Translation from: "Fortschritte der Medizin", 120th Edition, Original No. I/2003, 5 – 10.

The Effect of Ginkgo biloba on Healthy Elderly Subjects

A. Cieza, P. Maier, E. Pöppel [1]

Summary

Background and Aim: Over the past 25 years, numerous studies have confirmed the positive effect of the special ginkgo extract EGb 761® on the mental ability and emotional well-being of patients with cognitive disorders of vascular genesis, and Alzheimer-type dementia. The following study investigated the short-term effect of the special ginkgo extract EGb 761® on the subjective emotional well-being of healthy elderly subjects.
Study Population and Method: The study was designed as a randomised, placebo-controlled, double-blind, monocentre study with parallel groups. It included 66 healthy subjects of both sexes aged between 50 and 65 with no age-related cognitive impairments. For a period of 4 weeks, 34 subjects received a daily dose of 240 mg EGb 761®, and 32 a placebo. Prior to starting medication and after 28 days of treatment, subjects completed the following scales and questionnaires to establish subjective emotional well-being: The Profile of Mood States (POMS), the Self Rating Depression Scale (SDS), three Visual Analogue Scales to assess the quality of life (VAS-QoL), general health (VAS-GH) and mental health (VAS-MH), and a new instrument for assessing changes in general subjective well-being, the Subjective Intensity Score Mood (SIS Mood). Depending on the underlying distribution of the variables analysed, parametric (t-tests) or non-parametric tests (U-tests) were performed to compare mean values and distributions both within and between the treatment groups.
Results: The final examination revealed a statistically significant difference between the two groups for the VAS mental health and quality of life, as also for SIS Mood at the telephone interview in week 2. A comparison of baseline with the final examination within the groups showed a statistically significant improvement in the EGb 761® group for the variables: POMS-depression, fatigue, anger and SDS. For none of the variables investigated was a worsening observed in the EGb 761® group.
Conclusions: The results suggest a positive effect of EGb 761® on the subjective emotional well-being of healthy elderly persons.

Keywords: Ginkgo biloba – geriatric research – phytotherapy – well-being.

Submitted 16.9.2002 – Revision 26.1.2003 – Accepted 30.1.2003.

The scientific interest in the possibility of optimising cerebral performance and improving the emotional well-being of elderly people has increased dramatically over the past few years. This is certainly due to the continuously increasing numbers of elderly people in our society on the one hand, and a change in perspectives within geriatric research on the other. Current geriatric research is no longer primarily

[1] Dr. Alarcos Cieza (human biology), Petra Meier (M.Sc. psychology), Prof. Ernst Pöppel, Institute for Medical Psychology, Ludwig-Maximillian University Munich.

Tebonin®; manufacturer: Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe

See also summary with comment: A. Cieza et al.: "Older people feel mentally fitter". MMW-Fortschr. Med. 145 (2003), 150.

directed towards investigating the causal factors responsible for ageing but is also aimed at studying the bases of longevity and preservation of functional competence in old age. The search for possibilities of using or improving the individual's own capacities and competence is an important part of geriatric research.

This change in perspective can also be observed in clinical research. For several years, the number of clinical studies with target groups outside the so-called "ailing elderly" has increased. The latter is defined as the occurrence of pathological symptoms in the elderly surpassing those found at the usual level of biomedical and psychological changes resulting from the normal ageing process. Increasingly more clinical trials address the question of the extent to which specific interventions can combat the physical and psychic changes that normally occur during ageing.

As a consequence, our interest was focussed on the effect of Ginkgo special extract EGb 761® on mental functions or emotional mood of healthy subjects. The positive effect of the preparation on the psychic and emotional well-being of patients with disorders of vascular origin or Alzheimer-type dementia has already been demonstrated [5, 15, 17, 19].

Studies undertaken to date with healthy subjects showed positive effects of EGb 761® on the following functions:

- Memory performance (short-term and long-term memory) [8, 20],
- Fixation time of saccadic eye movements [16] and complex reaction times [1], which indicates more efficient central information processing,
- Vigilance, measured by the "Quantitative-Pharmaco-EEG" [12],
- Stimulus processing speed [14].

The effect of Ginkgo special extract on the emotional well-being of healthy elderly subjects has not been investigated to date, although this effect has been demonstrated in depressive patients [17, 19]. Some of the results of a study which investigated the effect of Ginkgo biloba extract EGb 761® on emotional well-being and mental function of healthy elderly subjects are presented here. The results reported only refer to emotional well-being.

Methods

Study Population

Elderly subjects between 50 and 65 years of age with no clinically relevant cardiovascular, pulmonary, neurological, endocrinological, renal, hepatic, gastrointestinal, haematological, oncological or psychiatric diseases or disorders, and in whom no age-related cognitive disorders were found (as assessed by cognitive minimal screening, CMS [7]), were included in the study. With the exception of hormonal treatment for women at the time of screening, no concomitant medication was allowed. In particular, drugs which influenced mood or psychic function were prohibited. In order to check this exclusion criterion, drug screening was performed for all patients during baseline screening and at the final investigation (Triage TM8 immunoassay, Diagnostica Merck).

The study protocol and the patients' statements of consent were submitted to the ethics committees in Baden-Württemberg and Bavaria. Written consent was obtained from all subjects.

Study Design

The study was a randomised, double-blind, placebo-controlled mono-centric study with fixed dosage. Treatment was carried out over four weeks. Prior to randomisation, a medical examination was performed, during which electrocardiogram, drug screening, blood count and urine status were documented.

The target variable, emotional well-being, was monitored one day before the start of medication (baseline examination, Day 0) and two hours after the last dose of medication (final examination, Day 28). These two examinations were performed for all patients at approx. 18:30 in order to prevent falsification of the results due to diurnal variations in physiological and biochemical functions.

Medication administration started one day after the baseline examination at 08:00 and finished on Day 28 at about 16:00. During the 28-day treatment phase, the subjects took the study medication regularly at 08:00 and 16:00. Tolerability of the preparation, compliance, and emotional well-being, as measured by the subjective

intensity score of mood (SIS-M) [2], were monitored by the physician in charge by telephone each week.

The study drugs were packed by the manufacturer, labelling was done according to Section 10 of the German Drug Law. The medication was administered in the form of film-coated tablets with a content of 120 mg dry extract of Ginkgo biloba leaves (35-67:1). The extract is standardised to 28.8 mg flavone glycosides and 7.2 mg terpene lactones per film-coated tablet. Taking two tablets/day is equivalent to a daily dose of 240 mg. The active substance and placebo did not differ in appearance, flavour or odour. Sequentially numbered packs of medication were given to the subjects in the order of their inclusion. The randomisation list, which assigned the medication number to each treatment, was produced using the SAS random number generator, program version 6.12. In order to ensure that the two treatment groups had the same sample size, block randomisation with a block size of 2 was performed.

Target variables

The emotional well-being of healthy elderly subjects was determined using the following methods:

- **The Profile of Mood States (POMS)** [2, 13] examines the emotional well-being and mood of a person. This is performed by means of a list of 35 adjectives whose relevance can be evaluated by the person on a five-point scale from “not at all” to “very much”. These 35 items are assigned to four sub-scales: depression, fatigue, vitality and angry mood. The interpretation of the scale scores is homogeneous. On all scales the following is applicable: the higher the score, the better the emotional well-being.

- **The Subjective Intensity Scale (SIS) – Well-being** [10] provides an assessment of current well-being in relation to previously determined well-being. The instructions for the subjects are: “Assuming your general well-being scored 100 points in your previous test, how many points does your general well-being score today?”

  If the subject feels a deterioration in well-being since the last test for example, the SIS would be less than 100 points. If well-being is considered to be improved, the

SIS would be over 100 points. The baseline value, i.e. assessment of well-being at the baseline examination, is taken as 100. The point difference between the raw values should represent a measure of the changes in well-being. In order to obtain the course of well-being in relation to the baseline score (100 points at baseline), the raw data are transformed into relative SIS scores. The following rule is applied: previous raw value/100 x current raw value = relative SIS-score.

- **The Self-rating Depression Scale (SDS)** [21] is a standardised procedure for self-assessment of depressive mood states and well-being. The SDS requires the subject to assess his/her mood state during the past week by evaluating the presence of specific symptoms on a four-point scale from “never or rarely” to “usually or always”. A total score summarises the data on the 20 items. The higher the score, the more depressed the mood of the subject.

- **Three Visual Analogue Scales (VAS)** [6, 18] are used to monitor the self-assessment of the subjects regarding their quality of life (VAS-QoL), their general state of health (VAS-GH) and their mental health (VAS-MH). Self-assessment is performed by placing a ball-point pen mark on a 100 mm line with the extremes “could not have been worse” and “could not have been better”. The distance between the point on the line and 0 is measured and documented as a value between 0 and 100. The higher the score the higher the self-assessed quality of life and therefore the better the general or mental health.

Statistical Analysis

In view of the pilot character of the study, confirmatory testing of hypotheses was not performed.

Based on a test power ($1-\beta$) of 0.8 and a level of significance (α) of 0.05, a sample size of 30 was calculated: i.e. a minimum of 30 subjects per group was necessary to detect a difference of 10 % in the mean of the variables.

The first step in the statistical analysis was to test the variables for normal distribution using the Kolmogorov-Smirnov test. A level of significance of 0.05 was chosen as a criterion to determine whether the variables were normally distributed. Depending on

the underlying distribution of the variables analysed, parametric or non-parametric tests were used.

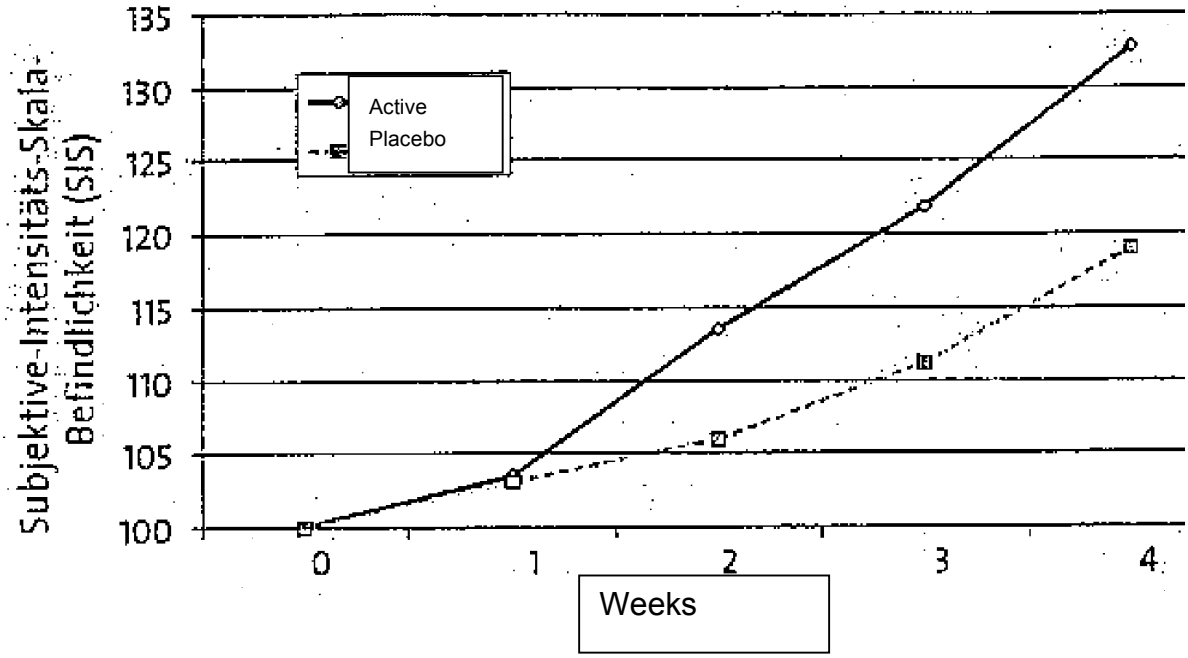
The adjusted t-test, which takes measurement errors into account, was used for normally distributed variables. Critical differences for both inter-group and intra-group comparisons were calculated on the basis of the reliability of the variables. A critical difference is the smallest difference which can be assessed as non-random, i.e. can be evaluated as evidence for a difference between the groups. If the observed difference is greater than the critical difference, the difference is statistically significant.

Inter- and intra-group differences were analysed by U-tests for non-normally distributed variables. If the intra-group comparison was statistically significant in the active substance group but not in the placebo group, this was taken to be evidence of a beneficial effect of EGb 761® with regard to the parameter tested. If the two treatment groups differed at the final examination but not at the baseline examination, this was also interpreted as evidence for a positive effect of EGb 761®.

Whether the subjects in the active substance group assessed their subjective well-being more positively than those in the placebo group after one, two, three or four weeks of treatment was examined for SIS well-being.

Fig. 1.

Subjective Intensity Scale Well-being, cumulative well-being improvement of both subject groups at weekly intervals.



Results

A total of 94 elderly subjects were screened for this study. 28 did not meet the inclusion and exclusion criteria and accordingly could not be enrolled in the treatment phase (Table 1).

Table 1: *Profile of the randomised controlled trial*

Number of persons recruited	94	
Number of persons not included	28	
Number of persons randomised	66	
	Active substance	Placebo
	34	32
Excluded after baseline examination	0	0
Excluded from analysis	0	0
Complete trial	34	32

After randomised assignment, 34 of the remaining 66 subjects were treated with EGb 761® and 32 received placebo. All subjects completed the treatment phase without serious protocol violations. The two treatment groups showed no significant differences with regard to age and sex (Table 2).

Table 2: *Characteristics of the subjects at the time of baseline examination*

	Total	**Active substance group**	**Placebo group**
Number of persons	66	34	32
- female (%)	37	20 (58.8)	17 (53.1)
- male (%)	29	14 (41.2)	15 (46.9)
Age [years]			
Mean (SD)			
- female		56.5 (3.8)	56.3 (3.8)
- male		55.1 (3.7)	57.3 (2.9)

The test of the interval scale variables for normal distribution showed that the data representing VAS were normally distributed. This was also true for the variables fatigue, vitality and angry mood on the POMS scale and for SDS data. The results for all scales on emotional well-being are given in Tables 3 – 6.

Table 3: *Non-normally distributed variable POMS-depression: Mean, standard deviation and p values for the intra- and inter-group comparison based on the U-test*

	Intra-group comparison				Inter-group comparison	
	Active substance group		Placebo group		Baseline	End
	Baseline	End	Baseline	End		
POMS depression	3.64 ± 0.44	3.77 ± 0.30	3.65 ± 0.30	3.71 ± 0.35		
p value	0.01		0.08		0.26	0.6

At all times, more marked improvements on the SIS-M scale compared with each previous time were shown for the patients treated with EGb 761® than for subjects receiving placebo (Fig. 1). After Week 2, the difference between active treatment and placebo groups was statistically significant (Table 4).

Table 4: *Non-normally distributed variables: Means, standard deviations and p values of inter-group comparison within the SIS well-being based on the U-test after one, two, three and four weeks of treatment*

	Inter-group comparison	
SIS well-being	Active substance group	Placebo group
- Baseline	100	100
- Week 1	103.53 ± 12.70	103.13 ± 11.76
p value	0.24	
- Week 2	109.97 ± 24.52	102.75 ± 14.88
p value	0.04	
- Week 3	108.29 ± 20.96	105.21 ± 17.23
p value	0.25	
- Week 4	110.93 ± 20.34	107.84 ± 32.94
p value	0.17	

The mood score on the POMS depression sub-scale showed a statistically significant increase under treatment with EGb 761®, the depression score in the SDS decreased correspondingly in a statistically significant manner. With placebo treatment, in contrast, neither score showed a statistically significant difference (Tables 3 and 6). This was also true for the POMS sub-scales angry mood and fatigue.

The subjects' self-assessment regarding their mental health and quality of life according to VAS was statistically significantly better for the active substance group than for the placebo group at the end of treatment.

The study subjects reported no evidence of severe drug-related adverse events. All adverse events occurring in the active substance group, for which a causal relationship with the test medication could not be excluded, corresponded to the known and very rare side effects of EGb 761® described in the manufacturer's brochure.

Table 5: *Normally distributed variables: Means and standard deviations at baseline and final examination according to treatment group*

	Baseline		End	
	Active	Placebo	Active	Placebo
Emotional well-being				
- POMS-fatigue	2.97 ± 0.65	3.02 ± 0.71	3.25 ± 0.56	3.28 ± 0.44
- POMS-vitality	2.33 ± 0.75	2.41 ± 0.58	2.38 ± 0.60	2.27 ± 0.65
- POMS-angry mood	3.23 ± 0.60	3.13 ± 0 54	3.46 ± 0.46	3.46 ± 0.45
- SDS	32.16 ± 5.24	32.24 ± 6.25	30.54 ±5.78	31.21 ± 6.00
VAS				
- VAS-MH	76.09 ± 16.00	74.16 ± 18.19	79.79 ± 14.29	74.00 ± 19.68
- VAS-GH	82.41 ± 15.73	79.13 ± 20.40	78.68 ± 19.87	77.78 ± 19.07
- VAS-QoL	74.91 ± 19.06	69.81 ± 17.38	77.94 ± 14.03	72.66 ± 16.79

Table 6: *Observed and critical differences for intra- and inter-group comparison*

	Intra-group comparison Active group Baseline vs. final examination		Inter-group comparison Final examination	
	Observed difference	Critical difference	Observed difference	Critical difference
Emotional well-being				
- POMS-fatigue	0.28*	0.17	0.04	0.14
- POMS-vitality	0.05	0.15	0.11	0.16
- POMS-angry mood	0.23*	0.17	0.00	0.14
- SDS	1.61*	0.94	0.66	1.16
VAS				
- VAS-MH	3.71	4.51	5.79*	5.11
- VAS-GH	3.74	7.39	0.90	6.45
- VAS-QoL	3.03	5.74	5.28*	4.87
* If the observed difference is greater than the critical difference, the difference is statistically significant.				

Discussion

The aim of this study was to investigate the influence of Ginkgo special extract EGb 761® on different aspects of well-being, mood, self-assessment of state of health and quality of life of healthy elderly subjects.

An improvement in emotional well-being and mood, with an early onset and continuous increase over the fours weeks of treatment, was found. This was clearly greater than placebo. It is possible that the effects of treatment were only inadequately reflected by the SIS-M, as the assessments were always made in comparison to the previous investigational point, i.e. the changes could actually be considered to be cumulative. After the subjects treated with EGb 761® experienced a more pronounced improvement in their mental well-being in the second week of treatment, all further relative improvements, which were numerically larger than

placebo in each case, can be interpreted as being of more relevance than the changes recorded under placebo (Fig. 1).

The improvements in mood, as measured by the POMS depression sub-scale, and the decrease in depressiveness, assessed by means of SDS, correlate with these findings.
In order to illustrate the results of the POMS depression scale, a study on cognitive behavioural therapy in the group in patients with breast cancer should be mentioned. In this study, a somewhat smaller change in the POMS depression sub-scale (0.16 compared to 0.23 in the present study) produced a significant result [4]. Although an antidepressant effect of EGb 761® in patients with a symptom complex of cerebral disorders and depressive mood has been shown in earlier studies [5, 17, 19], this is the first study which shows comparable effects on mental well-being and mood states in healthy elderly subjects.

That this is not just a numerical effect on sensitive, operationalised scales is demonstrated by the global self-assessment based on visual analogue scales, which was documented in parallel. Those subjects treated with EGb 761® were obviously aware of an improvement in their mental health and increase in quality of life, which can be considered as confirmation of the relevance of the effects described above.

If the fact that declining mental powers are associated with negative emotional well-being in old age [3, 9, 11] on the one hand, and that active measures to preserve mental powers can oppose a (sub-)depressive mood state on the other, are taken into account, this shows that early pathological developments can potentially be counteracted within the framework of an integrated treatment approach.

Literature List

1. Allain, H., Raul, P., Lieury, A. LeCoz, F., Gandon, J.M.: Effect of two doses of Ginkgo biloba Extract (EGb 761) on the Dual-Coding Test in elderly subjects. Clin. Ther. 15 (1993), 549–558.
2. Bullinger, M., Heinisch, M., Ludwig, M., Geier, S.: Skalen zur Erfassung des Wohlbefindens: psychometrische Analysen zum "Profile of Mood States" (POMS) und zum "Psychological General Well-Being Index" (PGWB). Z. Differentielle Diagnost. Psychol. 11 (1990), 53–61.
3. Carmelli, D., Swan, G. E., LaRue, A., Eslinger, P. J.: Correlates of change in cognitive function in survivors from the Western Collaborative Group Study. Neuroepidemiology 16 (1997), 285–295.
4. Edelman, S., Bell, D. R., Kidman, A. D.: A group cognitive behaviour therapy programme with metastatic breast cancer patients. Psycho-Oncology 8 (1999), 295–305.
5. Halama, P.: Was leistet der Spezialextrakt (EGb 761)?. Therapiewoche 40 (1990), 3760–3765.
6. Huskisson, E. C.: Measurement of pain. Lancet 4 (1974), 1127–1131.
7. Kessler, J., Grond, M., Schaaf, A.: Kognitives Minimal Screening (KMS). Beltz Test GmbH, Weinheim 1991.
8. Lacomblez, L., Warot, D., Tarrade, T., Puech, A. J.: Psychopharmacological effects of Ginkgo Biloba extract (EGb 761®) on healthy volunteers. Eur. J. Pharmacol. 183 (1990), 1460.
9. LaRue, A., Swan, G. E., Carmelli, D.: Cognition and depression in a cohort of aging men: results from the Western Collaborative Group Study. Psychol-Aging 10 (1995), 30–33.
10. Limm, H.: Der „Subjektive Intensitäts-Score" (SIS): ein neues Schmerzmeßinstrument. Verlag Dr. Kovac, Hamburg, 1999.
11. Luszcz, M. A., Bryan, J., Kent, P.: Predicting episodic memory performance of very old men and women: contributions from age, depression, activity, cognitive ability, and speed. Psychol-Aging 12 (1997), 340–351.
12. Luthringer, R., d'Arbigny, P., Machler, J. P.: Ginkgo biloba Extract (EGb 761®), EEG and event-related potentials mapping profile. In: Christen, Y., Courtois, Y., Droy-Lefaix, M. T. (eds.): Advances in Ginkgo biloba Extract Research, Vol. 4. Effects of Ginkgo biloba Extract on Aging and Age-Related Disorders. Elsevier, Paris 1995, S. 107–118.
13. McNair D., Lorr, N., Dropelman, L.: Manual for the Profile of Mood States. Education and Industrial Testing Service, San Diego, CA 1982.
14. Mix, J. A., Crews, W. D.: An examination of the efficacy of Ginkgo biloba Extract EGb 761 on the neuropsychologic functioning of cognitively intact older adults. J. Alternative Complement. Med. 6 (2000), 219–229.
15. Oken, B. S., Storzbach, B. M., Kaye, J. A.: The efficacy of Ginkgo biloba on cognitive function in Alzheimer Disease. Arch. Neurol. 55 (1998), 1409–1415.
16. Schaffler, K., Reeh, P. W.: Doppelblindstudie zur hypoxieprotektiven Wirkung eines standardisierten Ginkgo-Biloba-Präparates nach Mehrfachverabreichung an gesunden Personen. Arzneimittelforsch. 35 (1985), 1283–1286.
17. Schubert, H., Halama, P.: Primary therapy-resistant depressive instability in elderly patients with cerebral disorders: Efficacy of a combination of Ginkgo biloba extract EGb 761 with antidepressants. Geriatr. Forsch. 1 (1993), 45–53.
18. Scott, J., Huskisson, E. C.: Graphic representation of pain. Pain 2 (1974), 175–184.
19. Stocksmeier, U., Eberlein, M.: Depressive Verstimmung bei Hirnleistungsstörungen, Wirkung eines Ginkgo-biloba-Extraktes in Doppelblindstudie überprüft. TW Neurol. Psychiatr. 6 (1992), 74–76.
20. Subhan, Z., Hindmarch, I.: The psychopharmacological effects of Ginkgo biloba extract in normal healthy subjects. Int. J. Clin. Pharmacol. Res. 4 (1984), 89–93.
21. Zung, W. K.: A self-rating depression scale. Arch. Gen. Psychiatry 12 (1965), 63–70.

Acknowledgements:
We would like to thank both the investigating physicians who were involved with data collection, Dierk Schwender, Hospital for Anaesthesiology, LMU Munich, and Karin Meissner, Institute for Medical Psychology, LMU Munich.
The study was financed by Dr. Willmar Schwabe Pharmaceuticals.
The authors would like to thank the subjects for participating in the study, and members of the Institute for Medical Psychology's research group, especially Marion Pollok, Lisa Flammersfeld and Jasmin Heiss, for their support.

On behalf of the authors:

Petra Maier (M.Sc. Psychology), Institute for Med. Psychology, LMU Munich, Goethestr. 31, D-80336 Munich.