Quality of Life is Improved in Breast Cancer Patients by Standardised Mistletoe Extract PS76A2 during Chemotherapy and Follow-up: A Randomised, Placebo-controlled, Double-blind, Multicentre Clinical Trial

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Abstract. *The objective of this randomised, multicentre, double-blind clinical trial was to investigate the impact of PS76A2, an aqueous mistletoe extract standardised to mistletoe lectins, on quality of life (QoL) in breast cancer patients. A total of 352 patients were randomly allocated to 2 groups receiving PS76A2 (15 ng mistletoe lectin/0.5 ml) or matching placebo twice weekly for 4 to 6 cycles of CMF (cyclophosphamide, methotrexate, fluorouracil) chemotherapy followed by 2 months follow-up. The primary efficacy end-point was the change from baseline of 3 FACT-G subscales (physical, emotional and functional well-being) during the fourth CMF cycle. Secondary measures included GLQ-8 (8 linear analogue self-assessment scales), Spitzer's uniscale and haematological variables. The main variables of safety analysis were adverse events, including injection site reactions and clinical laboratory tests. The results showed that physical, emotional and functional well-being improved upon PS76A2, but deteriorated following placebo. The treatment differences were statistically significant for the 3 subscales as well as for the summary score FACT-G, which was analysed as O'Brien's rank sum of its 3 subscales. The total score increased by 4.40±11.28, indicating a higher QoL after PS76A2, but decreased by 5.11±11.77 with placebo ($p<0.0001$). The GLQ-8 sum of 8 LASA scales was analysed as a summary score of GLQ-5 (sum of item nos. 1, 5, 6, 7, 8) and GLQ-3 (sum of item nos. 2, 3, 4). GLQ-5 characterises typical aspects of QoL, while GLQ-3 consists of 3 side-effects of CMF (feeling sick, numbness or pins and needles, loss of hair). GLQ-5 decreased by 42.9±125.0 upon PS76A2, indicating an improvement in QoL, but increased by 60.3±94.0 upon placebo ($p<0.0001$). GLQ-3 deteriorated in both groups (PS76A2: 13.9±52.4; placebo: 34.5±57.0), but the differences in favour of PS76A2 were, nevertheless, statistically significant ($p=0.0007$). The total score GLQ-8 improved by 28.9±154.6 after PS76A2 and deteriorated by 94.8±141.1 after placebo ($p<0.0001$). Spitzer's uniscale improved by 12.2±30.7 upon PS76A2 and deteriorated by 10.8±26.1 with placebo ($p<0.0001$). After follow-up without chemotherapy, a significant treatment difference in favour of PS76A2 was determined by means of FACT-G, GLQ-8 and Spitzer's uniscale. PS76A2 was well tolerated in this trial, with the exception of slight local reactions in 17.6% of the PS76A2 group. In conclusion, PS76A2 (15 ng mistletoe lectin/0.5 ml twice weekly) was shown to be safe and effective in improving QoL in breast cancer patients during chemotherapy and follow-up.*

Aqueous mistletoe extracts are widely used in complementary cancer therapy as immunomodulating agents and biological response modifiers (1). About 70% of cancer patients nowadays use complementary treatments and, among those, mistletoe therapy is gaining importance, especially in women suffering from breast cancer. The reason for using mistletoe therapy is mainly to reduce the side-effects of standard chemotherapy and to improve the patient's immune status and quality of life (QoL) (2, 3). Since mistletoe lectins were identified as the main active principle of mistletoe extracts, there is increasing interest in clinical oncology about using preparations standardised to mistletoe lectins.

Mistletoe lectins belong to a group of ribosome-inactivating proteins (RIP) which specifically bind to the D-galactosidic and/or *N*-acetyl-D-galactosaminic cell surface residues of malignant tumour cells, immune cells and others. Mistletoe lectins are composed of a carbohydrate binding B chain, which mediates cellular uptake of the

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disulfide-bonded hololectin, and a cytotoxic A chain, which inhibits protein biosynthesis enzymatically, subsequently resulting in cell death *via* apoptosis or necrosis (4).

From experimental and clinical investigations, mistletoe extracts as well as isolated lectins were shown to have immunomodulatory potencies by enhancing the secretion of cytokines and the activity of immunological effector cells like natural killer cells and T lymphocytes. Moreover, inhibition of tumour cell proliferation and tumour growth has been shown in numerous *in vitro* and *in vivo* studies (4-8).

Based on current knowledge, a mistletoe preparation standardised to mistletoe lectins would be a promising candidate for cancer therapy in principle. So far, the results from the first pilot studies on a limited number of patients with malignant glioma or superficial urinary bladder carcinoma have indicated a positive impact on tumour progression (9-11), but this has to be confirmed in further clinical trials. On the other hand, improvement in QoL of cancer patients treated with mistletoe preparations is generally recognised, although significant evidence of its efficacy has been limited to some clinical trials including a GCP-conform dose-finding study with the standardised mistletoe extract used in this study (12-15).

The objective of this clinical trial was to confirm the efficacy of PS76A2, an aqueous mistletoe extract standardised to mistletoe lectins, on QoL in breast cancer patients during chemotherapy and follow-up at the clinically effective dosage identified in a previous study (15).

Materials and Methods

Study design and selection criteria. This was a prospective, randomised, double-blind, placebo-controlled, multicentre trial on women with operable breast cancer who were eligible for adjuvant CMF (cyclophosphamide, methotrexate, fluorouracil) chemotherapy. Patients were enrolled in 6 centres in Russia, Bulgaria and the Ukraine prior to the start of the first cycle of CMF therapy. The inclusion criteria were: TNM-classification pT1-T3 pN0-N+ (0-10 positive lymph nodes) pM0, including carcinoma *in situ*; pre-and perimenopausal patients aged between 18 and 55 years; patients who were intended to be treated with adjuvant CMF chemotherapy for at least 4 to 6 cycles; school education >7 years; written informed consent according to ICH-GCP and applicable national law. The exclusion criteria were: inability to answer the QoL scales; concomitant therapy with steroids (except on the day of *i.v.* chemotherapy) or biological response modifiers; concomitant malignancy; radiation therapy to the ipsilateral breast and lymph nodes with a total dose above 60 Gray prior to study enrolment; individual hypersensitivity to protein and mistletoe preparations; time-interval between breast surgery and start of chemotherapy less or equal to 1 week or more than 4 weeks; chronic progressive infections (*e.g.,* tuberculosis); alcohol consumption >50 g ethanol per day; drug and nicotine abuse >20 cigarettes per day; pregnancy or lactation; participation in another clinical trail.

The study was performed in accordance with GCP (Good Clinical Practice), the Declaration of Helsinki and the CONSORT statement. Prior to the start of the study, the approval of the ethics committees of the participating centres and the corresponding countries were obtained.

Patients were allocated to the treatment groups (PS76A2 or placebo) on the basis of a computer-generated randomisation list. They received either 0.5 ml of the study medication PS76A2 (aqueous mistletoe extract standardised to mistletoe lectin; MADAUS GmbH, Cologne, Germany; commercially available as Lektinol®) containing 30 ng mistletoe lectin/ml or 0.5 ml placebo subcutaneously twice weekly for 16 to 24 consecutive weeks during chemotherapy, followed by a chemotherapy-free phase of 2 months (follow-up). The study medications (PS76A2 or placebo) were identical in terms of appearance, colour and packaging. Each centre retained sealed emergency envelopes for each patient. The course of treatment was divided into 4 to 6 CMF chemotherapy cycles and 2 follow-up cycles (2 months) without chemotherapy. Each cycle lasted 28 days. The study medication was administered on days 1 and 4 of each week, and always before administration of CMF chemotherapy on the respective first day of each week. On days 1 and 8 of each cycle, the patient received the standard adjuvant CMF treatment consisting of 600 mg/m^2 cyclophosphamide, 40 mg/m^2 methotrexate and 600 mg/m^2 fluorouracil intravenously (*i.v.*). To prevent or reduce nausea or emesis, patients received 10 mg dexamethasone *i.v.* and 10 mg metoclopramide q.i.d. per os on the day of chemotherapy. In accordance with the previous dose-finding study, the main study parameters were determined on days 1 of each 4-week interval, on days 8 of the chemotherapy cycles (haematological efficacy data only) and on days 15 and 21 of the 4th cycle (total count: days 92 and 99) to quantify changes in QoL *versus* baseline (15). The respective days were day 1 of the 15th or 16th week (1 day after completion of the 14th or 15th study week). Therefore, the mean value of the study end-points on these 2 target visits was denoted as the mean control at week 15 or, in short, as control after 15 weeks. The last day of follow-up, *i.e.,* days 169 or 197 or 225 after 4, 5 or 6 CMF plus 2 follow-up cycles, was defined as the target day of the follow-up phase. A delayed start of chemotherapy (maximum 14 days) and an adjustment of dosages were permitted depending on the patient's condition. All treatment adjustments were thoroughly checked for accordance with the protocol.

Target parameters. Three subscales for physical well-being (7 items scored 0, 1, 2, 3, 4), emotional well-being (6 items) and functional well-being (7 items) of the validated FACT-G scale (Functional Assessment of Cancer Therapy-General) were accumulated according to O'Brien and used as the primary efficacy variable of this study (16-18). The fourth subscale for social / family well-being was not considered. The subscales of FACT-G ranged from 0 to 24 (emotional well-being) or 28 (physical and functional well-being), with 0 (24 or 28) representing the worst (best) QoL. Correspondingly, FACT-G ranged from 0 (worst) to 80 (best) QoL.

FACT-G was used as the primary outcome variable instead of the QoL assessment scales GLQ-8 (Global Quality of Life Scale) and Spitzer's uniscale, because this instrument was regarded to be more appropriate to cover QoL during chemotherapy as well as in the follow-up phase. The GLQ-8 sum of 8 linear analogue self-assessment (LASA) scales and Spitzer's uniscale were used as secondary outcome variables. Each of the 8 GLQ LASA scales and Spitzer's uniscale ranged from 0 (highest quality of life) to 100 (lowest quality of life) (19-23). Haematological efficacy parameters were leucocytes, granulocytes, lymphocytes, platelets and haemoglobin.

Primary study end-points. In accordance with the preceding dose-finding study, changes from baseline at week 15 were used as the main study end-points (15). Changes in FACT-G, analysed as the O'Brien rank-sum of its 3 subscales, were defined as the primary study end-point.

In an *a priori* ordered sequence, the level of FACT-G at the end of follow-up and the course of FACT-G over 4 or 6 CMF cycles with baseline as a covariate (analysis of covariance for repeated measurements) were used as further primary end-points. Furthermore, the subscales of FACT-G were analysed in a closed test procedure.

Secondary study end-points. The secondary study end-points related to GLQ-8 and Spitzer's uniscale were defined and analysed in accordance with FACT-G. Apart from GLQ-8, the so-called subscale GLQ-5 (sum of item nos. 1, 5, 6, 7, 8) was analysed as the QoL instrument while GLQ-3 (sum of item no. 2 feeling sick/nausea or vomiting, no. 3 numbness or pins and needles and no. 4 loss of hair) was mainly considered as the tolerability variable for chemotherapy.

The secondary study end-points of the haematological efficacy variables were minimum values in the course of treatment and time of first occurrence of leucopenia and/or granulocytopenia.

Exploratory data analysis. Further study outcome variables were analysed in the scope of the exploratory data analysis. These were: items of FACT-G and GLQ-8, respectively, Karnofsky scale, consumption of antiemetic and analgesic drugs, number of in-patient days, adverse events and laboratory tests.

Quality assurance. A system audit of the Contract Research Organisation (CRO), which was responsible for the recruitment of investigators and monitoring of the trial, was performed by the Quality Assurance Department of the sponsor. The Standard Operating Procedures (SOPs) of the CRO, the personnel and the offices were checked and judged to be adequate for the conduct of the study according to GCP. On-site audits of study centres were performed by the Quality Assurance Department of the sponsor. The data quality regarding source data verification, accuracy and completeness was judged excellent for all centres and no relevant violations of GCP were reported.

Statistical methods. The primary study end-point was analysed as O'Brien's rank-sum of the changes from baseline in physical, emotional and functional well-being after 15 weeks of treatment (18). The analysis of the corresponding single end-points was performed in a 'closed test procedure' suitable to control the type I-error rate (24). The further primary end-points were tested in an *a priori* fixed order: first, the level of FACT-G at the end of follow-up; second, the level of FACT-G in the course of 4 to 6 CMF cycles by means of the treatment factor of an ANCOVA for repeated measures and baseline as covariate. The distribution of ranks or rank-sums was compared by Mann-Whitney's *U*-test. Additionally, the following tests were used: the *t*-test for the comparison of means in both trial groups, the χ^2 test for the comparison of categorial data and the log-rank test for the comparison of Kaplan-Meier plots. All tests were carried out two-tailed on the significance level of $\alpha=0.05$.

The sample size was determined prospectively assuming a power of $1-\beta=0.8$, a standardised treatment difference of 0.35 and a drop-out rate of approximately 15%. By means of a protocol amendment, the resulting sample size of approximately N=300 was enlarged to N=352, because a higher drop-out rate in the follow-up phase was suspected.

Results

Patient distribution and baseline characteristics. Within the 6 centres participating in this study, a total of 352 patients were allocated to the PS76A2 (N=176) or the placebo (N=176) trial groups. All patients received trial medication and were eligible for safety analysis. The Full Analysis Set (FAS) of the study consisted of 337 patients treated with 4 cycles of CMF who reached the target visits 15 weeks after the start of CMF. In total, 207 patients were evaluable for 6 cycles of CMF. Of 337 completers of CMF chemotherapy, 331 started the follow-up period. Six patients were lost to follow-up: decision of patient (PS76A2 N=2; placebo N=1), serious adverse event (placebo N=1), patient moved (placebo N=2).

The treatment groups were well balanced with respect to demographics and medical history, except for the histological classification, there being a slightly lower rate of invasive ductal tumors in the placebo group (Table I). The target parameters, however, showed initial inhomogeneities indicating a stronger restriction of QoL in the PS76A2 group. Therefore, the planned evaluation had to be complemented by baseline adjusted analyses of variance.

Confirmatory statistics of primary study end-point (FAS, chemotherapy phase). The confirmatory analysis of the FACT-G total score was based on the O'Brien rank-sum of changes in 3 subscales for physical, emotional and functional well-being. This test resulted in a highly significant superiority of PS76A2 compared to the placebo ($p<0.0001$). In a subsequent closed test procedure, all 3 subscales were established to be significantly superior to the placebo ($p<0.0001$; Table II). The results were confirmed in an ANCOVA with baseline values as covariate, carried out because of the baseline heterogeneity of the QoL scales. The course of FACT-G over 4 and 6 cycles of CMF chemotherapy is depicted in Figure 1.

Confirmatory statistics of secondary study end-points (FAS, chemotherapy phase). The O'Brien rank-sum of changes from baseline after 15 weeks of treatment in GLQ-8 sum of 8 LASA scales and Spitzer's uniscale, used as primary end-point in the preceding dose-finding study, was analysed as a secondary end-point in this trial (15). The difference in favour of PS76A2 was highly significant ($p<0.0001$), as were both subsequent tests of the single end-points shown in Table II.

GLQ-5 (sum of item nos. 1, 5, 6, 7, 8) was prespecified as a further secondary end-point. The changes from baseline showed a marked improvement upon PS76A2, but a mean

Table I. *Demographic data and medical history.*

	PS76A2 (N=176)	Placebo (N=176)
Age (years)		
mean±SD	46.4±5.9	45.9±6.0
range	28 – 55	25 – 55
Body weight (kg)		
mean±SD	71.6±13.2	72.6±13.8
Type of mastectomy		
radical / simple	145 (82.4%)*	143 (81.3%)
segmental	31 (17.6%)	33 (18.8%)
Tumor classification		
pTis – T1c	38 (21.6%)	53 (30.1%)
pT2 – T2a	128 (72.7%)	116 (65.9%)
pT3	10 (5.7%)	7 (4.0%)
Lymph nodes		
pN0	109 (61.9%)	118 (67.0%)
pN+	67 (38.1%)	58 (33.0%)
Histological classification		
invasive ductal	136 (77.3%)	118 (67.0%)
other	40 (22.7%)	58 (33.0%)
Grading of malignancy		
well-differentiated	12 (7.6%)	10 (6.4%)
moderately-differentiated	82 (52.2%)	77 (49.4%)
poorly-differentiated	47 (29.9%)	48 (30.8%)
undifferentiated	16 (10.2%)	21 (13.5%)
not assessed	19	20
Family history	30 (17.0%)	25 (14.2%)
Radiation prior to study enrolment [maximum dosage: 58 Gy]	18 (10.2%)	17 (9.7%)

*Number of patients (percentage).

Table II. *Changes from baseline in FACT-G, GLQ-8 and Spitzer's uniscale after 15 weeks of treatment with PS76A2 or placebo, respectively (FAS) (means±SD).*

	PS76A2 (N=169)	Placebo (N=168)	*U*-test (*p*-value)
FACT-G total score	4.40±11.28	–5.11±11.77	<0.0001
Physical well-being	2.03±5.07	–2.33±5.10	<0.0001
Emotional well-being	1.43±4.11	–1.17±4.36	<0.0001
Functional well-being	0.94±4.15	–1.61±4.66	<0.0001
GLQ-8 (sum of 8 LASA scales)	–28.9±154.6	94.8±141.1	<0.0001
GLQ-5 (sum of items 1, 5, 6, 7, 8)	–42.9±125.0	60.3±94.0	<0.0001
GLQ-3 (sum of items 2, 3, 4)	13.9±52.4	34.5±57.0	0.0007
Spitzer's uniscale	–12.2±30.7	10.8±26.1	<0.0001

deterioration following placebo ($p<0.0001$; Table II). The remaining parameter GLQ-3 (sum of item nos. 2, 3, 4) worsened in both trial groups. A difference in favour of PS76A2 with respect to raw changes from baseline (*U*-test: $p=0.0007$) turned out to be a insignificant trend after adjustment for baseline values. However, GLQ-3 was not assumed to discriminate between both treatments and, therefore, was not intended as an end-point of the confirmatory statistics. The results concerning GLQ-8 and Spitzer's uniscale (4 cycles) were confirmed in an ANCOVA with baseline values as covariate (Figure 2).

Item analysis of FACT-G after 15 weeks of treatment (FAS, chemotherapy phase). The contribution of each individual item to the physical, emotional and functional well-being scale is represented in Table III. In the majority of cases, statistically significant differences were seen between PS76A2 and the placebo. The only exceptions were item no. 4 of physical well-being and item nos. 2 and 5 of emotional well-being. Regarding the placebo group, all items showed a more or less marked deterioration after 15 weeks of treatment as compared to the baseline. Following PS76A2, improved mean values were determined for most items.

Item analysis of GLQ-8 after 15 weeks of treatment (FAS, chemotherapy phase). The contribution of item nos. 1, 5, 6, 7 and 8 to GLQ-5 is represented in Table IV. The respective items improved upon PS76A2, but deteriorated in the placebo group ($p<0.0001$). Regarding item nos. 2, 3 and 4, slight deteriorations were seen in both groups, but all 3 variables showed mean advantages of PS76A2, except for item no. 4.

Confirmatory statistics of primary study end-point (FU set, follow-up phase). The O'Brien rank-sum of the FACT-G scales after a 2-month follow-up without chemotherapy showed statistically significant differences in favour of

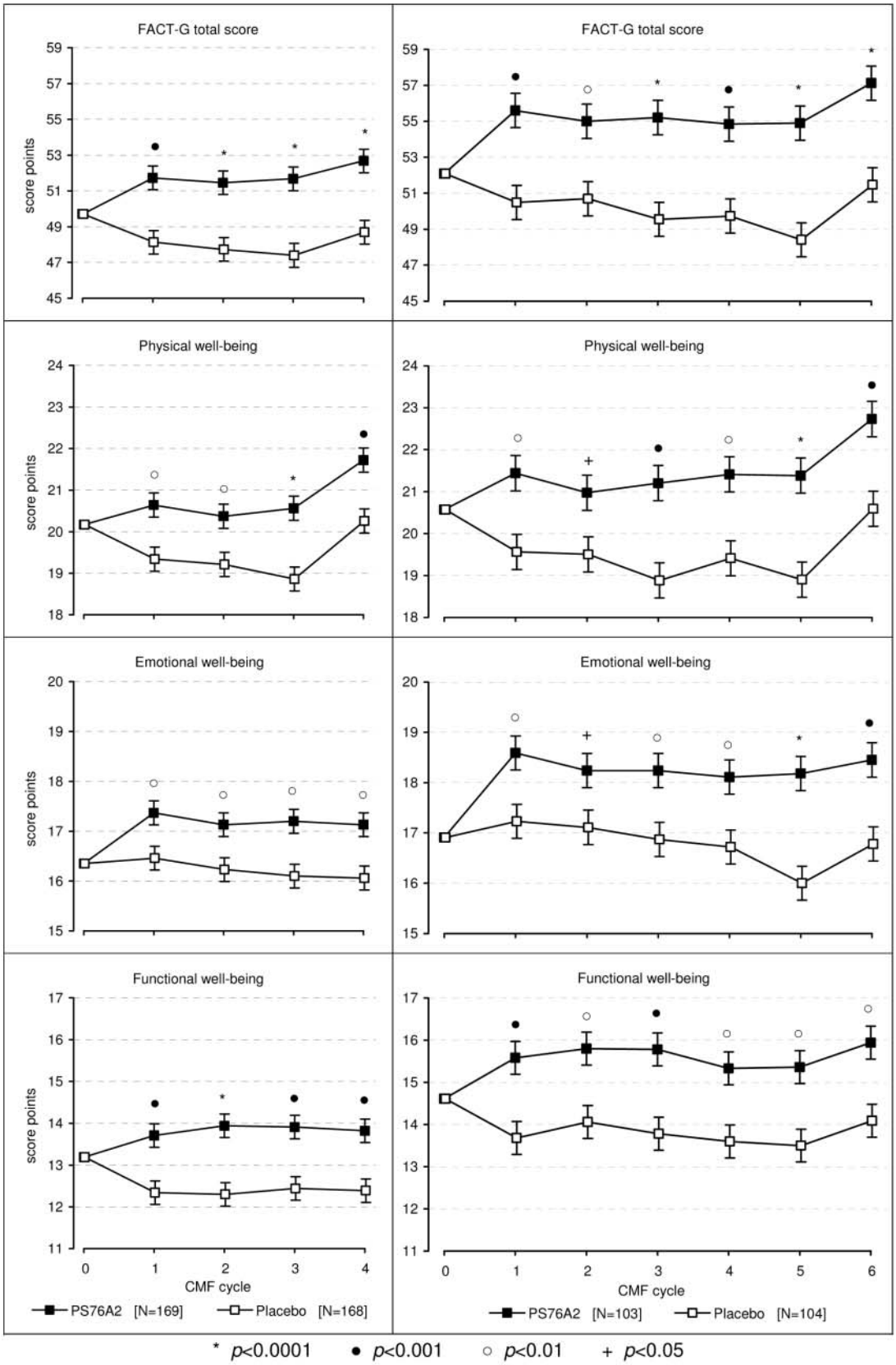

Figure 1. *Course of FACT-G over 4 (N=337) and 6 (N=207) CMF cycles (FAS; adjusted means±SEM).*

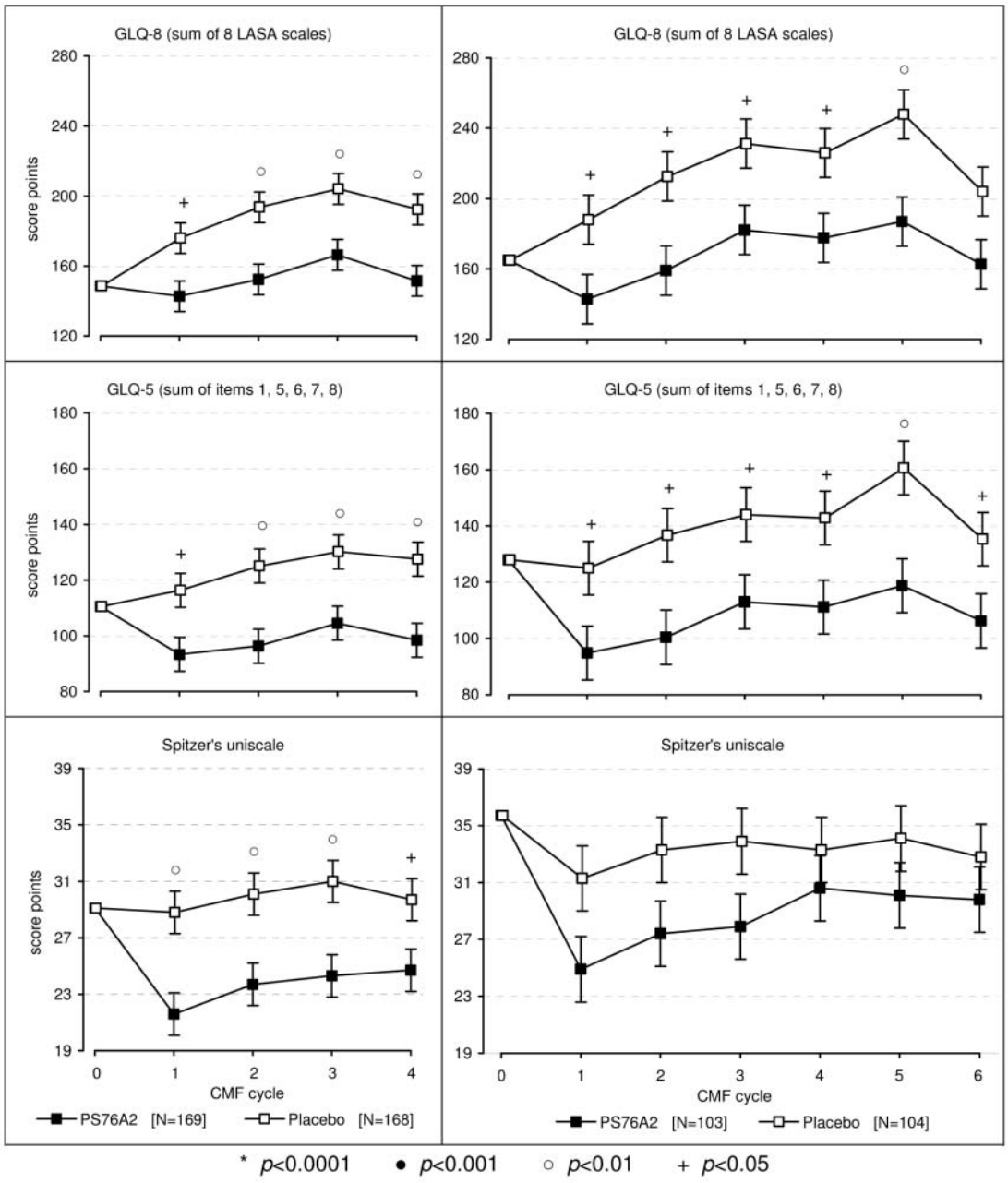

Figure 2. *Course of GLQ-8, GLQ-5 and Spitzer's uniscale over 4 (N=337) and 6 (N=207) CMF cycles (FAS; adjusted means±SEM).*

PS76A2 as compared to the placebo (*U*-test: $p=0.0311$). The levels were 55.27±9.73 (PS76A2) and 53.09±9.36 (placebo), respectively.

Item analysis of FACT-G after 2 months without chemotherapy (FU set, follow-up phase). The corresponding changes from baseline in the items and subscales of FACT-G at the end of follow-up showed significant differences in favour of PS76A2 for all physical and functional well-being items except for having pain (Table V). Regarding emotional well-being, a marked superiority of PS76A2 was seen for item no. 1 (I feel sad), no. 4 (I feel nervous) and no. 6 (I worry that my condition will get worse). The total improvement was 8.55±12.27 (PS76A2) and 0.34±10.14 (placebo), respectively.

Exploratory statistics of GLQ-8 and Spitzer's uniscale after 2 months without chemotherapy (FU set, follow-up phase). At the end of follow-up, GLQ-8 and Spitzer's uniscale showed

Table III. *Contribution of individual well-being items to changes from baseline after 15 weeks of treatment with PS76A2 or placebo, respectively (means±SD).*

No.	Item	PS76A2 (N=169)	Placebo (N=168)	*t*-test (*p*-value)
1	I have a lack of energy	0.47±1.21	–0.53±1.08	<0.0001
2	I have nausea	–0.17±1.16	–0.64±1.13	0.0002
3	Because of my physical condition, I have trouble meeting the needs of my family	0.64±1.14	–0.17±1.15	<0.0001
4	I have pain	0.07±0.80	–0.02±0.81	0.2676
5	I am bothered by side-effects of the treatment	0.27±1.13	–0.46±1.08	<0.0001
6	I feel ill	0.50±1.27	–0.32±1.04	<0.0001
7	I am forced to spend time in bed	0.25±0.90	–0.19±0.85	<0.0001
	Sum: Physical well-being	2.03±5.07	–2.33±5.10	<0.0001
1	I feel sad	0.43±1.17	–0.29±1.15	<0.0001
2	I am satisfied with how I am coping with my illness	–0.06±0.93	–0.05±1.06	0.9262
3	I am losing hope in the fight against my illness	0.00±0.92	–0.25±0.91	0.0098
4	I feel nervous	0.56±1.28	–0.21±1.14	<0.0001
5	I worry about dying	0.06±0.84	–0.10±0.93	0.1009
6	I worry that my condition will get worse	0.42±1.19	–0.27±1.16	<0.0001
	Sum: Emotional well-being	1.43±4.11	–1.17±4.36	<0.0001
1	I am able to work (including work at home)	0.20±0.77	–0.13±0.84	0.0003
2	My work (including work at home) is fulfilling	0.09±0.86	–0.17±0.94	0.0094
3	I am able to enjoy life	0.03±0.94	–0.29±0.94	0.0016
4	I have accepted my illness	0.03±0.86	–0.24±0.90	0.0052
5	I am sleeping well	0.17±1.03	–0.31±1.04	<0.0001
6	I am enjoying the things I usually do for fun	–0.01±0.88	–0.28±1.01	0.0106
7	I am content with the quality of my life right now	0.44±0.98	–0.20±1.19	<0.0001
	Sum: Functional well-being	0.94±4.15	–1.61±4.66	<0.0001

improved values with PS76A2, but deteriorations following placebo ($p<0.0001$; Table VI). This treatment difference was based on GLQ-5, while GLQ-3 showed an advantage only for item no. 2 (feeling sick/nausea or vomiting).

Table IV. *Contribution of individual GLQ-5 and GLQ-3 items to changes from baseline after 15 weeks of treatment with PS76A2 or placebo, respectively (means±SD).*

No.	Item	PS76A2 (N=169)	Placebo (N=168)	*t*-test (*p*-value)
1	Feeling anxious or depressed	–14.5±33.4	10.4±27.4	<0.0001
5	Tiredness	–10.6±31.6	14.0±26.7	<0.0001
6	Appetite or sense of taste	–8.0±28.8	12.7±23.8	<0.0001
7	Sexual interest or ability	–5.1±29.2	12.5±22.0	<0.0001
8	Thought of actually having treatment	–4.6±23.1	10.8±19.2	<0.0001
	Sum: GLQ-5 subscale	–42.9±125.0	60.3±94.0	<0.0001
2	Feeling sick (nausea or vomiting)	1.8±28.9	15.1±25.9	<0.0001
3	Numbness or pins and needles	1.6±21.9	6.8±22.4	0.0330
4	Loss of hair	10.5±23.5	12.5±23.5	0.4385
	Sum: GLQ-3 subscale	13.9±52.4	34.5±57.0	0.0007

Exploratory statistics of further efficacy parameters (FAS, FU set). No relevant differences were seen between the trial groups regarding the Karnofsky scale after chemotherapy and follow-up (data not shown). Changes in the parameters leucocytes, granulocytes, lymphocytes, platelets, haemoglobin, use of paracetamol or metoclopramide tablets, and the number of in-patient days were insignificant, too (data not shown).

Safety evaluation. All 352 patients were treated with at least 1 dose of study medication and, therefore, were included in the safety population. Ninety-six per cent (PS76A2) and 97.2% (placebo) of the patients received 4 to 6 cycles of adjuvant CMF chemotherapy and similar mean numbers of study medication injections during the chemotherapy phase: 40.8±9.1 (PS76A2) and 40.6±9.4 (placebo). In nearly all patients who participated in the follow-up phase, 16 further injections were administered: 97.0% (PS76A2) and 96.3% (placebo). Except for discontinuation of CMF before the target visits in week 15, all adjustments of CMF were in accordance with the prespecified treatment conditions and homogeneously distributed in both trial groups. Overall, the extent of drug exposure in terms of CMF chemotherapy, concomitant measures and study medication injections was fully comparable in both groups.

In all, 82 patients treated with PS76A2 (46.6%) and 63 patients receiving placebo (35.8%) experienced a total of 288 adverse events. In 253 instances, a connection with the

Table V. *Contribution of individual well-being items to changes from baseline after 2 months of follow-up with PS76A2 or placebo, but without chemotherapy (means±SD).*

No.	Item	PS76A2 (N=169)	Placebo (N=168)	*t*-test (*p*-value)
1	I have a lack of energy	0.77±1.26	–0.09±0.99	<0.0001
2	I have nausea	0.63±1.08	0.20±0.89	<0.0001
3	Because of my physical condition, I have trouble meeting the needs of my family	1.01±1.22	0.35±1.05	<0.0001
4	I have pain	0.26±0.93	0.24±0.83	0.8474
5	I am bothered by side-effects of the treatment	0.71±1.29	0.10±1.12	<0.0001
6	I feel ill	0.75±1.42	0.12±0.97	<0.0001
7	I am forced to spend time in bed	0.62±1.00	0.27±0.86	0.0006
	Sum: Physical well-being	4.75±5.57	1.20±4.45	<0.0001
1	I feel sad	0.64±1.26	0.04±0.95	<0.0001
2	I am satisfied with how I am coping with my illness	0.03±1.09	0.01±1.23	0.8520
3	I am losing hope in the fight against my illness	–0.04±1.19	–0.15±1.01	0.3903
4	I feel nervous	0.67±1.29	–0.10±0.94	<0.0001
5	I worry about dying	0.01±1.04	–0.15±1.02	0.1634
6	I worry that my condition will get worse	0.47±1.32	–0.09±1.12	<0.0001
	Sum: Emotional well-being	1.78±4.67	–0.44±3.83	<0.0001
1	I am able to work (including work at home)	0.29±0.88	0.06±0.88	0.0171
2	My work (including work at home) is fulfilling	0.32±0.94	–0.09±1.07	0.0003
3	I am able to enjoy life	0.23±1.10	–0.19±1.20	0.0010
4	I have accepted my illness	0.07±0.98	–0.18±0.92	0.0199
5	I am sleeping well	0.24±1.13	–0.12±1.09	0.0042
6	I am enjoying the things I usually do for fun	0.19±0.92	–0.14±1.10	0.0043
7	I am content with the quality of my life right now	0.69±1.07	0.23±1.20	0.0003
	Sum: Functional well-being	2.02±4.60	–0.42±5.07	<0.0001

Table VI. *Changes from baseline in GLQ-8 and Spitzer's uniscale after 2 months of follow-up with PS76A2 or placebo, but without chemotherapy (means±SD).*

No.	Item	PS76A2 (N=169)	Placebo (N=168)	*t*-test (*p*-value)
1	Feeling anxious or depressed	–18.3±35.6	3.6±22.0	<0.0001
5	Tiredness	–17.2±33.8	5.5±26.2	<0.0001
6	Appetite or sense of taste	–14.2±30.1	3.2±21.4	<0.0001
7	Sexual interest or ability	–5.6±31.4	10.5±25.6	<0.0001
8	Thought of actually having treatment	–7.5±25.0	3.8±17.0	<0.0001
	Sum: GLQ-5 subscale	–62.8±133.1	26.5±81.9	<0.0001
2	Feeling sick (nausea or vomiting)	–10.2±29.1	1.6±21.7	<0.0001
3	Numbness or pins and needles	0.7±23.0	1.9±20.8	0.6201
4	Loss of hair	1.7±21.4	4.2±14.9	0.2094
	Sum: GLQ-3 subscale	–7.9±51.8	7.6±45.2	0.0040
	GLQ-8 sum of 8 LASA scales	–70.7±166.3	34.2±116.8	<0.0001
	Spitzer's uniscale	–16.3±30.6	2.7±22.9	<0.0001

trial medication was rated improbable, not related or insufficient evidence, because the majority of events was clearly related to chemotherapy (Table VII). The rates of granulocytopenia / leucopenia were analysed by means of life-table-analysis and yielded a tendency in favour of PS76A2 (9.9%±2.3%) in comparison with the placebo (14.0%±2.7%), but this difference was not statistically significant (log-rank test: $p=0.2595$).

In 31 (17.6% PS76A2) and 3 (1.7% placebo) patients the relationship of adverse events to the trial medication was rated probable or possible, the discrepancy accounted for by the fact that injection site reactions did occur in 31 PS76A2-treated patients, but only in 2 placebo-treated cases ($p<0.0001$). This rate was well comparable with 17.9% reported in the dose-finding study after administration of PS76A2 (15). No patient stopped the trial medication due to local reactions. Other events at least possibly related to PS76A2 were reddening (not classified as injection site reaction) and allergic skin reaction (the patient decided to discontinue the trial drug administration due to this side-effect).

Similar changes of laboratory parameters, except for granulocytes, were seen in both groups. No changes to abnormal were seen in the PS76A2 group in case of normal pre-treatment findings, but in 7 placebo-treated patients, abnormally low values occurred. The changes from normal to abnormal were predominantly due to chemotherapy. No clinically relevant differences between PS76A2 and placebo were seen with respect to changes from baseline in vital signs.

Table VII. *Adverse events (MedDRA SOCs and selected high level terms).*

SOC / HLT	PS76A2 (N=176)	Placebo (N=176)	χ^2 test (p-value)
Blood and lymphatic system disorders	8 (4.5%)	7 (4.0%)	0.7919
Gastrointestinal disorders	20 (11.4%)	21 (11.9%)	0.8680
Nausea and vomiting symptoms	17 (9.7%)	17 (9.7%)	1.0000
General disorders and administration site conditions	56 (31.8%)	27 (15.3%)	0.0003
Febrile disorders	24 (13.6%)	24 (13.6%)	1.0000
Injection and infusion site reactions	31 (17.6%)	2 (1.1%)	<0.0001
Infections and infestations	11 (6.3%)	11 (6.3%)	1.0000
Investigations	23 (13.1%)	26 (14.8%)	0.6441
Liver function analyses	13 (7.4%)	10 (5.7%)	0.5176
Platelet analyses	1 (0.6%)	4 (2.3%)	0.1766
White blood cell analyses	12 (6.8%)	19 (10.8%)	0.1880
Metabolism and nutrition disorders	0	1 (0.6%)	0.3166
Musculoskeletal and connective tissue disorders	3 (1.7%)	0	0.0820
Nervous system disorders	14 (8.0%)	10 (5.7%)	0.3976
Headaches	14 (8.0%)	10 (5.7%)	0.3976
Skin and subcutaneous tissue disorders	12 (6.8%)	9 (5.1%)	0.4996
Vascular disorders	1 (0.6%)	1 (0.6%)	1.0000

Three serious adverse events were not related to the trial medication: 1 patient receiving PS76A2 was hospitalised for acute otitis; in the placebo group, 1 patient was hospitalised for a febrile neutropenia and another patient developed diabetes mellitus.

Discussion

Patients with operable breast cancer (stages II and III) are generally treated with adjuvant chemotherapy after the complete removal of the tumour and axillary lymph nodes (mastectomy or breast-conserving treatment) with the aim of prolonging the disease-free interval and improving the overall survival. Patients are afraid of the side-effects of chemotherapy and these side-effects and the patients' ability to cope with the diagnosis have a negative impact on the QoL and may lead to inadequate administration of chemotherapy, which results in a poorer prognosis (20, 21). Therefore, improvement of the QoL has become an important aim in the treatment of cancer patients.

For decades, there has been controversy about whether therapy with mistletoe extracts has any significant impact on tumour progression or the QoL of cancer patients. While to date antitumoral effects have not been shown in clinical trials on an adequate number of patients, there are promising results in the published literature regarding QoL (12-15). Now this prospective, randomised GCP study clearly demonstrated that PS76A2, a mistletoe extract preparation standardised to mistletoe lectin, significantly improved the QoL of breast cancer patients during adjuvant CMF chemotherapy and follow-up without chemotherapy ($p<0.0001$). This study further confirmed the results of a previous dose-finding study with PS76A2 following a very similar trial protocol where a dose-response relationship could be shown, indicating that the concentration of mistletoe lectin plays a major role in terms of the efficacy of mistletoe extract preparations in general (15, 25). In that previous study, the validated LASA scales GLQ-8 and Spitzer's uniscale had been shown to be suitable instruments to measure the effects of PS76A2 on the QoL during adjuvant CMF chemotherapy. Nevertheless, there is currently no gold standard covering all aspects of QoL in mistletoe therapy. In order to obtain more information on the possible effects of PS76A2 and its usefulness in complementary cancer therapy, it was therefore decided to include the FACT-G questionnaire as a primary efficacy variable to evaluate more specifically the influence on QoL in this clinical trial. GLQ-8 and Spitzer's uniscale were used again as secondary efficacy variables. All the instruments are well accepted and validated tools in oncology to assess QoL and proved to be sensitive to changes in the QoL (16, 17, 19, 20-23).

In this study, the FACT-G sum score as well as all 3 subscales (physical, emotional and functional well-being) were established to be significantly superior to the placebo ($p<0.0001$) during 4 or 6 CMF cycles as well as in the follow-up without chemotherapy. It is important that the majority of items was significantly improved by PS76A2, especially during chemotherapy, *e.g.,* I have lack of energy, I am bothered by side-effects of the treatment, I feel ill and I worry that my condition will get worse.

Most of the 8 items of GLQ-8 showed statistically significant differences ($p<0.0001$) between PS76A2 and

placebo during chemotherapy and follow-up, being largest for the items tiredness and feeling anxious or depressed. The GLQ-8 sum was analysed as 2 summary subscales, because GLQ-5 characterises typical aspects of QoL while GLQ-3 represents the side-effects of CMF chemotherapy. It is noteworthy that even those side-effects, especially nausea or vomiting ($p<0.0001$), were significantly improved by PS76A2 ($p=0.0007$). The effect on the item tiredness is of major importance, because more than three-quarters of cancer patients develop fatigue during the course of their disease or treatment. Furthermore, approximately one-third of the patients reported that fatigue strongly affected their daily routine. Even after the end of the cancer treatment, patients continued to feel a profound tiredness that affected almost all aspects of life. From the patients' point of view, tiredness, nausea and decreased sexual interest, all being significantly improved by PS76A2 during chemotherapy and follow-up ($p<0.0001$), are generally major problems of chemotherapy (26, 27). Significant improvement in the QoL ($p<0.0001$) following treatment with PS76A2 was also observed when using Spitzer's uniscale as the measuring instrument. Comparable effects of PS76A2 were seen in the previous dose-finding study regarding the LASA scales GLQ-8 and Spitzer's uniscale (15).

Summarising these findings, PS76A2 improved the QoL in patients with breast cancer receiving adjuvant CMF standard therapy and during follow-up without chemotherapy. It is important to stress that not only general well-being, but also the typical side-effects of chemotherapy improved significantly. Clinical studies with another standardised mistletoe extract preparation in patients with advanced breast or colorectal cancer supported the results of this study (12-14).

Apart from QoL, no relevant differences were detected in this study regarding changes from baseline after treatment for secondary variables (haematology, consumption of paracetamol or metoclopramide tablets, number of in-patient days). The compliance regarding administration of the trial medication was excellent. In contrast to other published QoL data from cancer trials, the documentation and completeness of the QoL data was very good in this study. This was achieved by intense monitoring and training of the investigators and study personnel.

The tolerability and safety of the trial medication was good. PS76A2-related local reactions at the injection sites did not lead to a discontinuation of treatment. Apart from this, no clinically relevant differences concerning adverse events and laboratory parameters between the groups with PS76A2 and placebo were recorded. The observed adverse events, predominantly of the haematological and gastrointestinal system, are anticipated adverse events of CMF chemotherapy and are not related to treatment with PS76A2.

In conclusion, the standardised mistletoe extract preparation PS76A2 (15 ng mistletoe lectin/0.5 ml twice weekly) was shown to be safe and effective in improving the QoL in breast cancer patients during CMF chemotherapy and follow-up.

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