standard of care in patients of the LEAP-study, where CEA and CUA were performed from the societal perspective. The societal perspective included the health

care costs among providers, the non-reimbursable out-of-pocket expenses of patients, and the employer costs of sick leave from work ('absenteeism') and lowered productivity while at work ('presenteeism'). As the UPDRS is frequently used in PD trials to assess treatment efficacy, the extra cost per unit decrease on the UPDRS 80 weeks after baseline was chosen as the CEA outcome measure. The extra costs per additional quality adjusted life year (QALY) during follow-up was chosen as the CUA outcome measure. The time horizon was restricted to the planned period of clinical follow-up of 80 weeks as patients from the early and delayed-start groups clinically did not differ significantly at this point, and no marked differences in resource use could be observed during the last half year of follow-up. Therefore, projections from a lifetime perspective based on modelling of the future disease course were considered obsolete. With a horizon of more than one year, the costs and effects during the weeks that fell in the second year of follow-up were discounted against 4% and 1.5% respectively – these yearly discount rates are common in Dutch health care research.

Cost components and resources

We included the health care costs of (a) levodopa treatment, including pharmacy delivery costs, (b) consultations by the neurologist, psychiatrist, rehabilitation specialist, general practitioner, company physician, emergency care, psychologist, Parkinson nurse, physiotherapist, occupational therapist, speech therapist, and social worker, (c) hospital day care treatment or inpatient stay, (d) institutionalized care other than hospitals, like a nursing home or rehabilitation center, (e) formal home care, and (f) devices supporting a patient's autonomy, like walking aids or an adjusted telephone. Out-of-pocket expenses concerned over-the-counter medication for extra, private help and adaptations at home. Questionnaires were used to collect data regarding the impact of early levodopa treatment on sickness leave from work. Both work absenteeism and presenteeism were questioned to be able to study productivity losses.

Measurements took place at weeks 22, 40, 56, 68, and 80. The recall period in the questionnaires was four weeks. The results were generalized to the period in-between successive measurements by multiplying the reported data with the length of the preceding time interval in weeks divided by four. Whether this led to an over- or underestimation was qualitatively

Table 1
Dutch unit costs (€) for resources used

Resource	Unit	Unit costs in 2017 euros*	Source
Levodopa			
Monthly costs	standard dose	11.40	www.medicijnkosten.nl
Pharmacy costs	delivery	6.37	Menzis
Consultations			
Neurologist	visit	101.28	DCM-2015
Psychiatrist	visit	96.16	DCM-2015
Rehabilitation specialist	visit	156.52	DCM-2015
General practitioner	visit	33.76	DCM-2015
Company physician	visit	45.84	DCM-2015/ expert opinion
Emergency care	visit	264.98	DCM-2015
Psychologist	visit	96.16	DCM-2015
Parkinson nurse	visit	66.50	DCM-2015
Physiotherapist	visit	33.76	DCM-2015
Occupational therapist	visit	33.76	DCM-2015
Speech therapist	visit	30.69	DCM-2015
Social worker	visit	66.50	DCM-2015
Out-of-pocket expenses			
Over-the-counter medication	mean monthly costs	reported	patient
Private home help	mean monthly costs	reported	patient
Productivity loss	Hour	35.55	DCM-2015

DCM, Dutch Costing Manual for health care research. *After price-indexing, based on yearly general consumer price indices for the Netherlands.

assessed by a separate question on the representativeness at the individual patient level of the use of resources during the recall period being substantially below, somewhat below, somewhat above or substantially above average.

Unit costs and costing

Unit costing was done in accordance with the most recent Dutch guideline on costing in health care research [4]. Units of volume measurement and unit costs are shown in Table 2. All unit costs were expressed for the reference year 2017 after price-indexing with general consumer price-index figures for the Netherlands, if sources with different base years were used.

The costs of levodopa/carbidopa treatment were based on prototyping, assuming an overall mean 100/25 mg three times per day dose per patient, including pharmacy dispensing fees depending on the mean total length of drug use during the follow-period per study group, starting with a higher fee for a first prescription and lower fees for each subsequent one at quarterly intervals. Unit costs for a consultation of the Parkinson nurse-specialist were aligned with unit costs of a social worker. Out-of-pocket expenses were gathered as reported by patients as monthly averages at the time of completion of the questionnaire.

In order to quantify productivity losses resulting from absenteeism and from presenteeism at work, we first determined the number of daily working hours for each patient with a paid job. Absenteeism was costed by multiplying the number of days absent from work with the patient's daily working hours. In case of presenteeism the score between 0 (could not do the work at all) and 10 (worked as usual) was used to derive the patient's daily working hours lost. The elasticity between hours absent and productivity is implicitly included in the valuation in Table 2. In case of sick leave, the average unit costs per lost working hour were taken, irrespective of age and sex. Costs were calculated as the sum of products of the volumes of resources used and their respective unit costs. Volumes of resource use and the costs are reported separately.

Patient outcomes

EQ-5D-3L health status data were gathered at baseline and at weeks 22, 40, 56, 68, and 80 [5]. The health utility of each EQ-5D health status scoring profile was determined by applying the available Dutch valuation algorithm [6]. The algorithm was based on the time trade-off elicitation technique of health state preferences during interviews with adults from the general population. The number of QALYs a patient generated during the 80 weeks of follow-up

Table 2
Mean use of resources by treatment group

	Early treatment (N _{max} = 212) Mean volume (BCa 95% CI)	Delayed treatment (N _{max} = 219) Mean volume (BCa 95% CI)	Difference* early minus delayed Mean volume [†] (BCa 95% CI)
Health care			
Levodopa	see text	see text	see text
Neurologist	3.5 (3.0, 4.1)	4.3 (3.7, 5.0)	-0.8 (-1.6, 0.0)
Psychiatrist	0.1 (0.0, 0.3)	0.2 (0.0, 0.5)	-0.1 (-0.4, 0.2)
Rehabilitation specialist	0.2 (0.1, 0.3)	0.6 (0.3, 1.0)	-0.4 (-0.9, 0.0)
General practitioner	1.4 (1.0, 1.8)	1.7 (1.2, 2.2)	-0.3 (-1.0, 0.4)
Company physician	0.6 (0.3, 0.9)	0.6 (0.3, 0.9)	-0.0 (-0.4, 0.4)
Emergency care	0.0 (0.0, 0.1)	0.1 (0.0, 0.2)	-0.1 (-0.2, 0.0)
Psychologist	0.8 (0.4, 1.2)	1.1 (0.7, 1.6)	-0.4 (-1.0, 0.3)
Parkinson nurse	1.7 (1.3, 2.0)	2.2 (2.6, 3.3)	-0.5 (-1.2, 0.1)
Physiotherapist	26.1 (21.2, 31.3)	33.3 (28.6, 38.3)	-7.3 (-14.5, -0.2)
Occupational therapist	1.0 (0.5, 1.4)	2.7 (1.6, 3.8)	-1.8 (-3.3, -0.4)
Speech therapist	0.7 (0.3, 1.1)	1.7 (0.9, 2.6)	-1.1 (-2.0, -0.1)
Social worker	0.5 (0.2, 0.9)	1.0 (0.4, 1.7)	-0.5 (-1.4, 0.3)
Productivity loss in hours			
Absenteeism	25.7 (15.3, 37.4)	11.3 (5.9, 18.0)	14.4 (1.8, 27.8)
Presenteeism	15.2 (9.6, 21.3)	16.1 (8.7, 25.2)	-1.0 (-11.4, 9.3)

*Differences rounded to zero keep their sign. [†]*p*-values are reported in Table 3.

was determined by interpolation between successive measurements and taking the area under the curve as the best estimate, weighted for the lengths of the periods between measurements and accounting for periods with utilities below zero. If only one of two neighboring measurements was available, no interpolation was performed and the available measurement was considered to represent the interpolated value. Because of the weighting by period length, this approach effectively restores interpolation for each triple of successively planned measurements of which the middle one is missing. Only in case of two non-available successive measurements interpolated data were missing. The patients' final scores were calculated by taking the weighted mean of available period scores. The maximum number of QALYs a patient could generate during 80 weeks of follow-up was 80/52.175 or 1.533 (undiscounted), or 79.58/52.175 or 1.525 (discounted).

Analyses

The health economic analyses were based on the intention-to-treat analysis data set. Results on costs, patient outcomes and differences between treatment groups are reported along with bias-corrected and accelerated 95% confidence intervals (BCa 95% CI). These confidence intervals were derived by drawing

2,500 samples of the same size as the original samples and with replacement, stratified by treatment group, academic versus non-academic hospital, age below or at least 65 years, and symptom duration shorter than or at least six months. *P*-values for differences by types of resources used are not reported, as *p*-values for the corresponding costs are identical.

No incremental cost-effectiveness and cost-utility ratios were calculated for the extra costs per extra unit decrease in UPDRS score or the extra costs per additional QALY. Both health outcome measures showed a near zero absolute difference between the study groups – see Results. Consequently, incremental analyses easily render into positive or negative infinity, leaving the health care policy maker and the interested medical professional in doubt whether early levodopa treatment should be regarded as respectively an inefficient or efficient alternative to delayed-start treatment. This could be overcome if a substantial cost difference was to be observed with a clear preference for one strategy over the other. In absence of a disease modifying effect of levodopa however, the hopes of observing such contrast were low.

Data sharing

De-identified data is available for academic research upon request by the corresponding author.

RESULTS

Patients

In the LEAP-study, 445 patients were assessed at baseline after initial enrolment, with 222 and 223 patients randomly assigned to the early-start, respectively delayed-start group. The CONSORT flow-diagram and descriptions of the demographic and baseline clinical characteristics of patients are reported elsewhere with the study groups showing similar profiles at baseline [1].

Resources use and costs

Use of health care resources was reported by 212 patients in the early-start group and 219 patients in the delayed-start group. The other 14 patients did not complete any questionnaire on health resource use during follow-up and were considered drop-outs for the cost analyses. Including drop-out, data were missing for 51 of 1,110 originally planned periods (4.59%, or 4.05% of person-years of follow-up) in the early-start and for 35 of 1,115 originally planned periods (3.14%, or 2.67% of person-years of follow-up) in the delayed-start group. Between 96.3% and 98.6% of patients at the successive measurements over time indicated that the use of resources during the recall period of the latest four weeks was similar to the preceding period.

Table 2 shows the mean use of resources by study group. Table 3 shows the corresponding costs. Tables 2 and 3 do not contain data on inpatient stays at a hospital ward, rehabilitation center or nursing home, because admissions in this cohort were rare, which is expected in early PD. Informal care from neighboring care givers was also still limited in scale. Walking aids and adjusted telephones too yet had to become popular in use.

Patients in the early-start group used levodopa for the full length of the follow-up period of 80 weeks. In the delayed-start group, 61% of patients started treatment in week 41; 17.9% already started with levodopa treatment between weeks 22 and 40 and were assumed to be on treatment for an average of 49 weeks; 21.1% already started with levodopa between weeks 4 and 22 and were assumed to be on treatment for an average of 64 weeks.

Patients in both treatment groups received most attention from the neurologist, Parkinson nurse, general practitioner, occupational therapist, psychologist, and, most dominantly, the physiotherapist.

Patients in the delayed-start group more often visited the physiotherapist (28%), occupational therapist, speech therapist, neurologist, Parkinson nurse, and social worker. This was the main reason that the mean health care costs (Table 3) were lower in the early-start group, saving on average €517 (undiscounted, $P=0.017$; discounted, €512 saved) per patient, despite the €105 higher levodopa drug costs in this group. The out-of-pocket expenses by patients for over-the-counter medication and extra help at home were limited in this relatively healthy Parkinson population and were similar for both study groups.

At baseline, 24% indicated to have a paid regular job (early-start group: 23.9%; delayed-start group: 24.2%). More patients in the early-start group ($N=24$; 10.8%) worked as an entrepreneur, compared with the delayed-start group ($N=9$; 4%). Patients in the early-start group generated 14.4 hours more productivity losses due to absenteeism than patients in the delayed-start group during the follow-up period 80 weeks. These extra two days of absence from work were averaged over all patients, meaning that the difference in the subpopulation with paid employment may be about 6 extra working days of productivity lost during 80 weeks of follow-up. On average, the costs of productivity loss because of absenteeism were €512 (undiscounted, $p=0.046$) higher in the early-start group. The costs of productivity losses due to presenteeism were similar for the two groups. The societal costs of early-start levodopa were similar to the costs of delayed-start levodopa: $-\text{€}59$ ($P=0.89$) per patient.

Health outcomes

Total UPDRS-scores at 80 weeks were available for 207 patients in the early-start group and 210 patients in the delayed-start group. The mean total UPDRS-score was 26.97 (BCa 95% CI: 25.10, 28.88) in the early-start group and 27.00 (BCa 95% CI: 25.11, 28.87) in the delayed-start group, a non-significant difference of -0.04 (BCa 95% CI: -2.76 , 2.74; $p=0.99$).

QALY scores for the follow-up period of 80 weeks could be calculated for all patients. Patients in the early-start group generated a weighted mean of 1.30 (BCa 95% CI: 1.26, 1.33) QALYs during follow-up versus 1.30 (BCa 95% CI: 1.27, 1.33) QALYs for patients in the delayed-start group, the difference of 0.00 (BCa 95% CI: -0.05 , 0.04; $p=0.89$) QALYs being negligible. The discounted QALY results were quite identical (not shown).

Table 3
Mean costs by treatment group

	Early treatment (N _{max} = 212) Mean costs (euros) (BCa 95% CI)	Delayed treatment (N _{max} = 219) Mean costs (euros) (BCa 95% CI)	Difference* early minus delayed Mean costs (euros) (BCa 95% CI; p)
Health care	1888 (1676, 2102)	2405 (2099, 2779)	-517 (-1007, -118; 0.017)
<i>Discounted</i>	1863 (1651, 2076)	2375 (2074, 2743)	-512 (-998, -118; 0.016)
Levodopa	257	151	105
Neurologist	357 (303, 415)	439 (375, 510)	-82 (-167, 5; 0.071)
Psychiatrist	12 (4, 22)	18 (2, 45)	-6 (-40, 18; 0.72)
Rehabilitation specialist	28 (8, 54)	91 (40, 157)	-62 (-143, 1; 0.13)
General practitioner	46 (33, 60)	56 (41, 74)	-10 (-34, 12; 0.38)
Company physician	28 (15, 42)	28 (16, 44)	-1 (-21, 19; 0.96)
Emergency care	9 (0, 19)	34 (12, 62)	-25 (-57, 5; 0.12)
Psychologist	73 (34, 119)	107 (63, 158)	-34 (-100, 33; 0.36)
Parkinson nurse	111 (88, 135)	146 (115, 178)	-35 (-80, 8; 0.11)
Physiotherapist	880 (716, 1,057)	1125 (965, 1293)	-246 (-489, -8; 0.047)
Occupational therapist	30 (15, 46)	89 (54, 130)	-60 (-111, -14; 0.025)
Speech therapist	20 (9, 33)	52 (29, 81)	-32 (-63, -4; 0.039)
Social worker	36 (15, 63)	67 (29, 115)	-31 (-91, 20; 0.26)
Out-of-pocket expenses	36 (18, 60)	55 (27, 88)	-19 (-64, 22; 0.39)
<i>Discounted</i>	35 (18, 59)	55 (26, 88)	-19 (-63, 22; 0.38)
Over-the-counter drugs	20 (9, 38)	14 (7, 22)	6 (-9, 26; 0.52)
Private help	16 (6, 30)	42 (14, 74)	-25 (-70, 10; 0.21)
Productivity loss	1453 (958, 2014)	976 (585, 1445)	477 (-195, 1169; 0.18)
<i>Discounted</i>	1439 (951, 1992)	968 (580, 1433)	472 (-192, 1157; 0.18)
Absenteeism	914 (544, 1329)	402 (211, 639)	512 (65, 987; 0.046)
Presenteeism	539 (342, 757)	574 (309, 897)	-35 (-405, 330; 0.86)
Societal costs	3377 (2819, 4008)	3436 (2889, 4052)	-59 (-829, 788; 0.89)
<i>Discounted</i>	3338 (2787, 3957)	3397 (2856, 4004)	-59 (-821, 782; 0.89)

*Differences rounded to zero keep their sign.

DISCUSSION

In the LEAP-study, there was no significant between-group difference on the UPDRS at week 80 between the early- and delayed-start groups. In the current sub-study, the societal costs were well balanced between the groups and no difference in QALYs was observed. From a strict economic point of view, early-start treatment with low dose levodopa in early PD can neither be regarded as a more, nor as a less efficient intervention than delayed-start treatment. When only the costs were studied for resources used after the first year of follow-up up to week 80 in a confirmatory sensitivity analysis, the differences between the study groups shrank disproportionately, and tended towards an even smaller range of differences in costs – from savings of €65 for physiotherapy in favor of the early-start group (€181 in the first year) to respectively extra costs of €89 due to absenteeism from work (€423 in the first year) for the early-start group. Discounting the costs generated during the final 28 out of 80 weeks of the observation period did not influence the interpretation of the data.

On average, the delayed treatment group showed a higher use of physiotherapy per patient during the

80 weeks of follow-up than the early treatment group with a relative increase in the number of visits by 28% (95% CI 1%–56%). If staff capacity is limited, early treatment may be part of a lean management strategy.

Because of the recall period of four weeks, which was chosen to mitigate a recall bias as much as possible, differences between groups could possibly have been amplified during longer intervals between measurements, despite the study being randomised and thus equally distributing any errors in measurements. However, the most direct impact of intermittent measurement over time with multipliers to achieve full coverage of the calendar period is the widening of the confidence interval of between-group differences. As a result, fewer between-group differences will be detected, if present – qualifying the approach as conservative. More measurements could have been done to minimize this conservatism, but because of the risk of attrition bias, only the minimum number of measurements necessary to be able to perform the primary clinical analysis were done. Further, more measurements would have meant more costs, which might have been problematic since the LEAP-study was an investigator-initiated trial on a relatively tight budget.

The fact that the early-start group included relatively more patients that were entrepreneurs (self-employed) among the patients with a paid job—which can only be explained by the randomization being unbalanced in this respect—might have affected the study results in favor of delayed treatment. If so, an explanation for this could be that when a somewhat higher labour participation of entrepreneurs is assumed, PD symptoms could possibly negatively influence the productivity in a relatively earlier stage than when having a lower labour participation. An explanation for this could be that entrepreneurs will not be able to work those extra hours or have earlier problems with combining work with appointments with a doctor or physiotherapist. A related explanation could be that entrepreneurs are by definition more focused on their productivity, which might result in a recall bias with a higher reported rate of absenteeism. However, patient numbers were too small for a thorough exploratory *post-hoc* subgroup analysis.

The observation that 39% of the patients in the delayed start-group started with levodopa in the placebo-controlled first 40 weeks could have resulted in reducing a difference between the early-start and delayed-start group. Per protocol, starting with levodopa in the first 40 weeks was allowed when patients experienced limitations in functional health. This closely resembles the way patients are treated in clinical practice. It further demonstrates that while ‘starting early’ is possible by indication, it is not pre-determined how much early one actually will have started at the individual patient level.

From an economic point of view, this study suggests that early treatment with levodopa is not more expensive compared to delayed treatment with levodopa, but also, that the clinically relevant effect of a low levodopa dose is not accompanied by a net reduction of costs, therefore seemingly not influencing the clinical decision whether to start early or later after diagnosis of PD. However, as treatment with levodopa is inexpensive, and patients in the early start-group showed improvement of symptoms and health-related quality of life and did not have a different side-effects profile at the end of the study [1], there are more arguments in favor of than against starting with levodopa early after diagnosis of PD. Furthermore, as patients in our study necessarily had insufficient disability to warrant treatment with Parkinson medication, it is possible that early treatment simply could not improve the capacity to work—consequently limiting the possibility of

showing cost-effectiveness of early treatment with levodopa.

Although the possible typically Dutch phenomenon where there is a well-integrated network of, for example, physiotherapists for the care of PD-patients, may be different from the situation for patients in other, less-developed countries in the world, we hypothesize that the results of this study probably can well be extrapolated to other countries, as patients in the placebo-controlled first 40 weeks of the study showed an improvement in symptoms and disease-related quality of life. To further investigate this, costing based on the guidelines of a specific country should be applied to our data. Finally, we expect that the unique data presented in this manuscript will function as a point of reference for clinicians and policymakers when comparing costs of current and future treatments for PD compared to the standard treatment with levodopa.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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