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Ginkgo biloba extract EGb 761® in the treatment of dementia: a pharmacoeconomic analysis of the Austrian setting

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Ginkgo-biloba-Extrakt EGb 761® in der Behandlung der Demenz: eine pharmakoökonomische Analyse bezogen auf Österreich

Zusammenfassung

Ziel Anhand von Daten aus drei klinischen Studien untersuchten wir die pharmakoökonomischen Auswirkungen der Behandlung nicht-institutionalisierter Demenzpatienten in Österreich mit einem Medikament, das den standardisierten Ginkgo-Extrakt EGb 761® enthält. In einer separaten Analyse verglichen wir die für die Erzielung eines Behandlungserfolges mit EGb 761® bzw. Cholinesterasehemmern entstehenden Kosten.

Methoden Unter Verwendung eines Modells mit festen Effekten wurde eine Metaanalyse von Daten zu Alltagsaktivitäten von 1201 Patienten mit Demenz durchgeführt, die für 22 bzw. 24 Wochen doppelblind entweder EGb 761® (240 mg/Tag) oder Placebo erhielten. Hieraus wurde die Verzögerung der Progression von Einbußen in den Alltagsaktivitäten geschätzt. Anhand der aktuellen österreichischen Erstattungsbeträge für Arzneimittel, Arzthonorare und Leistungen der Pflegeversicherung für sieben Pflegestufen wurden die Gesamtkosten für vier Szenarien berechnet. Für den Vergleich mit Cholinesterasehemmern wurden Daten aus Cochrane-Metaanalysen zum klinischen Globalurteil herangezogen und mit entsprechenden Daten aus den EGb 761®-Studien verglichen.

Ergebnisse und Diskussion Der Nutzen einer Behandlung mit EGb 761® (240 mg/Tag) entspricht einer Verzögerung der Progression von Einbußen in den Alltagsaktivitäten um 22,3 Monate gegenüber Placebogabe. Die Nettoeinsparungen bei Behandlung mit EGb 761® reichten von EUR 3692 bis EUR 29.577 und kamen vorwiegend durch späteren Eintritt in höhere Pflegestufen zustande. Ein zusätzlicher Therapieerfolg mit EGb 761® kostete EUR 530,88. In einem behelfsweisen Vergleich verursachte die Behandlung mit einem Cholinesterasehemmer höhere Kosten je Behandlungserfolg.

Schlüsselwörter: Demenz, Ginkgo biloba, EGb 761®, Pharmakoökonomie, Österreich

Summary

Objective We used efficacy data from three clinical trials to investigate the pharmacoeconomic implications of treating noninstitutionalized Austrian dementia patients with a drug based on EGb 761®, a standardized extract from *Gingkgo biloba*. In a separate analysis, we compared the pharmacoeconomic aspects of achieving treatment success with EGb 761® and cholinesterase inhibitors.

Methods A fixed-effect model was used to conduct a metaanalysis of activities of daily living data from 1,201 patients diagnosed with dementia and treated with either EGb 761® (240 mg/day) or matched placebo for 22 or 24 weeks under double-blind conditions. From this analysis, the delay in activities of daily living (ADL)-based disease progression was estimated. Current Austrian drug reimbursement prices, physician fees, and federal subsidies for seven stages of home care were applied to calculate overall costs in four scenarios. For the comparison with cholinesterase inhibitors, metaanalysis data pertaining to overall clinical impression as published by the Cochrane Group were compared to corresponding data from our EGb 761® studies.

Results and discussion The benefit of treatment with EGb 761® (240 mg/day) corresponds to a delay in ADL deterioration by 22.3 months compared to placebo. Overall net savings with EGb 761® treatment ranged from

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EUR 3,692 to EUR 29,577, mainly driven by delays in progression towards higher home care subsidies. For one additional therapy success with EGb 761®, EUR 530.88 was required. In a tentative cost comparison, cholinesterase inhibitors required higher expenses to achieve treatment success.

Keywords: Dementia, Ginkgo biloba, EGb 761®, Economics, Pharmaceutical, Austria

Introduction

EGb 761® is a dry extract from *Ginkgo biloba* leaves (drug-extract ratio 35–67:1; extraction solvent: acetone 60 % (w/w)) which is adjusted to 22.0–27.0 % ginkgo flavonoids calculated as ginkgo flavone glycosides and 5.0–7.0 % terpene lactones consisting of 2.8–3.4 % ginkgolides A, B, C and 2.6–3.2 % bilobalide and contains less than 5 ppm ginkgolic acids [1]. Drug products based on EGb 761® have been approved in several countries, including Austria, for the symptomatic treatment of progressive mental impairment in dementia syndromes, where they are to be used as a component of a general therapeutic concept to address Alzheimer's disease, vascular dementia, and mixed type dementia.

Pharmacoeconomic evaluations are gaining importance, especially in chronically progressive and currently incurable conditions such as dementia. In this setting, the central objective of such an evaluation has to be whether the funds spent on dementia medications can precipitate subsequent greater savings, making the use of the drug an economically attractive proposal. In the particular case of dementia, the bulk of savings would result from a deceleration of disease progression, thereby delaying the later and more expensive stages of home and institutional care.

Ten years ago, a first study analyzed the pharmacoeconomic aspects of an EGb 761® dementia drug in the specific Austrian scenario [2]. The evaluation—which was based on a daily dose of 120 mg, and on the home nursing subsidies rules and drug prices that were in place at that time—employed the Geriatric Evaluation by Relative's Rating Instrument (GERRI) instead of cognitive parameters as a measure of patient independence. This approach was also employed in a separate study that assessed the effect of treatment with EGb 761® 120 mg/day on the delay of progression through the stages of dementia-related dependency [3]. Several realistic scenarios featuring early or late initiation of treatment and either normal life expectancy or early death from other causes were simulated. Economic benefit of varying degrees was reported for all scenarios, with the largest saving occurring when treatment was initiated early, and in patients with Alzheimer's disease.

During the decade that has passed since, a daily dose twice as high (240 mg/day) as the one reported in the 2002 paper has been established as safe and effective through three randomized, placebo-controlled, and double-blind clinical studies [4–6]. A metaanalysis of clinical trials, conducted by the German Institute for Quality and Efficiency in Health Care (IQWiG) [7] found evidence of benefit from this high dose (but not the 120 mg/day dose) for the therapy dimensions "cognitive function" and "general psychopathological symptoms", as well as for the quality of life of caregivers.

While clinical studies [4–6] had not been designed as pharmacoeconomic studies, they do offer the opportunity of careful pharmacoeconomic interpretation if combined with economic parameters currently valid for Austria. We therefore present an analysis of economic benefits of treating Austrian dementia patients with EGb 761® at 240 mg/day, employing scenarios and methods similar to those used in [2] and [3]. In addition, we relate our results to pharmacoeconomic data for cholinesterase inhibitors.

Patients and methods

In three clinical studies [4–6], a total of 1,201 patients diagnosed with dementia (probable Alzheimer's disease, probable vascular dementia, or mixed-type) and exhibiting neuropsychiatric symptoms had been treated with either EGb 761® (240 mg/day) or matched placebo for 22 [4] or 24 weeks [5, 6] under double-blind conditions.

To estimate the delay in activities of daily living (ADL)-based disease progression from these three studies, we first conducted a metaanalysis with fixed effects and calculated the standardized means and standardized mean difference for the changes of ADL in and between the treatment groups, respectively. The standardized mean difference was then related to the deterioration under placebo, and multiplied with the mean duration of treatment (23.3 weeks) [3].

The calculated delay in ADL symptom progression as well as actual costs for treatment, consultation, and care was used to perform a pharmacoeconomic assessment of EGb 761® in the Austrian setting. We employed the same assumptions that had been used in [2]:

- The mean remaining life expectancy after the first occurrence of dementia symptoms was set at 7.3–10.6 years, using data reported for Alzheimer patients [8, 9].
- The progression through the seven stages of nursing and dependency as defined in Austria (see Table 2) was assumed to be approximately linear, resulting in 0.71–1.0 years spent in each stage.
- The delay in symptom progression is mostly achieved through treatment in early disease stages when nursing costs are still relatively low; assuming that treatment does not increase remaining life expectancy, this shortens the period spent in the most cost-intense late stages of dependency.

To obtain conservative treatment cost estimates for the specific situation in Austria, we used the reimbursement

Table 1. Federal home care subsidies in Austria as of January 1, 2012

Stage	Monthly care requirements (h)	Subsidies per month (€)
1	61–85	154.20
2	86–120	284.30
3	121–160	442.90
4	>160	664.30
5	>180	902.30
6	>180	1,260.00
7	>180	1,655.80

Note that to reach stages 5–7, an additional requirement for specifically qualified professional care has to be demonstrated

price for the largest package size of EGb 761® 80 mg tablets (Cerebokan) disregarding patient copayments as in the original analysis. For a daily dose of 240 mg, this results in annual medication costs of EUR 288.35, to which the costs for the visits at the doctor's office to refill the prescription has to be added. Based on the mean frequency of physician visits by Austrians aged 60 years and above [10], on the case fee for general practitioners (EUR 18.10 as on April 1, 2011), and the flat fee of EUR 3.96 for every calendar quarter with more than three patient visits, we arrived at physician-related additional costs of EUR 37.62 per patient and year.

Finally, the tabulated values for the federal nursing subsidies for home care as effective since January 1, 2012 [11] (see Table 1) were used in our calculation, disregarding any costs of family caregivers as in the original analysis. Additional subsidies that can be granted for particularly disabled patients, especially for those suffering from severe dementia, in the amount of 25 h/month were not included in our conservative calculation.

Based on the calculated delay in ADL-related disease progression and the actual costs for treatment, consultation, and care, we analyzed the first four scenarios that had been presented in [2].

In a cost-effectiveness analysis, we estimated the costs per additional clinically relevant response to treatment with EGb 761®. We therefore calculated numbers needed to treat (NNT) based on two response criteria. As suggested by an expert consensus group, we considered a ≥4 point improvement in the Neuropsychiatric Inventory (NPI) score [12] as a clinically relevant response. Moreover, in a naturally progressive disease, an improvement in the clinician's global judgment during the course of about half a year may be considered clinically relevant. We therefore calculated NNTs for improvement in the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change score (ADCS-CGIC <4) under EGb 761® therapy (The ADCS-CGIC rating [13] is based on a 7-point scale that is designed to capture only clinically relevant changes as assessed by a physician, spanning the range from 1 (marked improvement) to 7 (marked worsening); a rating of 4 represents no change). All physicians who made ratings in the course of the clinical studies [5, 6] had received specific expert training and written instructions how to apply the ADCS-CGIC. Combined differences between response rates and 95 % confidence intervals were computed according to the Mantel–Haenszel method in a fixed-effects model.

To compare the pharmacoeconomic benefit of EGb 761® treatment with that of cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), a type of analysis was needed that would allow such a comparison in the absence of common outcome parameters. Using EGb 761® studies [5] and [6] and the summary evaluation of the three above-mentioned cholinesterase inhibitors provided by the Cochrane Dementia and Cognitive Improvement Group [14], we calculated the number of patients to be treated to achieve an additional treatment success (NNT) defined as improvement in the clinician's global judgment. Similar to studies of cholinesterase inhibitors, these two studies used an unstructured clinician's global judgment comparable to the Clinician Interview-Based Impression of Change with caregiver interview (CIBIC-Plus). Since the clinician's global judgment was not assessed in an unstructured (CIBIC-Plus type) manner in study [4], this study could not be included in this analysis.

To calculate the NNTs for the cholinesterase inhibitors, we used analysis 1.07 from the Cochrane evaluation [14]; this compares the agents at their respective recommended dose with placebo according to the criterion "Improvement in the Clinician Interview-Based Impression of Change plus carer interview (CIBIC-Plus) after 6 months of treatment." We calculated odds ratios for each cholinesterase inhibitor in a metaanalysis with fixed effects (Mantel–Haenszel method). The odds ratios and the placebo responses from the individual studies were used to estimate NNTs and 95 % confidence intervals [15, 16]. Taking into account that no common outcome measures were available, this procedure was considered valid for the intended comparisons because the CIBIC-Plus and ADCS-CGIC scores are obtained in similar ways using physicians' and caregivers' impressions and are both designed to provide estimates for the global change of a dementia patient's condition under treatment.

As with EGb 761®, we used the Austrian reimbursement price (as of October 2011) for the largest package size of each cholinesterase inhibitor. Treatment costs for an additional responder were calculated by multiplying NNT and drug costs.

Results

Besides achieving cognitive improvements (as measured by the Short Cognitive Performance (SKT) score) and in the neuropsychiatric symptoms (as measured by the Neuropsychiatric Inventory (NPI) total score), EGb 761® had shown benefits in terms of activities of daily living (ADL) in each of the three studies [4–6] while patients treated with placebo declined on this dimension or maintained their status (see Table 2).

Table 2. Development of activities of daily living scores (mean ± SD) in patients receiving EGb 761® (240 mg/day) or placebo for 22 or 24 weeks

Study	Tool	EGb 761®		Placebo		*p*-value[a]
		Mean ± SD	*n*	Mean ± SD	*n*	
Napryeyenko et al. [4]	GBS-ADL	−1.86±2.70	198	+0.90±2.44	197	<0.001
Ihl et al. [5]	ADL-IS	−0.15±0.29	202	+0.01±0.32	202	<0.001
Herrschaft et al. [6]	ADL-IS	−0.11±0.38	200	+0.04±0.32	202	<0.001

GBS-ADL Gottfries-Bråne-Steen ADL subscale, *ADL-IS* ADL international scale

[a]*p*-value of the two-sided t-test for comparison of the treatment groups

The combined analysis of changes in ADL during randomized treatment resulted in a standardized difference of the means of −0.68 (EGb 761®: −0.51, placebo: +0.17) in favor of EGb 761®, which translates to a 22.3 month delay of ADL symptom progression.

EGb 761® cost versus home care subsidies

The following scenarios correspond to the first four scenarios presented in [2]:

1. Optimal (and probably most realistic) scenario: Duration of disease 9 years, starting with 2 years of complete independence followed by 7 years of increasing care requirements. Treatment with EGb 761® 240 mg/day commences together with disease symptoms (thus achieving the entire 22.3 months of treatment-related delay in progression during the period of independence), and continues until the end of nursing care stage 5; stages 6 and 7 are correspondingly shortened.
2. Accelerated scenario: Duration of disease 7 years, starting with 2 years of complete independence followed by 5 years of increasing care requirements. Treatment with EGb 761® 240 mg/day commences together with disease symptoms, thus achieving the entire 22.3 months of treatment-related delay in progression during the period of independence, and continues until the end of nursing care stage 5; stages 5–7 are correspondingly shortened.
3. Delayed therapy initiation: Duration of disease 9 years, starting with 2 years of complete independence, followed by 7 years of increasing care requirements. Treatment with EGb 761® 240 mg/day commences only when nursing care is already required, and is continued into stage 4. The treatment-related progression delay takes hold slowly while the patient passes through dependency stages 1–4; stages 5–7 are correspondingly shortened.
4. Early death: Treatment with EGb 761® 240 mg/day commences only when nursing care is already required, delaying progression into stage 2; the patient dies from comorbid causes in stage 3.

Scenarios (1) and (2) take full advantage of the fact that EGb 761® can already be prescribed at the earliest stages of dementia (actually, even prior to a clinical diagnosis of dementia). Because available data do not suggest a loss of effectiveness of EGb 761® treatment, these scenarios assume that treatment will be terminated as soon as the patient declines into severe dependency on intensive care (stages 6 and 7).

Table 3 shows the results of our analysis for the four EGb 761® treatment scenarios, broken down by drug and physician costs.

In all four scenarios, savings achieved in care subsidies drive overall net savings while treatment-related costs play a minor role. Although Scenario (1) requires the largest treatment-related investments, it is also the scenario with the greatest overall savings which result from the fact that the patient's independence (as defined by the fact that no care subsidies are being paid) is maintained longer. The situation is fundamentally the same in Scenario (2) where both the investments in treatment and the savings in care subsidies are lower because the disease course is accelerated. Scenario (3), which assumes disease progression dynamics similar to Scenario (1) but initiates EGb 761® therapy only when the patient already incurs care subsidy costs, shows reduced (but still substantial) overall savings. Even the most unfortunate Scenario (4), which is identical to Scenario (3) but assumes death from a comorbid disease while the patient requires stage 3 care, is associated with net savings.

In a marginal cost analysis, treatment with EGb 761® 240 mg/day saves EUR 887 in care subsidies for each month of delayed progression from the low or average care requirement stages 1–4 (mean subsidies, EUR 386) to stages 5–7 which have high care requirements and mean subsidies of EUR 1,273. This equals the expenses for 3.1 years of treatment with EGb 761®.

Table 3. Costs and savings related to treatment with EGb 761® in the four treatment scenarios

Scenario	Treatment duration (years)	Costs (€)			Savings (€)	
		EGb 761® drug (Cerebokan®)	Physician visits	Care subsidies (in stages)	Care subsidies (in stages)	Net
1	9	2,595.15	338.58	None	32,511.17 (6–7)	29,577.44
2	7	2,018.45	263.34	None	28,368.48 (5–7)	26,086.69
3	5.9	1,701.27	221.96	8,617.28 (1–4)	28,381.20 (5–7)	17,840.58
4	3	865.05	112.86	3,438.66 (1)	8,108.28 (2–3)	3,691.71

Table 4. Numbers needed to treat (NNT) calculated for the single studies and combined (Mantel–Haenszel method, fixed effects)

Study	Responder/N (response rate (%))		Difference of response rates (EGB 761®–Placebo) and 95 % CI (%)	NNT and 95 % CI
	EGb 761®	Placebo		
Improvement in NPI score ≥4				
Napryeyenko et al. [4]	149/198 (75.25)	14/197 (7.11)	68.15 (60.14; 76.15)	2 (1.3; 1.7)
Ihl et al. [5]	91/202 (45.05)	48/202 (23.76)	21.29 (10.96; 31.61)	5 (3.2; 9.1)
Herrschaft et al. [6]	113/200 (56.50)	78/202 (38.61)	17.89 (6.90; 28.87)	5 (3.5; 14.5)
Combined (MH, fixed)	*600*	*601*	*35.56 (31; 41)*	*3 (2.4; 3.2)*
Improvement in ADCS-CGIC score <4				
Ihl et al. [5]	109/202 (53.96)	52/202 (25.74)	28.22 (17.76; 38.67)	4 (2.6; 5.6)
Herrschaft et al. [6]	137/200 (68.50)	76/202 (37.62)	30.88 (20.27; 41.49)	4 (2.4; 4.9)
Combined (MH, fixed)	*402*	*404*	*29.55 (23; 36)*	*4 (2.8; 4.3)*

NPI neuropsychiatric inventory, *ADCS-CGIC* Alzheimer's disease cooperative study-clinical global impression of change

Table 5. Numbers needed to treat (NNT) computed from the odds ratios using analysis 1.07 from the Cochrane review [14], comparing cholinesterase inhibitors to placebo

Response criterion	Cholinesterase inhibitor	Odds ratio and 95 % CI (meta-analysis with fixed effects)	Placebo response rate[a] (%)	Response rate differences (Cholinesterase inhibitor - Placebo) and 95 % CI	NNT and 95 % CI
Improvement (CIBIC +)	Galantamine	1.29 (0.89–1.88)	13.78	3.34 (1.34; 9.30)	30 (10.7; 74.8)
			16.26	3.80 (1.54; 10.46)	27 (9.6; 65.0)
	Donepezil	2.23 (1.54–3.22)	11.18	10.72 (5.06; 17.67)	10 (5.7; 19.8)
			14.01	12.61 (6.04; 20.40)	8 (4.9; 16.5)
	Rivastigmine	1.47 (1.17–1.84)	15.18	5.62 (2.18; 9.54)	18 (10.5; 46.0)
			18.98	6.60 (2.58; 11.08)	16 (9.0; 38.7)
			20.00	6.84 (2.68; 11.45)	15 (8.7; 37.3)
			25.44	7.92 (3.15; 13.06)	13 (7.7; 31.7)

[a]Placebo response rates from the single trials included

Cost-effectiveness analysis

Table 4 shows the NNTs derived from the three EGb 761® studies [4–6] and from the metaanalysis of these trials. In the combined analysis, NNTs varied between 3 (at least 4-point improvement in the NPI) and 4 (improvement in the ADCS-CGIC, two studies [5, 6]). Costs for an additional treatment response can be calculated as product of the NNT and the costs for a 24-week treatment with EGb 761® (EUR 132.72, Table 6).

With NNTs between 2 and 6 in the individual studies, costs for one additional treatment response in terms of relevant improvement of neuropsychiatric symptoms range between EUR 265.44 and EUR 796.32. Costs per improvement in the ADCS-CGIC based on the NNTs from two studies [5, 6] amount to EUR 530.88 (Table 6).

Comparison with cholinesterase inhibitors

Table 5 shows the NNTs, as computed from the odds ratios reported or calculated for the three cholinesterase inhibitors using data of the Cochrane review [14]. Our analysis yielded NNTs between 8 and 30. To achieve a CIBIC-Plus improvement in one additional patient, the minimum number of patients who need to be treated is 27 for galantamine, 8 for donepezil, and 13 for rivastigmine (Table 5).

Table 6 compares the economic key parameters for the four analyzed antidementia agents. Various generic products will probably soon be available to substitute the three proprietary cholinesterase inhibitors. Since this scenery is in dynamic change, we have applied a strong discount (39.8 % of the originator drug price [17]) to all three cholinesterase inhibitors.

The data presented here allow the calculation of the cost associated with achieving an additional therapy success, based on the response criterion "improved global assessment" (based on the ADCS-CGIC for EGb 761®, and on the CIBIC-Plus for the cholinesterase inhibitors). Using the overall NNT from Table 5 for EGb 761®, and the minimum NNT from Table 6 for the cholinesterase inhibitors, we arrive at EUR 531 for one additional therapy success with EGb 761® while cholinesterase inhibitors require between EUR 3,849 and EUR 14,224.

Table 6. Daily and 24-week treatment course costs, and cost per additional treatment response, for EGb 761® 240 mg/day and the cholinesterase inhibitors at their recommended daily doses, based on Austrian drug prices [17]

Drug (active ingredient)	Strength per unit (mg)	Daily dose (mg)	Health insurance agency price (€)	NNT[a]	Cost (€)			Cost per additional response (€)	
					Per day	For 24 weeks	24 weeks generic pricing[b]		Generic pricing[b]
Cerebokan (EGb 761®)	80	240	15.8	4	0.79	132.72		530.88	
Reminyl (galantamine)	16	16	93.8	27	3.35	562.80	223.99	14,223.60	5,660.99
Aricept (donepezil)	10	10	266.9	8	3.18	533.80	212.45	4,270.40	1,699.62
Exelon (rivastigmine)	6	6	98.7	13	1.76	296.10	117.85	3,849.30	1,532.02

NNT numbers needed to treat
[a]NNT for one additional patient with improvement in clinical global judgment after 24 weeks of treatment
[b]39.8 % of the originator drug's price has been applied

Discussion

In the first part of this investigation, we have re-applied four EGb 761® treatment scenarios, identical to those that had been used ten years ago with a 120 mg/day dose, to data from a metaanalysis from three randomized placebo-controlled clinical efficacy studies that used a 240 mg/day dose. Obviously these scenarios represent special cases selected from a continuum of treatment possibilities; however, each one is based on assumptions that are frequently seen in the reality of dementia in the Austrian community.

In contrast to other pharmacoeconomic investigations which use cognitive scores as exclusive or dominant measures of treatment success, this part of our analysis focused exclusively on the delay in progression toward higher care requirements and dependency. Our conservative approach therefore did not (in this first analysis stage) take into account that EGb 761® treatment is also associated with clinically relevant improvements in neuropsychiatric symptom scores [18–20]. It is well known that neuropsychiatric symptoms place an especially heavy burden on caregivers, precipitate the prescription of reimbursable psychoactive drugs, and are a key factor in moving a dementia patient into institutional care [21, 22]. However, as there are insufficient data available concerning possible savings related to fewer prescriptions of psychiatric medications, and as the decision to institutionalize a dementia patient in a nursing home depends on additional criteria, we did not attempt to quantify these effects in terms of monetary savings.

Although we used a very conservative approach that considered only the EGb 761® drug, physician fees, and home care subsidies as cost factors, all scenarios achieved overall net savings. These ranged from 3,692 to 29,577 EUR, obviously exceeding the savings (EUR 910–12,153) achieved under identical scenarios for treatment with EGb 761® at 120 mg/day as reported in [2]. These additional net savings seem to be at least partly attributable to the higher delay in disease progression towards dependency on care achievable with the 240 mg/day dose, and on the increased care subsidies that had been implemented during the past ten years. Compared with these savings, the increased cost resulting from the doubled dose is of little relevance. Consistent with this, initiation of EGb 761® treatment prior to the onset of cost-generating care was the predominant driver for savings in spite of the longer duration of drug therapy.

In the second part of our analysis, we related treatment costs for EGb 761® 240 mg/day to the clinically relevant treatment responses achieved. Costs per one additional patient's improvement in neuropsychiatric symptoms that is considered clinically relevant by expert consensus [12] were found to be between EUR 265 and EUR 796. Again, it should be kept in mind that neuropsychiatric symptoms drive costs for both treatment and care, in that they determine treatment with psychoactive drugs and predict institutionalization. Yet, there are no reliable data to counterbalance costs against savings.

In the third part of our analysis, we compared treatment costs per additional clinically relevant treatment response for EGb 761® and for cholinesterase inhibitors. This analysis was necessarily less straightforward for three reasons. First, treatment success (defined as improvement in global impression scores) had been measured with compatible but different tools—the ADCS-CGIC for EGb 761®, and the CIBIC-Plus for the three cholinesterase inhibitors. Second, we had to compare two metaanalyses of clinical trials, an approach that has inherent drawbacks. In our particular case, the studies had been selected using different criteria: for EGb 761® two large double-blind studies that had used the 240 mg/day dose and a CIBIC type clinical global assessment took place had been included while the studies included in the cholinesterase inhibitor analysis had been selected according to the Cochrane Group's criteria. Third, none of the studies that provided the data for the comparison had been designed as pharmacoeconomic study; they were randomised placebo-controlled clinical efficacy studies.

However, we believe that—all limitations considered—our analysis is the best that can be done on the basis of the available data. The global impression as assessed by a clinician who briefly interviews the patient and his or her caregivers (but is not involved in the patient's treatment and is unaware of the results of the patient's cognitive test results) is generally regarded as a suitable measure of clinically relevant overall change and

is considered as the global endpoint for dementia drug studies by the European Medicines Agency [23].

Our results, expressed as costs to achieve an additional treatment success, showed an advantage for EGb 761®. We compute EUR 531 for one additional therapy success (defined as improvement in clinician's global judgment) with EGb 761® while cholinesterase inhibitors require between EUR 3,849 and EUR 14,224. We are aware that, as a result of what has been discussed above, these figures do not allow a precise quantitative pharmacoeconomic comparison between the two agent classes; however, we believe that they should be taken as a preliminary indication of pharmacoeconomic implications. It would be most interesting to reconduct our comparison once large studies using identical clinical outcome measures for EGb 761® 240 mg/day and cholinesterase inhibitors are available.

Beyond these caveats, simplifications and omissions were consciously made in this analysis. For example, we made no attempt to include the pharmacoeconomic implications of drug side effects and treatment noncompliance with the respective drug regimes. In the EGb 761® studies [4–6] side effects under active treatment had been essentially indistinguishable from those under placebo while this had not been the case for cholinesterase inhibitors [14], which would therefore be favored by our omission of these effects. Costs for physician visits, required to monitor therapy success and to refill the drug prescriptions, were not included because we assumed these to be the same for all treatments; again, these omissions are unlikely to skew the assessment in favor of EGb 761®. It would rather seem likely that side effects from cholinesterase inhibitors would precipitate unscheduled physician visits.

In summary, we have shown that overall savings can be achieved with EGb 761® 240 mg/day in the treatment of Austrian dementia patients under each of four investigated treatment scenarios, and we present a comparative analysis which—although it has inherent limitations resulting from the nature of the available clinical data—indicates a favorable cost comparison in relation to cholinesterase inhibitors.

Conflict of interest

Hermann Mucke has received consulting fees from a manufacturer of Ginkgo extracts and from a commercial provider of galantamine, and is a shareholder of a company that markets rivastigmine-based drugs. Michael Rainer has no conflict of interest related to the reported work. Sandra Schlaefke is an employee of Dr. Willmar Schwabe GmbH & Co. KG receiving a fixed salary.

References

1. Kleijnen J, Knipschild P. Ginkgo biloba for cerebral insufficiency. Br J Clin Pharmacol. 1992;34(4):352–8.
2. Hörr R, Kieser M. Pharmaco-economic evaluation of Ginkgo special extract EGb 761® for dementias in Austria. Wien Med Wochenschr. 2002;152(15–16):427–31 (in German).
3. Haan J, Hörr R. Delay in progression of dependency and need of care of dementia patients treated with Ginkgo special extract EGb 761®. Wien Med Wochenschr. 2004;154(21–22):511–4 (in German).
4. Napryeyenko O, Borzenko I, GINDEM-NP Study Group. Ginkgo biloba special extract in dementia with neuropsychiatric features. A randomised, placebo-controlled, double-blind clinical trial. Arzneimittelforschung. 2007;57(1):4–11.
5. Ihl R, Bachinskaya N, Korczyn AD, Vakhapova V, et al. on behalf of the GOTADAY Study Group. Efficacy and safety of a once-daily formulation of Ginkgo biloba extract EGb 761® in dementia with neuropsychiatric features: a randomized controlled trial. Int J Geriatr Psychiatry. 2011;26(11):1186–94.
6. Herrschaft H, Nacu A, Likhachev S, Sholomov I, Hoerr R, Schlaefke S. Ginkgo biloba extract EGb 761® in dementia with neuropsychiatric features: a randomized, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg. J Psychiatr Res. 2012;46(3):713–23.
7. Institute for Quality and Efficiency in Health Care (IQWiG). Ginkgo in Alzheimer's disease. Executive summary. IQWiG reports—Commission no. A05-19B. Version 1.0; Status: 29.09.2008.
8. Bracco L, Gallato R, Grigoletto F, et al. Factors affecting course and survival in Alzheimer's disease. A 9-year longitudinal study. Arch Neurol. 1994;51(12):1213–9.
9. Heyman A, Peterson B, Fillenbaum G, Pieper C. The consortium to establish a registry for Alzheimer's disease (CERAD). Part XIV: Demographic and clinical predictors of survival in patients with Alzheimer's disease. Neurology. 1996;46(3):656–60.
10. Statistik Austria. Gesundheitsbefragung 2006/07. Compiled July 18, 2008. http://www.statistik.at/web_de/static/ambulante_versorgung_200607_022268.pdf. WebCite Archive URL: http://www.webcitation.org/66Niy7Nu2. Accessed 18 Dec 2012.
11. Versicherungsanstalt für Eisenbahnen und Bergbau. Information über das Bundespflegegeld (Stand: 1. Jänner 2012). https://www.sozialversicherung.at/mediaDB/633780_Infoblatt%20Bundespflegegeld%20%20Stand%201.1.2010.pdf%20-%20Adobe%20Acrobat%20Professional.pdf. WebCite Archive URL: http://www.webcitation.org/66NiPxD1l. Accessed 18 Dec 2012.
12. Mega MS, Masterman DM, O'Connor SM, et al. The spectrum of behavioral responses to cholinesterase inhibitor therapy in Alzheimer disease. Arch Neurol. 1999;56(11):1388–93.
13. Schneider LS, Olin JT, Doody RS, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997;11(Suppl. 2):S22–32.
14. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006;1:CD005593. doi: 10.1002/14651858.CD005593.

15. Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, Guyatt GH, on behalf of the Cochrane Applicability and Recommendations Methods Group. Chapter 12: Interpreting results and drawing conclusions. Section 12.5.4.3. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions, version 5.1.0, updated March 2011. The Cochrane Collaboration. 2011. www.cochrane-handbook.org/. Accessed 1 Aug 2011.
16. Cates CJ. Simpson's paradox and calculation of number needed to treat from metaanalysis. BMC Med Res Methodol. 2002;2:1.
17. Österreichischer Apotheker-Verlag. Warenverzeichnis I des Österreichischen Apotheker-Verlages. Wien: Österreichische Apotheker-Verlagsgesellschaft mbH, Mai 2012. http://warenverzeichnis.apoverlag.at. Accessed 31 May 2012.
18. Scripnikov A, Khomenko A, Napryeyenko O, GINDEM-NP Study Group. Effects of Ginkgo biloba extract EGb 761® on neuropsychiatric symptoms of dementia: findings from a randomised controlled trial. Wien Med Wochenschr. 2007;157(13–14):295–300.
19. Bachinskaya N, Hoerr R, Ihl R. Alleviating neuropsychiatric symptoms in dementia: the effects of Ginkgo biloba extract EGb 761®. Findings from a randomized controlled trial. Neuropsychiatr Dis Treat. 2011;7:209–15.
20. Nacu A, Hörr R, Herrschaft H. Neuropsychiatric symptoms of dementia and related caregiver distress: effect of treatment by a once-daily formulation of Ginkgo biloba extract EGb 761®. Alzheimer's & Dementia. 2011;7(4 Suppl. 1):S785.
21. Gilley DW, Bienias JL, Wilson RS, et al. Influence of behavioral symptoms on rates of institutionalization for persons with Alzheimer's disease. Psychol Med. 2004;34(6):1129–35.
22. de Vugt ME, Stevens F, Aalten P, et al. A prospective study of the effects of behavioral symptoms on the institutionalization of patients with dementia. Int Psychogeriatr. 2005;17(4):577–89.
23. Committee for Medicinal Products for Human Use (CHMP). Guideline on medicinal products for the treatment of Alzheimer's disease and other dementias. Doc. Ref. CPMP/EWP/553/95 Rev. 1. London, 24 July 2008. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003562.pdf. Accessed 18 Dec 2012.