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Prospective, open, randomised, controlled clinical trial for the investigation of the efficacy and tolerability of a Mistletoe preparation in patients with malignant pleural effusions

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Prospective, open, randomised, controlled clinical trial for the investigation of the efficacy and tolerability of a Mistletoe preparation in patients with malignant pleural effusions

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1. Aim of the Study

The tolerability of mistletoe preparation compared to those of Doxycycline in intrapleural instillation in patients with malignant pleural effusions will be investigated. The aim of this study is to test the hypothesis that mistletoe in intrapleural instillation induces fewer side effects than Doxycycline. Further objective is to investigate the efficacy of mistletoe preparation compared to those of Doxycycline in intrapleural instillation in patients with malignant pleural effusions. The hypothesis is that mistletoe preparation in intrapleural instillation ensures the same or a better success of pleurodesis. Furthermore, the changes in the laboratory parameters (punctate fluid and blood examinations) will be investigated.

2. Design of trial

Phase IV prospective, controlled, randomised, open trial in 40 patients.
Patients will be randomised to one of the two treatment groups (Helixor or Doxycycline).

2.1. Trial plan and treatment schedules

2.1.1. Trial Plan

Table 65 and Table 66 in the Appendix contain the trial plans for both treatment groups which differ in the treatment schedule.

2.1.2. Treatment schedule of the trial group (Helixor)

All patients in the trial group (Helixor) receive their therapy according to the following scheme.

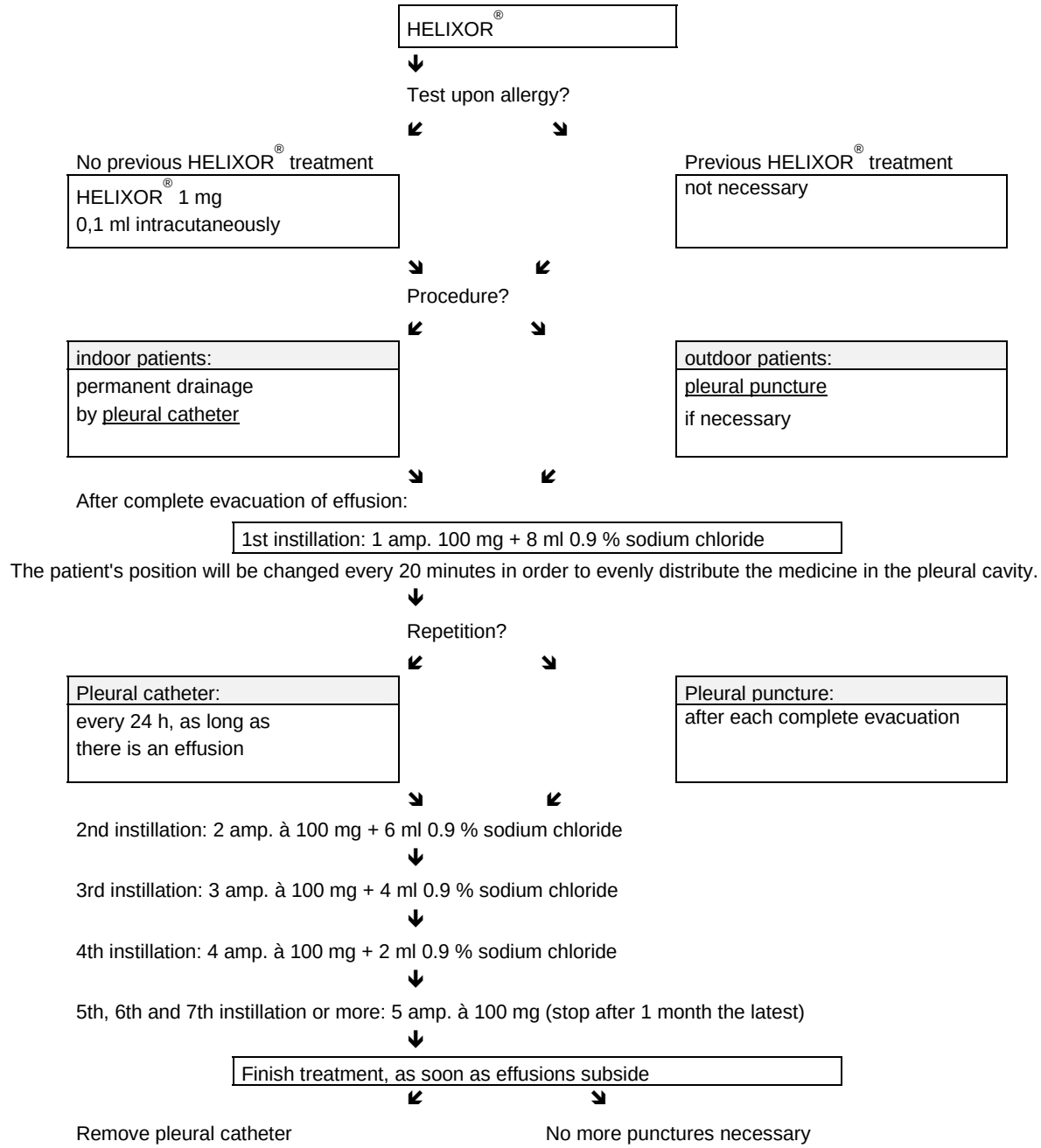

Table 1: Treatment schedule of the trial group (Helixor)

2.1.3. Treatment schedule of the control group (Doxycycline)

All patients in the control group receive a Vibramycin injection (active principle: Doxycycline) therapy according to standard intrapleural instillation therapy in Kangnam St. Mary's Hospital.

1		On first day, pleural catheter will be installed and then pleural effusion fluid will be naturally excreted for 1 day.
2		On second day, intrapleural instillation of Doxycycline will be conducted.
	a	Pre-treatment with Demerol (Pethidine-HCL) 50 mg by intramuscular injection.
	b	Preparation of treatment medicine: Doxycycline 500 mg + lidocaine 2% 2 mg/kg body weight + normal saline solution 100 ml.
	c	This medicine will be instilled through the pleural catheter and then the catheter will be clamped down.
	d	The patient's position will be changed every 20 minutes in order to evenly distribute the medicine in the pleural cavity.
	e	After 4 hours, the catheter will be opened in order to excrete the fluid.
3		The daily quantity of pleural effusion fluid will be documented and also thorax X-ray will be performed every 2 days.
4		After 7 days of examination, or later (but within 1 month) if the daily quantity of excreted fluid is > 100 ml or no pleurodesis formation is detectable by way of thorax X-ray, this treatment will be repeated one more time.

Table 2: Treatment schedule of the control group (Doxycycline)

2.2. Objectives

The tolerability of mistletoe preparation will be compared to the tolerability of Doxycycline in intrapleural instillation in patients with malignant pleural effusions. The primary objective is to answer the question, if mistletoe in intrapleural instillation induces fewer side effects compared to Doxycycline.

Further objective is to investigate the efficacy of mistletoe preparation compared to those of Doxycycline in intrapleural instillation in patients with malignant pleural effusions. The secondary objective is to answer the question, if mistletoe preparation in intrapleural instillation ensures the same or a better success of pleurodesis according to the WHO-criteria.

Furthermore, the changes in the laboratory parameters (punctate fluid and blood examinations) will be investigated.

2.3. Statistical Analysis

The primary analysis was done by the intention to treat principle. A sensitivity analysis was added for the analysis of the tolerability and the efficacy of mistletoe preparation.
In this particular trial the ITT population and the as treated population differ only in the treatment of two patients. One patient was randomised in the Helixor group and got Doxycycline instead of Helixor and the next patient was randomised in the Doxycycline group and got Helixor instead of Doxycycline.
This statistical report refers first on the as treated population for reasons of clinical interest and afterwards an account of the analysis using the ITT population is given.

2.3.1. Statistical Methods to analyse the trial population

The statistical analyses will be performed using SAS Version 8.02. To see if the two groups of patients treated with Helixor or Doxycycline seem to be equal, the demographic characteristics, the characteristics of physical condition and the history and extent of malignancy are summarized in tables. All p-values have to be interpreted as descriptive. This analysis has no confirmative power. In the following, the Mann-Whitney-Wilcoxon test was used for continuous data, and Fisher´s exact test for categorical data. Differences between screening and final investigation were analysed by paired t-test or the signed rank sum test. Individual information for each patient is listed at the end of this report.

2.3.2. Statistical Methods to analyse the tolerability of Mistletoe preparation

2.3.2.1 Side effects

Frequency tables of side effects by symptom (pain, burning, fever, others) and intensity will be presented for both treatment groups. In both treatment groups the tolerance rates (number of instillations without side effects / number of all instillations) for no pain, no burning and no fever will be calculated. The differences will be noted and confidence intervals will be constructed. The analysis is based on a test for correlated binary response discussed by Cochran [Cochran W. G., 1977]. Also a global tolerance rate (number of patients without side effects / number of all patients) will be given for each treatment group.
The mean severity of the side effects pain, burning and fever in both treatment groups will be analysed by the Mann-Whitney-Wilcoxon test.

2.3.2.2 Changes in laboratory parameters

- The following parameters (laboratory A) will be categorized as normal or not normal. Changes relative to baseline will be presented. The McNemar test will be used to compare paired proportions (normal at baseline / normal at the trial end); p-values can only be interpreted as descriptive.
  Laboratory A: blood sedimentation, hemoglobin, erythrocytes, thrombocytes, total leukocytes, neutrophils, eosinophils, basophils, monocytes, lymphocytes, creatinine, AST, ALT, γ-GT, lactate dehydrogenase, alkaline phosphatase
- Changes of the following parameters from baseline (prior to the first evacuation) to all following evacuations till the last evacuation will be tabulated.
  Laboratory B and C: tumor cells, eosinophils, neutrophils, lymphocytes, CD4, CD8, NK-cells, color and consistency of pleurate fluid. The parameters HLA-DR+ on T-Cells and Macrophages will be noted only once for the time prior to the first evacuation.

2.3.2.3 Safety evaluation

An assessment of incidence and severity of adverse events is given. The number of adverse events will be counted for each treatment group. Frequency tables of adverse events by body system and severity will be produced. Details to each adverse event will be listed.

The number of serious adverse events will be counted. Each serious adverse event will be described.

2.3.3. Statistical Methods to analyse the efficacy of Mistletoe preparation

Secondary endpoint is the success of pleurodesis, which is defined as:

- CR = no effusion ascertainable within four weeks after last evacuation.
- PR = further effusion ascertainable within four weeks after last evacuation, but no puncture required.
- NC = effusion requiring evacuation still present, no major change in volume.
- PD = increase in volume of effusion, need for evacuation.

According to these criteria, each patient that presents no ascertainable effusion within four weeks after last puncture is considered to be in complete remission, even in the case that a relapse should occur beyond this time interval.
A frequency table will be produced. The analysis will be done using the Chi squared test for trend. The Chi squared test for trend is used to assess a trend in proportions in a 2 x *k* table. The Chi squared test for trend is a more powerful test than the Chi squared test, if the outcome variable is an ordered categorical variable and incrising categories have a monotonous effect on the outcome, because this test uses this information about the ordering.
"Variation among groups can be subdivided into that due to a trend in proportions across the groups and the remainder. Although the value of Chi^2 for trend will always be less than Chi^2 for the overall comparison, the Chi squared test for trend is a powerful method of analysis because it yields a test statistic from a Chi squared distribution with one degree of freedom rather than k-1 degrees of freedom for the usual Chi squared test. If most of the variation is due to a trend across the groups, then the test for trend will yield a much smaller p value" [Douglas G. Altman, 1991].

3. Analysis of the as treated population

In this part "analysis of the as treated population" the parameter "group" means the treatment group, independent of the randomisation. So the Helixor group consists of 17 patients who got Helixor as treatment, including the one who was randomised for Doxycycline (patient number 4). Likewise in the Doxycycline group there are all 16 patients who got Doxycycline, including the one who was randomised for the Helixor group (patient number 5).

3.1. As treated Analysis of the trial population

33 patients were enrolled in the trial. Organizational reasons prevented from including the planned 40 patients. Of the 33 patients, 17 patients were randomised to the Helixor group, 16 to the Doxycycline group. The randomisation was done by a randomisation list. Two patients were not treated as allocated: patient number 4 got Helixor instead of Doxycycline, therefore the next patient (patient number 5) got Doxycycline instead of Helixor. One patient in the Doxycycline group did not receive the second Doxycycline instillation as allocated, because his treating physician decided that Doxycycline had failed and he switched to another therapeutical modality. The progress of patients through the trial shows Table 3.

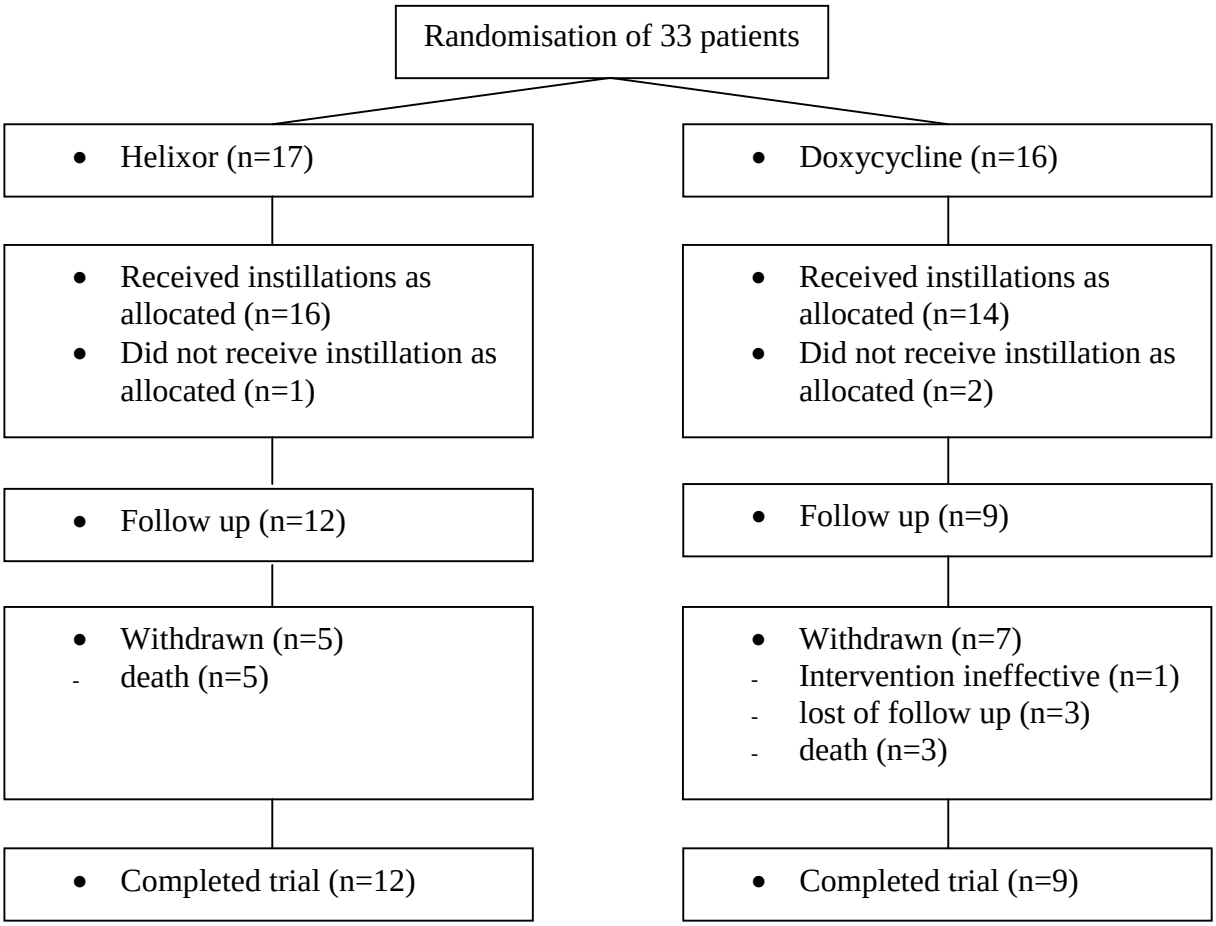

Table 3: As treated population: Progress of patients through the trial
n = number of patients

3.1.1. Violations of inclusion and exclusion criteria in the as treated population

One patient was marked not to be suitable for the trial, because he did not fulfill the inclusion criteria; his thrombocytes were 95 000/µl instead of 100 000/µl (Helixor, patient number 24). By screening the data there was another patient identified, who failed inclusion criteria, his hemoglobin was 9.8g/l instead of 10g/l (Doxycycline, patient number 20). None of these violations was classified to be relevant for the success of pleurodesis or the incidences or intensity of side effects. Therefore, all patients stayed in the as treated population.

3.1.2. Demography of the as treated population

The demography of the trial population is summarized in Table 4 and Table 5. As the explorative analysis shows, there seems to be no obvious difference between the Helixor and Doxycycline group except of smoking. There were more smokers (p-value = 0.039) in the Doxycycline group. For details see Listing 1.

	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
age	Helixor	17	0	58.7	11.5	33.0	52.0	58.0	68.0	76.0	0.068
[years]	Doxycycline	16	0	51.1	11.7	37.0	42.0	46.0	62.5	71.0	
	total	33	0	55.0	12.1	33.0	46.0	58.0	64.0	76.0	

Table 4: As treated population: Demographic characteristics I
n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, min = minimum, Q1 = 25th centiles, median = 50th centiles, Q3 = 75th centiles, max = maximum, p-value.

		Helixor N=17		Doxycycline N=16		total N=33		p-value
		N	%	N	%	N	%	
sex	female	9	52.9	8	50.0	17	51.5	1.000
	male	8	47.1	8	50.0	16	48.5	
alcohol	no	10	58.8	10	62.5	20	60.6	0.721
	rarely	7	41.2	5	31.3	12	36.4	
	regulary	0	0.0	1	6.3	1	3.0	
smoker	no	16	94.1	10	62.5	26	78.8	0.039
	yes	1	5.9	6	37.5	7	21.2	
profession		1	5.9	1	6.3	2	6.1	0.957
	DENTIST (RETIRED)	1	5.9	0	0.0	1	3.0	
	FARMER	1	5.9	1	6.3	2	6.1	
	HOUSEWIFE	8	47.1	5	31.3	13	39.4	
	NONE	4	23.5	3	18.8	7	21.2	
	NOT EMPLOYED	0	0.0	1	6.3	1	3.0	
	PAID EMPLOYEE	0	0.0	1	6.3	1	3.0	
	PLUMMER (PLUMBER*)	0	0.0	1	6.3	1	3.0	
	SALARY MAN	2	11.8	2	12.5	4	12.1	
	SALES MERCHANT	0	0.0	1	6.3	1	3.0	

Table 5: As treated population: Demographic characteristics II
n = number of patients
* in the original data “plummer” was noted as profession, but probably “plumber” was meant.

3.1.3. Characteristics of physical condition of the as treated population

The characteristics of physical condition are to be seen in Table 6, Table 7 and Table 8. No differences between the two groups are obvious. For details see Listing 2, Listing 4, Listing 5.

	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
height [cm]	Helixor	17	0	161.2	8.6	143.0	156.0	159.0	168.0	172.0	0.786
	Doxycycline	16	0	162.6	7.0	149.0	156.5	164.5	169.0	171.0	
	total	33	0	161.9	7.8	143.0	156.0	164.0	168.0	172.0	
weight [kg]	Helixor	17	0	57.4	10.1	39.8	52.0	55.0	62.0	80.0	0.900
	Doxycycline	16	0	56.8	9.5	40.0	50.5	56.5	64.5	77.0	
	total	33	0	57.1	9.7	39.8	52.0	55.0	63.1	80.0	
temperature [°C]	Helixor	17	0	36.5	0.2	36.0	36.3	36.5	36.7	36.8	0.078
	Doxycycline	16	0	36.7	0.4	36.0	36.4	36.8	37.0	37.2	
	total	33	0	36.6	0.3	36.0	36.4	36.6	36.8	37.2	
pulse [/min]	Helixor	17	0	84.0	15.6	60.0	76.0	80.0	88.0	132.0	0.187
	Doxycycline	16	0	86.2	6.7	72.0	83.0	87.0	92.0	96.0	
	total	33	0	85.1	12.0	60.0	78.0	85.0	90.0	132.0	
blood pressure systolic [mm Hg]	Helixor	17	0	115.3	17.4	90.0	100.0	120.0	130.0	140.0	0.769
	Doxycycline	16	0	114.3	12.9	100.0	105.0	110.0	120.0	140.0	
	total	33	0	114.8	15.1	90.0	100.0	110.0	120.0	140.0	
blood pressure diastolic [mm Hg]	Helixor	17	0	70.6	11.4	50.0	60.0	70.0	80.0	100.0	0.632
	Doxycycline	16	0	71.9	8.3	60.0	70.0	70.0	80.0	90.0	
	total	33	0	71.2	9.9	50.0	70.0	70.0	80.0	100.0	

Table 6: As treated population: Characteristics of physical conditions I
n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, min = minimum, Q1 = 25th centiles, median = 50th centiles, Q3 = 75th centiles, max = maximum, p-value.

		Helixor N=17		Doxycycline N=16		total N=33		p-value
		N	%	N	%	N	%	
Karnofsky Index [%]	50 %	1	5.9	1	6.3	2	6.1	0.145
	60 %	6	35.3	6	37.5	12	36.4	
	70 %	5	29.4	1	6.3	6	18.2	
	80 %	0	0.0	4	25.0	4	12.1	
	90 %	4	23.5	4	25.0	8	24.2	
	100 %	1	5.9	0	0.0	1	3.0	
additional disease	no	9	52.9	11	68.8	20	60.6	0.481
	yes	8	47.1	5	31.3	13	39.4	

Table 7: As treated population: Characteristics of physical conditions II
n = number of patients

		Helixor N=17		Doxycycline N=16		total N=33		p-value
		N	%	N	%	N	%	
nutritional status	normal	13	76.5	14	87.5	27	81.8	0.794
	not relevant	3	17.6	1	6.3	4	12.1	
	relevant	1	5.9	1	6.3	2	6.1	
skin	normal	16	94.1	16	100.0	32	97.0	1.000
	relevant	1	5.9	0	0.0	1	3.0	
edemas	normal	16	94.1	15	93.8	31	93.9	1.000
	not relevant	0	0.0	1	6.3	1	3.0	
	relevant	1	5.9	0	0.0	1	3.0	
lymphnodes	normal	16	94.1	16	100.0	32	97.0	1.000
	relevant	1	5.9	0	0.0	1	3.0	
head	normal	16	94.1	16	100.0	32	97.0	1.000
	relevant	1	5.9	0	0.0	1	3.0	
mucous membrane of mouth	normal	17	100.0	16	100.0	33	100.0	
thyroid	normal	17	100.0	15	93.8	32	97.0	0.485
	not relevant	0	0.0	1	6.3	1	3.0	
respiratory tract	normal	1	5.9	0	0.0	1	3.0	1.000
	not relevant	2	11.8	1	6.3	3	9.1	
	relevant	14	82.4	15	93.8	29	87.9	
heart	normal	16	94.1	16	100.0	32	97.0	1.000
	not relevant	1	5.9	0	0.0	1	3.0	
breasts	normal	13	76.5	15	93.8	28	84.8	0.335
	relevant	4	23.5	1	6.3	5	15.2	
abdomen	normal	14	82.4	16	100.0	30	90.9	0.352
	not relevant	1	5.9	0	0.0	1	3.0	
	relevant	2	11.8	0	0.0	2	6.1	
kidney region	normal	17	100.0	16	100.0	33	100.0	
spine	normal	16	94.1	16	100.0	32	97.0	1.000
	relevant	1	5.9	0	0.0	1	3.0	
extremities	normal	15	88.2	16	100.0	31	93.9	0.485
	relevant	2	11.8	0	0.0	2	6.1	
nervous system	normal	17	100.0	16	100.0	33	100.0	
urogenital system	normal	17	100.0	15	93.8	32	97.0	0.485
	relevant	0	0.0	1	6.3	1	3.0	
other		2	11.8	3	18.8	5	15.2	1.000
	normal	14	82.4	13	81.3	27	81.8	
	relevant	1	5.9	0	0.0	1	3.0	

Table 8: As treated population: Physical examinations
n = number of patients

In Listing 3, the kind of additional diseases before screening can be seen for both treatment groups.

3.1.4. Extent and history of malignancy of the as treated population

The following Table 9 describes the extent of malignancy. In the analysis of tumor stage, one patient had to be excluded from each treatment group. In the Helixor group, the tumor stage "TXN3M1" (patient number 6) was excluded from analysis and in the Doxycycline group the tumor stage "T4NXM1" (patient number 25) was excluded. No difference was seen neither for current tumor stage nor for number of metastases or for occurred combinations of localization of distant metastases. All patients suffered from pleural effusion.

		Helixor N=17		**Doxycycline N=16**		**Total N=33**		**p-value**
		N	%	N	%	N	%	
tumor stage	T1 N3 M1	0	0.0	1	6.7	1	3.2	0.142
	T2 N1 M1	0	0.0	1	6.7	1	3.2	
	T3 N0 M1	0	0.0	1	6.7	1	3.2	
	T3 N2 M1	0	0.0	1	6.7	1	3.2	
	T4 N0 M1	5	31.3	0	0.0	5	16.1	
	T4 N1 M1	3	18.8	2	13.3	5	16.1	
	T4 N2 M1	5	31.3	4	26.7	9	29.0	
	T4 N3 M1	3	18.8	5	33.3	8	25.8	
number of metastases	1	10	58.8	10	62.5	20	60.6	1.000
	2	4	23.5	5	31.3	9	27.3	
	3	2	11.8	1	6.3	3	9.1	
	4	1	5.9	0	0.0	1	3.0	
localization of metastasis	pleura	10	58.8	10	62.5	20	60.6	0.850
	pleura bones	2	11.8	4	25.0	6	18.2	
	pleura bones liver	1	5.9	0	0.0	1	3.0	
	pleura bones liver brain	1	5.9	0	0.0	1	3.0	
	pleura liver	1	5.9	1	6.3	2	6.1	
	pleura liver other	0	0.0	1	6.3	1	3.0	
	pleura lung bones	1	5.9	0	0.0	1	3.0	
	pleura lymphnodes	1	5.9	0	0.0	1	3.0	

Table 9: As treated population: Extent of malignancy
n = number of patients

The history of malignancy can be summarized as followed. In the Helixor group there were eleven patients who suffer from any kind of lung cancer (patient number 1, 9, 10, 11, 13, 14, 19, 22, 24, 26, 33), four with the diagnosis breast cancer (patient number 4, 8, 29, 32), one with a stomach cancer (patient number 3) and one with a cancer of unknown origin (patient number 6). In the Doxycycline group there were twelve lung-cancer-patients (patient number 2, 5, 7, 16, 18, 20, 21, 23, 27, 28, 30, 31), one breast-cancer-patient (patient number 12), one with a rectal tumor (patient number 17), one with the diagnosis cervix cancer (patient number 25), and one with the diagnosis adenocarcinoma of bartholin gland (patient number 15).
The time of diagnosis of primary tumor was between 1983 and 1999 for the Helixor group and between 1993 and 1999 for the Doxycycline group. The mean time since diagnosis was 24 months (median = two months) in the Helixor group and 5 months (median = one month) in the Doxycycline group. The minimum in both treatment groups was zero, i.e. the time of diagnosis and the beginning of the therapy was in the same month (Table 10).

	GROUP	**N**	**NMISS**	**MEAN**	**SDEV**	**MIN**	**Q1**	**MEDIAN**	**Q3**	**MAX**	**P-VALUE**
months since diagnosis	Helixor	17	0	23.9	51.3	0.0	1.0	2.0	12.0	192.0	0.245
	Doxycycline	16	0	5.4	8.4	0.0	0.0	1.0	9.0	24.0	
	total	33	0	14.9	37.9	0.0	0.0	1.0	11.0	192.0	

Table 10: As treated population: Time since diagnosis of primary tumor
n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, min = minimum, Q1 = 25^{th} centiles, median = 50^{th} centiles, Q3 = 75^{th} centiles, max = maximum, p-value.

In both treatment groups there were seven patients with no previous treatment (Helixor, patient number 1, 6, 11, 13, 14, 22, 33; Doxycycline, patient number 2, 7, 20, 21, 27, 28, 31), two patients with a previous operation (Helixor, patient number 3, 29; Doxycycline, patient number 12, 17), two patients with other previous treatments such as chemo-, hormone-, immuno- or other therapy (Helixor, patient number 9, 19; Doxycycline, patient number 16, 18). In the Helixor group there were also three patients with the combination "radiotherapy and others" (Helixor, patient number 10, 24, 26) while in the Doxycycline group there were four patients (Doxycycline, patient number 15, 23, 25, 30) with this combination. The Helixor group included also two patients with the combination "operation, radiotherapy and others" (Helixor, patient number 4, 32) and one patient with the combination "operation and other treatments" (Helixor, patient number 8). The patient number 5 (Doxycycline) had also "operation and other treatments" as previous treatment. For details of extent and history of malignancy see Listing 6.

3.1.5. Course of the illness of the as treated population

In the Appendix (Figure 5 till Figure 37) there is one figure for each patient with the following information:

- The legend informs about the treatment group and the patient number.
- The curve in the diagram shows the course of the patient's effusions of pleural fluid (volume in ml).
- The needles represent the instillations with Helixor or Doxycycline.
- One the second y-axis all results can be seen:
  - o The symbol " o " represents the efficacy of the treatment, ranged from CR to PD.
  - \+ The " + " marks the finding in the patients x-rays, as there is free, pleural effusion and unchanged finding.
  - * The " * " shows the reason for the end of trial. If there was not any trial plan violation during the trial, the end of trial was marked as a successful one. A trial plan violation was noted as failure. If the patient changed the location under treatment the end of trial was called "in other location". At last the reason for the end of trial could be the patient´s death.

For details of effusions, instillations and x-rays see Listing 7 and Listing 8.

The time of intrapleural instillations was not specified and was decided upon by the treating physician. Some patients did have previous effusions of pleural fluid or previous x-rays with finding of pleural effusion. So the time suffering from pleural effusion before starting the therapy was not equal for all patients. Also the amount of pleural effusion by starting the therapy was quite different. There was no definition of a minimum or maximum amount of pleural effusion in the trial plan.

The patients treated with Helixor could get one up to seven or even more instillations during the trial depending on the decision of the treating physician. In the Doxycycline group there were one or two instillations possible according to the trial plan. The dosing of Helixor and Doxycycline was given according to the trial plan. The average number of instillations was seven in the Helixor group and one in the Doxycycline group (Table 11).

	GROUP	N	NMISS	MEAN	SDEV	STD ERROR
number of instillations	Helixor	17	0	6.59	1.54	0.37
	Doxycycline	16	0	1.31	0.48	0.12

Table 11: As treated population: Average number of instillations
n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, std error = standard error.

Twelve patients of the Helixor group (patient number 1, 4, 6, 8, 9, 11, 13, 14, 19, 22, 26, 29) got seven instillations, two patients (patient number 33, 24) got more then seven (1x8 and 1x9 instillations) and three (patient number 10, 32, 3) got less (2x3 and 1x5 instillations).
In the Doxycycline group eleven patients (patient number 2, 5, 12, 15, 16, 18, 20, 21, 23, 25, 28) got one instillation and five (patient number 7, 17, 27, 30, 31) got two instillations. Listing 9 and Listing 10 contain a listing of concomitant medication for pain and for other indications in each treatment group sorted by investigation.

3.1.6. Final investigation of the as treated population

Table 12 contains the reasons for the end of the trial sorted by the number of instillations.

Helixor			Doxycycline		
17 patients			16 patients		
			1	instillation	
				successful end	7
				failure	1
				in another hospital under treatment	2
				death	1
			2	instillations	
				successful end	2
				in another hospital under treatment	1
				death	2
3	instillations				
	successful end	1			
	death	1			
5	instillations				
	death	1			
7	instillations				
	successful end	9			
	failure	1			
	death	2			
8	instillations				
	successful end	1			
9	instillations				
	death	1			

Table 12: As treated population: Number of instillations and reason for end of trial.

The end of the trial in the Helixor group was eleven times successful (no trial plan violation for patient number 1, 6, 8, 9, 11, 13, 14, 26, 29, 32, 33), and once failed. This trial plan violation for patient number 22 was a final investigation after nearly 6 months instead of 4 weeks. Five patients died in the Helixor group. Four of these five cases were connected to cancer disease (patient number 3, 4, 10, 24), one patient (patient number 19) died because of gastric ulcer bleeding.
The Doxycycline group ended nine times successful (patient number 5, 12, 15, 16, 18, 21, 27, 28, 31), one failure occurred. For patient number 25 the treating physician concluded that the pleurodesis had failed so he decided to switch to another therapeutical modality. Conservative management using frequent puncture was preferred instead of giving the second dose of Doxycycline. Three patients were treated in another location (patient number 2, 7, 20) and three patients died (patient number 17, 23, 30). All three deaths were connected to the cancer disease.

It was decided that the two patients with a trial plan violation (Helixor, patient number 22, Doxycycline, patient number 25) should stay in the as treated population.

Figure 1 and Figure 2 show the time on study for each patient. One patient in the Helixor group (patient number 22) got his last examination (follow up) after 180 days instead of 28 days. One patient in the Doxycycline group (patient number 20) moved to another hospital. Several telephone interviews gave information about the patient's physical condition; the last telephone interview was 329 days after the initial examination. The mean time on study in the Helixor group was 39 days and in the Doxycycline group it was 47 days (Table 13).

	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	P-VALUE
time on study	Helixor	17	0	39.2	39.5	7.0	12.0	36.0	41.0	180.0	0.745
(days)	Doxycycline	16	0	47.1	76.0	11.0	19.5	32.0	37.0	329.0	
	total	33	0	43.0	59.2	7.0	14.0	34.0	41.0	329.0	

Table 13: As treated population: Time on study

n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, min = minimum, Q1 = 25th centiles, median = 50th centiles, Q3 = 75th centiles, max = maximum, p-value.

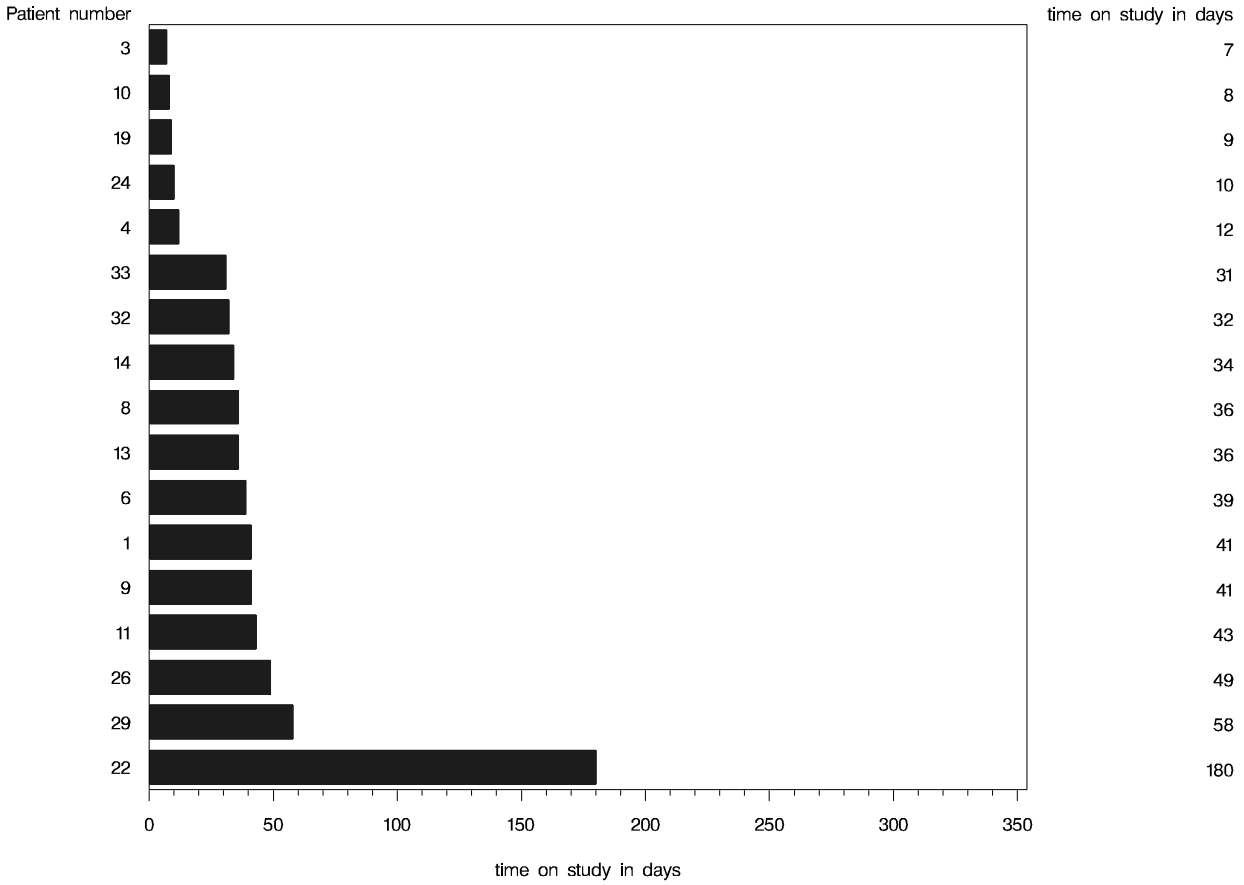

Figure 1: As treated population: Helixor: Time on study

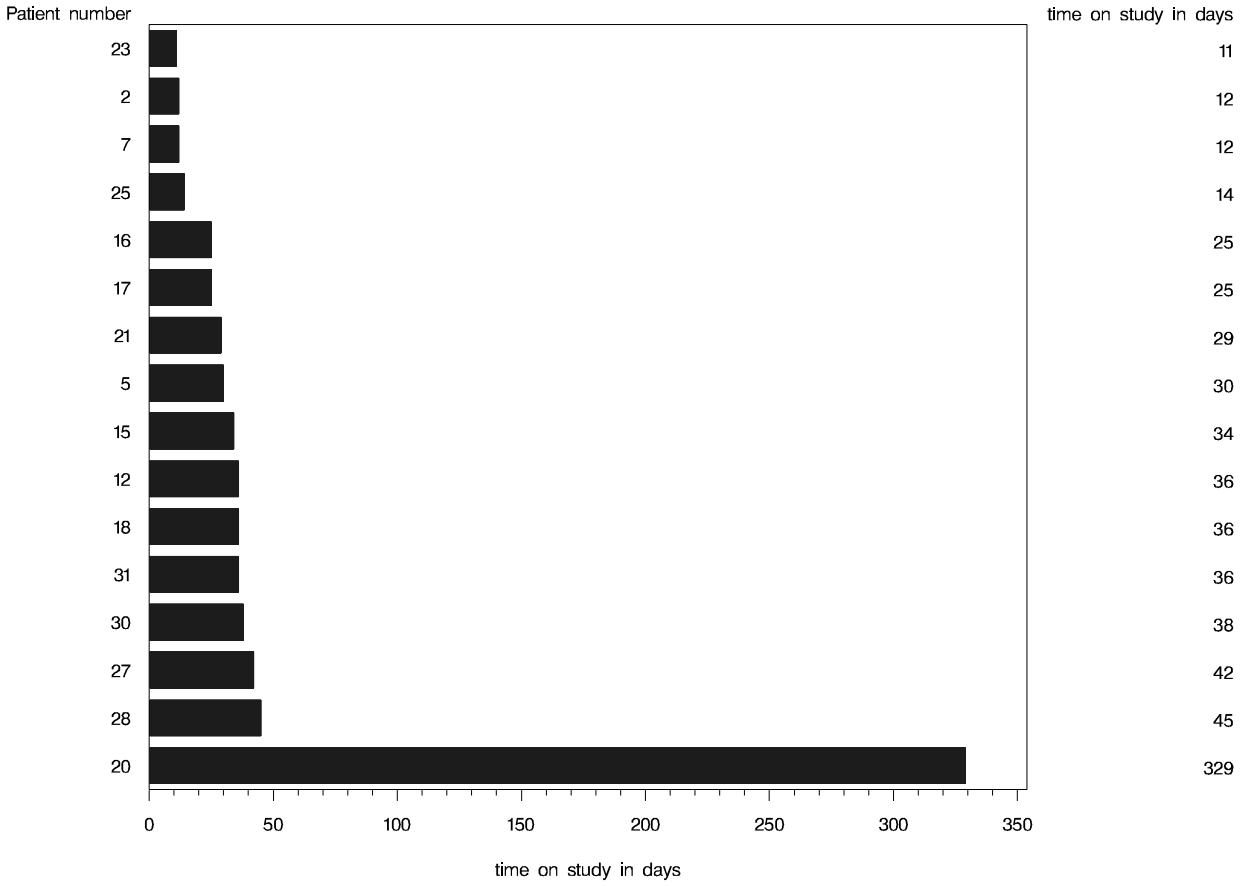

Figure 2: As treated population: Doxycycline: Time on study

Table 14 contains changes in weight, blood pressure systolic and diastolic, pulse, temperature and Karnofsky Index for both treatment groups. The paired t-test was used except for the analysis of the changes of the Karnofsky Index. There the signed rank sum test was used. No differences are obvious.

	Helixor					Doxycycline				
	N	**mean screening**	**mean final**	**mean difference**	**p-value**	**N**	**mean screening**	**mean final**	**mean difference**	**p-value**
blood pressure systolic [mm Hg]	12	116.7	114.2	-2.5	0.463	9	115.3	115.6	0.2	0.957
blood pressure diastolic [mm Hg]	12	71.7	73.3	1.7	0.504	9	72.2	72.2	0.0	1.000
pulse [/min]	12	80.2	81.4	1.3	0.564	9	87.1	86.6	-0.6	0.897
temperature [°C]	12	36.5	36.7	0.2	0.081	9	36.7	36.7	0.0	1.000
weight [kg]	11	60.1	59.0	-1.0	0.030	7	59.2	56.9	-2.3	0.057

	Helixor					Doxycycline				
	N	**median screening**	**median final**	**median difference**	**p-value**	**N**	**median screening**	**median final**	**median difference**	**p-value**
Karnofsky Index [%]	12	70	75	0	0.688	9	80	70	0	0.750

Table 14: As treated population: Changes between screening and final investigation
n = number of patients

To see if there is a difference between the mean differences between both treatment groups, the unpaired t-test was used for the parameters blood pressure systolic, blood pressure diastolic, pulse,

temperature and weight. The results are presented in Table 15, no differences are obvious. The Mann-Whitney-Wilcoxon test was used for the same analysis of the parameter Karnofsky Index, again no difference could be found (p=0,4221).

	mean difference Helixor	mean difference Doxycycline	mean difference between groups	confidence interval [95% CI]	p-value
blood pressure systolic [mm Hg]	-2.5	0.2	2.7	[-8.0 - 13.4]	0.600
blood pressure diastolic [mm Hg]	1.7	0.0	-1.7	[-8.9 - 5.6]	0.635
pulse [/min]	1.3	-0.6	-1.8	[-10.8 - 7.2]	0.681
temperature [°C]	0.2	0.0	-0.2	[-0.7 - 0.2]	0.313
weight [kg]	-1.0	-2.3	-1.3	[-3.2 - 0.7]	0.268

Table 15: As treated population: Comparison of the differences between the treatment groups
[95% CI] = 95% confidence interval

3.2. As treated analysis of the tolerability of Mistletoe preparation

3.2.1. Side effects in the as treated population

In both treatment groups the tolerance rates (number of instillations without side effects / number of all instillations) for no pain, no burning and no fever were calculated. There was a significant difference for pain between the two treatment groups. The difference was 0.65 [0.40 ; 0.90], (p-value < 0.0001) if the cut point was chosen as "severity 0" = "no side effect" (p-value = < 0.0001) and the difference reached 0.75 [0.49 ; 1.00], (p-value < 0.0001) if the cut point was chosen as "severity 0 and 1" = "no relevant side effect" (Table 16).
The probability to receive one instillation of Helixor without any pain (if the first definition is used "severity 0" = "no side effect") was 0.79, so the probability to receive the second instillation again without any pain is 0.62 (= 0.79^2), for the third painless instillation the probability can be calculated to 0.49 (= 0.79^3).
There was also a significant difference for burning of 0.33 [0.05 ; 0.60], (p-value = 0.020) for both cut points (Table 16).
Looking at the tolerance rates in the Helixor group, fever has the lowest rate. Regarding the confidence interval a difference between the two treatment groups could not be seen.

side effect	severity	Helixor tolerance rate [95% CI] n=112	Doxycycline tolerance rate [95% CI] n=21	difference	confidence interval [95% CI]	p-value
pain	1-4	0.79 [0.64 ; 0.95]	0.14 [-0.05 ; 0.33]	0.65	[0.40 ; 0.90]	< 0.0001
	2-4	0.94 [0.85 ; 1.03]	0.19 [-0.05 ; 0.43]	0.75	[0.49 ; 1.00]	< 0.0001
burning	1-4	0.95 [0.86 ; 1.04]	0.62 [0.36 ; 0.88]	0.33	[0.05 ; 0.60]	0.020
	2-4	0.95 [0.86 ; 1.04]	0.62 [0.36 ; 0.88]	0.33	[0.05 ; 0.60]	0.020
fever	1-4	0.77 [0.62 ; 0.92]	0.71 [0.49 ; 0.94]	0.06	[-0.21 ; 0.32]	0.696
	2-4	0.89 [0.82 ; 0.97]	0.81 [0.60 ; 1.02]	0.08	[-0-14 ; 0.31]	0.470

Table 16: Tolerance rates for the as treated population
[95% CI] = 95% confidence interval, n=number of instillations, (*this analysis was done by using s-plus)

A global tolerance rate (number of patients without side effects / number of all patients) is given for each treatment group in Table 17. In Table 18, the global tolerance rate was defined as number of patients without any relevant side effects (number of patients with none or light side effects / number of all patients). Using Fisher´s exact test, a difference between the treatment groups is to be seen for pain.

	severity	Helixor N=17		Doxycycline N=16		total N=33		p-value
		N	%	N	%	N	%	
pain	none	11	64.7	1	6.3	12	36.4	0.001
	light-unacceptable	6	35.3	15	93.8	21	63.6	.
burning	none	15	88.2	10	62.5	25	75.8	0.118
	light-unacceptable	2	11.8	6	37.5	8	24.2	.
fever	none	9	52.9	11	68.8	20	60.6	0.481
	light-unacceptable	8	47.1	5	31.3	13	39.4	.

Table 17: Global tolerance rates for the as treated population, success = no side effect
n = number of patients

	severity	Helixor N=17		Doxycycline N=16		total N=33		p-value
		N	%	N	%	N	%	
pain	none-light	15	88.2	2	12.5	17	51.5	< 0.0001
	moderate-unacceptable	2	11.8	14	87.5	16	48.5	.
burning	none-light	15	88.2	10	62.5	25	75.8	0.118
	moderate-unacceptable	2	11.8	6	37.5	8	24.2	.
fever	none-light	10	58.8	13	81.3	23	69.7	0.259
	moderate-unacceptable	7	41.2	3	18.8	10	30.3	.

Table 18: Global tolerance rates for the as treated population, success = no or light side effect
n = number of patients

The mean severity of a side effect was calculated as the mean of the individual patients means in order to adjust to an harmonious number of treatment instillations between treatment groups and individual patients. Table 19 shows that the mean severity of pain was higher in the Doxycycline group than in the Helixor group (p-value < 0.0001). Using the Mann-Whitney-Wilcoxon test no other differences were obvious. Details for each side effect present Table 20 and Listing 11.

side effect	severity	Helixor mean severity	Doxycycline mean severity	difference	confidence interval [95% CI]	p-value
pain	0-4	0.43	2.64	-2.21	[-2.95 , -1.47]	< 0.0001
burning	0-4	0.28	0.88	-0.6	[-1.37 , 0.19]	0.281
fever	0-4	0.42	0.48	-0.06	[-0.64 , 0.51]	0.567

Table 19: Mean severity of side-effects for the as treated population
[95% CI] = 95% confidence interval (*this analysis was done by using s-plus)

	severity	Helixor N=112		Doxycycline N=21		Total N=133	
		N	%	N	%	N	%
pain	none	89	79.5	3	14.3	92	69.2
	light	16	14.3	1	4.8	17	12.8
	moderate	2	1.8	1	4.8	3	2.3
	serious	4	3.6	12	57.1	16	12.0
	unacceptable	1	0.9	4	19.0	5	3.8
burning	none	106	94.6	13	61.9	119	89.5
	moderate	1	0.9	4	19.0	5	3.8
	serious	5	4.5	2	9.5	7	5.3
	unacceptable	0	0.0	2	9.5	2	1.5
fever	none	86	76.8	15	71.4	101	75.9
	light	14	12.5	2	9.5	16	12.0
	moderate	9	8.0	2	9.5	11	8.3
	serious	3	2.7	1	4.8	4	3.0
	unacceptable	0	0.0	1	4.8	1	0.8
other	none	108	96.4	19	90.5	127	95.5
	light	1	0.9	2	9.5	3	2.3
	moderate	3	2.7	0	0.0	3	2.3

Table 20: Frequency and severity of side effects for the as treated population
n = number of instillations

3.2.2. Changes in laboratory parameters of the as treated population

An overview about the laboratory parameters of laboratory A in both treatment groups for time of screening gives Table 21 and for time of the final investigation it is Table 22.

	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
blood	Helixor	15	2	65.4	34.4	14.0	28.0	65.0	96.0	123.0
sedimentation	Doxycycline	16	0	63.9	33.9	10.0	38.5	68.0	85.5	125.0
[mm/h]	total	31	2	64.6	33.6	10.0	32.0	66.0	91.0	125.0
hemoglobin	Helixor	17	0	11.6	1.0	10.0	10.8	11.7	12.4	13.3
[g/dl]	Doxycycline	16	0	12.0	1.4	9.8	11.1	11.8	12.8	14.4
	total	33	0	11.8	1.2	9.8	11.0	11.7	12.6	14.4
erythrocytes	Helixor	17	0	3.8	0.5	3.0	3.4	3.8	4.3	4.6
[10^6/µl]	Doxycycline	14	2	3.9	0.5	3.3	3.6	3.8	4.3	4.8
	total	31	2	3.8	0.5	3.0	3.5	3.8	4.3	4.8
thrombocytes	Helixor	17	0	263.9	92.2	95.0	202.0	261.0	297.0	439.0
[10^3/µl]	Doxycycline	16	0	289.7	67.8	160.0	249.5	273.0	339.5	429.0
	total	33	0	276.4	81.1	95.0	229.0	271.0	311.0	439.0
total	Helixor	17	0	7.7	3.1	3.3	5.7	7.4	9.7	14.9
leucocytes	Doxycycline	16	0	7.9	1.8	5.3	6.4	7.7	9.2	11.0
[10^3/µl]	total	33	0	7.8	2.5	3.3	6.1	7.4	9.4	14.9
neutrophils	Helixor	17	0	67.9	20.2	5.2	56.5	71.4	80.9	91.0
[%]	Doxycycline	16	0	74.1	8.9	59.7	66.6	73.8	81.7	90.3
	total	33	0	70.9	15.8	5.2	66.3	72.4	80.9	91.0
eosinophils	Helixor	17	0	3.0	3.5	0.2	0.5	1.0	5.2	10.2
[%]	Doxycycline	16	0	2.8	3.7	0.1	0.8	1.9	3.3	15.7
	total	33	0	2.9	3.5	0.1	0.5	1.4	3.8	15.7
basophils	Helixor	17	0	1.1	1.3	0.0	0.3	0.7	1.3	4.9
[%]	Doxycycline	16	0	1.2	1.0	0.0	0.4	0.8	2.4	2.9
	total	33	0	1.2	1.1	0.0	0.3	0.8	1.5	4.9
monocytes	Helixor	17	0	8.2	5.6	0.5	5.8	7.2	9.2	27.2
[%]	Doxycycline	16	0	7.6	3.1	0.6	5.8	7.4	9.8	13.7
	total	33	0	7.9	4.5	0.5	5.8	7.2	9.2	27.2
lymphocytes	Helixor	17	0	15.2	9.5	1.2	10.1	14.3	20.5	36.2
[%]	Doxycycline	16	0	14.7	7.2	4.2	8.2	15.0	22.0	25.8
	total	33	0	15.0	8.3	1.2	10.0	14.3	21.4	36.2
creatinine	Helixor	17	0	0.9	0.2	0.5	0.7	0.8	1.0	1.5
[mg/dl]	Doxycycline	16	0	0.8	0.2	0.5	0.7	0.8	1.0	1.0
	total	33	0	0.9	0.2	0.5	0.7	0.8	1.0	1.5
SGOT	Helixor	17	0	32.4	23.2	13.0	19.0	24.0	39.0	102.0
[IU/l]	Doxycycline	16	0	27.3	8.2	14.0	21.5	26.5	33.0	42.0
	total	33	0	29.9	17.5	13.0	20.0	26.0	36.0	102.0
SGPT	Helixor	17	0	26.2	11.0	11.0	13.0	27.0	35.0	44.0
[IU/l]	Doxycycline	16	0	28.3	16.0	2.0	14.0	26.5	43.0	50.0
	total	33	0	27.2	13.5	2.0	14.0	27.0	40.0	50.0
gamma-GT	Helixor	17	0	48.6	46.4	8.0	14.0	29.0	75.0	149.0
[IU/l]	Doxycycline	16	0	53.3	55.8	6.0	12.0	40.0	66.5	198.0
	total	33	0	50.9	50.4	6.0	12.0	34.0	69.0	198.0
LDH	Helixor	17	0	593.8	564.0	249.0	314.0	385.0	471.0	2042.0
[IU/l]	Doxycycline	16	0	616.2	625.1	216.0	298.0	430.0	611.0	2766.0
	total	33	0	604.6	585.1	216.0	304.0	402.0	571.0	2766.0
AP	Helixor	17	0	274.6	144.7	152.0	183.0	255.0	303.0	763.0
[IU/l]	Doxycycline	16	0	328.0	258.9	151.0	182.0	228.0	393.5	1204.0
	total	33	0	300.5	206.5	151.0	183.0	239.0	336.0	1204.0

Table 21: As treated population: Laboratory parameters at screening

n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, min = minimum, Q1 = 25^{th} centiles, median = 50^{th} centiles, Q3 = 75^{th} centiles, max = maximum.

	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
blood	Helixor	9	3	84.7	50.8	11.0	60.0	91.0	102.0	172.0
sedimentation	Doxycycline	7	2	71.3	39.1	16.0	46.0	72.0	91.0	140.0
[mm/h]	total	16	5	78.8	45.1	11.0	50.0	78.5	98.0	172.0
hemoglobin	Helixor	12	0	10.6	1.3	8.3	9.8	10.7	11.7	12.7
[g/dl]	Doxycycline	9	0	10.8	2.1	9.0	9.2	9.5	12.9	13.9
	total	21	0	10.7	1.7	8.3	9.4	10.3	11.8	13.9
erythrocytes	Helixor	12	0	3.5	0.4	2.8	3.0	3.5	3.9	4.0
[10^6/µl]	Doxycycline	8	1	3.4	0.7	2.6	2.9	3.1	4.1	4.6
	total	20	1	3.5	0.6	2.6	2.9	3.4	3.9	4.6
thrombocytes	Helixor	12	0	288.6	110.9	127.0	214.0	275.0	375.5	489.0
[10^3/µl]	Doxycycline	9	0	253.6	114.6	114.0	159.0	248.0	294.0	461.0
	total	21	0	273.6	111.1	114.0	213.0	257.0	350.0	489.0
total	Helixor	12	0	6.7	1.9	4.0	4.9	6.5	8.1	9.6
leucocytes	Doxycycline	9	0	7.1	2.2	1.4	7.2	7.6	8.0	8.6
[10^3/µl]	total	21	0	6.8	2.0	1.4	6.2	7.6	8.0	9.6
neutrophils	Helixor	12	0	63.9	22.1	5.2	58.1	66.9	76.6	95.0
[%]	Doxycycline	9	0	64.8	24.5	8.0	55.4	72.2	79.1	90.0
	total	21	0	64.3	22.6	5.2	56.9	68.9	78.0	95.0
eosinophils	Helixor	12	0	2.8	2.9	0.1	0.3	2.5	4.7	8.4
[%]	Doxycycline	9	0	2.4	3.0	0.0	0.5	1.0	2.7	9.3
	total	21	0	2.6	2.9	0.0	0.3	1.7	3.4	9.3
basophils	Helixor	12	0	0.7	0.7	0.0	0.1	0.8	1.0	2.1
[%]	Doxycycline	9	0	0.4	0.6	0.0	0.0	0.1	0.6	1.5
	total	21	0	0.6	0.7	0.0	0.0	0.6	1.0	2.1
monocytes	Helixor	12	0	7.0	3.8	0.4	4.7	7.3	9.8	13.4
[%]	Doxycycline	9	0	7.3	4.9	2.0	4.4	6.8	8.1	15.5
	total	21	0	7.2	4.2	0.4	4.4	7.2	9.8	15.5
lymphocytes	Helixor	12	0	17.6	10.8	0.5	11.3	17.5	23.5	38.3
[%]	Doxycycline	9	0	25.8	25.9	3.3	13.2	19.4	27.3	90.0
	total	21	0	21.1	18.7	0.5	12.6	19.4	23.8	90.0
creatinine	Helixor	12	0	0.8	0.2	0.5	0.6	0.8	1.0	1.4
[mg/dl]	Doxycycline	9	0	0.8	0.2	0.6	0.7	0.9	1.0	1.0
	total	21	0	0.8	0.2	0.5	0.7	0.8	1.0	1.4
SGOT	Helixor	12	0	27.3	12.4	14.0	18.5	23.0	34.5	52.0
[IU/l]	Doxycycline	9	0	32.0	10.3	19.0	23.0	32.0	38.0	47.0
	total	21	0	29.3	11.5	14.0	19.0	26.0	37.0	52.0
SGPT	Helixor	12	0	25.2	15.8	9.0	12.5	20.5	34.0	57.0
[IU/l]	Doxycycline	9	0	35.1	14.6	12.0	28.0	39.0	46.0	54.0
	total	21	0	29.4	15.7	9.0	14.0	28.0	41.0	57.0
gamma-GT	Helixor	12	0	32.8	22.3	1.0	15.0	30.5	57.0	63.0
[IU/l]	Doxycycline	8	1	133.9	169.9	22.0	25.0	56.5	211.0	464.0
	total	20	1	73.3	116.2	1.0	19.5	34.0	62.5	464.0
LDH	Helixor	12	0	413.7	206.7	248.0	291.5	367.5	465.5	1010.0
[IU/l]	Doxycycline	8	1	577.0	455.6	196.0	330.5	373.5	702.5	1607.0
	total	20	1	479.0	328.5	196.0	301.5	373.5	496.5	1607.0
AP	Helixor	12	0	263.9	59.7	185.0	231.5	258.0	281.5	380.0
[IU/l]	Doxycycline	9	0	450.3	286.6	174.0	246.0	312.0	537.0	955.0
	total	21	0	343.8	209.2	174.0	233.0	266.0	364.0	955.0

Table 22: As treated population: Laboratory parameters at final investigation

n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, min = minimum, Q1 = 25^{th} centiles, median = 50^{th} centiles, Q3 = 75^{th} centiles, max = maximum.

The laboratory parameters of laboratory A were categorized as normal range and deviation. For the following explorative analysis of changes of the laboratory parameters between screening and final investigation, the McNemar test was used. No indications can be found in Table 23 or Table 24 that there were obvious changes in the laboratory parameters in the Helixor group or in the Doxycycline group between screening and final investigation. Details can be seen in Listing 12.

HELIXOR parameter	N	Screening				Final				p-value
		normal range		deviation		normal range		deviation		
		N	%	N	%	N	%	N	%	
blood sedimentation	9	1	11.1	8	88.9	1	11.1	8	88.9	1.000
hemoglobin	12	5	41.7	7	58.3	2	16.7	10	83.3	0.250
erythrocytes	12	3	25.0	9	75.0	1	8.3	11	91.7	0.500
thrombocytes	12	12	100.0	0	0.0	10	83.3	2	16.7	0.500
Total leucocytes	12	7	58.3	5	41.7	10	83.3	2	16.7	0.375
neutrocytes	12	4	33.3	8	66.7	6	50.0	6	50.0	0.688
eosinophils	12	5	41.7	7	58.3	6	50.0	6	50.0	1.000
basophils	12	9	75.0	3	25.0	10	83.3	2	16.7	1.000
monocytes	12	6	50.0	6	50.0	5	41.7	7	58.3	1.000
lymphocytes	12	3	25.0	9	75.0	2	16.7	10	83.3	1.000
creatinine	12	10	83.3	2	16.7	11	91.7	1	8.3	1.000
SGOT	12	10	83.3	2	16.7	10	83.3	2	16.7	1.000
SGPT	12	11	91.7	1	8.3	9	75.0	3	25.0	0.500
gammaGT	12	11	91.7	1	8.3	8	66.7	4	33.3	0.250
LDH	12	11	91.7	1	8.3	9	75.0	3	25.0	0.500
Alkaline Phosphatase	12	8	66.7	4	33.3	6	50.0	6	50.0	0.500

Table 23: As treated population: Helixor: Changes in laboratory parameters (laboratory A)
n = number of patients

DOXYCYCLINE parameter	N	Screening				Final				p-value
		normal range		deviation		normal range		deviation		
		N	%	N	%	N	%	N	%	
blood sedimentation	7	0	0.0	7	100.0	0	0.0	7	100.0	0.500
hemoglobin	9	4	44.4	5	55.6	3	33.3	6	66.7	1.000
erythrocytes	8	2	25.0	6	75.0	1	12.5	7	87.5	1.000
thrombocytes	9	9	100.0	0	0.0	6	66.7	3	33.3	1.000
Total leucocytes	9	8	88.9	1	11.1	8	88.9	1	11.1	1.000
neutrocytes	9	3	33.3	6	66.7	3	33.3	6	66.7	1.000
eosinophils	9	6	66.7	3	33.3	4	44.4	5	55.6	0.688
basophils	9	5	55.6	4	44.4	7	77.8	2	22.2	0.625
monocytes	9	6	66.7	3	33.3	4	44.4	5	55.6	0.625
lymphocytes	9	2	22.2	7	77.8	2	22.2	7	77.8	1.000
creatinine	9	9	100.0	0	0.0	9	100.0	0	0.0	1.000
SGOT	9	8	88.9	1	11.1	5	55.6	4	44.4	0.250
SGPT	9	4	44.4	5	55.6	3	33.3	6	66.7	1.000
gammaGT	8	5	62.5	3	37.5	4	50.0	4	50.0	1.000
LDH	8	3	37.5	5	62.5	4	50.0	4	50.0	1.000
Alkaline Phosphatase	9	6	66.7	3	33.3	4	44.4	5	55.6	0.500

Table 24: As treated population: Doxycycline: Changes in laboratory parameters (laboratory A)
n = number of patients

The changes between screening and final investigation in the laboratory parameters of pleural fluid (laboratory B) are listed in Listing 13.

3.2.3. Safety evaluation of the as treated population

Table 25 contains the mean number of adverse events in both treatment groups, for details see Listing 14. Only three patients in the Helixor group had no adverse event (patient number 6, 22, 33), all other patients had at least one adverse event; the mean number in both treatment groups was three.

	MEAN	MIN	MAX
Helixor	3.1	0	10
Doxycycline	2.6	1	6

Table 25: As treated population: Mean number of adverse events
mean, min = minimum, max = maximum

Table 26 illustrates the incidence of adverse events in both treatment groups as well as the severity. In total there were 53 adverse events in the Helixor group and 41 in the Doxycycline group.

	Helixor							Doxycycline						
		light		moderate		severe			light		moderate		severe	
	N	N	%	N	%	N	%	N	N	%	N	%	N	%
BRUSTKORB BRENNSCHMERZ	6			1	16.7	5	83.3	8			4	50.0	4	50.0
DYSPNOE	6	1	16.7	1	16.7	4	66.7	3					3	100.0
FIEBER	19	8	42.1	8	42.1	3	15.8	6	2	33.3	2	33.3	2	33.3
HAEMATEMESIS BEI MAGENULKUS	1			1	100.0			0						
HUSTEN	0							1						
HYPOTENSION	1					1	100.0	0						
KOERPERGEFUEHL-VERAENDERUNG	0							1	1	100.0				
NAUSEA	1			1	100.0			0						
OBERBAUCH-BESCHWERDEN	0							1	1	100.0				
PLEURASCHMERZ	3			2	66.7	1	33.3	0						
SCHMERZ	11	6	54.5	1	9.1	4	36.4	9	1	11.1			8	88.9
SCHMERZ LOKAL	3	1	33.3	2	66.7			0						
SCHMERZEN BRUSTKORB	2	2	100.0					12			3	25.0	9	75.0

Table 26: As treated population: Adverse events
n = number of adverse events

This analysis (Table 25, Table 26) may be biased by the way of documenting an adverse event was done. For example: One patient (Helixor: patient number 1) had the adverse event “fever”, the duration of this adverse event was eight days (Listing 14). Another patient (Helixor: patient number 14) had the first adverse event “fever” on October 5th, the second adverse event “fever” on October 6th, the third one on October 7th and the last one on October 8th (Listing 14). If these four adverse events are really four different adverse events, or if it is one adverse event with the duration of four days, cannot be judged at the time of writing this report.

The adverse event “pain” was documented in different categories: “Brustkorb Brennschmerz”, “Pleuraschmerz”, “Schmerz”, “Schmerz local”, “Schmerzen Brustkorb”. Listing 14 shows that only two adverse events out of the category “Schmerzen Brustkorb” are not connected to the treatment. Both adverse events took place in the Doxycycline group. For all other adverse events in the categories named above the connection to the treatment was sure, probable, possible or not documented. For details see Listing 14.

The number of serious adverse events in the Helixor group was five (Helixor, patient number 3, 4, 10, 19, 24) while in the Doxycycline group there were three serious adverse events (patient number 17, 23, 30). The degree of severity was always “death” (Table 27). All patients suffered from dyspnea except one (Helixor, patient number 19). For this patient death was caused by hypotension due to hematemesis. In the Helixor group the five serious adverse events had taken place one or two days after the instillation of Helixor. In the Doxycycline group one serious adverse event followed a medication of Doxycycline (patient number 17), and two started before the first dose of Doxycycline (patient number 23, 30). The cancer diseases of the patient caused all eight serious adverse events. None of them was connected to the instillation of the medications. For details see Listing 14.

Group	Pat	symptom	last medication	begin of SAE	instillation	degree of severity	relation with therapy
Helixor	3	Dyspnea	25/05/97	26/05/97	5	death	none
	4	Dyspnea	22/07/97	23/07/97	7	death	none
	10	Dyspnea	11/02/98	12/02/98	3	death	none
	19	Hypotension due to Hematemesis	12/01/99	14/01/99	7	death	none
	24	Dyspnea, pain	10/04/99	10/04/99	6	death	none
Doxycycline	17	Dyspnea (due to general weakness)	19/12/98	02/01/99	2	death	none
	23	Dyspnoea		01/03/99		death	none
	30	Dyspnea and weakness		04/09/99		death	none

Table 27: As treated population: Serious adverse events

3.3. As treated analysis of the efficacy of Mistletoe preparation

The analysis was done using the Chi squared test for trend. Table 28 shows the efficacy parameters in both treatment groups. There could not be found a significant difference.

		Helixor N=17		Doxycycline N=16		total N=33		p-value
		N	%	N	%	N	%	
As treated population	missing	5		7		12	.	
	CR	11	91.7	5	55.6	16	76.2	0.116
	PR	0	0.0	2	22.2	2	9.5	
	NC	1	8.3	2	22.2	3	14.3	

Table 28: Efficacy, analysed for the as treated population
n = number of patients, CR=complete remission, PR=partial response, NC=no change

In the Helixor group containing 17 patients, an efficacy classified as CR could be seen eleven times, and the category NC could be observed once. It is to remember, that for five patients no efficacy was available, because these five patients died prior study termination. In the even smaller Doxycycline group out of 16 patients, seven missings occurred, because three patients died prior study termination, three patients went to an other hospital for further treatment and for one patient the treatment was terminated by the treating physician.

The remainder divided into five times CR, two times PR and two times NC. Interpretation should be done really carefully because of the small case-numbers.

The problem of regression towards the mean should be mentioned at this point [Bland J.M., Altman D.G., 1994]. One patient could have just a small pleural effusion and could not get better very much (for example patient 15, see Figure 26). So that patient would be valued as no change. Another one with a pleural effusion left at the end of trial would be valued as PR because at the beginning he felt even worse (patient number 16, see Figure 27). In Table 29 it can be seen that the range of the parameter “effusion in ml before the first instillation” was wide in both treatment groups. So in the analysis of efficacy, the effect caused by regression towards the mean and the treatment effect may overlap each other.

	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	P-VALUE
effusion [ml]	Helixor	17	0	221.4	334.8	3.5	30.0	70.0	300.0	1250.0	0.732
	Doxycycline	16	0	184.9	222.4	5.0	40.0	100.0	250.0	700.0	.
	total	33	0	203.7	282.1	3.5	30.0	100.0	300.0	1250.0	.

Table 29: As treated population: Effusion in ml before the first instillation
n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, min = minimum, Q1 = 25^{th} centiles, median = 50^{th} centiles, Q3 = 75^{th} centiles, max = maximum, p-value.

An examination for a monotonous trend between the efficacy and the parameter “months since diagnosis” was done. The results can be seen on frequency tables (Table 30, Table 31) for each

treatment group. But there was no effect, neither for the Helixor group nor for the Doxycycline group.

months since diagnosis	efficacy N=12			
	CR	PR	NC	total
0	4	0	0	4
1	3	0	0	3
8	1	0	0	1
10	1	0	0	1
18	0	0	1	1
111	1	0	0	1
192	1	0	0	1

Table 30: As treated population: Helixor: Fequency table of efficacy and months since diagnosis
n = number of patients, CR=complete remission, PR=partial response, NC=no change

months since diagnosis	efficacy N=9			
	CR	PR	NC	total
0	2	1	1	4
1	1	1	0	2
3	1	0	0	1
7	0	0	1	1
24	1	0	0	1

Table 31: As treated population: Doxycycline: Fequency table of efficacy and months since diagnosis
n = number of patients, CR=complete remission, PR=partial response, NC=no change

3.4. Conclusion of the analysis of the as treated population

The aim of this study was to test if the mistletoe preparation Helixor induces fewer side effects than Doxycycline and if Helixor reaches the same or better efficacy of pleurodesis than Doxycycline.

33 patients with malignant pleural effusion were enrolled in this trial. There should have been 40 patients enrolled, but for reasons of trial management this could not be realized. Two patients violated inclusion criteria. It was decided to keep these patients in the as treated population. Once, the treatment was done mistakenly, so patient number 4, who should get Doxycycline, got Helixor and therefore patient number 5 got Helixor instead of Doxycycline. In the as treated population the patients were analysed by their treatment group.

From the beginning of the trial there were a few obvious differences between the two treatment groups. In the Doxycycline group there were more smokers (Table 5). In the Helixor group there were only patients with current tumor stages T4 N0–3 M1 except one with the tumor stage TXN3M1, while in the Doxycycline group there were current tumor stages from T1-4, N0-3/X M1 (Table 9).

After enrolling a patient in the trial, the medical therapy was not started immediately. The time (and frequency) of intrapleural instillation of Helixor or Doxycycline was decided by the treating physician. So the time interval before starting the therapy was inharmonious for all patients. This can be seen in the graphics of patients' history (Figure 5 till Figure 37). Also, the parameter „effusion in ml before the first instillation" showed a wide range in both treatment groups (Table 29). So a comparison of time and severity in suffering from pleural effusion before starting the therapy was not analysed. There were no documentations of patients' management decisions and a scheme could not be identified.

The analysis of the tolerability was done by comparing the tolerance rates of Helixor and Doxycycline for no pain, no burning and no fever. If "no side effect" was defined as "severity 0",

the tolerance rate for no pain in the Helixor group was 0.79 [0.64 ; 0.95] with a significant difference of 0.65 [0.40 ; 0.90] to the Doxycycline group. If “no relevant side effect” was defined as “severity 0 or 1”, the tolerance rate of no pain in the Helixor group then was 0.94 [0.85 ; 1.03] with a significant difference of 0.75 [0.49 ; 1.00] to the Doxycycline group. This result contains the information for the probability to receive one instillation without any pain. In the Helixor group this probability is 0.79 if “no side effect“ is defined as “severity 0”. The probability for a second or third painless instillation can be calculated. Another advantage for Helixor could be identified as a significant difference of 0.33 [0.05 ; 0.60] for no burning (Table 46).
If the global tolerance rate (number of patients without side effects / number of all patients) for both groups were compared, an obvious advantage for the Helixor group could be seen for the side effect pain (Table 17, Table 18). Also, the mean severity of the side effect pain showed a significant lower level for the Helixor group (Table 19).

The number of adverse events was 53 for the Helixor group, containing five serious adverse events. In the Doxycycline group 41 adverse events were counted, including three serious adverse events (Table 26). All eight serious adverse events were deaths and caused by the cancer disease. None was connected to a medical instillation (Table 27).

The analysis of the efficacy showed no significant difference between the two treatment groups (Table 28).

4. Analysis of the ITT population

Here the term “group” means the randomisation group, independent of the treatment. So the Helixor group consists of 17 patients, who were randomised for Helixor, including the one who received Doxycycline (patient number 5). Likewise in the Doxycycline group all 16 patients were randomised for Doxycycline, including the one who was treated with Helixor (patient number 4).

4.1. ITT Analysis of the trial population

33 patients were enrolled in the trial. Organizational reasons prevented from including the planned 40 patients. Of the 33 patients, 17 patients were randomised to the Helixor group, 16 to the Doxycycline group. The randomisation was done by a randomisation list. Two patients were not treated as allocated: patient number 4 got Helixor instead of Doxycycline, therefore the next patient (patient number 5) got Doxycycline instead of Helixor. One patient in the Doxycycline group did not receive the second Doxycycline instillation as allocated, because his treating physician decided that Doxycycline had failed and he switched to another therapeutical modality. The progress of patients through the trial shows Table 32.

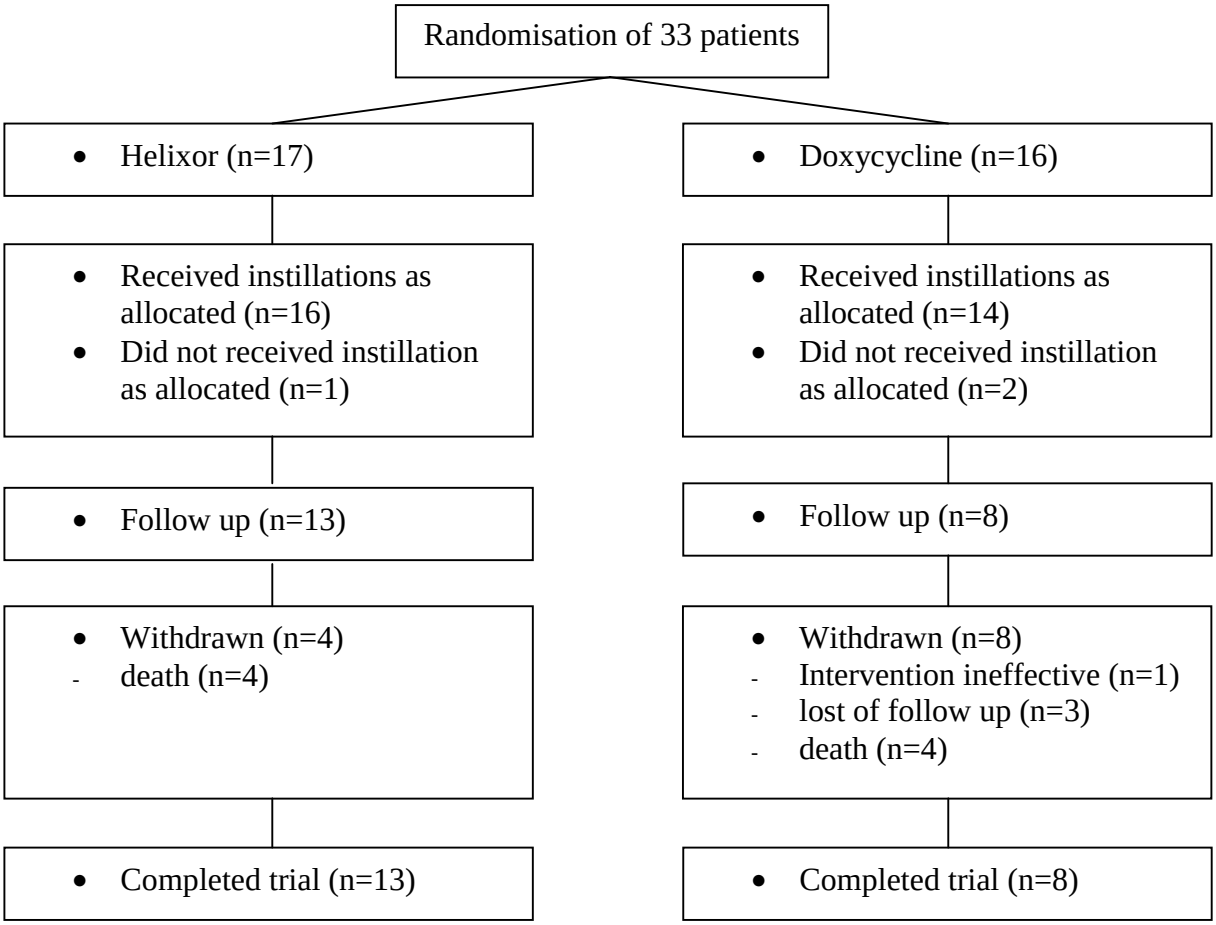

Table 32: ITT population: Progress of patients through the trial
n = number of patients

4.1.1. Violations of inclusion and exclusion criteria in the ITT population

One patient was marked not to be suitable for the trial, because he did not fulfill the inclusion criteria; his thrombocytes were 95 000/µl instead of 100 000/µl (Helixor, patient number 24). By screening the data there was another patient identified, who failed inclusion criteria, his hemoglobin was 9.8g/l instead of 10g/l (Doxycycline, patient number 20). None of these violations was classified to be relevant for the success of pleurodesis or the incidences or intensity of side effects. Therefore, all patients stayed in the ITT population.

4.1.2. Demography of the ITT population

The demography of the trial population is summarized in Table 33 and Table 34. As the explorative analysis shows, there seems to be no obvious difference between the Helixor and Doxycycline group except of age and smoking. There were more young patients (p-value = 0.009) and more smokers (p-value = 0.039) in the Doxycycline group. For details see Listing 1.

	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
age	Helixor	17	0	60.4	9.4	42.0	54.0	59.0	68.0	76.0	0.009
[years]	Doxycycline	16	0	49.4	12.2	33.0	41.0	46.0	61.0	71.0	
	total	33	0	55.0	12.1	33.0	46.0	58.0	64.0	76.0	

Table 33: ITT population: Demographic characteristics I
n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, min = minimum, Q1 = 25th centiles, median = 50th centiles, Q3 = 75th centiles, max = maximum, p-value.

		Helixor N=17		Doxycycline N=16		total N=33		p-value
		N	%	N	%	N	%	
sex	female	9	52.9	8	50.0	17	51.5	1.000
	male	8	47.1	8	50.0	16	48.5	
alcohol	no	10	58.8	10	62.5	20	60.6	0.721
	rarely	7	41.2	5	31.3	12	36.4	
	regulary	0	0.0	1	6.3	1	3.0	
smoker	no	16	94.1	10	62.5	26	78.8	0.039
	yes	1	5.9	6	37.5	7	21.2	
profession		1	5.9	1	6.3	2	6.1	0.891
	DENTIST (RETIRED)	1	5.9	0	0.0	1	3.0	
	FARMER	1	5.9	1	6.3	2	6.1	
	HOUSEWIFE	7	41.2	6	37.5	13	39.4	
	NONE	5	29.4	2	12.5	7	21.2	
	NOT EMPLOYED	0	0.0	1	6.3	1	3.0	
	PAID EMPLOYEE	0	0.0	1	6.3	1	3.0	
	PLUMMER (PLUMBER*)	0	0.0	1	6.3	1	3.0	
	SALARY MAN	2	11.8	2	12.5	4	12.1	
	SALES MERCHANT	0	0.0	1	6.3	1	3.0	

Table 34: ITT population: Demographic characteristics II
n = number of patients
* in the original data “plummer” was noted as profession, but probably “plumber” was meant.

4.1.3. Characteristics of physical condition of the ITT population

The characteristics of physical condition are to be seen in Table 35, Table 36 and Table 37. No differences between the two groups are obvious. Only the parameter pulse has a higher level in the Doxycycline group (p-value = 0.041). For details see Listing 2, Listing 4, Listing 5.

	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
height [cm]	Helixor	17	0	161.3	8.6	143.0	156.0	160.0	168.0	172.0	0.871
	Doxycycline	16	0	162.5	7.0	149.0	156.5	164.5	169.0	171.0	
	total	33	0	161.9	7.8	143.0	156.0	164.0	168.0	172.0	
weight [kg]	Helixor	17	0	56.7	10.7	39.8	52.0	54.9	62.0	80.0	0.540
	Doxycycline	16	0	57.5	8.8	40.0	52.5	56.5	64.5	77.0	
	total	33	0	57.1	9.7	39.8	52.0	55.0	63.1	80.0	
temperature [°C]	Helixor	17	0	36.5	0.3	36.0	36.3	36.5	36.7	37.0	0.123
	Doxycycline	16	0	36.6	0.4	36.0	36.4	36.8	36.9	37.2	
	total	33	0	36.6	0.3	36.0	36.4	36.6	36.8	37.2	
pulse [/min]	Helixor	17	0	81.1	9.5	60.0	76.0	80.0	88.0	100.0	0.041
	Doxycycline	16	0	89.3	13.2	72.0	84.0	88.0	92.0	132.0	
	total	33	0	85.1	12.0	60.0	78.0	85.0	90.0	132.0	
blood pressure systolic [mm Hg]	Helixor	17	0	116.5	16.2	90.0	110.0	120.0	130.0	140.0	0.463
	Doxycycline	16	0	113.0	14.2	90.0	100.0	110.0	120.0	140.0	
	total	33	0	114.8	15.1	90.0	100.0	110.0	120.0	140.0	
blood pressure diastolic [mm Hg]	Helixor	17	0	71.2	11.1	50.0	70.0	70.0	80.0	100.0	0.954
	Doxycycline	16	0	71.3	8.9	60.0	65.0	70.0	80.0	90.0	
	total	33	0	71.2	9.9	50.0	70.0	70.0	80.0	100.0	

Table 35: ITT population: Characteristics of physical conditions I

n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, min = minimum, Q1 = 25th centiles, median = 50th centiles, Q3 = 75th centiles, max = maximum, p-value.

		Helixor N=17		Doxycycline N=16		total N=33		p-value
		N	%	N	%	N	%	
Karnofsky Index [%]	50 %	1	5.9	1	6.3	2	6.1	0.439
	60 %	5	29.4	7	43.8	12	36.4	
	70 %	5	29.4	1	6.3	6	18.2	
	80 %	1	5.9	3	18.8	4	12.1	
	90 %	4	23.5	4	25.0	8	24.2	
	100 %	1	5.9	0	0.0	1	3.0	
additional disease	no	9	52.9	11	68.8	20	60.6	0.481
	yes	8	47.1	5	31.3	13	39.4	

Table 36: ITT population: Characteristics of physical conditions II

n = number of patients

		Helixor N=17		Doxycycline N=16		total N=33		p-value
		N	%	N	%	N	%	
nutritional status	normal	14	82.4	13	81.3	27	81.8	0.344
	not relevant	3	17.6	1	6.3	4	12.1	
	relevant	0	0.0	2	12.5	2	6.1	
skin	normal	17	100.0	15	93.8	32	97.0	0.485
	relevant	0	0.0	1	6.3	1	3.0	
edemas	normal	17	100.0	14	87.5	31	93.9	0.227
	not relevant	0	0.0	1	6.3	1	3.0	
	relevant	0	0.0	1	6.3	1	3.0	
lymphnodes	normal	16	94.1	16	100.0	32	97.0	1.000
	relevant	1	5.9	0	0.0	1	3.0	
head	normal	17	100.0	15	93.8	32	97.0	0.485
	relevant	0	0.0	1	6.3	1	3.0	
mucous membrane of mouth	normal	17	100.0	16	100.0	33	100.0	
thyroid	normal	16	94.1	16	100.0	32	97.0	1.000
	not relevant	1	5.9	0	0.0	1	3.0	
respiratory tract	normal	1	5.9	0	0.0	1	3.0	1.000
	not relevant	2	11.8	1	6.3	3	9.1	
	relevant	14	82.4	15	93.8	29	87.9	
heart	normal	16	94.1	16	100.0	32	97.0	1.000
	not relevant	1	5.9	0	0.0	1	3.0	
breasts	normal	14	82.4	14	87.5	28	84.8	1.000
	relevant	3	17.6	2	12.5	5	15.2	
abdomen	normal	15	88.2	15	93.8	30	90.9	1.000
	not relevant	1	5.9	0	0.0	1	3.0	
	relevant	1	5.9	1	6.3	2	6.1	
kidney region	normal	17	100.0	16	100.0	33	100.0	
spine	normal	17	100.0	15	93.8	32	97.0	0.485
	relevant	0	0.0	1	6.3	1	3.0	
extremities	normal	16	94.1	15	93.8	31	93.9	1.000
	relevant	1	5.9	1	6.3	2	6.1	
nervous system	normal	17	100.0	16	100.0	33	100.0	
urogenital system	normal	17	100.0	15	93.8	32	97.0	0.485
	relevant	0	0.0	1	6.3	1	3.0	
other		2	11.8	3	18.8	5	15.2	1.000
	normal	14	82.4	13	81.3	27	81.8	
	relevant	1	5.9	0	0.0	1	3.0	

Table 37: ITT population: Physical examinations
n = number of patients

In Listing 3, the kind of additional diseases before screening can be seen for both treatment groups.

4.1.4. Extent and history of malignancy of the ITT population

The following Table 38 describes the extent of malignancy. As the explorative analysis shows, there seem to be differences for current tumor stage (p-value = 0.030) between the Helixor and the Doxycycline group. In the analysis of tumor stage, one patient had to be excluded from each treatment group. In the Helixor group, the tumor stage “TXN3M1” (patient number 6) was excluded from analysis and in the Doxycycline group the tumor stage “T4NXM1” (patient number 25) was excluded. No difference was seen neither for number of metastases nor for occurred combinations of localization of distant metastases. All patients suffered from pleural effusion.

		Helixor N=17		Doxycycline N=16		Total N=33		p-value
		N	%	N	%	N	%	
tumor stage	T1 N3 M1	0	0.0	1	6.7	1	3.2	0.030
	T2 N1 M1	0	0.0	1	6.7	1	3.2	
	T3 N0 M1	0	0.0	1	6.7	1	3.2	
	T3 N2 M1	0	0.0	1	6.7	1	3.2	
	T4 N0 M1	5	31.3	0	0.0	5	16.1	
	T4 N1 M1	4	25.0	1	6.7	5	16.1	
	T4 N2 M1	5	31.3	4	26.7	9	29.0	
	T4 N3 M1	2	12.5	6	40.0	8	25.8	
number of metastases	1	11	64.7	9	56.3	20	60.6	0.820
	2	4	23.5	5	31.3	9	27.3	
	3	1	5.9	2	12.5	3	9.1	
	4	1	5.9	0	.	1	3.0	
localization of metastasis	pleura	11	64.7	9	56.3	20	60.6	0.779
	pleura bones	2	11.8	4	25.0	6	18.2	
	pleura bones liver	0	0.0	1	6.3	1	3.0	
	pleura bones liver brain	1	5.9	0	0.0	1	3.0	
	pleura liver	1	5.9	1	6.3	2	6.1	
	pleura liver other	0	0.0	1	6.3	1	3.0	
	pleura lung bones	1	5.9	0	0.0	1	3.0	
	pleura lymphnodes	1	5.9	0	0.0	1	3.0	

Table 38: ITT population: Extent of malignancy
n = number of patients

The history of malignancy can be summarized as followed. In the Helixor group there were twelve patients who suffer from any kind of lung cancer (patient number 1, 5, 9, 10, 11, 13, 14, 19, 22, 24, 26, 33), three with the diagnosis breast cancer (patient number 8, 29, 32), one with a stomach cancer (patient number 3) and one with a cancer of unknown origin (patient number 6). In the Doxycycline group there were eleven lung-cancer-patients (patient number 2, 7, 16, 18, 20, 21, 23, 27, 28, 30, 31), two breast-cancer-patients (patient number 4, 12), one with a rectal tumor (patient number 17), one with the diagnosis cervix cancer (patient number 25), and one with the diagnosis adenocarcinoma of bartholin gland (patient number 15).
The time of diagnosis of primary tumor was between 1983 and 1999 for the Helixor group and between 1993 and 1999 for the Doxycycline group. The mean time since diagnosis was 21 months in the Helixor group and eight months in the Doxycycline group, the median in both groups was one month. The minimum in both treatment groups was zero, i.e. the time of diagnosis and the beginning of the therapy was in the same month (Table 39).

	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	P-VALUE
months since diagnosis	Helixor	17	0	21.4	51.3	0.0	0.0	1.0	10.0	192.0	0.811
	Doxycycline	16	0	8.1	12.7	0.0	0.0	1.0	12.5	44.0	
	total	33	0	14.9	37.9	0.0	0.0	1.0	11.0	192.0	

Table 39: ITT population: Time since diagnosis of primary tumor
n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, min = minimum, Q1 = 25^{th} centiles, median = 50^{th} centiles, Q3 = 75^{th} centiles, max = maximum, p-value.

In both treatment groups there were seven patients with no previous treatment (Helixor, patient number 1, 6, 11, 13, 14, 22, 33; Doxycycline, patient number 2, 7, 20, 21, 27, 28, 31), two patients with a previous operation (Helixor, patient number 3, 29; Doxycycline, patient number 12, 17) , two patients with other previous treatments such as chemo-, hormone-, immuno- or other therapy (Helixor, patient number 9, 19; Doxycycline, patient number 16, 18), one patient with the combination “operation, radiotherapy and others” (Helixor, patient number 32; Doxycycline, patient number 4). In the Helixor group there were also three patients with the combination “radiotherapy and others” (Helixor, patient number 10, 24, 26) while in the Doxycycline group there were four patients (Doxycycline, patient number 15, 23, 25, 30) with this combination. The Helixor group included also two patients with the combination “operation and other treatments” (Helixor, patient number 5, 8).

For details of extent and history of malignancy see Listing 6.

4.1.5. Course of the illness of the ITT population

In the Appendix (Figure 5 till Figure 37) there is one figure for each patient with the following information:

- The legend informs about the treatment group and the patient number.
- The curve in the diagram shows the course of the patient's effusions of pleural fluid (volume in ml).
- The needles represent the instillations with Helixor or Doxycycline.
- One the second y-axis all results can be seen:
  - o The symbol " o " represents the efficacy of the treatment, ranged from CR to PD.
  - \+ The " + " marks the finding in the patients x-rays, as there is free, pleural effusion and unchanged finding.
  - * The " * " shows the reason for the end of trial. If there was not any trial plan violation during the trial, the end of trial was marked as a successful one. A trial plan violation was noted as failure. If the patient changed the location under treatment the end of trial was called "in other location". At last the reason for the end of trial could be the patient's death.

For details of effusions, instillations and x-rays see Listing 7 and Listing 8.

The time of intrapleural instillations was not specified and was decided upon by the treating physician. Some patients did have previous effusions of pleural fluid or previous x-rays with finding of pleural effusion. So the time suffering from pleural effusion before starting the therapy was not equal for all patients. Also the amount of pleural effusion by starting the therapy was quite different. There was no definition of a minimum or maximum amount of pleural effusion in the trial plan.

The patients treated with Helixor could get one up to seven or even more instillations during the trial depending on the decision of the treating physician. In the Doxycycline group there were one or two instillations possible according to the trial plan. The dosing of Helixor and Doxycycline was given according to the trial plan. The average number of instillations was six in the Helixor group and two in the Doxycycline group (Table 40).

	GROUP	N	NMISS	MEAN	SDEV	STD ERROR
number of instillations	Helixor	17	0	6.26	2.05	0.49
	Doxycycline	16	0	1.69	1.49	0.37

Table 40: ITT population: Average number of instillations
n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, std error = standard error.

Eleven patients of the Helixor group (patient number 1, 6, 8, 9, 11, 13, 14, 19, 22, 26, 29) got seven instillations, two patients (patient number 33, 24) got more then seven (1x8 and 1x9 instillations) and four patients (patient number 5, 10, 32, 3) got less (1x1, 2x3, 1x5 instillations). The patient (patient number 5) with one instillation is the one who was randomised wrongly and who was treated with Doxycycline instead of Helixor.
In the Doxycycline group ten patients (patient number 2, 12, 15, 16, 18, 20, 21, 23, 25, 28) got one instillation and five patients (patient number 7, 17, 27, 30, 31) got two instillations. The one (patient number 4) who received seven instillations is the one randomised wrongly and who was treated with Helixor instead of Doxycycline. Listing 9 and Listing 10 contain a listing of concomitant medication for pain and for other indications in each treatment group sorted by investigation.

4.1.6. Final investigation of the ITT population

Table 41 contains the reasons for the end of the trial sorted by the number of instillations. The first patient in the Helixor group and the last patient in the Doxycycline group are both marked with a star. These two patients are the ones who were treated mistakenly. So the one in the Helixor group (patient number 5) got one instillation of Doxycycline and the one in the Doxycycline group (patient number 4) got seven instillations of Helixor.

Helixor		Doxycycline	
17 patients		16 patients	
1* instillation		1 instillation	
successful end according WHO	1	successful end	6
		failure	1
		in another hospital under treatment	2
		death	1
		2 instillations	
		successful end	2
		in another hospital under treatment	1
		death	2
3 instillations			
successful end	1		
death	1		
5 instillations			
death	1		
7 instillations		7* instillations	
successful end	9	death	1
failure	1		
death	1		
8 instillations			
successful end	1		
9 instillations			
death	1		

Table 41: ITT population: Number of instillations and reason for end of trial.
The "*" marks the two patients treated by mistake.

The end of the trial in the Helixor group was twelve times successful (no trial plan violation for patient number 1, 5, 6, 8, 9, 11, 13, 14, 26, 29, 32, 33), and once failed. This trial plan violation for patient number 22 was a final investigation after nearly 6 months instead of 4 weeks. Four patients died in the Helixor group. Three of these four cases were connected to cancer disease (patient number 3, 10, 24), one patient (patient number 19) died because of gastric ulcer bleeding.
The Doxycycline group ended eight times successful (patient number 12, 15, 16, 18, 21, 27, 28, 31), one failure occurred. For patient number 25 the treating physician concluded that the pleurodesis had failed so he decided to switch to another therapeutical modality. Conservative management using frequent puncture was preferred instead of giving the second dose of Doxycycline. Three patients were treated in another location (patient number 2, 7, 20) and four patients died (patient number 4, 17, 23, 30). All four deaths were connected to the cancer disease.

It was decided that the two patients with a trial plan violation (Helixor, patient number 22, Doxycycline, patient number 25) should stay in the ITT population.

Figure 3 and Figure 4 show the time on study for each patient. One patient in the Helixor group (patient number 22) got his last examination (follow up) after 180 days instead of 28 days. One

patient in the Doxycycline group (patient number 20) moved to another hospital. Several telephone interviews gave information about the patient's physical condition; the last telephone interview was 329 days after the initial examination. The mean time on study in the Helixor group was 40 days and in the Doxycycline group it was 46 days (Table 42).

	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	P-VALUE
time on study	Helixor	17	0	40.2	39.0	7.0	30.0	36.0	41.0	180.0	0.588
(days)	Doxycycline	16	0	46.0	76.4	11.0	13.0	31.5	37.0	329.0	
	total	33	0	43.0	59.2	7.0	14.0	34.0	41.0	329.0	

Table 42: ITT population: Time on study

n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, min = minimum, Q1 = 25th centiles, median = 50th centiles, Q3 = 75th centiles, max = maximum, p-value.

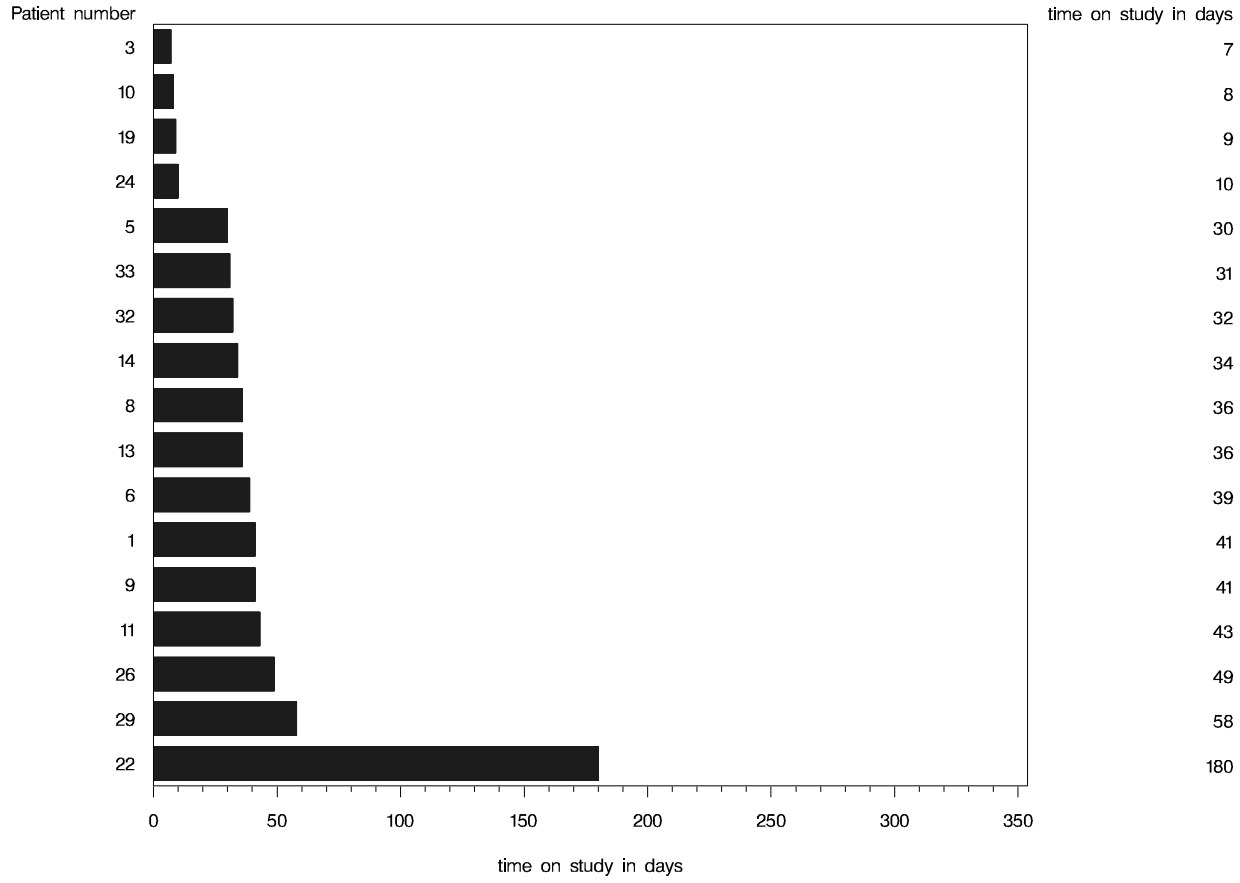

Figure 3: ITT population: Helixor: Time on study

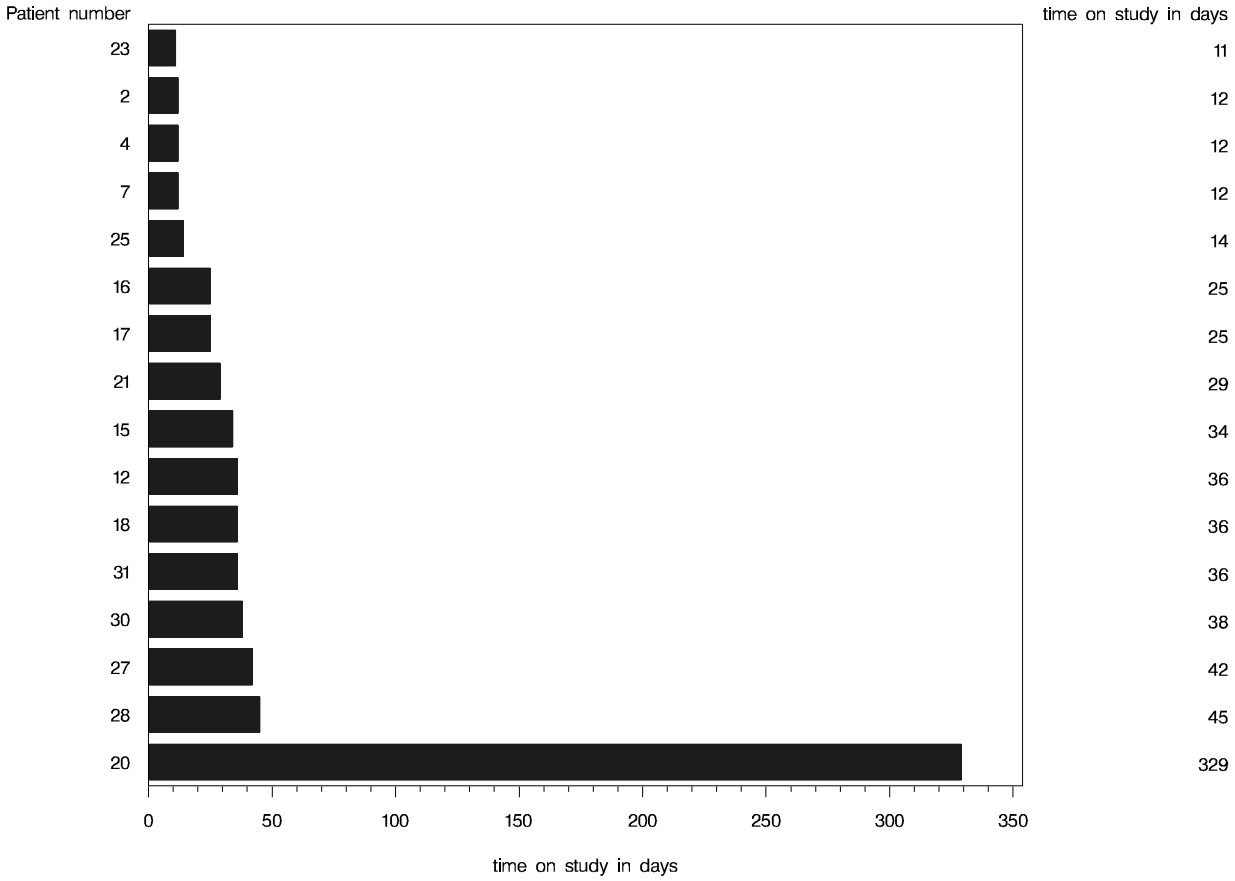

Figure 4: ITT population: Doxycycline: Time on study

Table 43 contains changes in weight, blood pressure systolic and diastolic, pulse, temperature and Karnofsky Index for both treatment groups. The paired t-test was used except for the analysis of the changes of the Karnofsky Index. There the signed rank sum test was used. No differences are obvious except of weight. In both treatment groups, the patients lost weight.

	Helixor					Doxycycline				
	N	**mean screening**	**mean final**	**mean difference**	**p-value**	**N**	**mean screening**	**mean final**	**mean difference**	**p-value**
blood pressure systolic [mm Hg]	13	116.2	114.6	-1.5	0.636	8	116.0	115.0	-1.0	0.821
blood pressure diastolic [mm Hg]	13	71.5	73.1	1.5	0.502	8	72.5	72.5	0.0	1.000
pulse [/min]	13	80.3	81.9	1.6	0.427	8	87.8	86.4	-1.4	0.775
temperature [°C]	13	36.5	36.7	0.2	0.207	8	36.6	36.7	0.1	0.749
weight [kg]	12	58.6	57.7	-0.9	0.035	6	61.9	59.2	-2.7	0.049

	Helixor					Doxycycline				
	N	**median screening**	**median final**	**median difference**	**p-value**	**N**	**median screening**	**median final**	**median difference**	**p-value**
Karnofsky Index [%]	13	70	80	0	0.688	8	75	70	0	0.750

Table 43: ITT population: Changes between screening and final investigation
n = number of patients

To see if there is a difference between the mean differences between both treatment groups, the unpaired t-test was used for the parameters blood pressure systolic, blood pressure diastolic, pulse,

temperature and weight. The results are presented in Table 44, no differences are obvious. The Mann-Whitney-Wilcoxon test was used for the same analysis of the parameter Karnofsky Index, again no difference could be found (p=0.440).

	mean difference Helixor	mean difference Doxycycline	mean difference between groups	confidence interval [95% CI]	p-value
blood pressure systolic [mm Hg]	-1.5	-1.0	0.5	[-10.4 - 11.5]	0.919
blood pressure diastolic [mm Hg]	1.5	0.0	-1.5	[-8.9 - 5.8]	0.667
pulse [/min]	1.6	-1.4	-3.0	[-12.1 - 6.2]	0.565
temperature [°C]	0.2	0.1	-0.1	[-0.6 - 0.4]	0.680
weight [kg]	-0.9	-2.7	-1.8	[-3.7 - 0.1]	0.159

Table 44: ITT population: Comparison of the differences between the treatment groups
[95% CI] = 95% confidence interval

4.2. Analysis of the tolerability of Mistletoe preparation

4.2.1. Side effects

The following analysis was performed on the ITT and on the as treated population.
In both treatment groups the tolerance rates (number of instillations without side effects / number of all instillations) for no pain, no burning and no fever were calculated. There was a significant difference for pain between the two treatment groups in the ITT population. The difference was 0.63 [0.42 ; 0.85] if the cut point was chosen as "severity 0" = "no side effect" (p-value = < 0.0001) and the difference reached 0.51 [0.14 ; 0.89] if the cut point was chosen as "severity 0 and 1" = "no relevant side effect" (p-value = 0.007) (Table 45).
The probability to receive one instillation of Helixor without any pain (if the first definition is used "severity 0" = "no side effect") was 0.82, so the probability to receive the second instillation again without any pain is 0.67 (= 0.82^2), for the third painless instillation the probability can be calculated to 0.55 (= 0.82^3).
For the as treated population the difference for pain was 0.65 [0.40 ; 0.90], (p-value < 0.0001) for the first cut point and 0.75 [0.49 ; 1.00], (p-value < 0.0001) for cut point two. There was also a significant difference for burning of 0.33 [0.05 ; 0.60], (p-value = 0.020) for both cut points in the as treated population (Table 46).

side effect	severity	Helixor tolerance rate [95% CI] n=106	Doxycycline tolerance rate [95% CI] n=27	difference	confidence interval [95% CI]	p-value
pain	1-4	0.82 [0.67 ; 0.97]	0.19 [0.03 ; 0.34]	0.63	[0.42 ; 0.85]	< 0.0001
	2-4	0.92 [0.83 ; 1.03]	0.41 [0.04 ; 0.77]	0.51	[0.14 ; 0.89]	0.007
burning	1-4	0.93 [0.84 ; 1.03]	0.74 [0.50 ; 0.98]	0.19	[-0.07 ; 0.46]	0.149
	2-4	0.93 [0.84 ; 1.03]	0.74 [0.50 ; 0.98]	0.19	[-0.07 ; 0.46]	0.149
fever	1-4	0.78 [0.63 ; 0.93]	0.67 [0.46 ; 0.88]	0.11	[-0.14 ; 0.37]	0.376
	2-4	0.89 [0.80 ; 0.97]	0.85 [0.70 ; 1.01]	0.04	[-0.14 ; 0.21]	0.696

Table 45: Tolerance rates for the ITT population
[95% CI] = 95% confidence interval, n=number of instillations, (*this analysis was done by using s-plus)

side effect	severity	Helixor tolerance rate [95% CI] n=112	Doxycycline tolerance rate [95% CI] n=21	difference	confidence interval [95% CI]	p-value
pain	1-4	0.79 [0.64 ; 0.95]	0.14 [-0.05 ; 0.33]	0.65	[0.40 ; 0.90]	< 0.0001
	2-4	0.94 [0.85 ; 1.03]	0.19 [-0.05 ; 0.43]	0.75	[0.49 ; 1.00]	< 0.0001
burning	1-4	0.95 [0.86 ; 1.04]	0.62 [0.36 ; 0.88]	0.33	[0.05 ; 0.60]	0.020
	2-4	0.95 [0.86 ; 1.04]	0.62 [0.36 ; 0.88]	0.33	[0.05 ; 0.60]	0.020
fever	1-4	0.77 [0.62 ; 0.92]	0.71 [0.49 ; 0.94]	0.06	[-0.21 ; 0.32]	0.696
	2-4	0.89 [0.82 ; 0.97]	0.81 [0.60 ; 1.02]	0.08	[-0-14 ; 0.31]	0.470

Table 46: Tolerance rates for the as treated population
[95% CI] = 95% confidence interval, n=number of instillations, (*this analysis was done by using s-plus)

A global tolerance rate (number of patients without side effects / number of all patients) is given for each treatment group in Table 47. In Table 48, the global tolerance rate was defined as number of patients without any relevant side effects (number of patients with none or light side effects / number of all patients). Using Fisher´s exact test, a difference between the treatment groups is to be seen for pain.

	severity of the side effect	Helixor N=17		Doxycycline N=16		total N=33		p-value
		N	%	N	%	N	%	
pain	none	11	64.7	1	6.3	12	36.4	0.001
	light-unacceptable	6	35.3	15	93.8	21	63.6	.
burning	none	14	82.4	11	68.8	25	75.8	0.438
	light-unacceptable	3	17.6	5	31.3	8	24.2	.
fever	none	9	52.9	11	68.8	20	60.6	0.481
	light-unacceptable	8	47.1	5	31.3	13	39.4	.

Table 47: Global tolerance rates for the ITT population, success = no side effect
n=number of patients

	severity of the side effect	Helixor N=17		Doxycycline N=16		total N=33		p-value
		N	%	N	%	N	%	
pain	none-light	14	82.4	3	18.8	17	51.5	< 0.001
	moderate-unacceptable	3	17.6	13	81.3	16	48.5	.
burning	none-light	14	82.4	11	68.8	25	75.8	0.438
	moderate-unacceptable	3	17.6	5	31.3	8	24.2	.
fever	none-light	10	58.8	13	81.3	23	69.7	0.259
	moderate-unacceptable	7	41.2	3	18.8	10	30.3	.

Table 48: Global tolerance rates for the ITT population, success = no or light side effect
n=number of patients

The mean severity of a side effect was calculated as the mean of the individual patients means in order to adjust to an harmonious number of treatment instillations between treatment groups and individual patients. In Table 49 and Table 50, it can be seen that the mean severity of pain was higher in the Doxycycline group than in the Helixor group (p-value < 0.0001). Using the Mann-Whitney-Wilcoxon test no other differences were obvious. If the t-test had been used, there would have been found a p-value of 0.03 for burning (Table 49), that is why the confidence interval does not contain the zero (see * in Table 49).

side effect	severity	Helixor mean severity	Doxycycline mean severity	difference	confidence interval [95% CI]	p-value
pain	0-4	0.30	2.78	-2.48	[-3.10 , -1.87]	< 0.0001
burning	0-4	0.17	1	-0.83	[-1.58 , -0.08]*	0.072
fever	0-4	0.34	0.56	-0.22	[-0.80 , 0.35]	0.728

Table 49: Mean severity of side-effects for the ITT population
[95% CI] = 95% confidence interval (*this analysis was done by using s-plus)

side effect	severity	Helixor mean severity	Doxycycline mean severity	difference	confidence interval [95% CI]	p-value
pain	0-4	0.43	2.64	-2.21	[-2.95 , -1.47]	< 0.0001
burning	0-4	0.28	0.88	-0.6	[-1.37 , 0.19]	0.281
fever	0-4	0.42	0.48	-0.06	[-0.64 , 0.51]	0.567

Table 50: Mean severity of side-effects for the as treated population
[95% CI] = 95% confidence interval (*this analysis was done by using s-plus)

Details for each side effect can be seen in Table 51, Table 52 and Listing 11.

	severity	Helixor N=106		Doxycycline N=27		Total N=133	
		N	%	N	%	N	%
pain	none	87	82.1	5	18.5	92	69.2
	light	11	10.4	6	22.2	17	12.8
	moderate	2	1.9	1	3.7	3	2.3
	serious	5	4.7	11	40.7	16	12.0
	unacceptable	1	0.9	4	14.8	5	3.8
burning	none	99	93.4	20	74.1	119	89.5
	moderate	2	1.9	3	11.1	5	3.8
	serious	5	4.7	2	7.4	7	5.3
	unacceptable	0	0.0	2	7.4	2	1.5
fever	none	83	78.3	18	66.7	101	75.9
	light	11	10.4	5	18.5	16	12.0
	moderate	9	8.5	2	7.4	11	8.3
	serious	3	2.8	1	3.7	4	3.0
	unacceptable	0	0.0	1	3.7	1	0.8
other	none	102	96.2	25	92.6	127	95.5
	light	1	0.9	2	7.4	3	2.3
	moderate	3	2.8	0	0.0	3	2.3

Table 51: Frequency and severity of side effects for the ITT population
n = number of instillations

	severity	Helixor N=112		Doxycycline N=21		Total N=133	
		N	%	N	%	N	%
pain	none	89	79.5	3	14.3	92	69.2
	light	16	14.3	1	4.8	17	12.8
	moderate	2	1.8	1	4.8	3	2.3
	serious	4	3.6	12	57.1	16	12.0
	unacceptable	1	0.9	4	19.0	5	3.8
burning	none	106	94.6	13	61.9	119	89.5
	moderate	1	0.9	4	19.0	5	3.8
	serious	5	4.5	2	9.5	7	5.3
	unacceptable	0	0.0	2	9.5	2	1.5
fever	none	86	76.8	15	71.4	101	75.9
	light	14	12.5	2	9.5	16	12.0
	moderate	9	8.0	2	9.5	11	8.3
	serious	3	2.7	1	4.8	4	3.0
	unacceptable	0	0.0	1	4.8	1	0.8
other	none	108	96.4	19	90.5	127	95.5
	light	1	0.9	2	9.5	3	2.3
	moderate	3	2.7	0	0.0	3	2.3

Table 52: Frequency and severity of side effects for the as treated population
n = number of instillations

4.2.2. Changes in laboratory parameters of the ITT population

An overview about the laboratory parameters of laboratory A in both treatment groups for time of screening gives Table 53 and for time of the final investigation it is Table 54.

	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
blood	Helixor	15	2	62.9	36.3	14.0	27.0	65.0	96.0	123.0
sedimentation	Doxycycline	16	0	66.3	31.9	10.0	49.0	68.0	85.5	125.0
[mm/h]	total	31	2	64.6	33.6	10.0	32.0	66.0	91.0	125.0
hemoglobin	Helixor	17	0	11.7	1.0	10.0	10.8	12.0	12.6	13.3
[g/dl]	Doxycycline	16	0	11.9	1.4	9.8	11.1	11.6	12.5	14.4
	total	33	0	11.8	1.2	9.8	11.0	11.7	12.6	14.4
erythrocytes	Helixor	17	0	3.8	0.5	3.0	3.4	3.9	4.3	4.6
[10^6/µl]	Doxycycline	14	2	3.9	0.5	3.3	3.5	3.8	4.3	4.8
	total	31	2	3.8	0.5	3.0	3.5	3.8	4.3	4.8
thrombocytes	Helixor	17	0	255.9	95.1	95.0	193.0	259.0	287.0	439.0
[10^3/µl]	Doxycycline	16	0	298.3	58.3	212.0	260.0	283.0	339.5	429.0
	total	33	0	276.4	81.1	95.0	229.0	271.0	311.0	439.0
total	Helixor	17	0	7.6	3.0	3.3	5.7	7.3	8.1	14.9
leucocytes	Doxycycline	16	0	8.0	1.8	5.3	6.4	8.2	9.5	11.0
[10^3/µl]	total	33	0	7.8	2.5	3.3	6.1	7.4	9.4	14.9
neutrophils	Helixor	17	0	67.2	19.8	5.2	56.5	71.4	80.1	91.0
[%]	Doxycycline	16	0	74.9	9.2	59.7	66.6	75.3	83.2	90.3
	total	33	0	70.9	15.8	5.2	66.3	72.4	80.9	91.0
eosinophils	Helixor	17	0	3.1	3.4	0.2	0.6	1.2	5.2	10.2
[%]	Doxycycline	16	0	2.6	3.8	0.1	0.5	1.6	3.1	15.7
	total	33	0	2.9	3.5	0.1	0.5	1.4	3.8	15.7
basophils	Helixor	17	0	1.1	1.3	0.0	0.3	0.7	1.3	4.9
[%]	Doxycycline	16	0	1.2	1.0	0.0	0.4	0.8	2.4	2.9
	total	33	0	1.2	1.1	0.0	0.3	0.8	1.5	4.9
monocytes	Helixor	17	0	8.1	5.8	0.5	5.8	7.2	9.2	27.2
[%]	Doxycycline	16	0	7.8	2.8	3.2	5.8	7.4	9.8	13.7
	total	33	0	7.9	4.5	0.5	5.8	7.2	9.2	27.2
lymphocytes	Helixor	17	0	15.5	9.4	1.2	10.1	14.7	20.5	36.2
[%]	Doxycycline	16	0	14.4	7.3	4.2	8.2	12.7	22.0	25.8
	total	33	0	15.0	8.3	1.2	10.0	14.3	21.4	36.2
creatinine	Helixor	17	0	0.9	0.2	0.5	0.7	0.9	1.0	1.5
[mg/dl]	Doxycycline	16	0	0.8	0.2	0.5	0.7	0.8	0.9	1.0
	total	33	0	0.9	0.2	0.5	0.7	0.8	1.0	1.5
SGOT	Helixor	17	0	27.9	14.7	13.0	19.0	24.0	26.0	72.0
[IU/l]	Doxycycline	16	0	32.0	20.4	14.0	21.5	28.0	36.5	102.0
	total	33	0	29.9	17.5	13.0	20.0	26.0	36.0	102.0
SGPT	Helixor	17	0	26.4	11.3	11.0	13.0	27.0	35.0	44.0
[IU/l]	Doxycycline	16	0	28.1	15.9	2.0	14.0	26.5	41.5	50.0
	total	33	0	27.2	13.5	2.0	14.0	27.0	40.0	50.0
gamma-GT	Helixor	17	0	44.7	46.9	8.0	14.0	23.0	42.0	149.0
[IU/l]	Doxycycline	16	0	57.4	54.7	6.0	12.0	47.0	72.0	198.0
	total	33	0	50.9	50.4	6.0	12.0	34.0	69.0	198.0
LDH	Helixor	17	0	493.1	431.7	249.0	304.0	371.0	435.0	2042.0
[IU/l]	Doxycycline	16	0	723.1	708.9	216.0	302.0	477.5	649.5	2766.0
	total	33	0	604.6	585.1	216.0	304.0	402.0	571.0	2766.0
AP	Helixor	17	0	265.9	146.1	152.0	180.0	223.0	274.0	763.0
[IU/l]	Doxycycline	16	0	337.3	255.6	151.0	201.5	253.0	393.5	1204.0
	total	33	0	300.5	206.5	151.0	183.0	239.0	336.0	1204.0

Table 53: ITT population: Laboratory parameters at screening

n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, min = minimum, Q1 = 25^{th} centiles, median = 50^{th} centiles, Q3 = 75^{th} centiles, max = maximum.

	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
blood	Helixor	9	4	84.7	50.8	11.0	60.0	91.0	102.0	172.0
sedimentation	Doxycycline	7	1	71.3	39.1	16.0	46.0	72.0	91.0	140.0
[mm/h]	total	16	5	78.8	45.1	11.0	50.0	78.5	98.0	172.0
hemoglobin	Helixor	13	0	10.5	1.4	8.3	9.7	10.3	11.6	12.7
[g/dl]	Doxycycline	8	0	11.0	2.2	9.0	9.3	9.9	13.4	13.9
	total	21	0	10.7	1.7	8.3	9.4	10.3	11.8	13.9
erythrocytes	Helixor	13	0	3.4	0.5	2.6	2.9	3.5	3.8	4.0
[10^6/µl]	Doxycycline	7	1	3.6	0.7	2.9	3.0	3.2	4.4	4.6
	total	20	1	3.5	0.6	2.6	2.9	3.4	3.9	4.6
thrombocytes	Helixor	13	0	278.6	112.1	127.0	213.0	257.0	350.0	489.0
[10^3/µl]	Doxycycline	8	0	265.4	116.5	114.0	177.5	270.0	326.5	461.0
	total	21	0	273.6	111.1	114.0	213.0	257.0	350.0	489.0
total	Helixor	13	0	6.7	1.9	4.0	5.0	6.8	7.9	9.6
leucocytes	Doxycycline	8	0	7.1	2.3	1.4	7.4	7.7	8.3	8.6
[10^3/µl]	total	21	0	6.8	2.0	1.4	6.2	7.6	8.0	9.6
neutrophils	Helixor	13	0	65.1	21.6	5.2	59.3	68.6	78.0	95.0
[%]	Doxycycline	8	0	63.0	25.5	8.0	53.5	71.9	77.5	90.0
	total	21	0	64.3	22.6	5.2	56.9	68.9	78.0	95.0
eosinophils	Helixor	13	0	3.0	2.8	0.1	0.3	2.5	5.2	8.4
[%]	Doxycycline	8	0	2.0	3.1	0.0	0.4	0.9	2.2	9.3
	total	21	0	2.6	2.9	0.0	0.3	1.7	3.4	9.3
basophils	Helixor	13	0	0.7	0.6	0.0	0.1	0.6	1.0	2.1
[%]	Doxycycline	8	0	0.4	0.7	0.0	0.0	0.1	0.8	1.5
	total	21	0	0.6	0.7	0.0	0.0	0.6	1.0	2.1
monocytes	Helixor	13	0	7.1	3.6	0.4	5.4	7.4	9.8	13.4
[%]	Doxycycline	8	0	7.3	5.2	2.0	3.2	5.9	11.3	15.5
	total	21	0	7.2	4.2	0.4	4.4	7.2	9.8	15.5
lymphocytes	Helixor	13	0	17.3	10.4	0.5	12.6	14.5	23.2	38.3
[%]	Doxycycline	8	0	27.3	27.2	3.3	12.5	19.6	30.7	90.0
	total	21	0	21.1	18.7	0.5	12.6	19.4	23.8	90.0
creatinine	Helixor	13	0	0.8	0.2	0.5	0.7	0.8	1.0	1.4
[mg/dl]	Doxycycline	8	0	0.8	0.2	0.6	0.6	0.8	1.0	1.0
	total	21	0	0.8	0.2	0.5	0.7	0.8	1.0	1.4
SGOT	Helixor	13	0	28.2	12.2	14.0	19.0	26.0	36.0	52.0
[IU/l]	Doxycycline	8	0	31.3	10.8	19.0	22.5	28.5	41.0	47.0
	total	21	0	29.3	11.5	14.0	19.0	26.0	37.0	52.0
SGPT	Helixor	13	0	26.4	15.7	9.0	14.0	21.0	35.0	57.0
[IU/l]	Doxycycline	8	0	34.4	15.4	12.0	21.0	37.0	46.5	54.0
	total	21	0	29.4	15.7	9.0	14.0	28.0	41.0	57.0
gamma-GT	Helixor	13	0	33.9	21.7	1.0	15.0	31.0	53.0	63.0
[IU/l]	Doxycycline	7	1	146.3	179.5	22.0	24.0	66.0	339.0	464.0
	total	20	1	73.3	116.2	1.0	19.5	34.0	62.5	464.0
LDH	Helixor	13	0	410.1	198.3	248.0	309.0	367.0	438.0	1010.0
[IU/l]	Doxycycline	7	1	607.0	483.5	196.0	294.0	376.0	767.0	1607.0
	total	20	1	479.0	328.5	196.0	301.5	373.5	496.5	1607.0
AP	Helixor	13	0	262.8	57.3	185.0	233.0	250.0	276.0	380.0
[IU/l]	Doxycycline	8	0	475.4	295.7	174.0	229.5	416.0	691.5	955.0
	total	21	0	343.8	209.2	174.0	233.0	266.0	364.0	955.0

Table 54: ITT population: Laboratory parameters at final investigation

n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, min = minimum, Q1 = 25^{th} centiles, median = 50^{th} centiles, Q3 = 75^{th} centiles, max = maximum.

The laboratory parameters of laboratory A were categorized as normal range and deviation. For the following explorative analysis of changes of the laboratory parameters between the screening and final investigation, the McNemar test was used. No indications can be found in Table 55 or Table 56, that there were obvious changes in the laboratory parameters in the Helixor group or in the Doxycycline group between screening and final investigation. Details can be seen in Listing 12.

Helixor parameter	N	Screening				Final				p-value
		normal range		deviation		normal range		deviation		
		N	%	N	%	N	%	N	%	
blood sedimentation [mm/h]	9	1	11.1	8	88.9	1	11.1	8	88.9	1.000
hemoglobin [g/dl]	13	6	46.2	7	53.8	2	15.4	11	84.6	0.125
erythrocytes [10^6/µl]	13	3	23.1	10	76.9	1	7.7	12	92.3	0.500
thrombocytes [10^3/µl]	13	13	100.0	.	.	11	84.6	2	15.4	0.500
total leucocytes [10^3/µl]	13	8	61.5	5	38.5	11	84.6	2	15.4	0.375
neutrocytes [%]	13	4	30.8	9	69.2	6	46.2	7	53.8	0.688
eosinophils [%]	13	5	38.5	8	61.5	6	46.2	7	53.8	1.000
basophils [%]	13	10	76.9	3	23.1	11	84.6	2	15.4	1.000
monocytes [%]	13	6	46.2	7	53.8	6	46.2	7	53.8	1.000
lymphocytes [%]	13	3	23.1	10	76.9	2	15.4	11	84.6	1.000
creatinine [mg/dl]	13	11	84.6	2	15.4	12	92.3	1	7.7	1.000
SGOT [IU/l]	13	11	84.6	2	15.4	10	76.9	3	23.1	1.000
SGPT [IU/l]	13	11	84.6	2	15.4	9	69.2	4	30.8	0.500
gammaGT [IU/l]	13	12	92.3	1	7.7	9	69.2	4	30.8	0.250
LDH [IU/l]	13	12	92.3	1	7.7	10	76.9	3	23.1	0.500
alkaline phosphatase [IU/l]	13	9	69.2	4	30.8	7	53.8	6	46.2	0.500

Table 55: ITT population: Helixor: Changes in laboratory parameters (laboratory A)
n = number of patients

Helixor parameter	N	Screening				Final				p-value
		normal range		deviation		normal range		deviation		
		N	%	N	%	N	%	N	%	
blood sedimentation [mm/h]	7	.	.	7	100.0	.	.	7	100.0	0.500
hemoglobin [g/dl]	8	3	37.5	5	62.5	3	37.5	5	62.5	1.000
erythrocytes [10^6/µl]	7	2	28.6	5	71.4	1	14.3	6	85.7	1.000
thrombocytes [10^3/µl]	8	8	100.0	.	.	5	62.5	3	37.5	1.000
total leucocytes [10^3/µl]	8	7	87.5	1	12.5	7	87.5	1	12.5	1.000
neutrocytes [%]	8	3	37.5	5	62.5	3	37.5	5	62.5	1.000
eosinophils [%]	8	6	75.0	2	25.0	4	50.0	4	50.0	0.688
basophils [%]	8	4	50.0	4	50.0	6	75.0	2	25.0	0.625
monocytes [%]	8	6	75.0	2	25.0	3	37.5	5	62.5	0.250
lymphocytes [%]	8	2	25.0	6	75.0	2	25.0	6	75.0	1.000
creatinine [mg/dl]	8	8	100.0	.	.	8	100.0	.	.	1.000
SGOT [IU/l]	8	7	87.5	1	12.5	5	62.5	3	37.5	0.500
SGPT [IU/l]	8	4	50.0	4	50.0	3	37.5	5	62.5	1.000
gammaGT [IU/l]	7	4	57.1	3	42.9	3	42.9	4	57.1	1.000
LDH [IU/l]	7	2	28.6	5	71.4	3	42.9	4	57.1	1.000
alkaline phosphatase [IU/l]	8	5	62.5	3	37.5	3	37.5	5	62.5	0.500

Table 56: ITT population: Doxycycline: Changes in laboratory parameters (laboratory A)
n = number of patients

The changes between screening and final investigation in the laboratory parameters of pleural fluid (laboratory B) are listed in Listing 13.

4.2.3. Safety evaluation of the ITT population

Table 57 contains the mean number of adverse events in both treatment groups, for details see Listing 14. Only three patients in the Helixor group had no adverse event (patient number 6, 22, 33), all other patients had at least one adverse event; the mean number in both treatment groups was three.

	MEAN	MIN	MAX
Helixor	2.8	0	10
Doxycycline	2.9	1	10

Table 57: ITT population: Mean number of adverse events
mean, min = minimum, max = maximum

Table 58 illustrates the incidence of adverse events in both treatment groups as well as the severity. In total there were 47 adverse events in both treatment groups.

	Helixor							Doxycycline						
		light		moderate		severe			light		moderate		severe	
	N	N	%	N	%	N	%	N	N	%	N	%	N	%
BRUSTKORB BRENNSCHMERZ	7	.	.	2	28.6	5	71.4	7	.	.	3	42.9	4	57.1
DYSPNOE	5	1	20.0	.	.	4	80.0	4	.	.	1	25.0	3	75.0
FIEBER	16	5	31.3	8	50.0	3	18.8	9	5	55.6	2	22.2	2	22.2
HAEMATEMESIS BEI MAGENULKUS	1	.	.	1	100.0	.	.	0	.	.	.	.	.	.
HUSTEN	0							1						
HYPOTENSION	1	.	.	.	.	1	100.0	0	.	.	.	.	.	.
KOERPERGEFUEHL-VERAENDERUNG	0	.	.	.	.	.	.	1	1	100.0	.	.	.	.
NAUSEA	1	.	.	1	100.0	.	.	0	.	.	.	.	.	.
OBERBAUCH-BESCHWERDEN	0	.	.	.	.	.	.	1	1	100.0	.	.	.	.
PLEURASCHMERZ	3	.	.	2	66.7	1	33.3	0	.	.	.	.	.	.
SCHMERZ	9	3	33.3	1	11.1	5	55.6	11	4	36.4	.	.	7	63.6
SCHMERZ LOKAL	3	1	33.3	2	66.7	.	.	0	.	.	.	.	.	.
SCHMERZEN BRUSTKORB	1	.	.	1	100.0	.	.	13	2	15.4	2	15.4	9	69.2

Table 58: ITT population: Adverse events
n = number of adverse events

This analysis (Table 57, Table 58) may be biased by the way of documenting an adverse event. For example: One patient (Helixor: patient number 1) had the adverse event “fever”, the duration of this adverse event was eight days (Listing 14). Another patient (Helixor: patient number 14) had the first adverse event “fever” on October 5th, the second adverse event “fever” on October 6th, the third one on October 7th and the last one on October 8th (Listing 14). If these four adverse events are really four different adverse events, or if it is one adverse event with the duration of four days, cannot be judged at the time of writing this report.

The number of serious adverse events in both treatment groups was four (Helixor, patient number 3, 10, 19, 24; Doxycycline, patient number 4, 17, 23, 30); the degree of severity was always “death” (Table 59). All patients suffered from dyspnea except one (Helixor, patient number 19). For this patient death was caused by hypotension due to hematemesis. In the Helixor group the four serious adverse events had taken place one or two days after the instillation of Helixor. In the Doxycycline group two serious adverse events followed a medication of Doxycycline (patient number 4, 17), and two started before the first dose of Doxycycline (patient number 23, 30). The cancer diseases of the patient caused all eight serious adverse events. None of them was connected to the instillation of the medications. For details see Listing 14.

Group	Pat	symptom	last medication	begin of SAE	instillation	degree of severity	relation with therapy
Helixor	3	Dyspnea	25/05/97	26/05/97	5	death	none
	10	Dyspnea	11/02/98	12/02/98	3	death	none
	19	Hypotension due to Hematemesis	12/01/99	14/01/99	7	death	none
	24	Dyspnea, pain	10/04/99	10/04/99	6	death	none
Doxycycline	4	Dyspnea	22/07/97	23/07/97	7	death	none
	17	Dyspnea (due to general weakness)	19/12/98	02/01/99	2	death	none
	23	Dyspnoea		01/03/99		death	none
	30	Dyspnea and weakness		04/09/99		death	none

Table 59: ITT population: Serious adverse events

4.3. Analysis of the efficacy of Mistletoe preparation

The analysis was done for the ITT population and the as treated population using the Chi squared test for trend. Table 60 and Table 61 show the efficacy parameters in both treatment groups. There could not be found a significant difference between both groups neither in the ITT analysis nor in the as treated analysis.

		Helixor N=17		Doxycycline N=16		total N=33		p-value
		N	%	N	%	N	%	
ITT	missing	4		8		12	.	
population	CR	12	92.3	4	50.0	16	76.2	0.066
	PR	0	0.0	2	25.0	2	9.5	
	NC	1	7.7	2	25.0	3	14.3	

Table 60: Efficacy, analysed for the ITT population
n = number of patients, CR=complete remission, PR=partial response, NC=no change

As treated	missing	5		7		12	.	
population	CR	11	91.7	5	55.6	16	76.2	0.116
	PR	0	0.0	2	22.2	2	9.5	
	NC	1	8.3	2	22.2	3	14.3	

Table 61: Efficacy, analysed for the as treated population
n = number of patients, CR=complete remission, PR=partial response, NC=no change

The problem of regression towards the mean should be mentioned at this point [Bland J.M., Altman D.G., 1994]. One patient could have just a small pleural effusion and could not get better very much (for example patient 15, see Figure 26). So that patient would be valued as no change. Another one with a pleural effusion left at the end of trial would be valued as PR because at the beginning he felt even worse (patient number 16, see Figure 27). In Table 62, it can be seen that the range of the parameter “effusion in ml before the first instillation” was wide in both treatment groups. So in the analysis of efficacy, the effect caused by regression towards the mean and the treatment effect may overlap each other.

	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	P-VALUE
effusion [ml]	Helixor	17	0	233.1	348.4	3.5	30.0	70.0	300.0	1250.0	0.773
	Doxycycline	16	0	172.4	195.5	5.0	40.0	100.0	250.0	700.0	.
	total	33	0	203.7	282.1	3.5	30.0	100.0	300.0	1250.0	.

Table 62: ITT population: Effusion in ml before the first instillation
n = number of patients, nmiss = number of missing data, mean, sdev = standard deviation, min = minimum, Q1 = 25^{th} centiles, median = 50^{th} centiles, Q3 = 75^{th} centiles, max = maximum, p-value.

An examination for a monotonous trend between the efficacy and the parameter “months since diagnosis” was done. The results can be seen in frequency tables (Table 63, Table 64) for each

treatment group. But there was no effect, neither for the Helixor group nor for the Doxycycline group.

months since diagnosis	efficacy N=13			
	CR	PR	NC	total
0	5	0	0	5
1	3	0	0	3
8	1	0	0	1
10	1	0	0	1
18	0	0	1	1
111	1	0	0	1
192	1	0	0	1

Table 63: ITT population: Helixor: Fequency table of efficacy and months since diagnosis
n = number of patients, CR=complete remission, PR=partial response, NC=no change

months since diagnosis	efficacy N=8			
	CR	PR	NC	total
0	1	1	1	3
1	1	1	0	2
3	1	0	0	1
7	0	0	1	1
24	1	0	0	1

Table 64: ITT population: Doxycycline: Fequency table of efficacy and months since diagnosis
n = number of patients, CR=complete remission, PR=partial response, NC=no change

4.4. Conclusion

The aim of this study was to test if the mistletoe preparation Helixor induces fewer side effects than Doxycycline and if Helixor reaches the same or better efficacy of pleurodesis than Doxycycline.

33 patients with malignant pleural effusion were enrolled in this trial. There should have been 40 patients enrolled, but for reasons of trial management this could not be realized. Two patients violated inclusion criteria. It was decided to keep these patients in the ITT population and in the as treated population. Once, the treatment was done mistakenly, so patient number 4, who should get Doxycycline, got Helixor and therefore patient number 5 got Helixor instead of Doxycycline. In the ITT analysis these patients stayed in their random groups, in the as treated population the patients were analysed by their treatment group.

From the beginning of the trial there were a few obvious differences between the two treatment groups. In the Doxycycline group there were more young patients (Table 33) and more smokers (Table 34) and the parameter pulse obtained a higher level (Table 35). In the Helixor group there were only patients with current tumor stages T4 N0–3 M1 except one with the tumor stage TXN3M1, while in the Doxycycline group there were current tumor stages from T1-4, N0-3/X M1 (Table 38).

After enrolling a patient in the trial, the medical therapy was not started immediately. The time (and frequency) of intrapleural instillation of Helixor or Doxycycline was decided by the treating physician. So the time interval before starting the therapy was inharmonious for all patients. This can be seen in the graphics of patients' history (Figure 5 till Figure 37). Also, the parameter „effusion in ml before the first instillation" showed a wide range in both treatment groups (Table 62). So a comparison of time and severity in suffering from pleural effusion before starting the therapy was not analysed. There were no documentations of patients' management decisions and a scheme could not be identified.

The analysis of the tolerability was done by comparing the tolerance rates of Helixor and Doxycycline for no pain, no burning and no fever. If "no side effect" was defined as "severity 0", the tolerance rate for no pain in the Helixor group was 0.82 [0.67 ; 0.97] with a significant difference of 0.63 [0.42 ; 0.85] to the Doxycycline group. If "no relevant side effect" was defined as "severity 0 or 1", the tolerance rate of no pain in the Helixor group was 0.92 [0.83 ; 1.02] with a significant difference of 0.51 [0.14 ; 0.89] to the Doxycycline group (Table 45). This result contains the information for the probability to receive one instillation without any pain. In the Helixor group this probability is 0.82 if "no side effect" is defined as "severity 0". The probability for a second or third painless instillation can be calculated.
For the as treated population the results were similar. The significant difference for the second definition was even 0.75 [0.49 ; 1.00]. In the as treated population an advantage for Helixor could be identified with a significant difference of 0.33 [0.05 ; 0.60] for no burning (Table 46).
If the global tolerance rate (number of patients without side effects / number of all patients) for both groups were compared, an obvious advantage for the Helixor group could be seen for the side effect pain (Table 47, Table 48). Also, the mean severity of the side effect pain showed a significant lower level for the Helixor group (Table 49, Table 50).

For the ITT population, the number of adverse events in each treatment group was 47, containing four serious adverse events in each group. In the as treated population the number of adverse events was 53 for the Helixor group, containing five serious adverse events. In the Doxycycline group 41 adverse events were counted, including three serious adverse events (Table 58). All eight serious

adverse events were deaths and caused by the cancer disease. None was connected to a medical instillation (Table 59).

The analysis of the efficacy showed no significant difference between the two treatment groups (Table 60 and Table 61).

5. Appendix

Trial Plan (HELIXOR®)						
	SCR	**I/1**	**2 to 7 or more**	**II to V**	**FO**	**FINAL**
Investigation	**Screening**	**Investigation prior to 1st instillation. First instillation**	**Current instillation**	**Current investigation**	**Follow-up**	**Final investigation**
Instruction	X					
Informed consent	X					
Inclusion/Exclusion criteria	X					
Demographic data	X					
Karnofsky-Index	X					X
General Anamnesis/ Tumor-Anamnesis	X					
Height	X					
Weight / Physical examination	X					X
Vital signs	X					X
Pregnancy test	X					
Laboratory A[1]	X					X
Laboratory B[2]		X				
Laboratory C[3]				X		
Thorax X-ray	X	X[4]		X[5]		X
Daily amount of pleura fluid[6]			X			
Previous intrapleural treatments	X					
Medication	X					
Concomitant Medication				X		X
HELIXOR instillation		X	X[7]			
Relapsing effusion					X	
Adverse events / Toxicity		◄———	———	———	———	———►

[1] Blood: blood sedimentation, Hb, diff. blood count, creatinine, SGOT/SGPT, γ-GT, alc. phosphatase, LDH .
[2] Punctate: tumor cells, neutrophils, eosinophils, lymphocytes, HLA-DR on T-cells (HLA-DR+/CD3), macrophages, CD4, CD8, NK-Cells + including amount of punctate and visual examination of color and consistency.
[3] Punctate: tumor cells, neutrophils, eosinophils, lymphocytes CD4, CD8, NK-Cells + including amount of punctate and visual examination of color and consistency once a week.
[4] Thorax X-ray will be performed twice: prior to first puncture/catheterization (during screening) and immediately consecutive to it.
[5] Thorax X-ray will be performed every week, as far as no pleurodesis can be detected.
[6] Amount of pleural fluid will be documented daily; as far as no pleurodesis can be detected.
[7] HELIXOR® instillation should be performed as often as possible.

Table 65: Trial plan of the Helixor group

Trial Plan (Doxycycline)							
	SCR	**1**	**2**	**3**	**4**	**FO**	**FINAL**
Investigation	**Screening**	**Investigation prior to 1st instillation. First**	**Investigation between 1st and 2nd instillation**	**Investigation prior to 2nd instillation. Second instillation.**	**Investigation consecutive to 2nd instillation**	**Follow-up**	**Final investigation**
Instruction	X						
Informed consent	X						
Inclusion/Exclusion criteria	X						
Demographic data	X						
Karnofsky-Index	X						X
General Anamnesis/ Tumor-Anamnesis	X						
Height	X						
Weight / Physical examination	X						X
Vital signs	X						X
Pregnancy test	X						
Laboratory A[1]	X						X
Laboratory B[2]		X					
Laboratory C[3]				X			
Thorax X-ray	X	X[4]	X[5]		X[5]		X
Daily amount of pleural fluid[6]			X		X		
Previous intrapleural treatments	X						
Medication	X						
Concomitant Medication				X			X
Doxycycline instillation		X		X			
Relapsing effusion						X	
Adverse events/ Toxicity		←	—	—	—	—	→

[1] Blood: blood sedimentation, Hb, diff. blood count, creatinine, SGOT/SGPT, γ-GT, alc. phosphatase, LDH .
[2] Punctate: tumor cells, neutrophils, eosinophils, lymphocytes, HLA-DR on T-cells (HLA-DR+/CD3), macrophages, CD4, CD8, NK-Cells + including amount of punctate and visual examination of color and consistency.
[3] Punctate: tumor cells, neutrophils, eosinophils, lymphocytes, CD4, CD8, NK-Cells + including amount of punctate and visual examination of color and consistency once a week.
[4] Thorax X-ray will be performed twice: prior to first puncture/catheterization (during screening) and immediately consecutive to it.
[5] Thorax X ray will be performed every 2 days, as far as no pleurodesis can be detected; after 2nd instillation up to a total of 7 days.
[6] Amount of pleural fluid will be documented daily; after 2nd instillation daily up to a total of 7 days.

Table 66: Trial plan of the Doxycycline group

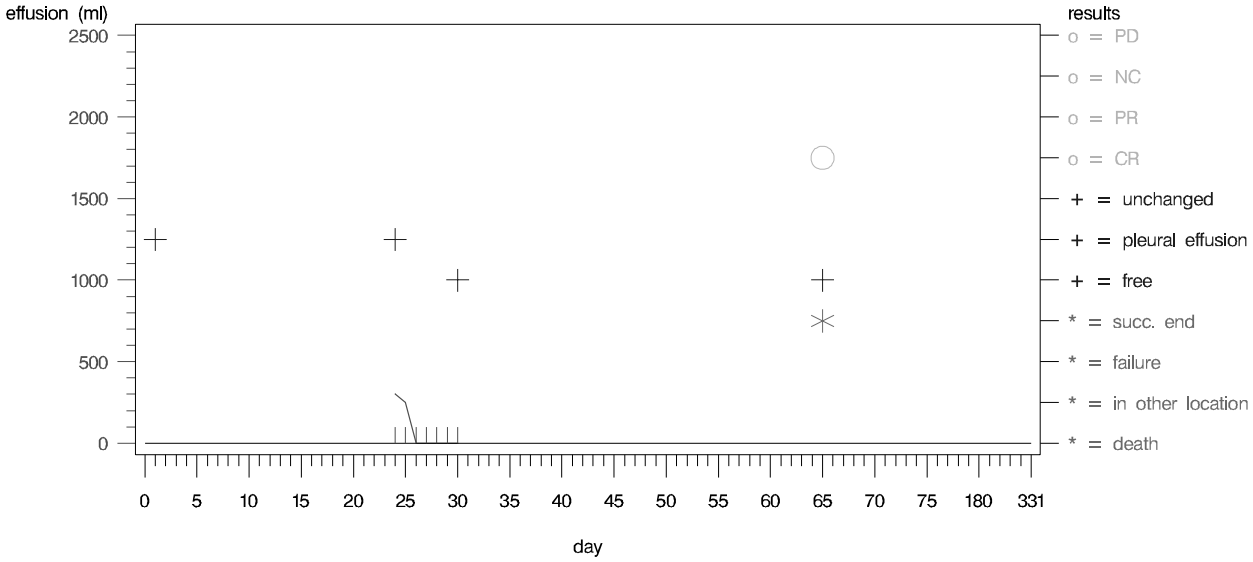

Figure 5: Helixor group: Course of illness of patient 1

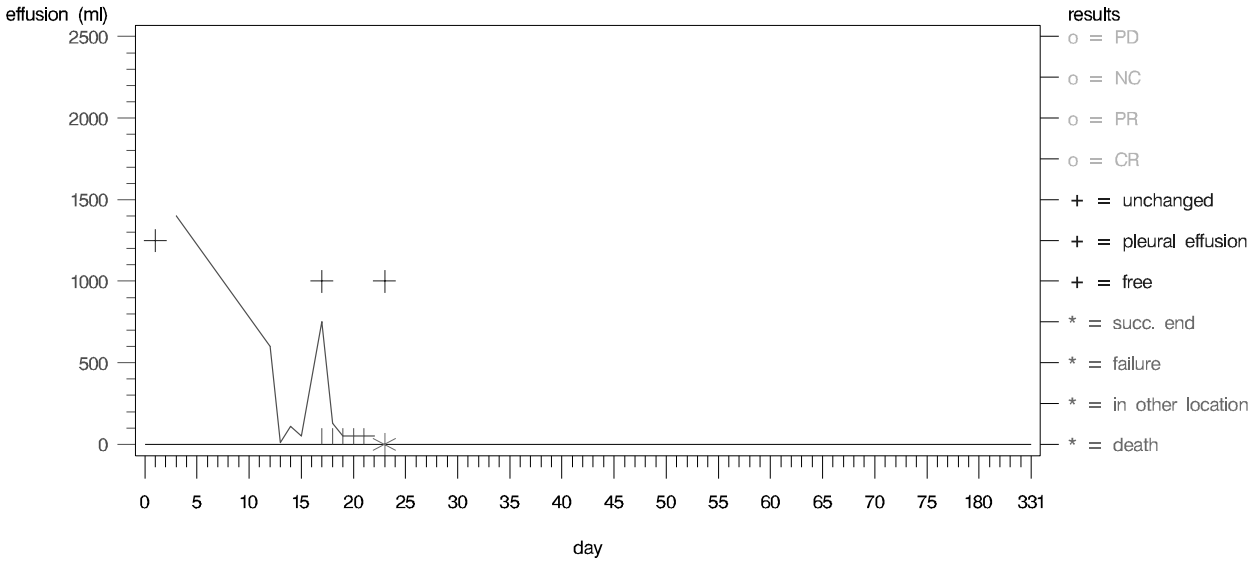

Figure 6: Helixor group: Course of illness of patient 3

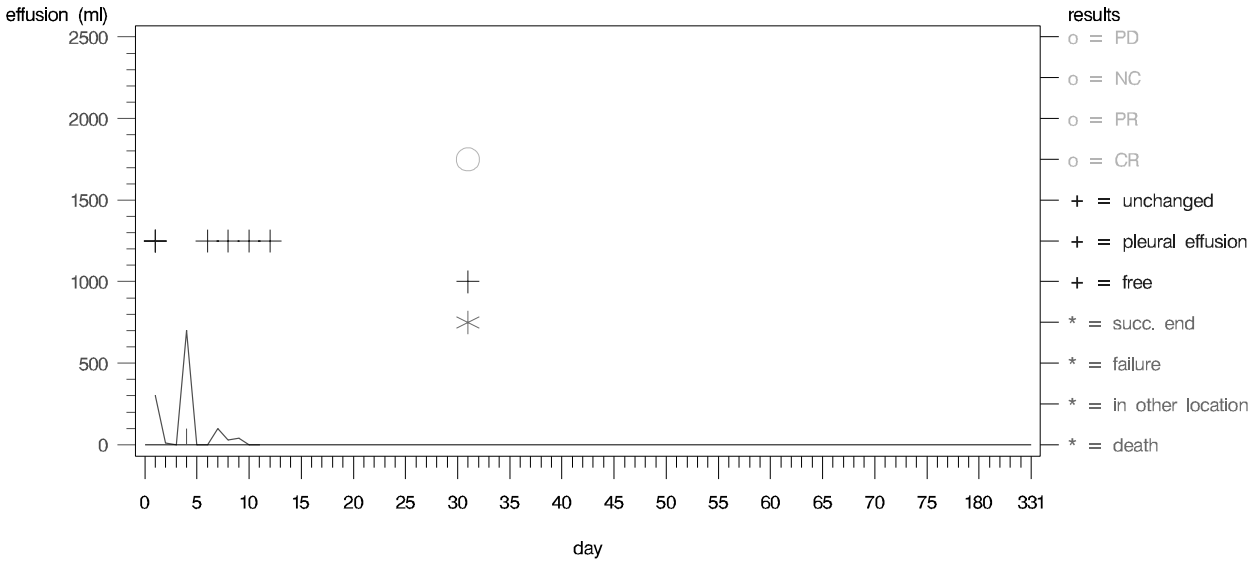

Figure 7: Helixor group: Course of illness of patient 5
(Patient was randomised in the Helixor group, but received Doxycycline.)

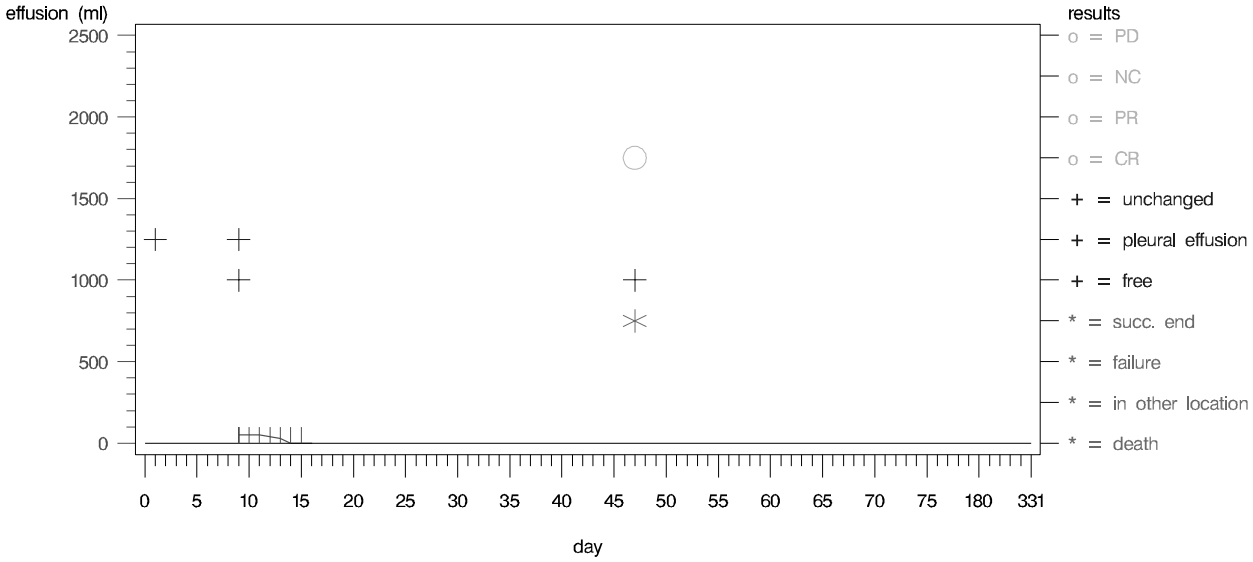

Figure 8: Helixor group: Course of illness of patient 6

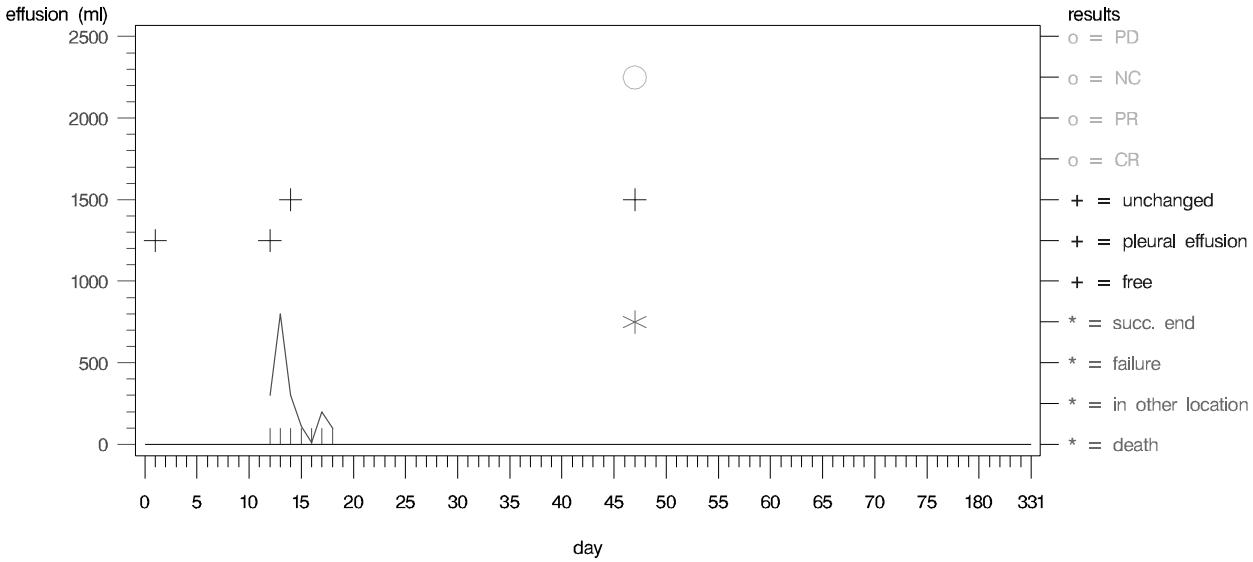

Figure 9: Helixor group: Course of illness of patient 8

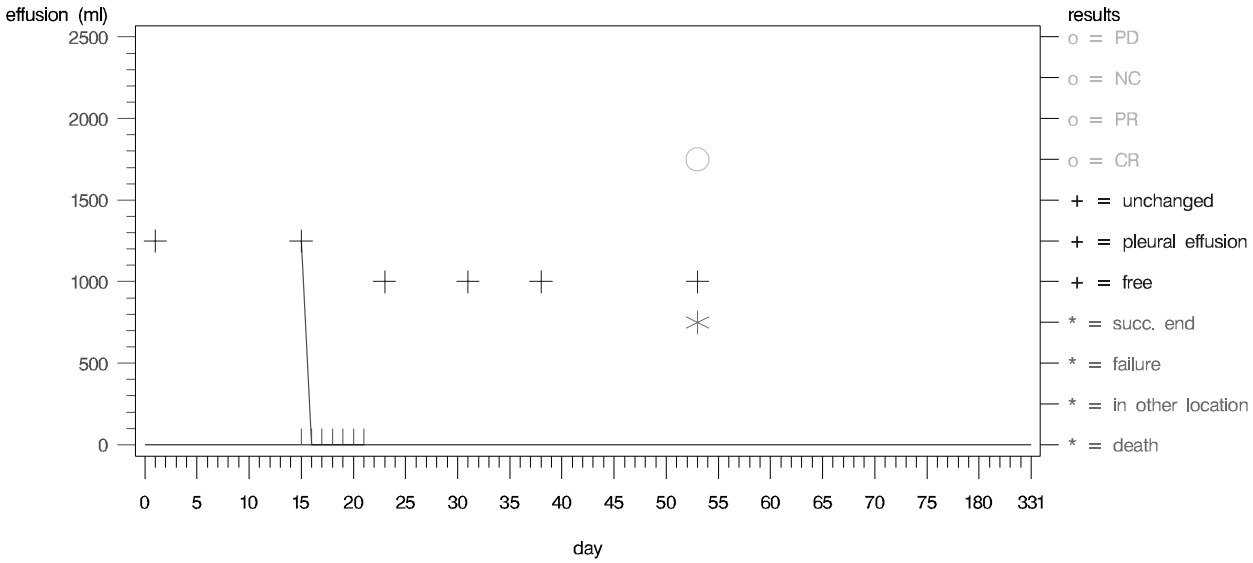

Figure 10: Helixor group: Course of illness of patient 9

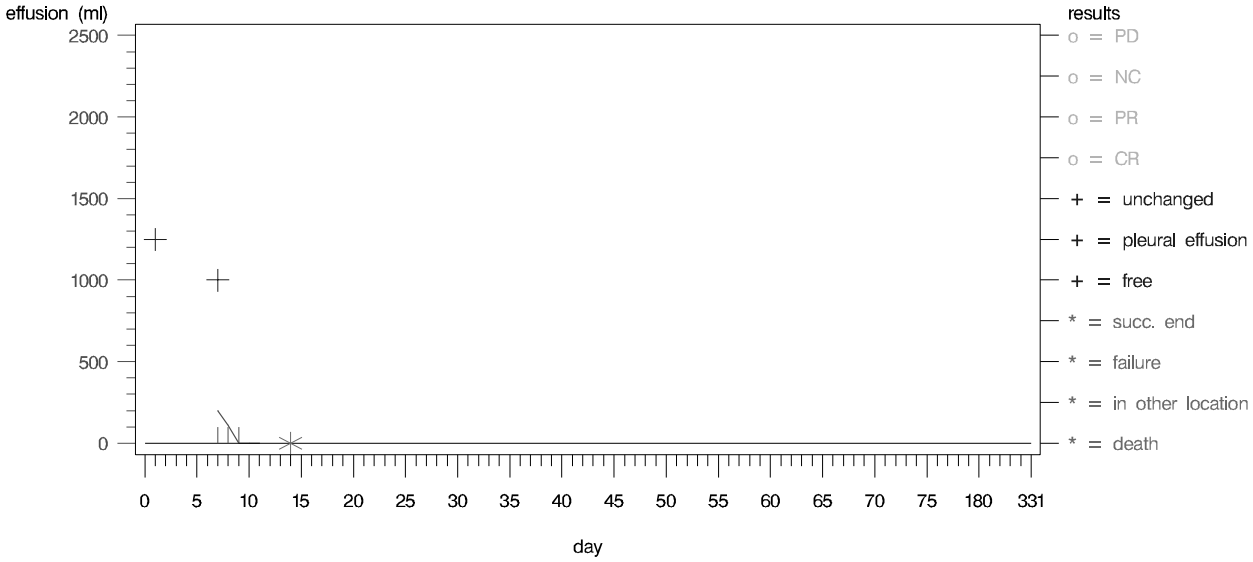

Figure 11: Helixor group: Course of illness of patient 10

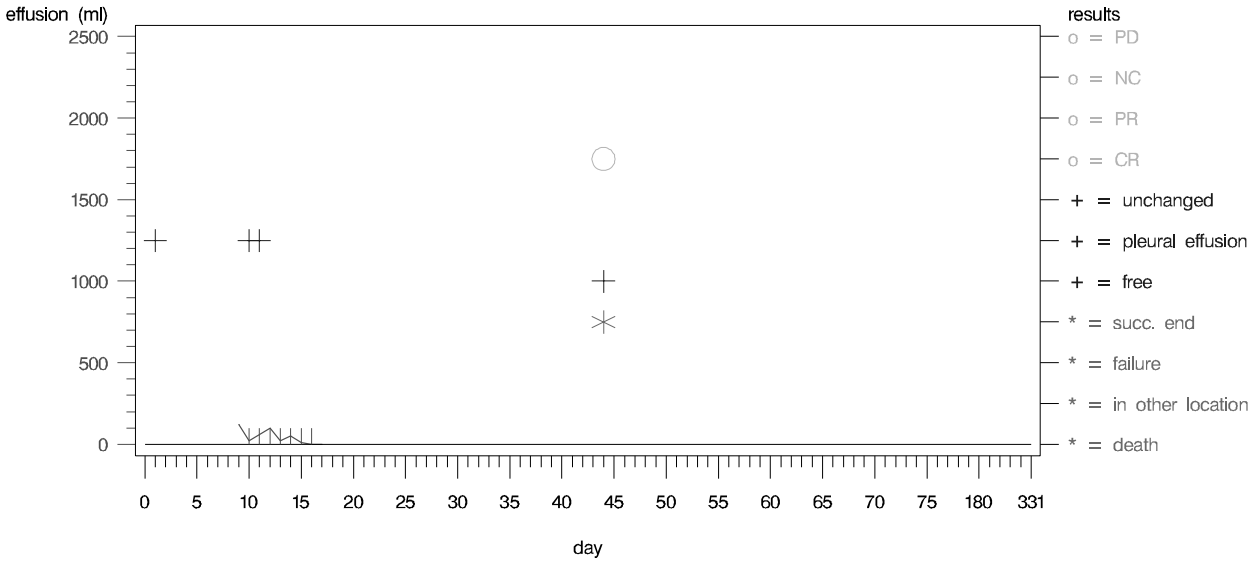

Figure 12: Helixor group: Course of illness of patient 11

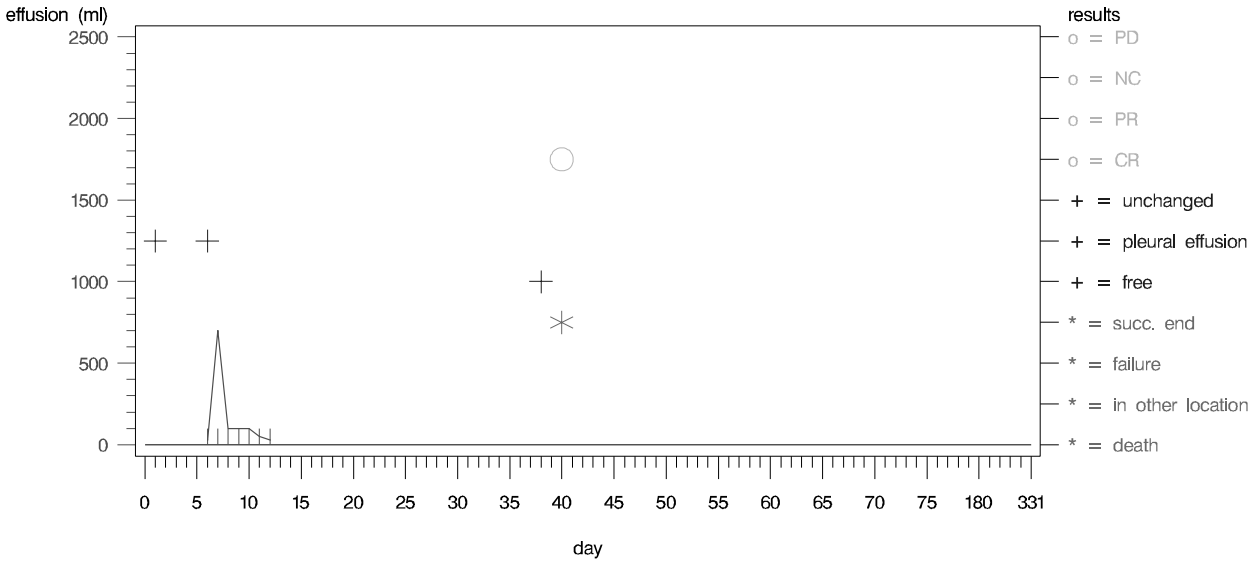

Figure 13: Helixor group: Course of illness of patient 13

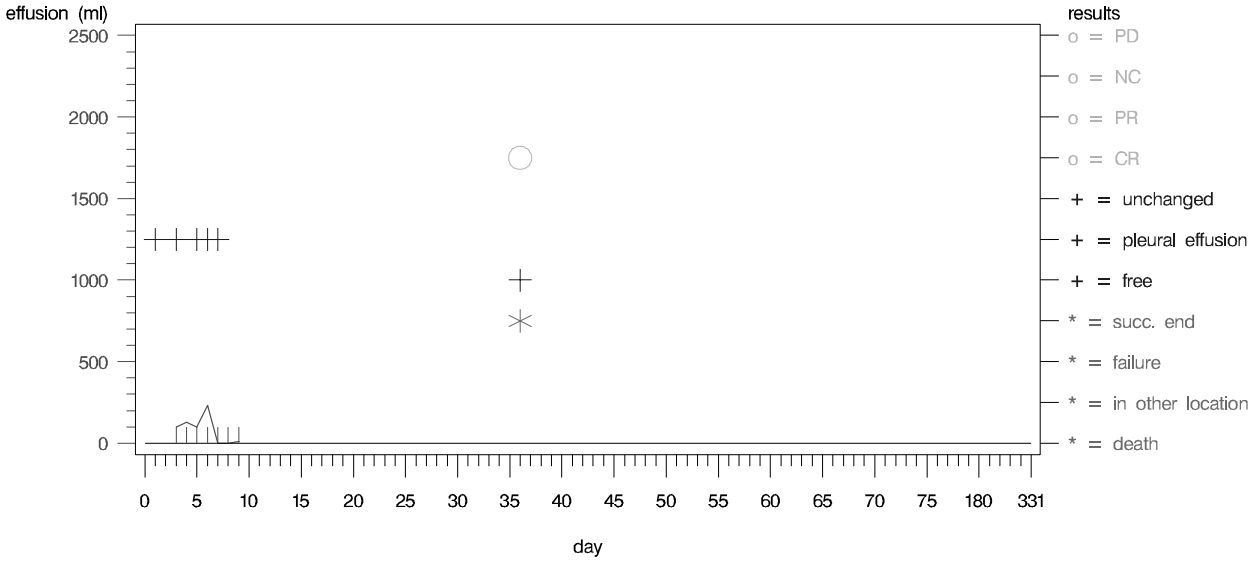

Figure 14: Helixor group: Course of illness of patient 14

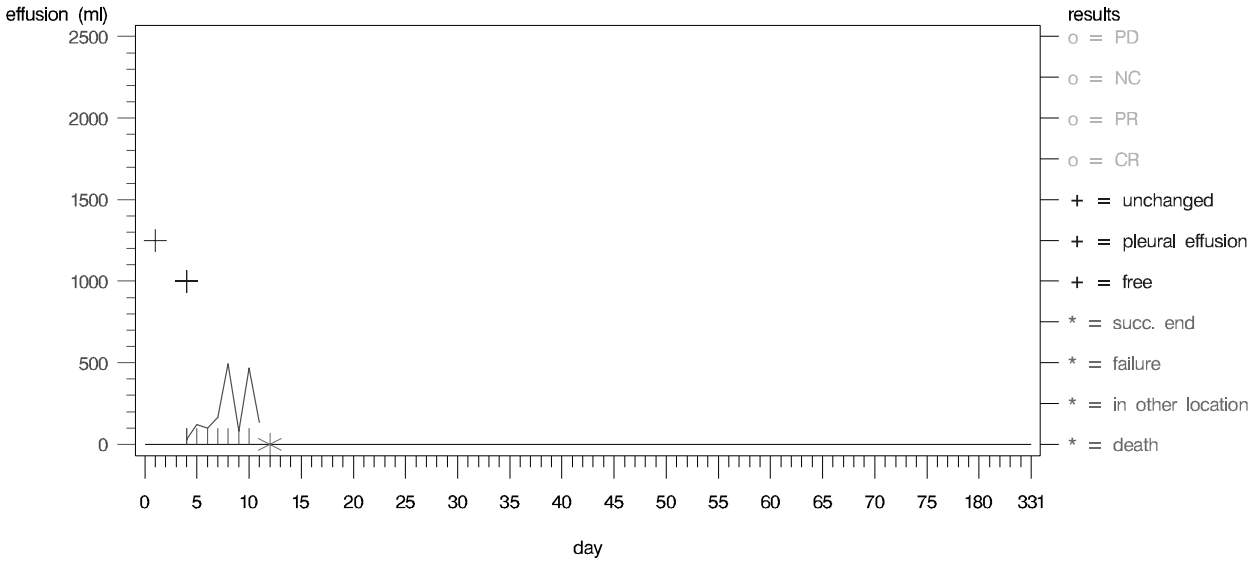

Figure 15: Helixor group: Course of illness of patient 19

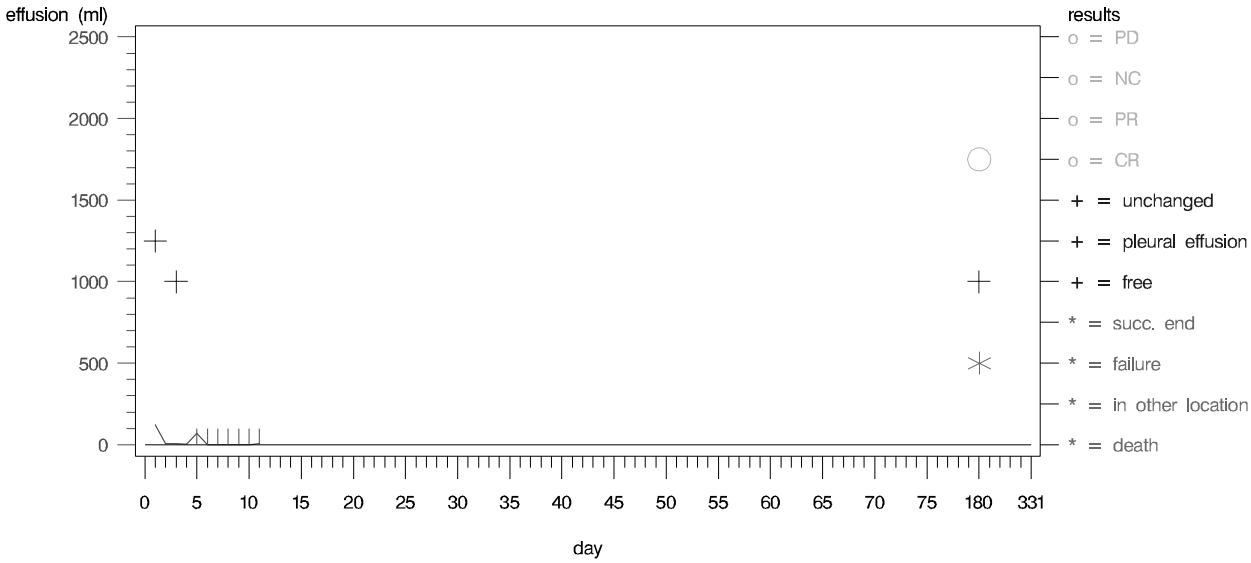

Figure 16: Helixor group: Course of illness of patient 22

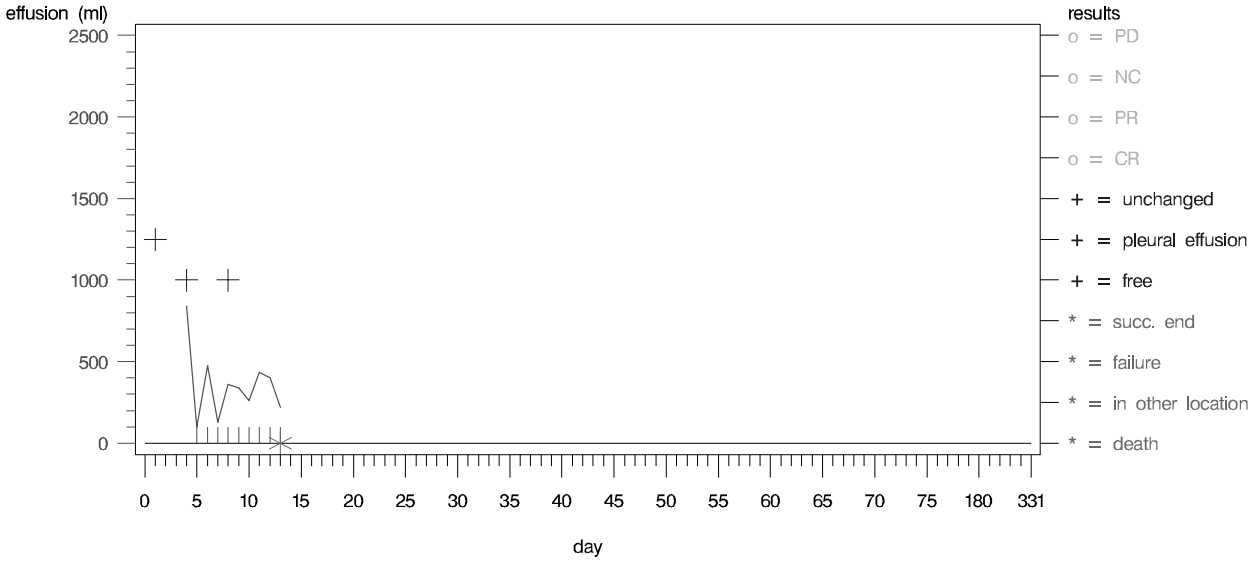

Figure 17: Helixor group: Course of illness of patient 24

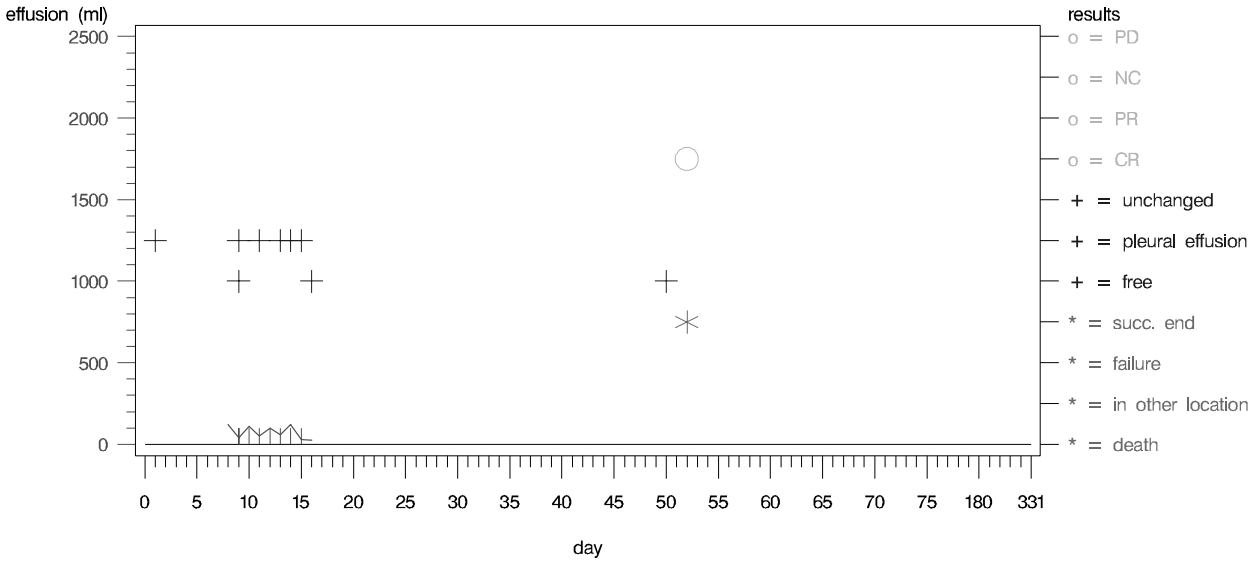

Figure 18: Helixor group: Course of illness of patient 26

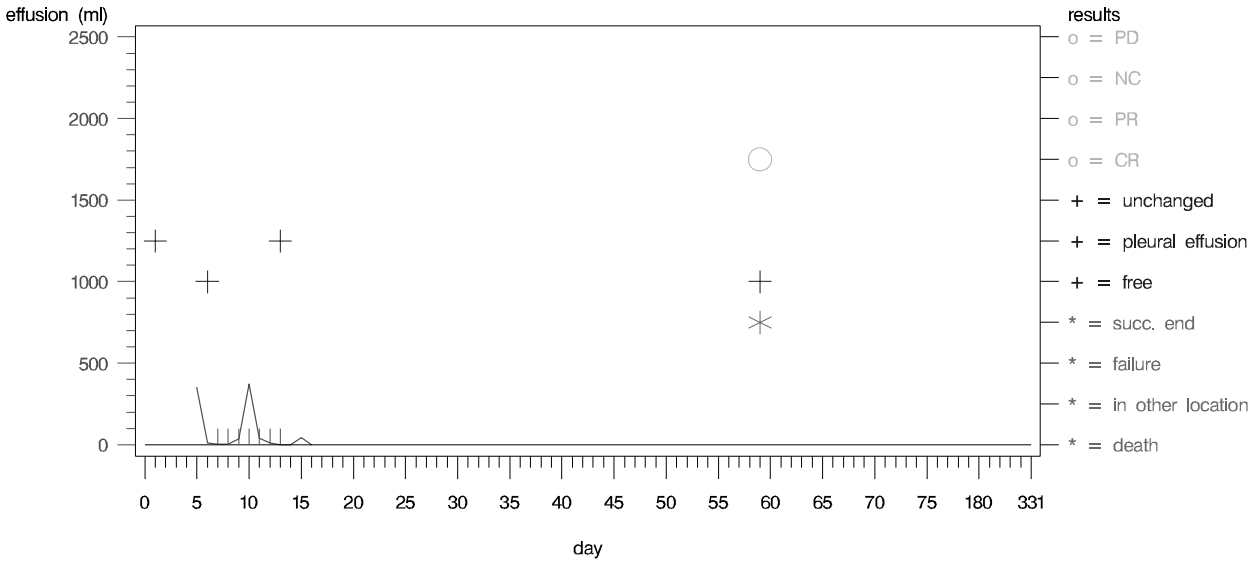

Figure 19: Helixor group: Course of illness of patient 29

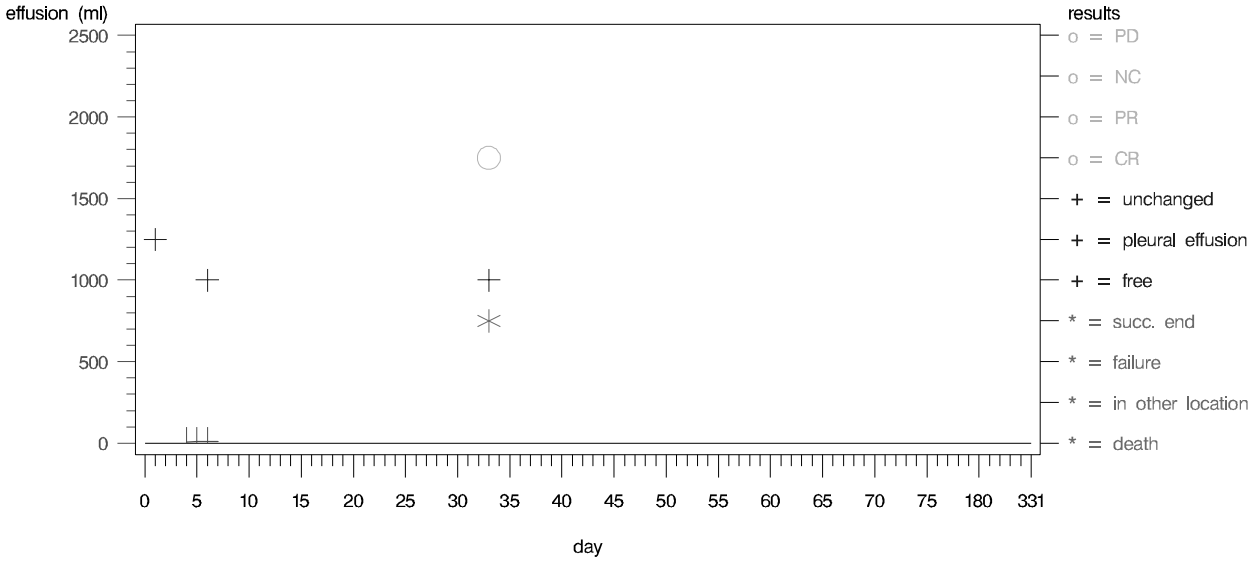

Figure 20: Helixor group: Course of illness of patient 32

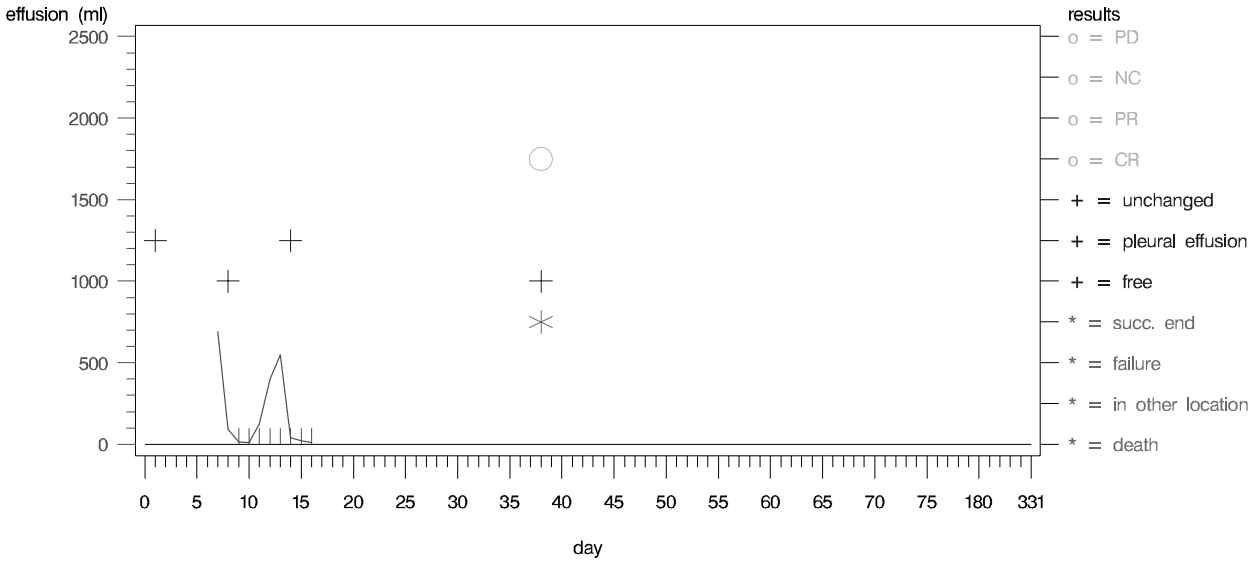

Figure 21: Helixor group: Course of illness of patient 33

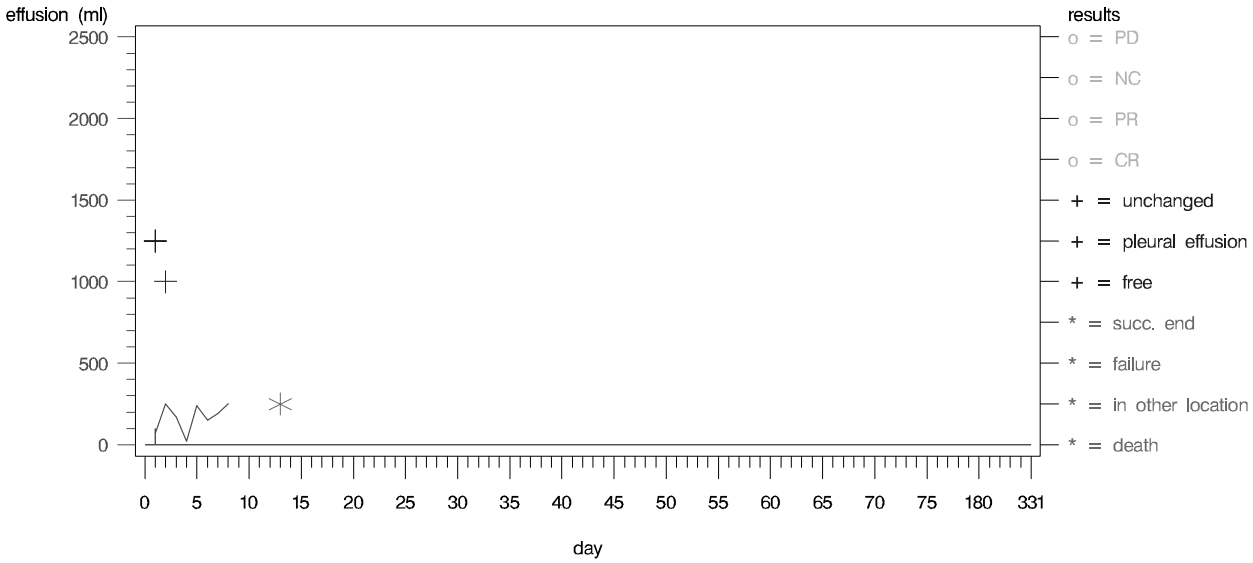

Figure 22: Doxycycline group: Course of illness of patient 2

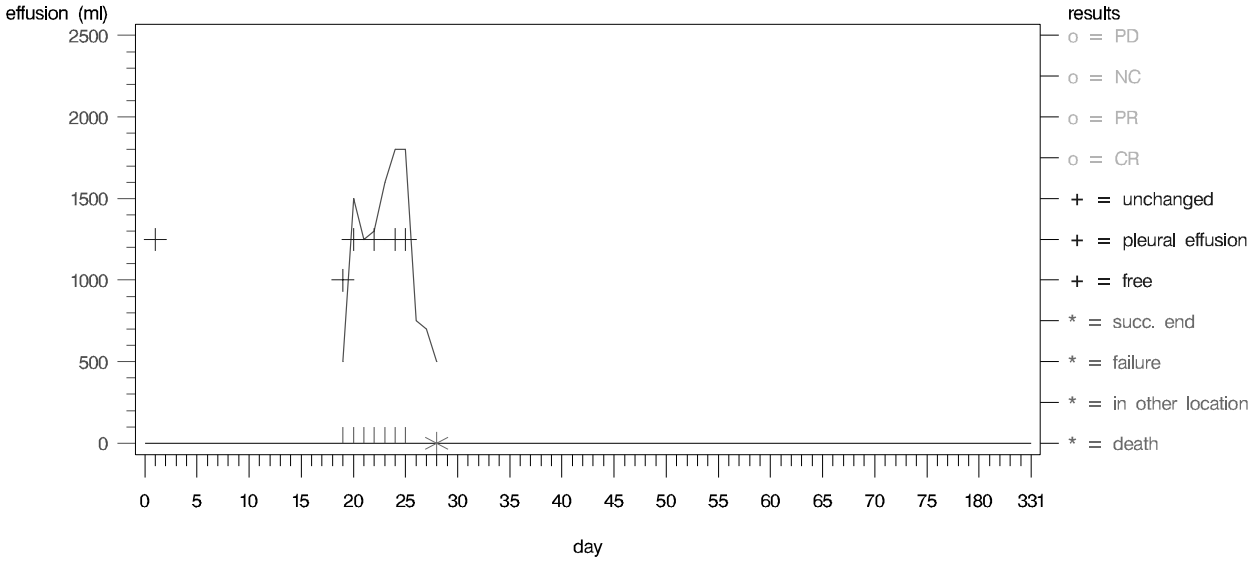

Figure 23: Doxycycline group: Course of illness of patient 4
(Patient was randomised in the Doxycycline group, but received Helixor.)

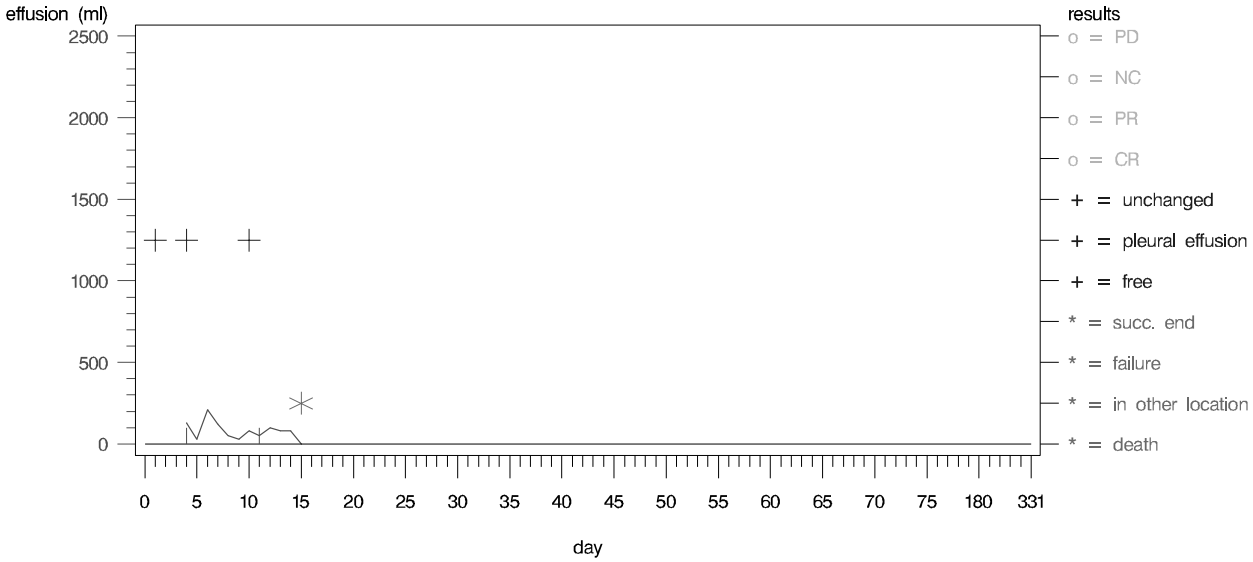

Figure 24: Doxycycline group: Course of illness of patient 7

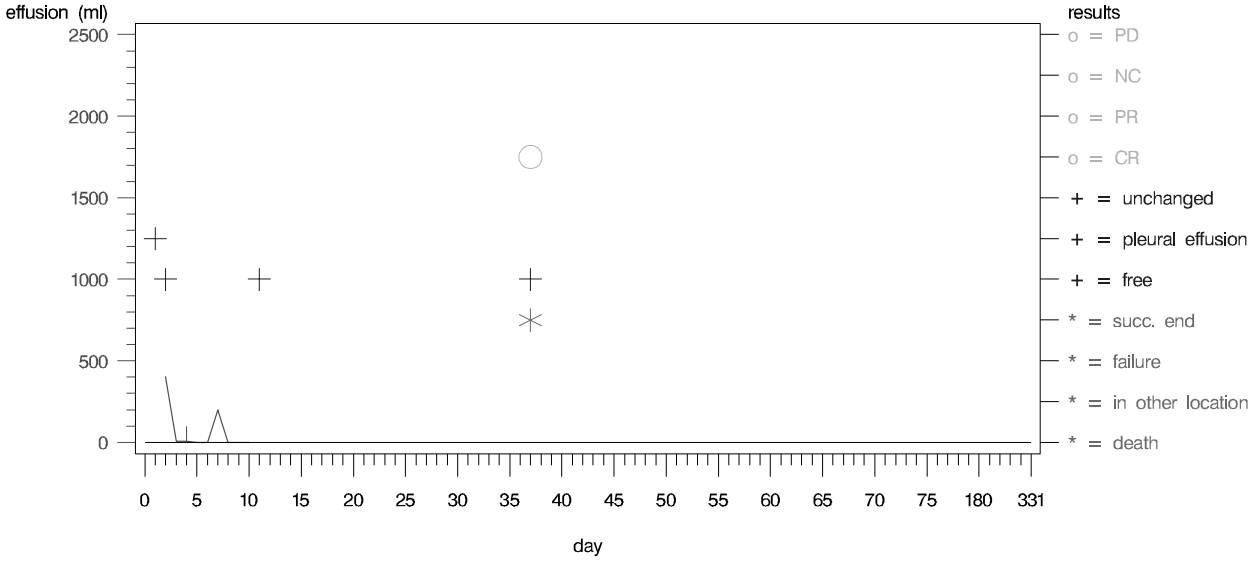

Figure 25: Doxycycline group: Course of illness of patient 12

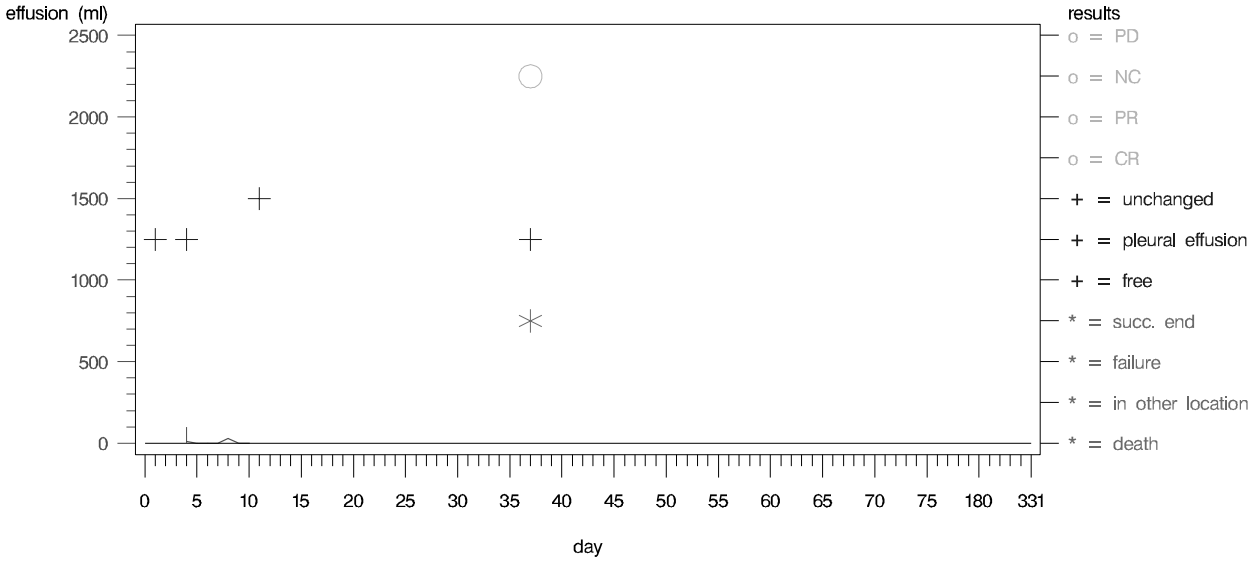

Figure 26: Doxycycline group: Course of illness of patient 15

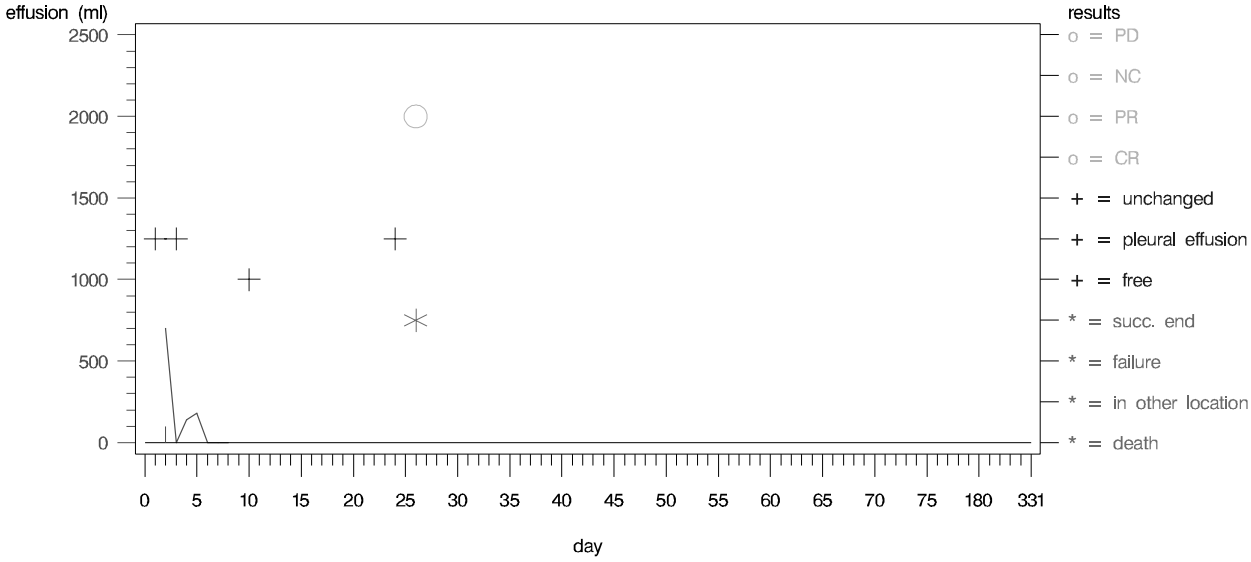

Figure 27: Doxycycline group: Course of illness of patient 16

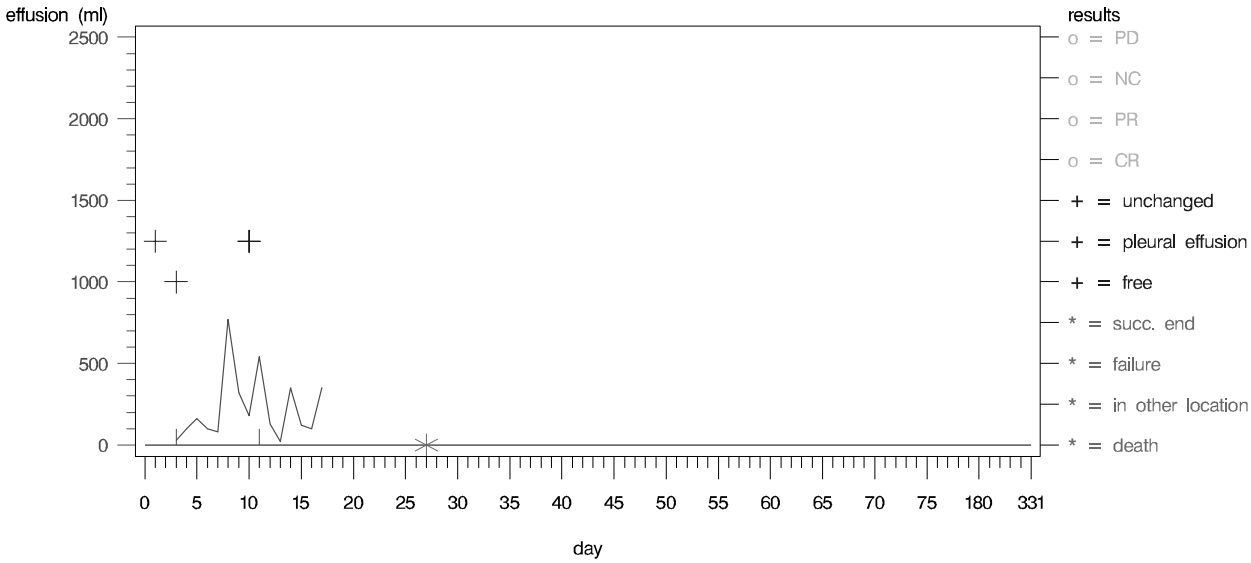

Figure 28: Doxycycline group: Course of illness of patient 17

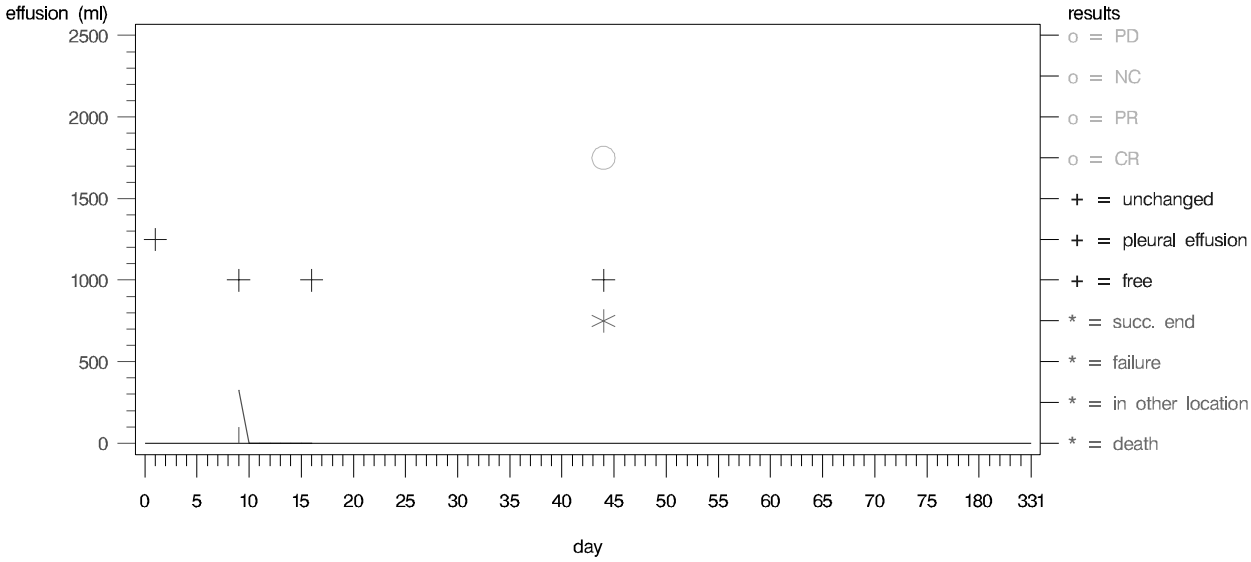

Figure 29: Doxycycline group: Course of illness of patient 18

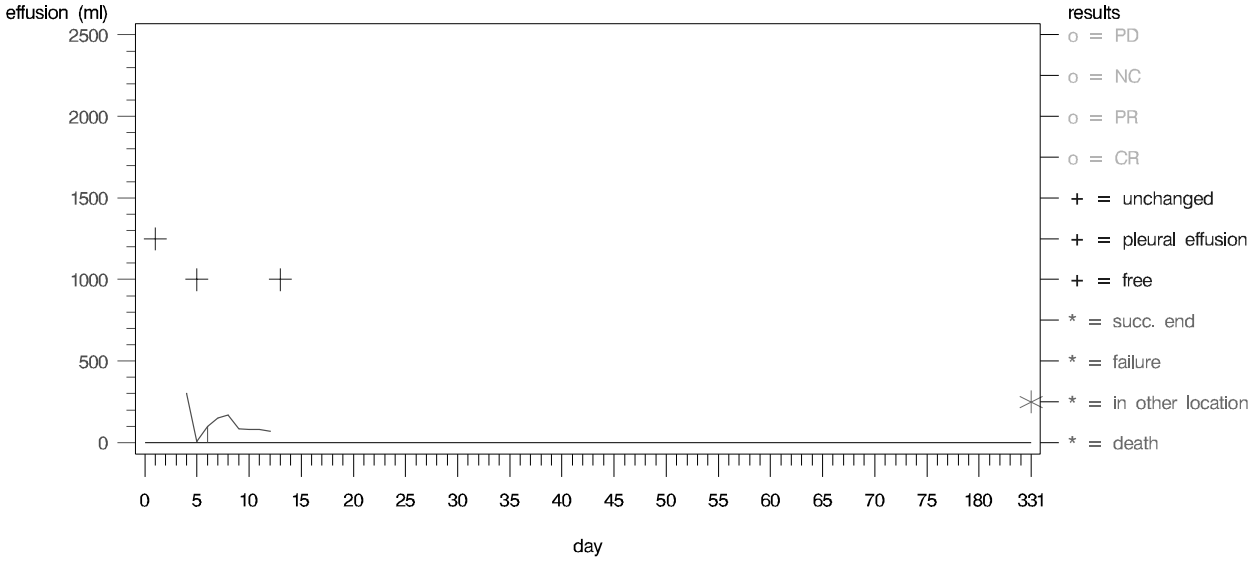

Figure 30: Doxycycline group: Course of illness of patient 20

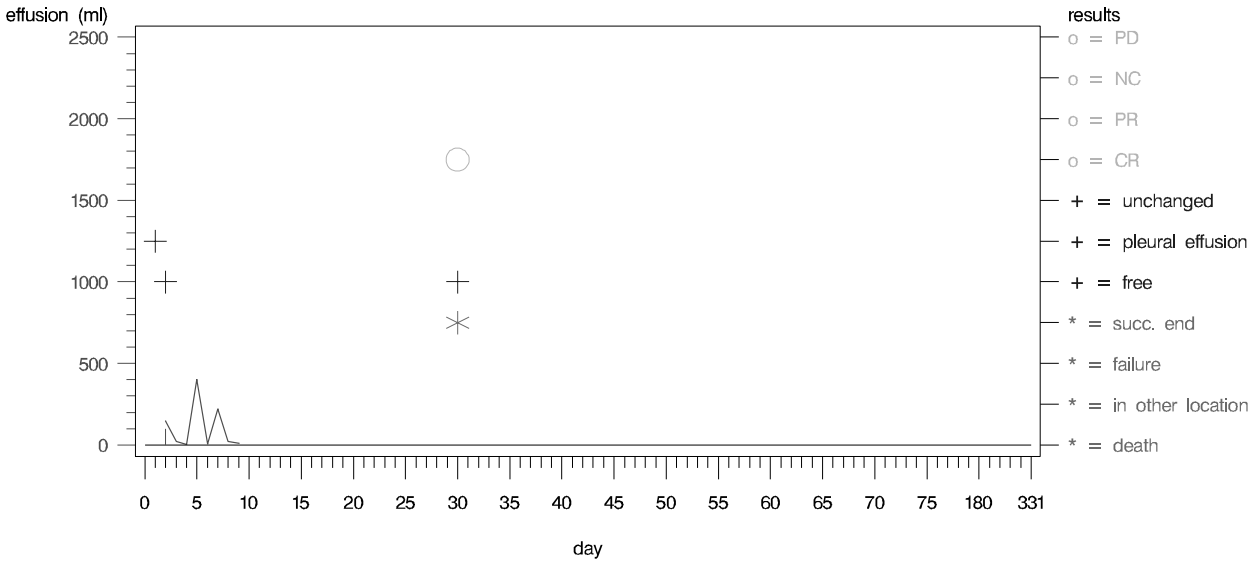

Figure 31: Doxycycline group: Course of illness of patient 21

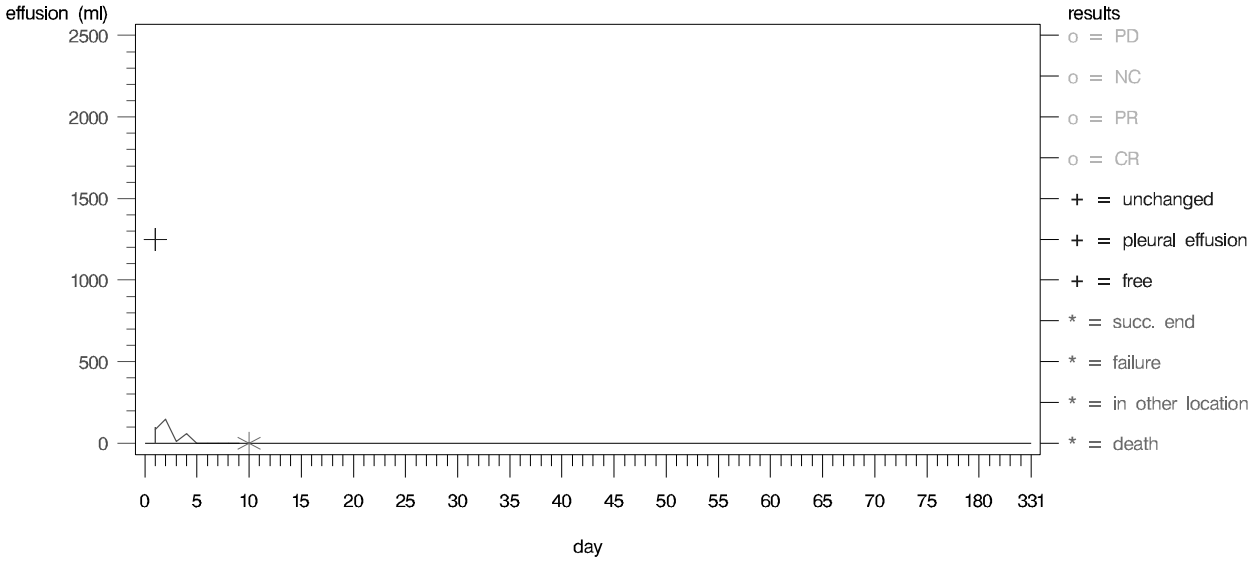

Figure 32: Doxycycline group: Course of illness of patient 23

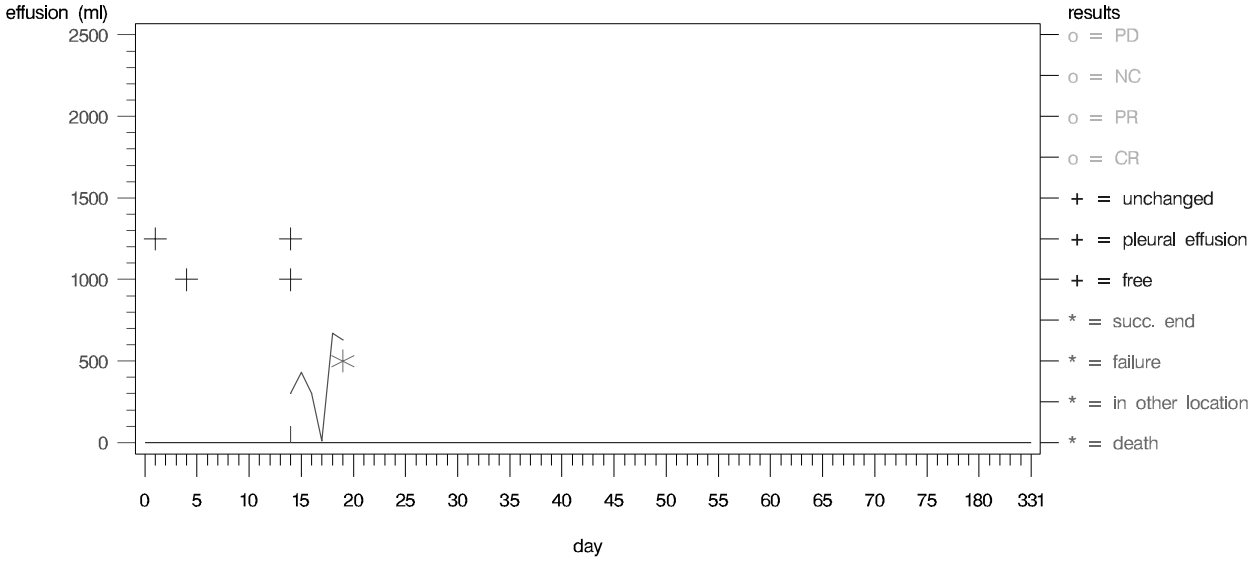

Figure 33: Doxycycline group: Course of illness of patient 25

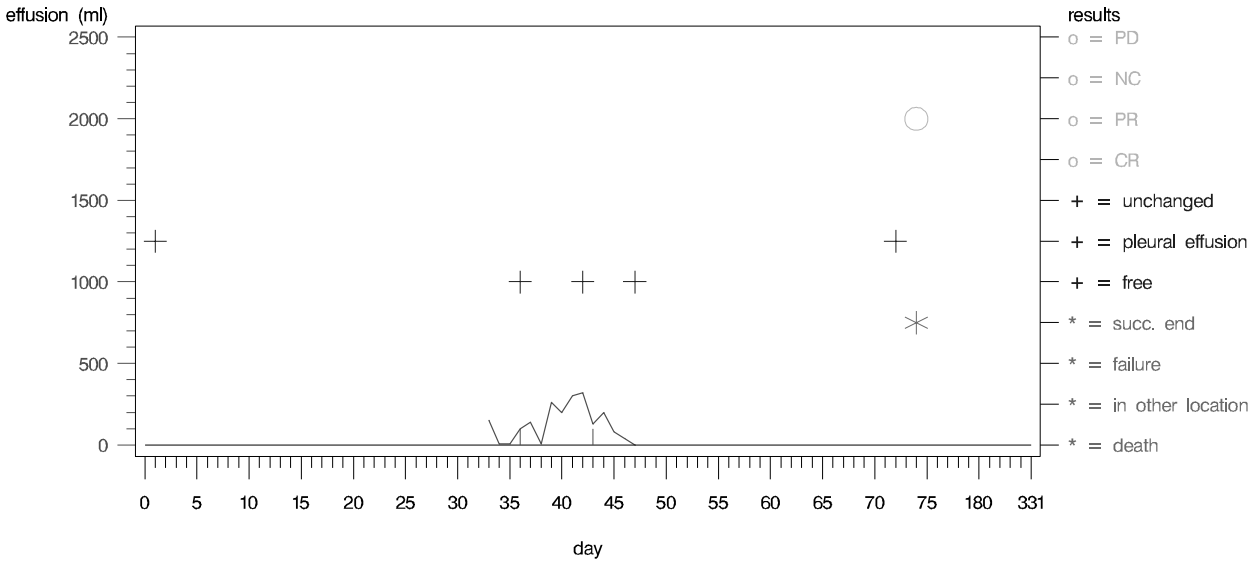

Figure 34: Doxycycline group: Course of illness of patient 27

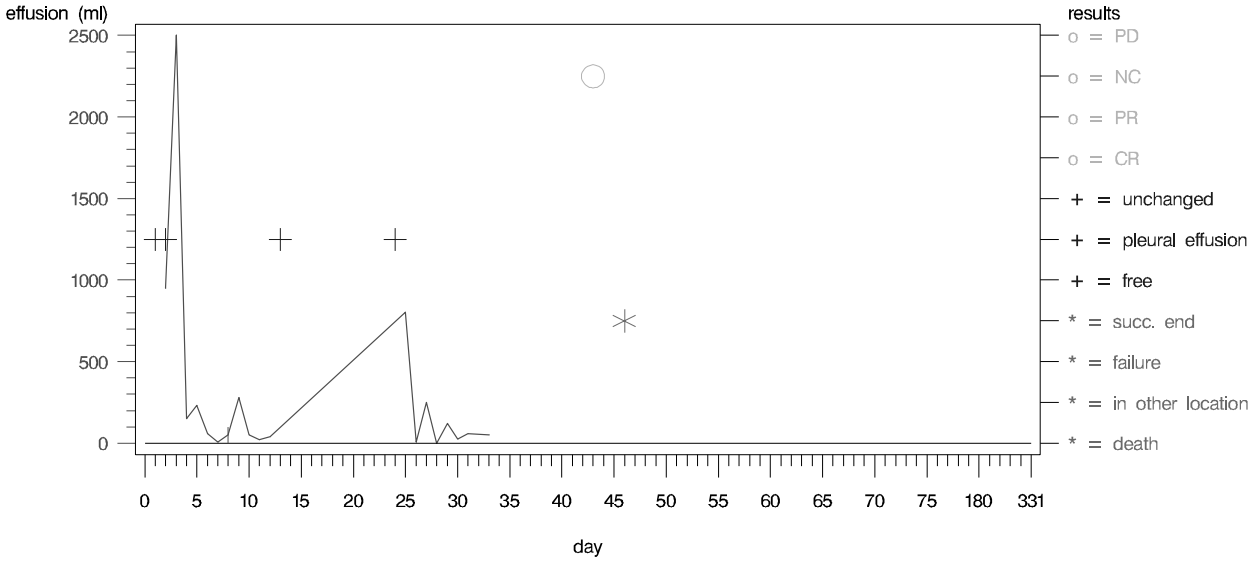

Figure 35: Doxycycline group: Course of illness of patient 28

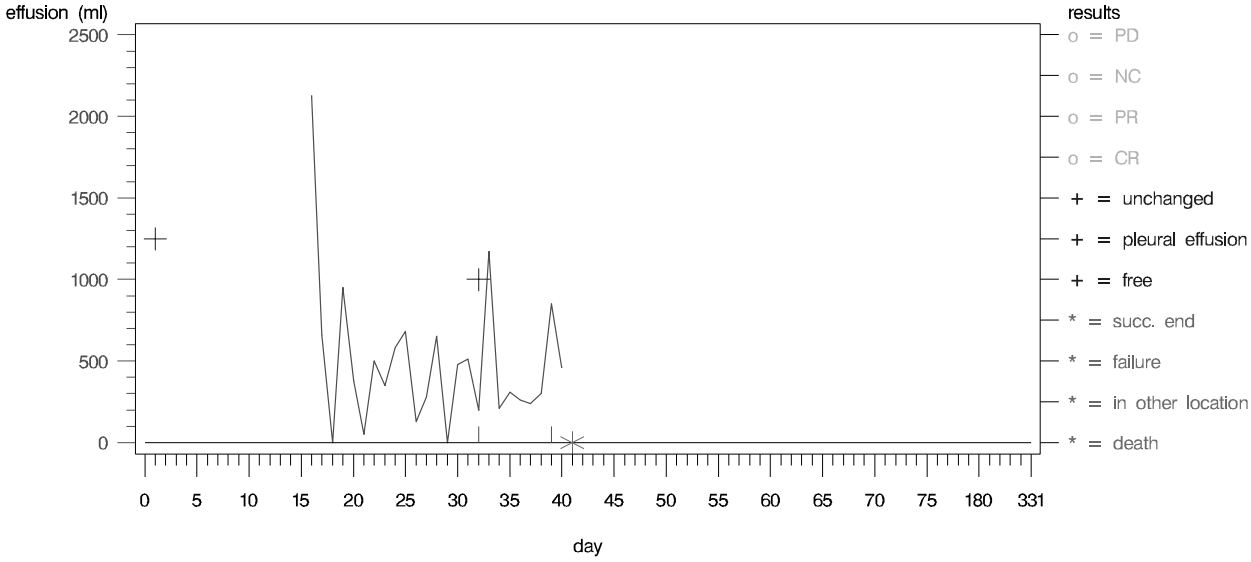

Figure 36: Doxycycline group: Course of illness of patient 30

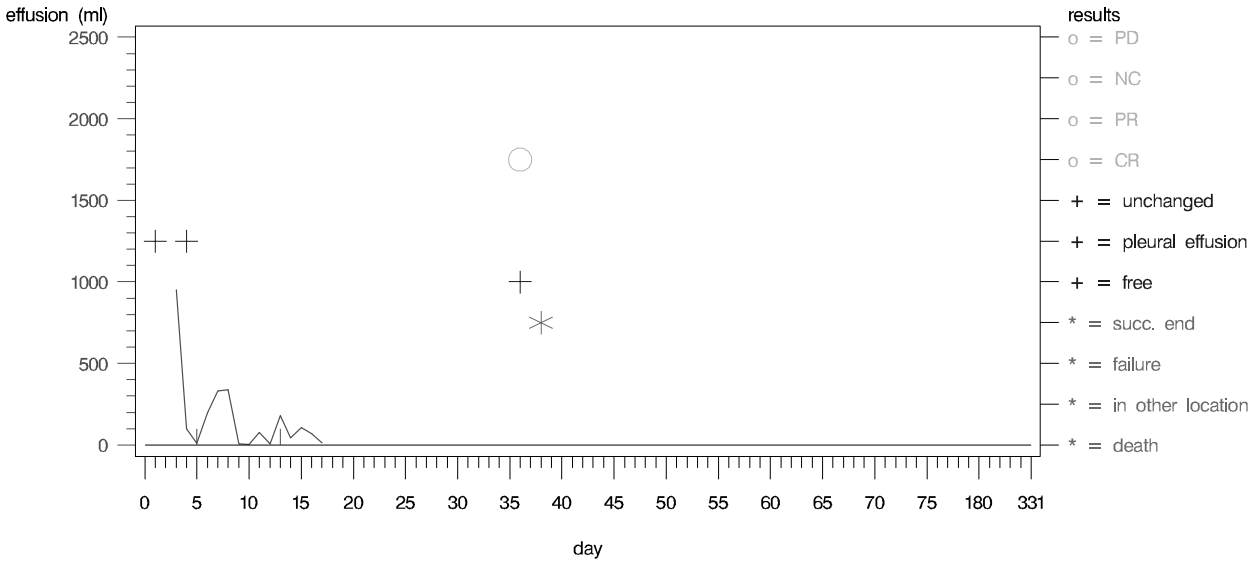

Figure 37: Doxycycline group: Course of illness of patient 31

6. Literature

- Bland J.M., Altman D.G. (1994). Statistic Notes: Regression towards the mean. BMJ 308: 1499
- Bland J.M., Altman D.G. (1994). Statistic Notes: Some examples of regression towards the mean. BMJ 309: 780
- Altman D.G. (1991). Practical statistics for medical research.
- Cochran W.G. (1977). Sampling Techniques. John Wiley & Sons. Third Edition.

7. Listings

Remark:
In the following listings, the parameter “group” is the treatment group, in which the patient was randomised. Patient number 5 was randomised in the Helixor group, but he received Doxycycline as treatment. Patient number 4 was randomised in the Doxycyline group, but he received Helixor as treatment.

Listing 1: Demographic characteristics

Group	Pat	date of birth	age [years]	sex	profession	alcohol consumption	smoker
Helixor	1	10/08/54	42	male	SALARY MAN	rarely	no
	3	17/07/42	54	male	NONE	rarely	no
	5	03/05/36	61	female	NONE	no	no
	6	15/08/25	72	female	HOUSEWIFE	no	no
	8	29/12/44	52	female	HOUSEWIFE	rarely	no
	9	22/01/38	59	female	HOUSEWIFE	no	no
	10	11/01/46	52	male	NONE	rarely	no
	11	23/01/22	76	female		rarely	no
	13	12/02/24	74	male	NONE	rarely	no
	14	18/02/34	64	female	HOUSEWIFE	no	no
	19	07/06/30	68	male	NONE	rarely	yes
	22	10/02/40	58	male	SALARY MAN	no	no
	24	20/04/28	70	male	DENTIST (RETIRED)	no	no
	26	11/08/40	58	male	FARMER	no	no
	29	18/07/38	60	female	HOUSEWIFE	no	no
	32	05/11/40	58	female	HOUSEWIFE	no	no
	33	24/02/51	48	female	HOUSEWIFE	no	no
Doxycycline	2	05/12/54	42	female	HOUSEWIFE	no	no
	4	28/02/64	33	female	HOUSEWIFE	no	no
	7	27/07/60	37	female	HOUSEWIFE	no	no
	12	25/03/61	37	female	HOUSEWIFE	no	no
	15	11/12/55	42	female	HOUSEWIFE	no	no
	16	03/10/51	46	female	SALARY MAN	rarely	no
	17	15/02/29	69	male	NONE	rarely	no
	18	05/04/32	66	male	NONE	rarely	yes
	20	10/03/52	46	female	HOUSEWIFE	no	no
	21	06/02/52	46	male	SALARY MAN	rarely	yes
	23	18/08/40	58	male	SALES MERCHANT	no	yes
	25	02/10/27	71	female		no	no
	27	24/01/52	47	male	PLUMBER	rarely	yes
	28	07/08/34	64	male	FARMER	regulary	yes
	30	03/03/53	46	male	NOT EMPLOYED	no	no
	31	26/02/59	40	male	PAID EMPLOYEE	no	yes

Listing 2: Characteristics of physical condition

Group	Pat.	examination	date	height [cm]	weight [kg]	temperature [°C]	pulse [/min]	blood pressure sys. [mm Hg]	blood pressure diast. [mm Hg]	Karnofsky Index [%]
Helixor	1	Screening	19/04/97	169.0	77.0	36.7	76	120	70	90
		Final	30/05/97	.	75.0	36.7	80	130	70	90
		final-screen	.	.	-2.0	0.0	4	10	0	0
	3	Screening	20/05/97	172.0	45.0	36.2	76	140	80	60
		Final	27/05/97	.	.	.	.	.	.	.
		final-screen	.	.	.	.	.	.	.	.
	5	Screening	25/08/97	160.0	42.8	37.0	82	110	70	80
		Final	24/09/97	.	43.0	36.4	88	120	70	80
		final-screen	.	.	0.2	-0.6	6	10	0	0
	6	Screening	09/09/97	149.0	57.0	36.5	88	120	70	70
		Final	18/10/97	.	57.5	36.5	84	110	80	70
		final-screen	.	.	0.5	0.0	-4	-10	10	0
	8	Screening	14/10/97	159.0	54.9	36.2	68	140	100	60
		Final	19/11/97	.	.	36.5	90	130	90	70
		final-screen	.	.	.	0.3	22	-10	-10	10
	9	Screening	16/11/97	156.0	53.6	36.3	90	90	60	70
		Final	27/12/97	.	53.6	36.3	88	100	60	80
		final-screen	.	.	0.0	0.0	-2	10	0	10
	10	Screening	08/02/98	170.0	52.0	36.8	88	120	70	60
		Final	.	.	.	.	.	.	.	.
		final-screen	.	.	.	.	.	.	.	.
	11	Screening	13/02/98	143.0	52.1	36.5	84	90	50	90
		Final	28/03/98	.	51.0	37.8	80	90	60	100
		final-screen	.	.	-1.1	1.3	-4	0	10	10
	13	Screening	28/09/98	168.0	52.0	36.7	88	110	70	70
		Final	03/11/98	.	50.0	37.0	92	100	70	60
		final-screen	.	.	-2.0	0.3	4	-10	0	-10
	14	Screening	01/10/98	156.0	62.0	36.5	60	130	80	70
		Final	04/11/98	.	61.0	36.5	60	130	80	70
		final-screen	.	.	-1.0	0.0	0	0	0	0
	19	Screening	05/01/99	168.0	50.0	36.7	80	100	60	60
		Final	.	.	.	.	.	.	.	.
		final-screen	.	.	.	.	.	.	.	.
	22	Screening	29/01/99	172.0	80.0	36.8	80	130	80	90
		Final	27/07/99	.	78.0	37.4	78	120	80	90
		final-screen	.	.	-2.0	0.6	-2	-10	0	0
	24	Screening	03/04/99	167.0	58.0	36.3	90	110	70	60
		Final	.	.	.	.	.	.	.	.
		final-screen	.	.	.	.	.	.	.	.
	26	Screening	07/05/99	165.0	64.0	36.4	74	110	70	70
		Final	25/06/99	.	60.0	36.0	76	110	70	60
		final-screen	.	.	-4.0	-0.4	2	0	0	-10
	29	Screening	06/07/99	159.0	63.1	36.4	74	140	80	100
		Final	02/09/99	.	63.5	36.6	70	130	80	100
		final-screen	.	.	0.4	0.2	-4	-10	0	0
	32	Screening	05/09/99	150.0	39.8	36.4	100	120	70	50
		Final	07/10/99	.	39.5	36.4	103	100	60	60
		final-screen	.	.	-0.3	0.0	3	-20	-10	10
	33	Screening	05/10/99	159.0	60.0	36.0	80	100	60	90
		Final	05/11/99	.	60.0	36.6	76	120	80	90
		final-screen	.	.	0.0	0.6	-4	20	20	0
Doxycycline	2	Screening	21/05/97	157.0	55.0	37.2	86	110	70	90
		Final	02/06/97	.	.	.	.	.	.	.
		final-screen	.	.	.	.	.	.	.	.

Group	Pat.	examination	date	height [cm]	weight [kg]	temperature [°C]	pulse [/min]	blood pressure sys. [mm Hg]	blood pressure diast. [mm Hg]	Karnofsky Index [%]
Doxycycline	4	Screening Final final-screen	13/07/97 . .	159.0 . .	55.0 . .	36.8 . .	132 . .	90 . .	60 . .	60 . .
	7	Screening Final final-screen	10/09/97 . .	153.0 . .	59.0 . .	36.8 . .	72 . .	110 . .	70 . .	80 . .
	12	Screening Final final-screen	28/07/98 02/09/98 .	167.0 . .	49.0 47.0 -2.0	37.0 36.6 -0.4	92 92 0	100 110 10	60 60 0	60 50 -10
	15	Screening Final final-screen	07/10/98 10/11/98 .	156.0 . .	54.0 50.0 -4.0	36.9 36.3 -0.6	92 116 24	120 140 20	80 90 10	60 40 -20
	16	Screening Final final-screen	29/09/98 24/10/98 .	166.0 . .	60.4 60.0 -0.4	36.6 36.5 -0.1	84 85 1	100 100 0	70 70 0	70 70 0
	17	Screening Final final-screen	10/12/98 . .	160.0 . .	40.0 . .	36.0 . .	96 . .	140 . .	90 . .	60 . .
	18	Screening Final final-screen	04/01/99 09/02/99 .	170.0 . .	65.0 62.0 -3.0	36.4 36.5 0.1	88 82 -6	120 110 -10	70 80 10	60 70 10
	20	Screening Final final-screen	23/01/99 . .	155.0 . .	48.0 . .	36.4 . .	88 . .	110 . .	70 . .	80 . .
	21	Screening Final final-screen	28/01/99 26/02/99 .	164.0 . .	66.0 66.0 0.0	36.0 36.4 0.4	84 80 -4	130 130 0	80 80 0	80 70 -10
	23	Screening Final final-screen	25/03/99 . .	171.0 . .	65.0 . .	36.6 . .	85 . .	120 . .	80 . .	60 . .
	25	Screening Final final-screen	27/04/99 . .	149.0 . .	52.0 . .	36.8 . .	76 . .	100 . .	60 . .	50 . .
	27	Screening Final final-screen	10/05/99 21/06/99 .	165.0 . .	58.0 . .	36.2 36.8 0.6	78 76 -2	138 120 -18	80 70 -10	90 90 0
	28	Screening Final final-screen	17/05/99 01/07/99 .	168.0 . .	64.0 . .	36.8 38.0 1.2	90 90 0	110 110 0	70 70 0	90 90 0
	30	Screening Final final-screen	11/08/99 . .	170.0 . .	53.0 . .	36.8 . .	92 . .	100 . .	60 . .	60 . .
	31	Screening Final final-screen	25/08/99 30/09/99 .	170.0 . .	77.0 70.0 -7.0	37.0 36.4 -0.6	94 70 -24	110 100 -10	70 60 -10	90 100 10

Listing 3: Additional diseases before screening

Group	Pat	disease, previous operation	since	still persistent
Helixor	1	Gastritis	10/95	yes
	3	Stomach Ca. Billroth op	3/97	na
		Old Tuberculosis	3/90	no
		Emphysema	3/90	yes
	5	non toxic multinodular goiter	7/93	yes
		gastritis	5/95	yes
	6	Gastritis	9/94	yes
	8	Atrial fibrillation	./.	yes
	24	Diabetes mellitus	3/99	yes
	26	Myocardial infarction	2/87	yes
	32	Diabetes mellitus	./.	yes
Doxycycline	2	Gastritis	2/92	yes
	4	Lumpectomy with lymph node dissection	11/93	yes
	7	Dyspepsia	8/97	yes
	12	Modified radical mastectomy due to Breast cancer	7/96	yes
	21	Appendectomy due to acute appendicitis	2/89	no

Listing 4: Physical examinations part 1

Group	Pat.	examination	date	Nutritional status	Skin	Edemas	Lymphnodes	head	Mucous membrane of the mouth	Thyroid	Resp. tract/ lung
Helixor	1	Screening Final	19/04/97 30/05/97	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.
	3	Screening Final	20/05/97 27/05/97	not rel. .	normal .	normal .	normal .	normal .	normal .	normal .	rel. .
	5	Screening Final	25/08/97 24/09/97	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	not rel. not rel.	rel. rel.
	6	Screening Final	09/09/97 18/10/97	normal normal	normal normal	normal normal	rel. rel.	normal normal	normal normal	normal normal	not rel. not rel.
	8	Screening Final	14/10/97 19/11/97	normal rel.	normal not rel.	normal rel.	normal normal	normal normal	normal normal	normal normal	normal not rel.
	9	Screening Final	16/11/97 27/12/97	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. not rel.
	10	Screening Final	08/02/98 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	rel. .
	11	Screening Final	13/02/98 28/03/98	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	not rel. not rel.
	13	Screening Final	28/09/98 03/11/98	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.
	14	Screening Final	01/10/98 04/11/98	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.
	19	Screening Final	05/01/99 .	not rel. .	normal .	normal .	normal .	normal .	normal .	normal .	rel. .
	22	Screening Final	29/01/99 27/07/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.
	24	Screening Final	03/04/99 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	rel. .
	26	Screening Final	07/05/99 25/06/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.
	29	Screening Final	06/07/99 02/09/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.
	32	Screening Final	05/09/99 07/10/99	not rel. normal	normal not rel.	normal not rel.	normal normal	normal normal	normal normal	normal normal	rel. rel.
	33	Screening Final	05/10/99 05/11/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.
Doxycycline	2	Screening Final	21/05/97 02/06/97	normal .	normal .	normal .	normal .	normal .	normal .	normal .	rel. .
	4	Screening Final	13/07/97 .	rel. .	rel. .	rel. .	normal .	rel. .	normal .	normal .	rel. .
	7	Screening Final	10/09/97 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	not rel. .
	12	Screening Final	28/07/98 02/09/98	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.
	15	Screening Final	07/10/98 10/11/98	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.
	16	Screening Final	29/09/98 24/10/98	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.

Group	Pat.	examination	date	Nutritional status	Skin	Edemas	Lymphnodes	head	Mucous membrane of the mouth	Thyroid	Resp. tract/ lung
Doxycycline	17	Screening Final	10/12/98 .	not rel. .	normal .	not rel. .	normal .	normal .	normal .	normal .	rel. .
	18	Screening Final	04/01/99 09/02/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.
	20	Screening Final	23/01/99 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	rel. .
	21	Screening Final	28/01/99 26/02/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. normal
	23	Screening Final	25/03/99 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	rel. .
	25	Screening Final	27/04/99 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	rel. .
	27	Screening Final	10/05/99 21/06/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.
	28	Screening Final	17/05/99 01/07/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.
	30	Screening Final	11/08/99 .	rel. .	normal .	normal .	normal .	normal .	normal .	normal .	rel. .
	31	Screening Final	25/08/99 30/09/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.

Listing 5: Physical examinations part 2

Group	Pat.	examination	date	Heart	Breasts	Abdomen	Kidney region	Spine	Extremities	Nervous system	Urogenital system	Other
Helixor	1	Screening Final	19/04/97 30/05/97	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal
	3	Screening Final	20/05/97 27/05/97	normal .	normal .	not rel. .	normal .	normal .	normal .	normal .	normal .	. .
	5	Screening Final	25/08/97 24/09/97	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal
	6	Screening Final	09/09/97 18/10/97	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal
	8	Screening Final	14/10/97 19/11/97	normal normal	rel. rel.	normal normal	normal normal	normal normal	rel. rel.	normal normal	normal normal	normal normal
	9	Screening Final	16/11/97 27/12/97	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal
	10	Screening Final	08/02/98 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .
	11	Screening Final	13/02/98 28/03/98	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal
	13	Screening Final	28/09/98 03/11/98	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	. normal
	14	Screening Final	01/10/98 04/11/98	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal
	19	Screening Final	05/01/99 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .
	22	Screening Final	29/01/99 27/07/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal
	24	Screening Final	03/04/99 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .
	26	Screening Final	07/05/99 25/06/99	not rel. not rel.	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal .
	29	Screening Final	06/07/99 02/09/99	normal normal	rel. rel.	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal
	32	Screening Final	05/09/99 07/10/99	normal normal	rel. rel.	rel. rel.	normal normal	normal normal	normal not rel.	normal normal	normal normal	rel. rel.
	33	Screening Final	05/10/99 05/11/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal
Doxycycline	2	Screening Final	21/05/97 02/06/97	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .
	4	Screening Final	13/07/97 .	normal .	rel. .	rel. .	normal .	rel. .	rel. .	normal .	normal .	normal .
	7	Screening Final	10/09/97 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .
	12	Screening Final	28/07/98 02/09/98	normal normal	rel. rel.	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal
	15	Screening Final	07/10/98 10/11/98	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	rel. rel.	. .
	16	Screening Final	29/09/98 24/10/98	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal
	17	Screening Final	10/12/98 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .

Group	Pat.	examination	date	Heart	Breasts	Abdomen	Kidney region	Spine	Extremities	Nervous system	Urogenital system	Other
Doxycyline	18	Screening Final	04/01/99 09/02/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal
	20	Screening Final	23/01/99 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .
	21	Screening Final	28/01/99 26/02/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal
	23	Screening Final	25/03/99 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .
	25	Screening Final	27/04/99 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .
	27	Screening Final	10/05/99 21/06/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	. normal
	28	Screening Final	17/05/99 01/07/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal
	30	Screening Final	11/08/99 .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	normal .	. .
	31	Screening Final	25/08/99 30/09/99	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal	normal normal

Listing 6: Extent and history of malignancy

Group	Pat	Diagnosis	time of diagnosis	months since diagnosis	tumor stage	distant metastases	Previous treatment
Helixor	1	Adenocarcinoma of lung cancer	3/97	1	T4 N2 M1	pleura	no
	3	Stomach Ca.	3/97	2	T4 N2 M1	pleura	op
	5	Bronchoalveolar cell carcinoma with right pleural effusion	8/97	0	T4 N1 M1	pleura	op other
	6	Metastasis of unknown origin with left pleural metastasis and cervix lymphnode metastasis	8/97	1	TX N3 M1	pleura lymphnodes	no
	8	Breast cancer	4/96	18	T4 N2 M1	pleura bones	op other
	9	Adenocarcinoma of lung cancer	1/97	10	T4 N0 M1	pleura lung bones	other
	10	Small cell lung cancer	2/97	12	T4 N2 M1	pleura	radiotherapy other
	11	Lung cancer	2/98	0	T4 N1 M1	pleura	no
	13	Adenocarcinoma of lung cancer	9/98	0	T4 N0 M1	pleura liver	no
	14	Bronchoalveolar carcinoma (lung ca.)	9/98	1	T4 N1 M1	pleura	no
	19	Adenocarcinoma of lung cancer	12/98	1	T4 N3 M1	pleura	other
	22	Lung cancer (squamous cell type)	1/99	0	T4 N1 M1	pleura	no
	24	Lung cancer (squamous cell type)	10/98	6	T4 N0 M1	pleura	radiotherapy other
	26	Lung cancer (squamous cell type)	9/98	8	T4 N2 M1	pleura	radiotherapy other
	29	Breast cancer	/83	192	T4 N0 M1	pleura bones	op
	32	Breast cancer	6/90	111	T4 N3 M1	pleura bones liver brain	op radiotherapy other
	33	Adenocarcinoma of lung cancer	10/99	0	T4 N0 M1	pleura	no
Doxycycline	2	Adenocarcinoma of lung ancer with malignant pleural effusion (right)	5/97	0	T4 N3 M1	pleura	no
	4	Breast cancer (invasive ductal cancer)	11/93	44	T4 N3 M1	pleura bones liver	op radiotherapy other
	7	Adenocarcinoma of lung with malignant pleural effusion	9/97	0	T4 N1 M1	pleura bones	no
	12	Breast cancer (with malignant pleural effusion and bone metastaseses)	7/96	24	T2 N1 M1	pleura bones	op
	15	Adenocarcinoma of bartholin gland	3/98	7	T3 N0 M1	pleura	radiotherapy other
	16	Adenocarcinoma of lung	9/98	0	T4 N2 M1	pleura bones	other
	17	Rectal Ca with malignant pleural effusion	11/98	1	T3 N2 M1	pleura liver other	op
	18	Adenocarcinoma of lung cancer with liver metastasis	10/98	3	T4 N3 M1	pleura liver	other
	20	Adenocarcinoma of lung cancer	1/99	0	T4 N2 M1	pleura bones	no
	21	Adenocarcinoma of lung cancer	1/99	0	T4 N2 M1	pleura	no
	23	Lung cancer (small cell type, extensive stage)	1/98	14	T4 N3 M1	pleura	radiotherapy other

Group	Pat	Diagnosis	time of diagnosis	months since diagnosis	tumor stage	distant metastases	Previous treatment
Doxycyline	25	Cerxic cancer	4/97	24	T4 NX M1	pleura	radiotherapy other
	27	Adenocarcinoma of lung cancer	4/99	1	T1 N3 M1	pleura	no
	28	Lung cancer (squamous cell type)	5/99	0	T4 N2 M1	pleura	no
	30	Adenocarcinoma of lung cancer	9/98	11	T4 N3 M1	pleura	radiotherapy other
	31	Adenocarcinoma of lung cancer	7/99	1	T4 N3 M1	pleura	no

Listing 7: Effusion and instillations

Group	Pat	date	instillation no	method	effusion [ml]	dosage [mg]	volume [ml]
Helixor	1	19/04/97	1	catheter (pigtail)	300	100	2
		20/04/97	2	catheter	250	200	4
		21/04/97	3	catheter	0	300	6
		22/04/97	4	catheter	0	400	8
		23/04/97	5	catheter	0	500	10
		24/04/97	6	catheter	0	500	10
		25/04/97	7	catheter	0	500	10
	3	07/05/97	.	puncture	1400		
		16/05/97	.	catheter	600		
		17/05/97	.	catheter	10		
		18/05/97	.	catheter	110		
		19/05/97	.	catheter	50		
		21/05/97	1	catheter	750	100	2
		22/05/97	2	catheter	130	200	4
		23/05/97	3	catheter	50	300	6
		24/05/97	4	catheter	50	400	8
		25/05/97	5	catheter	50	500	10
		26/05/97	.	catheter	50		
	5	25/08/97	.	catheter (pigtail)	300		
		26/08/97	.	catheter	10		
		27/08/97	.	catheter	0		
		28/08/97	1	catheter	700		
		29/08/97	.	catheter	0		
		30/08/97	.	catheter	0		
		31/08/97	.	catheter	100		
		01/09/97	.	catheter	30		
		02/09/97	.	catheter	40		
		03/09/97	.	catheter removal	0		
		04/09/97	.	puncture	0		
	6	10/09/97	1	catheter	50	100	2
		11/09/97	2	catheter	50	200	4
		12/09/97	3	catheter	50	300	6
		13/09/97	4	catheter	40	400	8
		14/09/97	5	catheter	30	500	10
		15/09/97	6	catheter	0	500	10
		16/09/97	7	catheter	0	500	10
		17/09/97	.	catheter	0		
	8	15/10/97	1	catheter (pigtail)	300	100	2
		16/10/97	2	catheter	800	200	4
		17/10/97	3	catheter	300	300	6
		18/10/97	4	catheter	110	400	8
		19/10/97	5	catheter	10	500	10
		20/10/97	6	catheter	200	500	10
		21/10/97	7	catheter	100	500	10
	9	19/11/97	1	catheter	1250	100	2
		20/11/97	2	catheter	0	200	4
		21/11/97	3	catheter	0	300	6
		22/11/97	4	catheter	0	400	8
		23/11/97	5	catheter	0	500	10
		24/11/97	6	catheter	0	500	10
		25/11/97	7	catheter	0	500	10
	10	09/02/98	1	catheter	200	100	2
		10/02/98	2	catheter	110	200	4
		11/02/98	3	catheter	0	300	6
		12/02/98	.	catheter	0		
		13/02/98	.	catheter	0		
	11	21/02/98	.	catheter	120		
		22/02/98	1	catheter	20	100	2
		23/02/98	2	catheter	60	200	4
		24/02/98	3	catheter	100	300	6
		25/02/98	4	catheter	20	400	8
		26/02/98	5	catheter	50	500	10
		27/02/98	6	catheter	10	500	10
		28/02/98	7	catheter	0	500	10
		01/03/98	.	catheter	0		
	13	30/09/98	1	catheter	30	100	2
		01/10/98	2	catheter	700	200	4
		02/10/98	3	catheter	100	300	6
		03/10/98	4	catheter	100	400	8
		04/10/98	5	catheter	100	500	10
		05/10/98	6	catheter	50	500	10
		06/10/98	7	catheter	30	500	10

Group	Pat	date	instillation no	method	effusion [ml]	dosage [mg]	volume [ml]
Helixor	14	02/10/98	1	catheter	100	100	2
		03/10/98	2	catheter	130	200	4
		04/10/98	3	catheter	100	300	6
		05/10/98	4	catheter	230	400	8
		06/10/98	5	catheter	0	500	10
		07/10/98	6	catheter	0	500	10
		08/10/98	7	catheter	10	500	10
	19	06/01/99	1	catheter	30	100	2
		07/01/99	2	catheter	120	200	4
		08/01/99	3	catheter	100	300	6
		09/01/99	4	catheter	165	400	8
		10/01/99	5	catheter	492	500	10
		11/01/99	6	catheter	80	500	10
		12/01/99	7	catheter	468	500	10
		13/01/99	.	catheter	135		
		14/01/99	.	catheter	.		
	22	28/01/99	.	catheter	120		
		29/01/99	.	catheter	5		
		30/01/99	.	catheter	7		
		31/01/99	.	catheter	4		
		01/02/99	1	catheter	70	100	2
		02/02/99	2	catheter	0	200	4
		03/02/99	3	catheter	0	300	6
		04/02/99	4	catheter	1	400	8
		05/02/99	5	catheter	0	500	10
		06/02/99	6	catheter	0	500	10
		07/02/99	7	catheter	5	500	10
		08/02/99	.	catheter removal	.		
	24	04/04/99	.	catheter (pigtail)	840		
		05/04/99	1	catheter	100	100	2
		06/04/99	2	catheter	475	200	4
		07/04/99	3	catheter	130	300	6
		08/04/99	4	catheter	362	400	8
		09/04/99	5	catheter	340	500	10
		10/04/99	6	catheter	260	500	10
		11/04/99	7	catheter	435	500	10
		12/04/99	8	catheter	400	500	10
		13/04/99	9	catheter	220	500	10
	26	12/05/99	.	catheter	120		
		13/05/99	1	catheter	40	100	2
		14/05/99	2	catheter	110	200	4
		15/05/99	3	catheter	52	300	6
		16/05/99	4	catheter	100	400	8
		17/05/99	5	catheter	60	500	10
		18/05/99	6	catheter	122	500	10
		19/05/99	7	catheter	28	500	10
		20/05/99	.	catheter	25		
		21/05/99	.	catheter removal	.		
	29	10/07/99	.	catheter (pigtail)	350		
		11/07/99	.	catheter	10		
		12/07/99	1	catheter	3.5	100	2
		13/07/99	2	catheter	3	200	4
		14/07/99	3	catheter	35	300	6
		15/07/99	4	catheter	370	400	8
		16/07/99	5	catheter	40	500	10
		17/07/99	6	catheter	10	500	10
		18/07/99	7	catheter	0	500	10
		19/07/99	.	catheter	0		
		20/07/99	.	US guided puncture	45		
		21/07/99	.	catheter	0		
		22/07/99	.	catheter removal	.		
	32	08/09/99	1	catheter	5	100	2
		09/09/99	2	catheter	10	200	4
		10/09/99	3	catheter	10	300	6
		11/09/99	.	catheter	10		
		12/09/99	.	catheter removal	.		

Group	Pat	date	instillation no	method	effusion [ml]	dosage [mg]	volume [ml]
Helixor	33	05/10/99	.	catheter	690		
		06/10/99	.	catheter	90		
		07/10/99	1	catheter	15	100	2
		08/10/99	2	catheter	10	200	4
		09/10/99	3	catheter	125	300	6
		10/10/99	4	catheter	400	400	8
		11/10/99	5	catheter	550	500	10
		12/10/99	6	catheter	40	500	10
		13/10/99	7	catheter	20	500	10
		14/10/99	8	catheter	10	500	10
Doxycycline	2	21/05/97	1	catheter	70		
		22/05/97	.	catheter	250		
		23/05/97	.	catheter	170		
		24/05/97	.	catheter	20		
		25/05/97	.	catheter	238		
		26/05/97	.	catheter	150		
		27/05/97	.	catheter	190		
		28/05/97	.	catheter	250		
	4	16/07/97	1	catheter	500	100	2
		17/07/97	2	catheter	1500	200	4
		18/07/97	3	catheter	1250	300	6
		19/07/97	4	catheter	1300	400	8
		20/07/97	5	catheter	1600	500	10
		21/07/97	6	catheter	1800	500	10
		22/07/97	7	catheter	1800	500	10
		23/07/97	.	catheter	750		
		24/07/97	.	catheter	700		
		25/07/97	.	catheter	500		
	7	11/09/97	1	catheter	130		
		12/09/97	.	catheter	30		
		13/09/97	.	catheter	210		
		14/09/97	.	catheter	120		
		15/09/97	.	catheter	50		
		16/09/97	.	catheter	30		
		17/09/97	.	catheter	80		
		18/09/97	2	catheter	50		
		19/09/97	.	catheter	100		
		20/09/97	.	catheter	80		
		21/09/97	.	catheter	80		
		22/09/97	.	catheter	0		
	12	29/07/98	.	catheter	400		
		30/07/98	.	catheter	5		
		31/07/98	1	catheter	5		
		01/08/98	.	catheter	0		
		02/08/98	.	catheter	0		
		03/08/98	.	catheter	200		
		04/08/98	.	catheter	0		
		05/08/98	.	catheter	0		
		06/08/98	.	catheter	0		
	15	08/10/98	1	catheter	10		
		09/10/98	.	catheter	0		
		10/10/98	.	catheter	0		
		11/10/98	.	catheter	0		
		12/10/98	.	catheter	30		
		13/10/98	.	catheter	0		
		14/10/98	.	catheter	0		
	16	30/09/98	1	catheter	700		
		01/10/98	.	catheter	0		
		02/10/98	.	catheter	140		
		03/10/98	.	catheter	180		
		04/10/98	.	catheter	0		
		05/10/98	.	catheter	0		
		06/10/98	.	catheter	0		

Group	Pat	date	instillation no	method	effusion [ml]	dosage [mg]	volume [ml]
Doxycycline	17	11/12/98	1	catheter	30		
		12/12/98	.	catheter	100		
		13/12/98	.	catheter	160		
		14/12/98	.	catheter	100		
		15/12/98	.	catheter	80		
		16/12/98	.	catheter	770		
		17/12/98	.	catheter	320		
		18/12/98	.	catheter	180		
		19/12/98	2	catheter	540		
		20/12/98	.	catheter	130		
		21/12/98	.	catheter	20		
		22/12/98	.	catheter	350		
		23/12/98	.	catheter	120		
		24/12/98	.	catheter	100		
		25/12/98	.	catheter	350		
	18	05/01/99	1	catheter	325		
		06/01/99	.	catheter	0		
		07/01/99	.	catheter	0		
		08/01/99	.	catheter	0		
		09/01/99	.	catheter	0		
		10/01/99	.	catheter	0		
		11/01/99	.	catheter	0		
		12/01/99	.	catheter	0		
	20	25/01/99	.	catheter	300		
		26/01/99	.	catheter	5		
		27/01/99	1	catheter	100		
		28/01/99	.	catheter	150		
		29/01/99	.	catheter	168		
		30/01/99	.	catheter	85		
		31/01/99	.	catheter	80		
		01/02/99	.	catheter	80		
		02/02/99	.	catheter	70		
	21	29/01/99	1	catheter (pigtail)	145		
		30/01/99	.	catheter	22		
		31/01/99	.	catheter	3		
		01/02/99	.	catheter	400		
		02/02/99	.	catheter	7		
		03/02/99	.	catheter	220		
		04/02/99	.	catheter	20		
		05/02/99	.	catheter	10		
	23	27/03/99	1	catheter (pigtail)	84		
		28/03/99	.	catheter	146		
		29/03/99	.	catheter	10		
		30/03/99	.	catheter	60		
		31/03/99	.	catheter	0		
		01/04/99	.	catheter	0		
		02/04/99	.	catheter	0		
		03/04/99	.	catheter	0		
		04/04/99	.	catheter	0		
	25	06/05/99	1	catheter (pigtail)	300		
		07/05/99	.	catheter	430		
		08/05/99	.	catheter	300		
		09/05/99	.	catheter	10		
		10/05/99	.	catheter	670		
		11/05/99	.	catheter	630		
	27	11/05/99	.	catheter	150		
		12/05/99	.	catheter	5		
		13/05/99	.	catheter	5		
		14/05/99	1	catheter	100		
		15/05/99	.	catheter	140		
		16/05/99	.	catheter	5		
		17/05/99	.	catheter	260		
		18/05/99	.	catheter	200		
		19/05/99	.	catheter	300		
		20/05/99	.	catheter	320		
		21/05/99	2	catheter	130		
		22/05/99	.	catheter	200		
		23/05/99	.	catheter	80		
		24/05/99	.	catheter	40		
		25/05/99	.	catheter	0		
		26/05/99	.	catheter removal	.		

Group	Pat	date	instillation no	method	effusion [ml]	dosage [mg]	volume [ml]
Doxycycline	28	18/05/99	.	catheter (pigtail)	950		
		19/05/99	.	catheter	2500		
		20/05/99	.	catheter	150		
		21/05/99	.	catheter	230		
		22/05/99	.	catheter	60		
		23/05/99	.	catheter	7		
		24/05/99	1	catheter	50		
		25/05/99	.	catheter	280		
		26/05/99	.	catheter	50		
		27/05/99	.	catheter	20		
		28/05/99	.	catheter	40		
		29/05/99	.	catheter removal	.		
		10/06/99	.	catheter	804		
		11/06/99	.	catheter	5		
		12/06/99	Urolanase	catheter	250		
		13/06/99	.	catheter	0		
		14/06/99	Urolanase	catheter	120		
		15/06/99	.	catheter	25		
		16/06/99	.	catheter	60		
		17/06/99	.	catheter	.		
		18/06/99	Urolanase	catheter	50		
	30	24/08/99	.	catheter (pigtail)	2125		
		25/08/99	.	catheter	660		
		26/08/99	.	catheter	0		
		27/08/99	.	catheter	950		
		28/08/99	.	catheter	380		
		29/08/99	.	catheter	50		
		30/08/99	.	catheter	500		
		31/08/99	.	catheter	350		
		01/09/99	.	catheter	580		
		02/09/99	.	catheter	680		
		03/09/99	.	catheter	130		
		04/09/99	.	catheter	280		
		05/09/99	.	catheter	650		
		06/09/99	.	catheter	0		
		07/09/99	.	catheter	480		
		08/09/99	.	catheter	510		
		09/09/99	1	catheter	200		
		10/09/99	.	catheter	1170		
		11/09/99	.	catheter	210		
		12/09/99	.	catheter	310		
		13/09/99	.	catheter	260		
		14/09/99	.	catheter	238		
		15/09/99	.	catheter	300		
		16/09/99	2	catheter	850		
		17/09/99	.	catheter	460		
	31	26/08/99	.	catheter	950		
		27/08/99	.	catheter	100		
		28/08/99	1	catheter	10		
		29/08/99	.	catheter	200		
		30/08/99	.	catheter	330		
		31/08/99	.	catheter	338		
		01/09/99	.	catheter	8		
		02/09/99	.	catheter	2		
		03/09/99	.	catheter	75		
		04/09/99	.	catheter	5		
		05/09/99	2	catheter	180		
		06/09/99	.	catheter	45		
		07/09/99	.	catheter	106		
		08/09/99	.	catheter	70		
		09/09/99	.	catheter	13		
		10/09/99	.	catheter removal	.		

Listing 8: X-rays

Group	Pat	examination	date	finding	finding date	site	distance [cm]	detectable
Helixor	1	Screening	19/04/97	pleural effusion	27/03/97	right		no
		Inv.I/1	19/04/97	pleural effusion	19/04/97	right	1	no
		Inv.II	20/04/97	free	25/04/97	missing		
		Final	30/05/97	free	30/05/97	missing		
	3	Screening	20/05/97	pleural effusion	05/05/97	right		
		Inv.I/1	21/05/97	free	21/05/97	missing	0	no
		Inv.II	26/05/97	free	27/05/97	missing		no
	5	Screening	25/08/97	pleural effusion	25/08/97	right		
		Inv.I/1	25/08/97	pleural effusion	25/08/97	right	1.5	no
		Inv.II	04/09/97	pleural effusion	30/08/97	right		
			04/09/97	pleural effusion	01/09/97	right		
			04/09/97	pleural effusion	03/09/97	right		
			04/09/97	pleural effusion	05/09/97	right		
		Final	24/09/97	free	24/09/97	missing		
	6	Screening	09/09/07	pleural effusion	02/09/97	left		
		Inv.I/1	10/09/97	pleural effusion	10/09/97	left	1	no
		Inv.II	12/09/97	free	10/09/97	left		
		Final	18/10/97	free	18/10/97	left		
	8	Screening	14/10/97	pleural effusion	04/10/97	left		
		Inv.I/1	15/10/97	pleural effusion	15/10/97	left	2	yes
		Inv.II	21/10/97	unchanged	17/10/97	missing		
		Final	19/11/97	unchanged	19/11/97	missing		
	9	.	.	free	05/12/97			
		.	.	free	12/12/97			
		Screening	16/11/97	pleural effusion	05/11/97	left		
		Inv.I/1	19/11/97	pleural effusion	19/11/97	left	0.5	yes
		Inv.II	27/11/97	free	27/11/97			
		Final	27/12/97	free	27/12/97			
	10	Screening	08/02/98	pleural effusion	03/02/98	left		
		Inv.I/1	09/02/98	free	09/02/98	left		no
	11	Screening	13/02/98	pleural effusion	13/02/98	right		
		Inv.I/1	22/02/98	pleural effusion	22/02/98		2	yes
		Inv.II	23/02/98	pleural effusion	23/02/98	right	1.5	yes
		Final	28/03/98	free	28/03/98		0.5	no
	13	Screening	28/09/98	pleural effusion	25/09/98	left		
		Inv.I/1	30/09/98	pleural effusion	30/09/98	left	1	yes
		Final	03/11/98	free	01/11/98	missing		
	14	Screening	01/10/98	pleural effusion	30/09/98	left		
		Inv.I/1	02/10/98	pleural effusion	02/10/98		1.4	no
		Inv.III	04/10/98	pleural effusion	04/10/98	left	1	no
		Inv.IV	05/10/98	pleural effusion	05/10/98	left	1	no
		Inv.V	06/10/98	pleural effusion	06/10/98		1	no
		Final	04/11/98	free	04/11/98			

Group	Pat	examination	date	finding	finding date	site	distance	detectable
Helixor	19	Screening	05/01/99	pleural effusion	03/01/99	left		
		Inv.I/1	06/01/99	free	06/01/99	missing		
		Inv.II	07/01/99	free	06/01/99	missing		
		Inv.III	08/01/99	free	06/01/99	missing		
		Inv.IV	09/01/99	free	06/01/99	missing		
		Inv.VI	11/01/99	free	06/01/99	missing		
		Inv.VII	12/01/99	free	06/01/99	missing		
	22	Screening	29/01/99	pleural effusion	28/01/99	right		
		Inv.I/1	.	free	30/01/99	missing		
		Final	27/07/99	free	26/07/99	missing		
	24	Screening	03/04/99	pleural effusion	01/04/99	left		
		Inv.I/1	04/04/99	free	04/04/99			no
		Inv.IV	08/04/99	free	08/04/99			
	26	Screening	07/05/99	pleural effusion	05/05/99	right		
		Inv.I/1	13/05/99	free	13/05/99	missing	0	no
		Inv.II	14/05/99	pleural effusion	13/05/99	double-sided		
		Inv.III	15/05/99	pleural effusion	15/05/99	double-sided		
		Inv.IV	17/05/99	pleural effusion	17/05/99	double-sided		
		Inv.V	18/05/99	pleural effusion	18/05/99	double-sided		
		Inv.VI	19/05/99	pleural effusion	19/05/99	double-sided		
		Inv.VII	20/05/99	free	20/05/99	missing		
		Final	25/06/99	free	23/06/99	missing		
	29	Screening	06/07/99	pleural effusion	06/07/99	right		
		Inv.I/1	10/07/99	free	11/07/99			no
		Inv.VII	18/07/99	pleural effusion	18/07/99	right		
		Final	02/09/99	free	02/09/99			
	32	Screening	05/09/99	pleural effusion	05/09/99	left		
		Inv.III	10/09/99	free	10/09/99	missing		
		Final	07/10/99	free	07/10/99	missing		
	33	Screening	05/10/99	pleural effusion	29/09/99	left		
		Inv.I/1	06/10/99	free	06/10/99	left	1	
		Inv.VI	12/10/99	pleural effusion	12/10/99	left		
		Final	05/11/99	free	05/11/99	left		
Doxycycline	2	Screening	21/05/97	pleural effusion	21/05/97	right		
		Inv.prior 1.Inst.	21/05/97	pleural effusion	21/05/97	right	1	yes
		Inv.betw.1./2.Inst.	28/05/97	free	22/05/97	missing		
	4	Screening	13/07/97	pleural effusion	28/06/97	right		
		Inv.I/1	16/07/97	free	16/07/97	missing		no
		Inv.II	17/07/97	pleural effusion	17/07/97	right		
		Inv.IV	19/07/97	pleural effusion	19/07/97	right		
		Inv.VI	21/07/97	pleural effusion	21/07/97	right		
		Inv.VII	22/07/97	pleural effusion	22/07/97	right		
	7	Screening	10/09/97	pleural effusion	08/09/97	right		
		Inv.prior 1.Inst.	11/09/97	pleural effusion	11/09/97	right	0.8	yes
		Inv.betw.1./2.Inst.	17/09/97	pleural effusion	17/09/97	right		
	12	Screening	28/07/98	pleural effusion	28/07/98	left		
		Inv.prior 1.Inst.	29/07/98	free	29/07/98	missing		
		Inv.betw.1./2.Inst.	07/08/98	free	07/08/98	missing		
		Final	02/09/98	free	02/09/98	right		

Group	Pat	examination	date	finding	finding date	site	distance	detectable
Doxycycline	15	Screening	07/10/98	pleural effusion	05/10/98	left		
		Inv.prior 1.Inst.	08/10/98	pleural effusion	08/10/98	left	1.5	yes
		Inv.betw.1./2.Inst.	15/10/98	unchanged	15/10/98	missing		
		Final	10/11/98	pleural effusion	10/11/98	left		
	16	Screening	29/09/98	pleural effusion	29/09/98	left		
		Inv.prior 1.Inst.	30/09/98	pleural effusion	01/10/98		0.5	yes
		Inv.betw.1./2.Inst.	08/10/98	free	08/10/98			
		Final	24/10/98	pleural effusion	22/10/98	left		
	17	Screening	10/12/98	pleural effusion	09/12/98	right		
		Inv.prior 1.Inst.	11/12/98	free	11/12/98	missing	0	no
		Inv.betw.1./2.Inst.	18/12/98	pleural effusion	18/12/98	right		
		Inv.consec.2.Inst.	25/12/98	pleural effusion	18/12/98	right		
	18	Screening	04/01/99	pleural effusion	28/12/98	right		
		Inv.prior 1.Inst.	05/01/99	free	05/01/99	missing		no
		Inv.betw.1./2.Inst.	12/01/99	free	12/01/99	missing		
		Final	09/02/99	free	09/02/99	missing		
	20	Screening	23/01/99	pleural effusion	22/01/99	right		
		Inv.prior 1.Inst.	25/01/99	free	26/01/99	missing		no
		Inv.betw.1./2.Inst.	03/02/99	free	03/02/99	missing		
	21	Screening	28/01/99	pleural effusion	28/01/99	left		
		Inv.prior 1.Inst.	29/01/99	free	29/01/99	missing		
		Final	26/02/99	free	26/02/99	missing		
	23	Screening	25/03/99	pleural effusion	27/03/99	right		
		Inv.prior 1.Inst.	27/03/99	pleural effusion	27/03/99	left		no
	25	Screening	27/04/99	pleural effusion	23/04/99	double-sided		
			27/04/99	free	26/04/99	right		no
		Inv.prior 1.Inst.	06/05/99	free	06/05/99	right		
			06/05/99	pleural effusion	06/05/99	left		
	27	Screening	10/05/99	pleural effusion	09/04/99	left		
		Inv.prior 1.Inst.	14/05/99	free	14/05/99	missing	0	no
		Inv.betw.1./2.Inst.	20/05/99	free	20/05/99	missing		
		Inv.consec.2.Inst.	01/06/99	free	25/05/99	missing		
		Final	21/06/99	pleural effusion	19/06/99	left		
	28	Screening	17/05/99	pleural effusion	17/05/99	right		
		Inv.prior 1.Inst.	18/05/99	pleural effusion	18/05/99	right		yes
		Inv.betw.1./2.Inst.	30/05/99	pleural effusion	29/05/99	right		
		Final	01/07/99	pleural effusion	09/06/99	right		
	30	Screening	11/08/99	pleural effusion	09/08/99	left		
		Inv.prior 1.Inst.	09/09/99	free	09/09/99	left		no
	31	Screening	25/08/99	pleural effusion	24/08/99	right		
		Inv.prior 1.Inst.	26/08/99	pleural effusion	27/08/99	right	0.5	no
		Final	30/09/99	free	28/09/99	missing		

Listing 9: Concomitant medication for pain

Group	Pat	examination	name	dosage	Application	since	taking concluded	Indication
Helixor	5	Screening	Almagel	60 ml	p.o.	19/08/97	yes	Epigastric pain
		Inv.prior 2.Inst.	Acetaminophen	6	p.o.	29/08/97	yes	pain
			Famotidine	40 mg	p.o.	28/08/97	yes	epigastric pain
	8	Final	Morphine	30 mg	p. o.	19/11/97	no	Dyspnea
	9	Screening	Acetaminophen	1800 mg	p.o.	05/11/97	no	Analgesics
	13	Final	Ibuprofen	1800 mg	p.o.	29/10/98	no	Pain
			Almagel	2 Tab.	p.o.	29/10/98	no	Epigastric pain
	14	Screening	Almagel	45 ml	p.o.	21/09/98	no	Epigastric pain
		Inv.III	Demerol	50 mg	i.m.	04/10/98	no	Burning
		Inv.IV	Demerol	25 mg	i.m.	05/10/98	no	Burning
		Inv.V	Valentac	75 mg	i.m.	06/10/98	no	Burning
		Inv.VI	Valentac	75 mg	i.m.	07/10/98	no	Burning
		Inv.VII	Valentac	75 mg	i.m.	08/10/98	no	Burning
	19	Screening	Tyrenol	1800 mg	p.o.	01/01/99	no	General ache
			Mylanta	40 ml	p.o.	01/01/99	no	Epigastric pain
	24	Screening	Brufen	1200 mg	p.o.	04/03/99	.	pain control
	26	Screening	Valentac			05/05/99	.	pain control
			Ibuprofen			05/05/99	.	pain control
			Fentunyl patch			05/05/99	.	pain control
		Inv.II	Valentac		i.m.	13/05/99	no	Pain
		Final	MS-Contin	20 mg		11/06/99	.	Pain control
			Brufen	2400 mg		28/05/99	.	Analgesics
	29	Inv.II	Acetaminophen	1800 mg	p.o.	10/07/99	no	Analgesics
		Inv.IV	Valentac	75 mg	i.m.	15/07/99	no	Analgesics
		Inv.VI	Codenal	60 mg	p.o.	17/07/99	yes	Analgesics
Doxycycline	7	Inv.prior 2.Inst.	Demerol	50 mg	p.o.	11/09/97	no	Right chest pain
			Demerol	50 mg	p.o.	18/09/97	no	Right chest pain
	12	Screening	Acetaminophen	800 mg	p.o.	28/07/98	no	pain
		Final	Ibuprofen	1800 mg	p.o.	15/08/98	no	pain
	15	Final	Demerol	50 mg	i.v.	08/10/98	no	Pain
	16	Inv.prior 1.Inst.	Demerol	75 mg	i.m.	30/09/98	no	Chest pain
	17	Inv.prior 2.Inst.	Demerol	75 mg	i.m.	11/12/98	no	Chest pain
			Demerol	50 mg	i.v.	19/12/98	no	Chest pain
	18	Final	Codeine	180 mg	p.o.	22/01/99	yes	Pain
			Demerol	75 mg	i.m.	05/01/99	no	Chest pain
	20	Inv.prior 2.Inst.	Demerol	75 mg	i. m.	27/01/99	no	chest pain
	21	Screening	Codeine	80 mg	p.o.	22/01/99	.	chest pain
			Almagel	60 ml	p.o.	22/01/99	.	epigastric pain
		Inv.prior 2.Inst.	Demerol	50 mg	i.v.	29/01/99	yes	chest pain
	23	Screening	Morphine	3 mg	i. v.	19/03/99	yes	pain
	27	Final	Brufen	1800 mg	p.o.	21/05/99	yes	Analgesics
	30	Screening	Morphine	18 mg	i. v.	11/08/99	yes	pain control

Listing 10: Other concomitant medication

Group	Pat	examination	name	dosage	Application	since	taking concluded	indication
Helixor	1	Screening	Gaspylor	2 g	p.o.	28/03/97	yes	Digestive
			Ranitidine	300 mg	p.o.	28/03/97	yes	Antiulcer
			Rulid	500 mg	p.o.	28/03/97	yes	Infection
			Cefminox	2 g	i.v.	18/04/97	yes	Infection
		Inv.II	Cefminox	2 g	i.v.	18/04/97	yes	Respiratory tract infection
			Astromycin	400 mg	i.v.	20/04/97	yes	Respiratory tract infection
	3	Screening	Cefminox	2 g	i. v.	05/05/97	no	Respiratory tract infection
			Astromycin	400 mg	i. v.	05/05/97	no	Respiratory tract infection
			Lasix	20 mg	p. o.	05/05/97	no	Hypertension
			Spironolactone	25 mg	p. o.	05/05/97	no	Hypertension
	5	Screening	Muteran	600 mg	p.o.	19/08/97	yes	Mucolyte
			Pancreon	825 mg	p.o.	19/08/97	yes	Digestive
			Cisapride	15 mg	p.o.	19/08/97	yes	Dyspepsia
			Prednisolone	10 mg	p.o.	23/08/97	yes	poor appetite
		Inv.prior 2.Inst.	Sucralfate	20 ml	p.o.	28/08/97	yes	gastric coating agent
			Ciprobay	500 mg	p.o.	28/08/97	yes	sputum
	6	Screening	Bizolvon	24 mg	p. o.	04/09/97	no	Cough
			Vit B Complex	50 mg	p. o.	04/09/97	no	Fatigue
			Phazyme	195 mg	p. o.	04/09/97	no	Digestive
			Famotidine	40 mg	p. o.	04/09/97	no	Antiulcer
		Inv.II	Vit B Complex	50 mg	p. o.	04/09/97	no	Fatigue
			Phazyme	195 mg	p. o.	04/09/97	no	Digestive
			Famotidine	40 mg	p. o.	04/09/97	no	Ulcer
			Dihydroxycodeine	10 mg	p. o.	08/09/97	no	Cough
	8	Screening	Enalapril	10 mg	p. o.	04/10/97	.	Hypertension
			Digoxin	0,125 mg	p.o.	04/10/97	.	Atrial fibrillation with rapid response
			Nifedipine	30 mg	p.o.	04/10/97	.	Hypertension
	9	Screening	Cofrel	120 mg	p.o.	05/11/97	no	Respiratory tract infection
			Airtal	120 mg	p.o.	05/11/97	yes	Bony metastasis of left humerus shaft
			Cisapride	30 mg	p.o.	05/11/97	yes	Digestive
		Inv.II	Cefminox	2 g	i.v.	27/11/97	yes	fever
	10	Screening	Cefaclor	750 mg	p. o.	30/01/98	no	Antibiotics
			Muteran	600 mg	p. o.	30/01/98	no	Respiratory tract infection
			Cofrel	60 mg	p. o.	30/01/98	no	Cough
			Pancreon F	825 mg	p. o.	30/01/98	no	Digestive
	11	Screening	INH	300 mg	p.o.	13/02/98	no	pulmonary tuberculosis
			W-RFP	600 mg	p.o.	13/02/98	no	pulmonary tuberculosis
			Myambutol	800 mg	p.o.	13/02/98	no	pulmonary tuberculosis
			Theophylline	300 mg	p.o.	13/02/98	no	Asthma
			Ranitidine	300 mg	p.o.	13/02/98	no	Antiulcer
			Mylanta	400 mg	p.o.	13/02/98	no	Digestive
	13	Screening	N-Acetylcysteine	600 mg	p.o.	18/09/98	.	Mucolytics
			Formoterol fumasate	40 mg	p.o.	18/09/98	.	Bronchodilator
		Final	Indigestion	10 mg	p.o.	29/10/98	no	Indigestion

Group	Pat	examination	name	dosage	Application	since	taking concluded	indication
Helixor	14	Screening	Ambroxol	90 mg	p.o.	21/09/98	no	Mucolytics
		Inv.V	Unasyn	4,5 g	i.v.	06/10/98	no	Fever
		Inv.VI	Unasyn	4,5 g	i.v.	07/10/98	no	Fever
	19	Screening	Muteran	600 mg	p. o.	01/01/99	no	Mucolytic
		Inv.IV	Sucralfate	35 ml	p. o.	09/01/99	no	Gastric ulcer
			Omeprazole	20 mg	p. o.	09/01/99	no	Gastric ulcer
	22	.				.	.	
	24	Screening	Cough syrup	80 ml	p.o.	10/03/99	.	Cough
			Cofrel	3 Tab.	p.o.	04/03/99	.	Cough
			Roxol	3 Tab.	p.o.	04/03/99	.	Thick secretion
			Muteran	3 Tab.	p.o.	04/03/99	.	Thick secretion
			Rulid	2 Tab.	p.o.	04/03/99	.	Antibiotics + toilet
			Antibro	1 g	p.o.	10/03/99	.	Diarrhea
		Inv.II	Codein	80 mg	p.o.	06/04/99	yes	Cough
			Diamicron	80 mg	p.o.	06/04/99	yes	Diabetes mellitus
		Inv.IV	Macperan	30 mg	i.v.	08/04/99	yes	Nausea
			Prepulsid	15 mg	p.o.	08/04/99	.	Indigestion
			Phazyme	3 Tab.	p.o.	08/04/99	.	Indigestion
		Inv.VI	Ciprobay	2 Tab.	p.o.	10/04/99	yes	Fever
		Inv.VII	O2 supply	2l /min	through nasal plug	11/04/99	yes	Dyspnea
	26	Screening	Verapamil		14.04.99	.	yes	Antiangina drug
			Aspirin		14.04.99	.	.	Antiangina drug
			Sigmart		14.04.99	.	.	Antiangina drug
			Carsodil		14.04.99	.	.	Antiangina drug
			Xanax		14.04.99	.	.	Antidepressent
			Topotecan		07.05.99	.	.	Antineoplastic
		Inv.II.	Itraconuval	100 mg	p.o.	14/05/99	yes	Antifungal Agent
			Leucogen	400 mg	s.c.	14/05/99	yes	Hemopoietic stimulant
		Inv.V	Roxol	3 Tab.	p.o.	18/05/99	.	Mucolytics
		Final	Packed red cells			28/05/99	.	Anemia
			Curan	300 mg		11/06/99	.	Antiulcer
			Magmil	1500 mg		11/06/99	.	Stool softenner
			Alaxyl	10 g		11/06/99	.	Laxatives
	29	Inv.II	Bestase	3 Tab.	p.o.	11/07/99	yes	Digestives
		Inv.V	Furomarin	2 g	i.v.	16/07/99	.	Antibiotics
			Amikin	750 mg	i.v.	16/07/99	.	Antibiotics
		Final	Tamoxifen	20 mg	p.o.	26/08/99	yes	Anti cancer agent
	32	Screening	Curan	300 mg	p. o.	05/09/99	yes	Antiulcer
			Bisolvon	16 mg	i. v.	05/09/99	yes	Mucolytics
			Unasyn		i. v.	05/09/99	yes	Antibiotics
			Aminofusin	1000 ml	i. v.	05/09/99	yes	Parenteral nutrition
			Intralipos	500 ml	i. v.	05/09/99	yes	Parenteral nutrition
			Haloperidol	5 mg	i.v.	05/09/99	yes	Antiepilepsy drug
			Beastase	3	p.o.	05/09/99	yes	Digestive
			Lasix	20 mg	p.o.	05/09/99	yes	Diuretics

Group	Pat	examination	name	dosage	Application	since	taking concluded	indication
Helixor	32	Final	Aminofusion	1000 ml	i. v.	19/09/99	yes	Parenteral nutrition
			Intralipos	500 ml	i.v.	19/09/99	yes	Parenteral nutrition
			Ibuprofen	2400 mg	p. o.	21/09/99	yes	Analgesics
			Lisapride	15 mg	p. o.	23/09/99	yes	Motility
	33	Screening	Cough syrup	80 cc	p. o.	28/09/99	yes	antitussive
			Rulid	300 mg	p. o.	28/09/99	yes	Antibiotics, upper airway infection
		Inv.V	Taxotere	144 mg	i. v.	11/10/99	yes	anticancer drug
			Carboplatin	32 mg	i. v.	11/10/99	yes	anticancer drug
			Eronisetron	3 mg	i. v.	11/10/99	yes	antiemetics
			Lasix	20 mg	i. v.	11/10/99	.	diuretics
			Dexamethasone	16 mg	p. o.	11/10/99	yes	steroid
		Inv.VI	Rulid	300 mg	p. o.	12/10/99	yes	antibiotics
Doxycycline	2	Screening	Cefminox	2 g	i.v.	09/05/97	no	Respiratory tract infection
			Theophylline	300 mg	p.o.	12/05/97	no	Asthma
			Ambroxol	45 mg	p.o.	12/05/97	no	Cough
			Cough syrup	80	p.o.	12/05/97	no	Cough
			Phazyme	200 mg	p.o.	12/05/97	no	Digestive
			Diazepam	4 mg	p.o.	12/05/97	no	Anxiety
			Mylanta	40 ml	p.o.	12/05/97	no	Antiacid
		Inv.betw.1./2.Inst.	Ranitidine	300 mg	p.o.	22/05/97	no	Antiulcer
	4	Screening	Total parenteral nutrition	1l	i. v.	26/06/97	no	Cachexia
			Gaspylor	2 g	p.o.	26/06/97	no	Digestive
			Essentiale forte	2 g	p.o.	26/06/97	no	Liver disease
	7	Screening	Muteram	600 mg	p.o.	25/08/97	no	Mucolytics
			Cofirel	60 mg	p.o.	25/08/97	no	Cough
			Cisapride	15 mg	p.o.	25/08/97	no	Dyspepsia
			Cough syrup	80 cc	p.o.	31/08/97	no	Cough
			Codeine	120 mg	p.o.	10/09/97	no	Cough
	12	Inv.prior 2.Inst.	Alprazolam	0,75 mg	p.o.	03/08/98	.	Anxiety
	15	Screening	Cough Syrup	80 cc	p.o.	25/09/98	yes	Cough
	16	Screening	N-acetylcysteine	600 mg	p.o.	29/09/98	no	Mucolytics
			Diazepam	6 mg	p.o.	29/09/98	no	Anxiolytics
			Triazolam	0,25 mg	p.o.	29/09/98	no	Hypnotic agent
	17	Screening	Theophylline	200 mg	p.o.	30/11/98	no	bronchodilator
			Polybutin	600 mg	p.o.	30/11/98	no	gastro-intestine tract motility agent
			Almagel	60 ml	p.o.	30/11/98	no	anti-acid
	18	Screening	Cough syrup	80 ml	p.o.	28/12/98	.	Cough control
			Muteran	600 mg	p.o.	28/12/98	.	Mucolytics
			Cofrel	60 mg	p.o.	28/12/98	.	Cough control
	20	Screening	Transamine	3 T.	p. o.	22/01/99	yes	blood tinged sputum
			Ambroxol	3 T.	p. o.	22/01/99	yes	Mucolytic
			Cofrel	3 T.	p. o.	22/01/99	yes	Anti-tussive
			Cough-syrup	80	p. o.	21/01/99	yes	Anti-tussive

Group	Pat	examination	name	dosage	Application	since	taking concluded	indication
Doxycycline	21	Screening	Cofrel	120 mg	p.o.	22/01/99	.	cough
			cough syrup	80	p.o.	22/01/99	.	cough
	23	Screening	Ranitidine	300 mg	p. o.	28/02/99	yes	Antiulcer
			Codeine	80 mg	p. o.	28/02/99	yes	Antitussive
			Cough syrup	120	p. o.	28/02/99	yes	Cough
			Mylanta	60 ml	p. o.	28/02/99	yes	Antiacid
	25	Screening	Gentamicin	160 mg	i.v.	29/03/99	no	Antibiotics
			Cefotaxine	1,5 g	i.v.	29/03/99	no	Antibiotics
			Clindamycin	600 mg	i.v.	29/03/99	no	Antibiotics
			Roxol	3 Tab.	p.o.	23/04/99	yes	Mucolytics
			Beptase	3 Tab.	p.o.	23/04/99	yes	Digestive
			Budesonide Nebulizer	2 mg	Inhaler	23/04/99	no	Steroid
			Azeptin	2 Tab.	p.o.	23/04/99	yes	Antihistamine
			Atock Fometerol	1 Tab.	p.o.	23/04/99	yes	Bronchodilator
			Spara	20 mg	p.o.	27/04/99	yes	Antibiotics
		Inv.prior 2.Inst.	Lasix	20 mg		05/05/99	yes	Diuretics
			Aldacton	50 mg		05/05/99	yes	Diuretics
	27	Screening	Aminofusin	500 ml	i.v.	07/05/99	.	Hyperalimentation
			Intralopos	250 ml	i.v.	07/05/99	.	Hyperalimentation
			Cofrel	3	p.o.	07/05/99	.	Antitussiva
			Cough Syrup	80 cc	p.o.	07/05/99	.	Antitussiva
			Roxol	3	p.o.	07/05/99	.	Mucolytics
			Polybutin	3	p.o.	07/05/99	.	gastrointestinal motility
		Inv.prior 2.Inst.	Navelbin	24,5 mg	i.v.	14/05/99	.	Anti cancer drug
			Cisplatin	32,6 mg	i.v.	14/05/99	.	Anti cancer drug
			Grunisetron	1	p.o.	15/05/99	.	Antiemetics
		Final	Cofrel	3	p.o.	21/05/99	no	Antitussiva
			Dicetel	3	p.o.	21/05/99	no	Gastrointestinal motility
			Bearse	3	p.o.	21/05/99	no	Digestives
			Cravit	300 mg	p.o.	21/05/99	no	Antibiotics
			Cough Syrup	80 cc	p.o.	21/05/99	no	Antitussiva
	28	Screening	Cofrel	3	p.o.	17/05/99	.	Antitussiva
			Mucotenal	3	p.o.	17/05/99	.	Mucolytics
			Intralipos	500 ml	i.v.	17/05/99	.	Parenteral nutrition
			Aminofusin	500 ml	i.v.	17/05/99	.	Parenteral nutrition
	30	Screening	Magmil	1500 mg	p. o.	11/08/99	yes	laxative
			Araxyl	5 g	p. o.	11/08/99	yes	laxative
			Diazepam	6 mg	p. o.	11/08/99	yes	sedative
			Cofrel	60 mg	p. o.	11/08/99	yes	Antitussive
			Curan	300 mg	i.v.	11/08/99	yes	Anti ulcer drug
			Lasix	40 mg	p. o.	11/08/99	yes	diuretics
			Aminophylline	500 mg	i.v.	11/08/99	yes	dyspnea
			Cough syrup	60 mg	p. o.	11/08/99	yes	Antitussive
		Inv.prior 2.Inst.	Unasyn	3000 mg	i. v.	23/08/99	yes	Antibiotics
			Codein	80 mg	p. o.	23/08/99	yes	Antitussive
			Solucotef	100 mg	i. v.	28/08/99	yes	steroid
			Oxygen	5 l/mi	nasal plug	25/08/99	yes	pneumothorax

Group	Pat	examination	name	dosage	Application	since	taking concluded	indication
Doxycycline	31	Screening	Cofrel	60 mg	p.o.	24/08/99	.	Antitussiva
			Cough Syrup	80 ml	p.o.	24/08/99	.	Antitussiva
			Bearse	3	p.o.	24/08/99	.	Digestiva
			Curan	300 mg	p.o.	24/08/99	.	Anti ulcer drug
		Inv.prior 2.Inst.	Navelbin	27,9 mg	i.v.	31/08/99	yes	Anti cancer drug
			Cisplatin	37,2 mg	i.v.	31/08/99	yes	Anti cancer drug

Listing 11: Side effects

Group	Pat	examination	no	date	pain	burning	fever	other
Helixor	1	Inv.I/1	1	19/04/97	light	none	light	
		Inv.II	2	20/04/97	light	none	light	
		Inv.III	3	21/04/97	light	none	light	
		Inv.IV	4	22/04/97	light	none	light	
		Inv.V	5	23/04/97	light	none	light	
		Inv.VI	6	24/04/97	light	none	moderate	
		Inv.VII	7	25/04/97	light	none	moderate	
	3	Inv.I/1	1	21/05/97	none	none	none	
		Inv.II	2	22/05/97	none	none	none	
		Inv.III	3	23/05/97	none	none	none	
		Inv.IV	4	24/05/97	none	none	none	
		Inv.V	5	25/05/97	none	none	none	
	5	Inv.prior 1.Inst.	1	28/08/97	serious	moderate	moderate	
	6	Inv.I/1	1	10/09/97	none	none	none	
		Inv.II	2	11/09/97	none	none	none	
		Inv.III	3	12/09/97	none	none	none	
		Inv.IV	4	13/09/97	none	none	none	
		Inv.V	5	14/09/97	none	none	none	
		Inv.VI	6	15/09/97	none	none	none	
		Inv.VII	7	16/09/97	none	none	none	
	8	Inv.I/1	1	15/10/97	light	none	none	
		Inv.II	2	16/10/97	none	none	none	
		Inv.III	3	17/10/97	none	none	none	
		Inv.IV	4	18/10/97	none	none	none	
		Inv.V	5	19/10/97	none	none	none	
		Inv.VI	6	20/10/97	none	none	none	
		Inv.VII	7	21/10/97	none	none	none	
	9	Inv.I/1	1	19/11/97	none	none	none	
		Inv.II	2	20/11/97	none	none	none	
		Inv.III	3	21/11/97	none	none	none	
		Inv.IV	4	22/11/97	none	none	light	
		Inv.V	5	23/11/97	none	none	none	
		Inv.VI	6	24/11/97	none	none	moderate	
		Inv.VII	7	25/11/97	none	none	light	
	10	Inv.I/1	1	09/02/98	none	none	none	
		Inv.II	2	10/02/98	none	none	none	
		Inv.III	3	11/02/98	none	none	none	
	11	Inv.I/1	1	22/02/98	none	none	none	
		Inv.II	2	23/02/98	none	none	none	
		Inv.III	3	24/02/98	none	none	none	
		Inv.IV	4	25/02/98	none	none	none	
		Inv.V	5	26/02/98	none	none	none	
		Inv.VI	6	27/02/98	none	none	none	
		Inv.VII	7	28/02/98	none	none	moderate	
	13	Inv.I/1	1	30/09/98	none	none	light	
		Inv.II	2	01/10/98	none	none	none	
		Inv.III	3	02/10/98	none	none	light	
		Inv.IV	4	03/10/98	none	none	none	
		Inv.V	5	04/10/98	none	none	none	
		Inv.VI	6	05/10/98	none	none	serious	
		Inv.VII	7	06/10/98	none	none	moderate	
	14	Inv.I/1	1	02/10/98	none	none	none	
		Inv.II	2	03/10/98	none	none	none	
		Inv.III	3	04/10/98	none	serious	none	
		Inv.IV	4	05/10/98	none	serious	moderate	
		Inv.V	5	06/10/98	none	serious	serious	
		Inv.VI	6	07/10/98	none	serious	serious	
		Inv.VII	7	08/10/98	none	serious	moderate	
	19	Inv.I/1	1	06/01/99	none	none	none	
		Inv.II	2	07/01/99	none	none	none	
		Inv.III	3	08/01/99	none	none	none	
		Inv.IV	4	09/01/99	none	none	none	
		Inv.V	5	10/01/99	none	none	none	
		Inv.VI	6	11/01/99	none	none	none	
		Inv.VII	7	12/01/99	none	none	none	
	22	Inv.I/1	1	01/02/99	none	none	none	
		Inv.II	2	02/02/99	none	none	none	
		Inv.III	3	03/02/99	none	none	none	
		Inv.IV	4	04/02/99	none	none	none	
		Inv.V	5	05/02/99	none	none	none	
		Inv.VI	6	06/02/99	none	none	none	
		Inv.VII	7	07/02/99	none	none	none	

Group	Pat	examination	no	date	pain	burning	fever	other
Helixor	24	Inv.I/1	1	05/04/99	light	none	light	
		Inv.II	2	06/04/99	light	none	light	
		Inv.III	3	07/04/99	light	none	none	
		Inv.IV	4	08/04/99	none	none	none	
		Inv.V	5	09/04/99	none	none	none	
		Inv.VI	6	10/04/99	none	none	none	
		Inv.VII	7	11/04/99	none	none	none	
		Inv.add.	8	12/04/99	none	none	none	
		9	9	13/04/99	none	none	none	
	26	Inv.I/1	1	13/05/99	unacceptable	none	none	
		Inv.II	2	14/05/99	serious	none	none	
		Inv.III	3	15/05/99	none	none	none	
		Inv.IV	4	16/05/99	none	none	none	
		Inv.V	5	17/05/99	none	none	none	
		Inv.VI	6	18/05/99	none	none	none	
		Inv.VII	7	19/05/99	none	none	none	
	29	Inv.I/1	1	12/07/99	serious	none	none	light
		Inv.II	2	13/07/99	none	none	none	
		Inv.III	3	14/07/99	none	none	none	
		Inv.IV	4	15/07/99	serious	none	none	moderate (right shoulder pain)
		Inv.V	5	16/07/99	moderate	none	moderate	moderate (pain at inspiration)
		Inv.VI	6	17/07/99	serious	none	none	moderate (right shoulder pain)
		Inv.VII	7	18/07/99	moderate	none	none	
	32	Inv.I/1	1	08/09/99	none	none	none	
		Inv.II	2	09/09/99	none	moderate	none	
		Inv.III	3	10/09/99	none	none	none	
	33	Inv.I/1	1	07/10/99	none	none	none	
		Inv.II	2	08/10/99	none	none	none	
		Inv.III	3	09/10/99	none	none	none	
		Inv.IV	4	10/10/99	none	none	none	
		Inv.V	5	11/10/99	none	none	none	
		Inv.VI	6	12/10/99	none	none	none	
		Inv.VII	7	13/10/99	none	none	none	
		Inv.add.	8	14/10/99	none	none	none	
Doxycycline	2	Inv.prior 1.Inst.	1	21/05/97	moderate	moderate	light	
	4	Inv.I/1	1	16/07/97	light	none	none	
		Inv.II	2	17/07/97	none	none	light	
		Inv.III	3	18/07/97	none	none	none	
		Inv.IV	4	19/07/97	light	none	moderate	
		Inv.V	5	20/07/97	light	none	none	
		Inv.VI	6	21/07/97	light	none	light	
		Inv.VII	7	22/07/97	light	none	light	
	7	Inv.prior 1.Inst.	1	11/09/97	serious	moderate	light	
		IInv.prior 2.Inst.	2	18/09/97	serious	moderate	none	
	12	Inv.prior 1.Inst.	1	31/07/98	serious	none	none	
	15	Inv.prior 1.Inst.	1	08/10/98	serious	none	none	
	16	Inv.prior 1.Inst.	1	30/09/98	serious	none	none	
	17	Inv.prior 1.Inst.	1	11/12/98	serious	none	none	
		Inv.prior 2.Inst.	2	19/12/98	serious	none	none	
	18	Inv.prior 1.Inst.	1	05/01/99	serious	none	none	
	20	Inv.prior 1.Inst.	1	27/01/99	serious	none	none	
	21	Inv.prior 1.Inst.	1	29/01/99	serious	none	none	
	23	Inv.prior 1.Inst.	1	27/03/99	unacceptable	serious	moderate	
	25	Inv.prior 1.Inst.	1	06/05/99	serious	none	none	
	27	Inv.prior 1.Inst.	1	14/05/99	unacceptable	unacceptable	unacceptable	
		Inv.prior 2.Inst.	2	21/05/99	unacceptable	unacceptable	serious	
	28	Inv.prior 1.Inst.	1	24/05/99	unacceptable	serious	none	
	30	Inv.prior 1.Inst.	1	09/09/99	none	none	none	light (Foreign body sensation)
		Inv.prior 2.Inst.	2	16/09/99	none	none	none	
	31	Inv.prior 1.Inst.	1	28/08/99	light	none	none	light
		Inv.prior 2.Inst.	2	05/09/99	none	none	none	

Listing 12: Changes in laboratory parameters (laboratory A)

Group	Pat.	Time	Date	blood sedimentation [mm/h]	Hb [g/dl]	erythro-cytes [10^6/µl]	thrombo-cytes [10^3/µl]	total leuco-cytes [10^3/µl]	neutro-philes [%]	eosino-philes [%]	baso-philes [%]	mono-cytes [%]	lympho-cytes [%]
Helixor	1	Screening Final final-screen	19/04/97 30/05/97	71 h 172 h 101	12.4 l 10.0 l -2.4	4.36 l 3.13 l -1.23	261 127 l -134	7.4 4.0 l -3.4	5.2 l 65.2 60.0	0.4 l 0.3 l -0.1	0.1 0.9 0.8	0.5 l 9.8 h 9.3	1.2 l 23.8 l 22.6
	3	Screening	20/05/97	16 h	13.3	4.58	259	8.1	71.4 h	0.6 l	4.9 h	8.9 h	14.2 l
	5	Screening Final final-screen	20/08/97 22/09/97	20 h . .	12.8 9.0 l -3.8	3.88 l 2.62 l -1.26	160 159 -1	7.3 7.1 -0.2	72.4 h 79.1 h 6.7	3.1 h 5.2 h 2.1	0.7 0.6 -0.1	0.6 l 7.9 7.3	16.2 l 13.2 l -3.0
	6	Screening Final final-screen	08/09/97 18/10/97	65 h 60 h -5	12.6 11.8 l -0.8	4.31 3.76 l -0.55	265 489 h 224	10.1 h 8.2 -1.9	74.2 h 68.9 -5.3	1.2 2.4 1.2	0.3 0.9 0.6	10.0 h 13.4 h 3.4	14.3 l 14.5 l 0.2
	8	Screening Final final-screen	14/10/97 18/11/97	. . .	12.2 11.1 l -1.1	3.88 l 3.45 l -0.43	246 215 -31	6.9 6.2 -0.7	82.5 h 5.2 l -77.3	0.7 l 0.1 l -0.6	0.7 0.0 -0.7	5.7 0.4 l -5.3	10.4 l 0.5 l -9.9
	9	Screening Final final-screen	16/11/97 27/12/97	96 h . .	10.0 l 11.0 l 1.0	3.20 l 3.39 l 0.19	287 257 -30	6.1 5.0 -1.1	80.1 h 81.1 h 1.0	10.1 h 0.3 l -9.8	0.3 2.1 h 1.8	8.7 h 3.9 l -4.8	10.1 l 12.6 l 2.5
	10	Screening	07/02/98	69 h	10.6 l	3.30 l	202	14.9 h	91.0 h	0.2 l	0.0	5.8	3.0 l
	11	Screening Final final-screen	12/02/98 28/03/98	57 h 77 h 20	12.0 10.3 l -1.7	4.29 3.78 l -0.51	303 338 35	4.6 l 4.8 l 0.2	52.0 l 59.3 7.3	6.4 h 8.4 h 2.0	3.0 h 1.7 h -1.3	7.1 7.4 0.3	31.5 23.2 l -8.3
	13	Screening Final final-screen	28/09/98 03/11/98	60 h . .	11.3 l 9.8 l -1.5	3.61 l 3.54 l -0.07	376 401 25	11.6 h 9.6 -2.0	69.3 68.6 -0.7	3.8 h 2.5 -1.3	1.0 1.0 0.0	4.5 7.2 2.7	21.4 l 20.7 l -0.7
	14	Screening Final final-screen	01/10/98 04/11/98	14 94 h 80	11.7 l 11.6 l -0.1	3.80 l 3.98 l 0.18	193 410 217	4.0 l 7.8 3.8	54.6 l 65.2 10.6	10.2 h 7.2 h -3.0	1.2 h 0.1 -1.1	9.2 h 7.0 -2.2	24.8 l 20.5 l -4.3
	19	Screening	05/01/99	.	10.1 l	3.41 l	208	3.3 l	56.5	0.6 l	0.2	27.2 h	15.5 l
	22	Screening Final final-screen	29/01/99 27/07/99	113 h 134 h 21	12.4 l 8.3 l -4.1	3.95 l 2.86 l -1.09	439 350 -89	11.5 h 9.4 -2.1	71.3 h 75.2 h 3.9	5.2 h 5.9 h 0.7	0.1 0.0 -0.1	7.3 5.4 -1.9	16.1 l 13.5 l -2.6
	24	Screening	03/04/99	123 h	10.4 l	2.97 l	95 l	7.4	86.0 h	6.8 h	1.5	7.2	3.8 l
	26	Screening Final final-screen	04/05/99 24/06/99	107 h 91 h -16	10.8 l 9.0 l -1.8	3.18 l 2.85 l -0.33	150 216 66	5.7 6.8 1.1	71.0 78.0 h 7.0	0.4 1.0 0.6	1.3 1.0 -0.3	12.6 h 10.0 h -2.6	14.7 l 10.0 l -4.7
	29	Screening Final final-screen	06/07/99 02/09/99	27 h 11 -16	12.6 12.2 -0.4	4.30 4.03 -0.27	189 154 -35	4.9 4.2 -0.7	51.8 48.7 l -3.1	2.0 2.5 0.5	0.8 0.6 -0.2	9.2 h 9.9 h 0.7	36.2 38.3 2.1
	32	Screening Final final-screen	05/09/99 07/10/99	78 h 102 h 24	11.4 l 9.7 l -1.7	3.66 l 2.88 l -0.78	437 213 -224	6.8 7.9 1.1	80.9 h 95.0 h 14.1	1.0 0.1 -0.9	2.3 h 0.0 -2.3	5.8 1.5 l -4.3	10.0 l 3.4 l -6.6

Group	Pat.	Time	Date	blood sedimentation [mm/h]	Hb [g/dl]	erythro-cytes [10^6/µl]	thrombo-cytes [10^3/µl]	total leuco-cytes [10^3/µl]	neutro-philes [%]	eosino-philes [%]	baso-philes [%]	mono-cytes [%]	lympho-cytes [%]
Helixor	33	Screening Final final-screen	28/09/99 05/11/99	28 h 21 h -7	12.8 12.7 -0.1	3.86 l 3.92 l 0.06	280 293 13	8.1 6.2 -1.9	71.7 56.9 -14.8	0.5 3.4 2.9	0.6 0.6 0.0	6.7 8.7 2.0	20.5 30.4 9.9
Doxycycline	2	Screening	21/05/97	106 h	10.5 l	3.44 l	429	7.9	66.3	3.8 h	1.4 h	11.2 h	17.3 l
	4	Screening	13/07/97	57 h	11.4 l	3.55 l	297	9.7	84.8 h	0.4 l	0.5	3.2 l	11.1 l
	7	Screening	09/09/97	14	12.0	3.77 l	273	5.5	67.5	3.6 h	2.5 h	5.0	21.4 l
	12	Screening Final final-screen	27/07/98 02/09/98	75 h 72 h -3	11.9 l 9.4 l -2.5	3.77 l 2.96 l -0.81	293 461 h 168	8.8 7.7 -1.1	72.8 h 72.2 h -0.6	15.7 h 2.7 -13.0	2.5 h 1.4 h -1.1	7.2 4.4 -2.8	15.7 l 19.4 l 3.7
	15	Screening Final final-screen	07/10/98 10/11/98	66 h . .	12.1 9.2 l -2.9	3.85 l 2.93 l -0.92	246 240 -6	7.3 1.4 l -5.9	85.8 h 90.0 h 4.2	0.5 l 1.0 0.5	2.2 h 0.0 -2.2	5.7 2.0 l -3.7	5.8 l 7.0 l 1.2
	16	Screening Final final-screen	29/09/98 24/10/98	45 h 54 h 9	11.6 l 12.9 1.3	3.46 l 3.68 l 0.22	267 248 -19	5.8 8.5 2.7	66.8 71.7 h 4.9	1.9 0.5 l -1.4	2.9 h 0.0 -2.9	5.8 8.1 h 2.3	22.6 l 19.7 l -2.9
	17	Screening	10/12/98	10	11.6 l	.	212	11.0 h	90.3 h	0.2 l	0.4	4.9	4.2 l
	18	Screening Final final-screen	31/12/98 28/01/99	91 h 91 h 0	10.1 l 10.3 l 0.2	. . .	370 115 l -255	6.5 7.6 1.1	80.6 h 8.0 l -72.6	2.7 0.0 l -2.7	0.4 0.0 -0.4	6.2 2.0 l -4.2	10.1 l 90.0 h 79.9
	20	Screening	23/01/99	76 h	9.8 l	3.34 l	253	5.3	77.2 h	1.4	0.3	6.9	14.2 l
	21	Screening Final final-screen	28/01/99 26/02/99	53 h 46 h -7	14.3 13.9 -0.4	4.58 4.63 0.05	273 294 21	10.8 h 7.6 -3.2	74.8 h 55.4 -19.4	2.1 0.3 l -1.8	0.8 1.5 h 0.7	11.5 h 15.5 h 4.0	10.8 l 27.3 16.5
	23	Screening	25/03/99	125 h	11.1 l	3.86 l	311	8.4	83.6 h	0.1	0.5	7.7	8.1 l
	25	Screening	27/04/99	32 h	13.7	4.78	331	9.4	66.0	1.0	0.0	10.0 h	23.0
	27	Screening Final final-screen	07/05/99 19/06/99	80 h 140 h 60	12.8 l 9.0 l -3.8	4.34 l 3.24 l -1.10	271 359 88	6.3 8.6 2.3	63.0 73.4 10.4	1.9 1.7 -0.2	0.8 0.2 -0.6	8.2 6.8 -1.4	25.8 17.9 l -7.9
	28	Screening Final final-screen	17/05/99 30/06/99	103 h 80 h -23	11.0 l 9.5 l -1.5	3.58 l 3.06 l -0.52	348 292 -56	7.5 7.2 -0.3	75.8 h 81.5 h 5.7	1.3 0.8 -0.5	1.0 0.0 -1.0	13.7 h 14.4 h 0.7	8.2 l 3.3 l -4.9
	30	Screening	10/08/99	70 h	11.5 l	3.64 l	369	9.0	82.8 h	0.3	0.3	9.5 h	7.1 l
	31	Screening Final final-screen	24/08/99 27/09/99	57 h 16 h -41	14.4 13.9 -0.5	4.60 4.42 l -0.18	229 114 l -115	9.5 8.0 -1.5	59.7 51.6 -8.1	4.8 9.3 h 4.5	2.9 h 0.1 -2.8	7.8 5.0 -2.8	24.8 34.0 9.2

Group	Pat.	Time	Date	creatinine [mg/dl]	SGOT [IU/l]	SGPT [IU/l]	g-GT [IU/l]	LDH [IU/l]	AP [IU/l]
Helixor	1	Screening	19/04/97	0.96	22	30	34	405	266 h
		Final	30/05/97	1.36 h	18	14	37	381	266 h
		final-screen		0.40	-4	-16	3	-24	0
	3	Screening	20/05/97	0.84	18	12	23	315	303 h
	5	Screening	20/08/97	0.97	26	43 h	8	304	173
		Final	22/09/97	1.00	38 h	41 h	47	367	250
		final-screen		0.03	12	-2	39	63	77
	6	Screening	08/09/97	0.67	19	13	10	385	223
		Final	18/10/97	0.55	28	20	15	394	250
		final-screen		-0.12	9	7	5	9	27
	8	Screening	14/10/97	0.89	24	11	20	301	165
		Final	18/11/97	1.00	19	9	1	354	233
		final-screen		0.11	-5	-2	-19	53	68
	9	Screening	16/11/97	1.00	44 h	28	42	978 h	356 h
		Final	27/12/97	1.01	47 h	57 h	63 h	1010 h	364 h
		final-screen		0.01	3	29	21	32	8
	10	Screening	07/02/98	0.88	72 h	35 h	127 h	2042 h	402 h
	11	Screening	12/02/98	0.54	20	13	8	287	208
		Final	28/03/98	0.69	19	9	9	248	230
		final-screen		0.15	-1	-4	1	-39	22
	13	Screening	28/09/98	0.83	26	27	16	471	169
		Final	03/11/98	0.92	36	33	30	500 h	187
		final-screen		0.09	10	6	14	29	18
	14	Screening	01/10/98	0.73	26	25	14	371	152
		Final	04/11/98	0.82	52 h	50 h	31	493 h	241
		final-screen		0.09	26	25	17	122	89
	19	Screening	05/01/99	0.64	46 h	44 h	88 h	484 h	255 h
	22	Screening	29/01/99	1.30 h	39 h	41 h	42	358	190
		Final	27/07/99	0.73	20	35 h	61 h	274	276 h
		final-screen		-0.57	-19	-6	19	-84	86
	24	Screening	03/04/99	1.06	20	36 h	125 h	282	274 h
	26	Screening	04/05/99	1.03	13	20	11	249	258 h
		Final	24/06/99	0.76	16	18	15	249	287 h
		final-screen		-0.27	3	-2	4	0	29
	29	Screening	06/07/99	0.72	24	31	14	314	180
		Final	02/09/99	0.75	26	21	17	314	185
		final-screen		0.03	2	-10	3	0	5
	32	Screening	05/09/99	1.50 h	18	26	149 h	402	763 h
		Final	07/10/99	0.54	14	11	53 h	438	380 h
		final-screen		-0.96	-4	-15	-96	36	-383
	33	Screening	28/09/99	0.67	18	13	29	435	183
		Final	05/11/99	0.53	33	25	62 h	309	268 h
		final-screen		-0.14	15	12	33	-126	85

Group	Pat.	Time	Date	creatinine [mg/dl]	SGOT [IU/l]	SGPT [IU/l]	g-GT [IU/l]	LDH [IU/l]	AP [IU/l]
Doxycycline	2	Screening	21/05/97	0.50	26	18	69 h	312	336 h
	4	Screening	13/07/97	0.75	102 h	40 h	75 h	2015 h	321 h
	7	Screening	09/09/97	0.86	17	14	11	406	156
	12	Screening	27/07/98	0.93	29	10	12	501 h	426 h
		Final	02/09/98	0.76	47 h	12	26	767 h	537 h
		final-screen		-0.17	18	2	14	266	111
	15	Screening	07/10/98	0.72	36	40 h	75 h	2766 h	361 h
		Final	10/11/98	0.60	45 h	28	.	.	520 h
		final-screen		-0.12	9	-12	.	.	159
	16	Screening	29/09/98	1.01	24	22	44	358	151
		Final	24/10/98	0.93	19	14	24	371	174
		final-screen		-0.08	-5	-8	-20	13	23
	17	Screening	10/12/98	0.72	39 h	40 h	50	571 h	1204 h
	18	Screening	31/12/98	0.82	37 h	46 h	166 h	676 h	474 h
		Final	28/01/99	0.89	37 h	54 h	464 h	1607 h	846 h
		final-screen		0.07	0	8	298	931	372
	20	Screening	23/01/99	0.73	14	12	12	292	212
	21	Screening	28/01/99	1.03	27	43 h	28	276	214
		Final	26/02/99	0.99	32	46 h	83 h	294	312 h
		final-screen		-0.04	5	3	55	18	98
	23	Screening	25/03/99	1.00	42 h	50 h	198 h	1240 h	474 h
	25	Screening	27/04/99	0.48 l	20	2 l	12	265	153
	27	Screening	07/05/99	0.77	17	14	61 h	216 l	239
		Final	19/06/99	0.67	23	47 h	339 h	196 l	955 h
		final-screen		-0.10	6	33	278	-20	716
	28	Screening	17/05/99	0.73	23	31	6	623 h	191
		Final	30/06/99	0.60	25	35 h	22	638 h	246
		final-screen		-0.13	2	4	16	15	55
	30	Screening	10/08/99	0.94	29	19	36	454	267 h
	31	Screening	24/08/99	0.85	30	49 h	64 h	599 h	217
		Final	27/09/99	1.01	22	39 h	66 h	376	213
		final-screen		0.16	-8	-10	2	-223	-4

Listing 13: Changes in laboratory parameters (laboratory B)

Group	Pat	examination	Date	punctate [ml]	color	consistency	tumor cells	neutro-phils	eosino-philes	lympho-cytes	HLA-DR+	macro-phages	CD4	CD8	NK-CD16	NK-CD56
Helixor	1	Inv.I/1	19/04/97	300	amber	turbid	none	3	1	96	.	0	.	.	.	.
		Inv.II	20/04/97	250	yellow	turbid	none	15	8	77	.	.	.	.	.	.
	3	Inv.I/1	21/05/97	750	yellow	cloudy	none	37	0	.	6.2	0	44.8	28.7	12	.
		Inv.II	26/05/97	50	bloody	turbid	none	37	0	63	.	.	47.5	29.8	2.2	.
	5	Inv.prior 1.Inst.	25/08/97	300	yellow	cloudy	none	31	6	63	1.4	0	25.4	40.7	.	3.6
		Inv.prior 2.Inst.	31/08/97	100	yellow	turbid (cloudy)	none	6	1	85	.	.	.	.	.	.
	6	Inv.I/1	10/09/97	50	amber	cloudy	few	94	0	6	2.3	0	26.5	9.9	.	5.1
		Inv.II	12/09/97	50	yellow	cloudy	none	95	0	5	.	.	.	.	.	.
	8	Inv.I/1	15/10/97	300	amber	turbid	isolated	26	.	74	0.3	0	31.7	15	.	3.5
		Inv.II	21/10/97	100	bloody	turbid	few	26	0	74	.	.	39.4	14.2	.	3.5
	9	Inv.I/1	19/11/97	1250	yellowish	cloudy	none	1	0	99	.	0	.	.	.	.
	10	Inv.I/1	09/02/98	200	bloody	cloudy	none	98	0	2	.	0	2.9	2.9	.	0.3
	11	Inv.I/1	22/02/98	20	yellow	turbid	many	1	29	70	.	0	59.6	20.5	.	.
		Inv.II	23/02/98	60			.	.	.	.	.	.	48.2	14.7	.	.
		Inv.IV	25/02/98	20			.	.	.	.	.	.	41.9	13.8	.	.
		Inv.V	26/02/98	50			.	.	.	.	.	.	51.7	15.2	.	.
		Inv.VI	27/02/98	10			.	.	.	.	.	.	53.4	11.6	.	.
	13	Inv.I/1	30/09/98	30	bloody	turbid	many	0	0	100	.	0	46	30.4	0.3	.
	14	Inv.I/1	02/10/98	100	amber	turbid	many	18	8	67	23.1	0	52.9	13.2	6.8	.
		Inv.II	03/10/98	130	yellow	turbid	many	.	.	.	.	.	52.7	10.2	0.2	.
		Inv.III	04/10/98	100	yellow	turbid	many	56	0	26	.	.	65.1	12	3.7	.
		Inv.IV	05/10/98	230	yellow	turbid	many	.	.	.	.	.	.	.	.	.
	19	Inv.I/1	06/01/99	30	yellow	turbid	many	83	0	15	9.3	0	65.9	13.8	2.5	.
		Inv.II	07/01/99	120	yellow	turbid	many	60	0	40	.	.	.	.	.	.
		Inv.III	08/01/99	100	yellow	turbid	many	53	0	33	9	.	0.9	14.9	2.4	.
		Inv.VI	11/01/99	80	yellow	turbid	many	58	0	37	45.8	.	0.3	17.1	1.2	.
		Inv.VII	12/01/99	468	yellow	turbid	few	72	0	19	56.6	.	0.6	13.1	10.4	.
		Inv.add.	13/01/99	135	yellow	turbid	few	16	0	84	49.8	.	63.7	16.5	2.7	.
	22	Inv.I/1	01/02/99	70	bloody	turbid	many	4	22	74	39.2	0	51.2	17	.	.
	24	Inv.I/1	04/04/99	840	yellow	turbid	none	81	0	19	2.6	0	42	49.1	3.1	.
		Inv.II	06/04/99	475	yellow	turbid	none	77	0	23	.	.	43.4	50	0.8	.
		Inv.IV	08/04/99	362	yellow	turbid	.	.	.	.	4.1	.	42.5	51.5	2.4	.
		Inv.V	09/04/99	340	yellow	clear	.	59	0	41	1.8	.	43.1	50.8	1.4	.
		Inv.VI	10/04/99	260	yellow	turbid	none	20	0	80	.	.	.	.	.	.
		Inv.VII	12/04/99	400	yellow	clear	none	0	0	98	1.3	.	58.3	37	2	.
	26	Inv.I/1	11/05/99	120	yellow	clean	none	0	0	100	0.9	0	44.7	27.5	10.2	.
		Inv.II	14/05/99	110	yellow	clean	none	.	.	.	.	.	.	.	.	.
		Inv.III	15/05/99	52	yellow	clear	.	.	.	.	0.9	.	41.6	28.7	6.1	.
		Inv.IV	17/05/99	60	yellow	clear	none	88	0	12	.	.	36.6	17.1	9.3	.
		Inv.V	18/05/99	122	yellow	clear	none	66	0	34	0.9	.	7	2.6	18	.
		Inv.VI	19/05/99	28	yellow	clear	none	89	0	11	4.4	.	4.5	1.4	14.3	.

Group	Pat	examination	Date	punctate	color	consistency	tumor cells	neutro-phils	eosino-philes	lympho-cytes	HLA-DR+	macro-phages	CD4	CD8	NK-CD16	NK-CD56
Helixor	29	Inv.I/1	10/07/99	350	yellow	clean	.	2	0	98	1	0	60.7	12	.	.
		Inv.IV	15/07/99	370	yellow	turbid	.	.	.	.	.	.	58.6	11.1	.	.
	32	Inv.I/1	08/09/99	5	straw	turbid	.	100	0	0	1.12	0	0.6	1.3	.	.
		Inv.III	10/09/99	10	bloody	turbid	.	100	0	0	.	.	.	.	.	.
	33	Inv.I/1	06/10/99	90			.	.	.	.	0.09	0	.	.	.	.
		Inv.II	08/10/99	10	yellow	turbid	.	56	0	36	.	.	.	.	.	.
		Inv.III	09/10/99	125	yellow	turbid	.	67	0	26	.	.	.	.	.	.
		Inv.V	11/10/99	550	yellow	turbid	.	32	1	63	.	.	.	.	.	.
		Inv.VI	12/10/99	40	yellow	turbid	.	51	0	49	.	.	.	.	.	.
		Inv.VII	13/10/99	20	yellow	turbid	.	67	0	27	.	.	.	.	.	.
		Inv.add.	14/10/99	10	yellow	turbid	.	92	2	6	.	.	.	.	.	.
Doxycycline	2	Inv.prior 1.Inst.	21/05/97	70	bloody	cloudy	none	15	16	69	3.9	0	52	12.4	23	.
		Inv.prior 2.Inst.	22/05/97	250	dark brown	turbid	.	.	.	.	.	.	31.3	11.9	8.9	.
	4	Inv.I/1	16/07/97	500	amber	cloudy	few	35	0	65	2.2	0	48.8	31.7	3.4	.
		Inv.II	17/07/97	1500	bloody	turbid	.	50	3	40	.	.	.	.	.	.
	7	Inv.prior 1.Inst.	11/09/97	130	amber	cloudy	none	19	29	52	0	0	2	7.4	.	3.3
		Inv.prior 2.Inst.	12/09/97	30	amber	cloudy	none	85	0	15	.	.	.	.	.	.
	12	Inv.prior 1.Inst.	29/07/98	400	yellow	turbid	none	24	0	76	0.6	0	48.79	22.26	3.9	.
		Inv.prior 2.Inst.	03/08/98	200	brown	turbid	none	62	7	31	.	.	.	.	.	.
	15	Inv.prior 1.Inst.	08/10/98	10	yellow	turbid	many	20	0	80	.	0	.	.	1.6	.
	16	Inv.prior 1.Inst.	30/09/98	700	amber	turbid	numerous	71	0	29	.	0	.	.	.	.
	17	Inv.prior 1.Inst.	11/12/98	30	yellow	turbid	none	34	0	66	31.7	0	48	13.8	2.2	.
		Inv.prior 2.Inst.	19/12/98	540	yellow	clean	none	0	0	100	.	.	44.2	27.2	0.4	.
	18	Inv.prior 1.Inst.	05/01/99	325	bloody	turbid	many	0	0	100	.	0	.	.	.	.
	20	Screening	25/01/99	300	yellow	turbid	many	0	1	99	.	0	43.4	36	.	.
		Inv.prior 2.Inst.	01/02/99	80	yellow	turbid	many	.	.	.	.	.	55.9	32.9	.	.
	21	Inv.prior 1.Inst.	29/01/99	145	yellow	turbid	none	0	0	100	2.1	0	6.9	4.9	2.5	.
	23	Inv.prior 1.Inst.	27/03/99	84	yellow	clear	none	2	0	98	2.1	0	34.9	49.7	5.5	.

Group	Pat	examination	Date	punctate	color	consistency	tumor cells	neutro-phils	eosino-philes	lympho-cytes	HLA-DR+	macro-phages	CD4	CD8	NK-CD16	NK-CD56
Doxycycline	25	Inv.prior 1.Inst.	06/05/99	330	yellow	turbid	numerous	2	0	98	4.9	0	48.1	39.5	3.6	.
		Inv.prior 2.Inst.	10/05/99	670	yellow-milky	clear	many	5	.	90	1.3	.	50.1	34	3.6	.
	27	Inv.prior 1.Inst.	11/05/99	150	yellow	clear	none	0	0	100	0.7	0	65.1	18.8	2.9	.
		Inv.prior 2.Inst.	20/05/99	320	dark brown	cloudy	none	4	0	96	7.3	.	58.1	17	5.4	.
	28	Inv.prior 1.Inst.	24/05/99	50	yellow	turbid	none	14	0	86	14.9	0	43.1	13.2	6.5	.
	30	Inv.prior 1.Inst.	24/08/99	2125	amber	turbid	many	20	1	79	0.16	0	33.9	32.1	.	.
		Inv.prior 2.Inst.	15/09/99	300	bloody	cloudy	isolated	24	0	68	.	.	.	.	.	.
	31	Inv.prior 1.Inst.	26/08/99	950	amber	turbid	many	20	1	79	6.1	0	33.8	17.3	.	.
		Inv.prior 2.Inst.	03/09/99	75	bloody	cloudy	.	1	10	71	.	.	.	.	.	.

Listing 14: Adverse events

Group	Pat	symptom	WHO	begin	end	intensity	degree	connection	sae	duration	evolution	measures	cancelling	Re-expo
Helixor	1	fever	FIEBER	19/04/97	26/04/97	moderate	not serious	probable	no	hours	occasional	suppl. medication	na	yes
		Pain (Side effect intrapleural instillation)	SCHMERZ	19/04/97	25/04/97	light	.	.	no	.	.	.	.	.
	3	Dyspnea	DYSPNOE	26/05/97	27/05/97	severe	death	none	yes	days	permanent	interruption	na	na
	5	Burning	BRUSTKORB BRENNSCHMERZ	28/08/97	.	moderate	.	.	no	.	.	.	.	.
		Fever (Side effect intrapleural instillation)	FIEBER	28/08/97	.	moderate	.	.	no	.	.	.	.	.
		pain	SCHMERZ	28/08/97	.	severe	.	.	no	.	.	.	.	.
		Chest pain	SCHMERZEN BRUSTKORB	29/08/97	29/08/97	moderate	not serious	probable	no	hours	occasional	none	na	na
	8	Pain (Side effect intrapleural instillation)	SCHMERZ	15/10/97	.	light	.	.	no	.	.	.	.	.
		Dyspnoea	DYSPNOE	21/10/97	.	severe	not serious	none	no	weeks	permanent	none	na	na
	9	Fever (Side effect intrapleural instillation)	FIEBER	22/11/97	.	light	.	.	no	.	.	.	.	.
		fever	FIEBER	24/11/97	27/11/97	moderate	not serious	not evaluable	no	days	permanent	suppl. medication	yes	no
	10	Dyspnea	DYSPNOE	12/02/98	16/02/98	severe	death	none	yes	days	unknown	.	.	na
	11	Fever (Side effect intrapleural instillation)	FIEBER	28/02/98	.	moderate	.	.	no	.	.	.	.	.
	13	Fever (38° C)	FIEBER	30/09/98	30/09/98	light	not serious	probable	no	hours	unique	none	na	na
		Fever 37,8° C (Side effect intrapleural instillation)	FIEBER	02/10/98	.	light	.	.	no	.	.	.	.	.
		Fever 39,6° C (Side effect intrapleural instillation)	FIEBER	05/10/98	.	severe	.	.	no	.	.	suppl. medication	.	.

Group	Pat	symptom	WHO	begin	end	intensity	degree	connection	sae	duration	evolution	measures	cancelling	Re-expo
Helixor	13	Fever (Side effect intrapleural instillation)	FIEBER	06/10/98	.	moderate	.	.	no	.	.	.	.	.
	14	Burning	BRUSTKORB BRENNSCHMERZ	04/10/98	04/10/98	severe	not serious	probable	no	minutes	unique	suppl. medication	na	na
		Burning (Side effect intrapleural instillation)	BRUSTKORB BRENNSCHMERZ	05/10/98	.	severe	.	.	no	.	.	.	.	.
		Fever	FIEBER	05/10/98	.	moderate	not serious	not evaluable	no	hours	unknown	none	na	na
		Burning (Side effect intrapleural instillation)	BRUSTKORB BRENNSCHMERZ	06/10/98	.	severe	.	.	no	.	.	.	.	.
		Fever (Side effect intrapleural instillation)	FIEBER	06/10/98	.	severe	.	.	no	.	.	.	.	.
		Burning (Side effect intrapleural instillation)	BRUSTKORB BRENNSCHMERZ	07/10/98	.	severe	.	.	no	.	.	.	.	.
		Fever (Side effect intrapleural instillation)	FIEBER	07/10/98	.	severe	.	.	no	.	.	.	.	.
		Burning (Side effect intrapleural instillation)	BRUSTKORB BRENNSCHMERZ	08/10/98	.	severe	.	.	no	.	.	.	.	.
		Fever (Side effect intrapleural instillation)	FIEBER	08/10/98	.	moderate	.	.	no	.	.	.	.	.
	19	Hematemesis	HAEMATEMESIS BEI MAGENULKUS	08/01/99	08/01/99	moderate	not serious	not evaluable	no	days	unique	suppl. medication	no	no
		Hypotension due to Hematemesis	HYPOTENSION	14/01/99	14/01/99	severe	death	none	yes	hours	permanent	suppl. medication	na	na
	24	Fever, light (Side effect pleural instillation)	FIEBER	05/04/99	.	light	.	.	no	.	.	.	.	.

Group	Pat	symptom	WHO	begin	end	intensity	degree	connection	sae	duration	evolution	measures	cancelling	Re-expo
Helixor	24	Pain	SCHMERZ	05/04/99	07/04/99	light	not serious	sure	no	minutes	occasional	none	no	na
		Fever, light (Side effect intrapleural instillation)	FIEBER	06/04/99	.	light	.	.	no	.	.	.	.	.
		Nausea, abdominal distension	NAUSEA	08/04/99	08/04/99	moderate	not serious	none	no	hours	frequent	suppl. medication	na	na
		Dyspnea, pain	DYSPNOE	10/04/99	14/04/99	severe	death	none	yes	days	unique	suppl. medication	na	na
	26	Pain	SCHMERZ	13/05/99	13/05/99	severe	not serious	sure	no	seconds	unique	suppl. medication	no	yes
		Pain (Side effect intrapleural instillation)	SCHMERZ	14/05/99	.	severe	.	.	no	.	.	.	.	.
		Dull pain and dyspnea	DYSPNOE	20/05/99	20/05/99	light	not serious	possible	no	minutes	unique	none	no	yes
	29	pain	SCHMERZ	12/07/99	.	severe	.	.	no	.	.	.	.	.
		Right shoulder pain	SCHMERZ LOKAL	12/07/99	12/07/99	light	not serious	sure	no	minutes	unique	none	no	yes
		Pain	SCHMERZ	15/07/99	15/07/99	severe	not serious	sure	no	hours	occasional	suppl. medication	no	yes
		Right shoulder pain	SCHMERZ LOKAL	15/07/99	15/07/99	moderate	not serious	probable	no	hours	occasional	suppl. medication	no	yes
		Pleural Pain	PLEURASCHMERZ	16/07/99	16/07/99	moderate	not serious	sure	no	hours	frequent	none	na	yes
		fever	FIEBER	16/07/99	.	moderate	.	.	no	.	.	.	.	.
		Pain at inspiration	SCHMERZ	16/07/99	16/07/99	moderate	not serious	possible	no	hours	frequent	none	na	yes
		Pleural pain	PLEURASCHMERZ	17/07/99	17/07/99	severe	not serious	possible	no	hours	frequent	suppl. medication	na	no
		Right shoulder pain	SCHMERZ LOKAL	17/07/99	17/07/99	moderate	not serious	sure	no	hours	unique	suppl. medication	na	yes
		Pleural pain	PLEURASCHMERZ	18/07/99	18/07/99	moderate	not serious	possible	no	minutes	unique	none	no	na
	32	Burning (Side effect intrapleural instillation)	BRUSTKORB BRENNSCHMERZ	09/09/99	.	moderate	.	.	no	.	.	.	.	.

Group	Pat	symptom	WHO	begin	end	intensity	degree	connection	sae	duration	evolution	measures	cancelling	Re-expo
Doxy-cycline	2	Chest pain	SCHMERZEN BRUSTKORB	21/05/97	21/05/97	moderate	not serious	possible	no	days	afer each appl.	none	na	na
		Burning (Side effect intrapleural instillation)	BRUSTKORB BRENNSCHMERZ	21/05/97	.	moderate	.	.	no	.	.	.	.	.
		Fever (Side effect intrapleural Instillation)	FIEBER	21/05/97	.	light	.	.	no	.	.	.	.	.
		Epigastric soreness	OBERBAUCHBESCHWERDEN	22/05/97	30/05/97	light	not serious	not evaluable	no	hours	occasional	suppl. medication	no	no
	4	Chest Pain	SCHMERZEN BRUSTKORB	16/07/97	16/07/97	light	not serious	probable	no	minutes	unique	none	na	no
		Fever	FIEBER	17/07/97	17/07/97	light	not serious	not evaluable	no	hours	frequent	none	na	na
		Fever	FIEBER	19/07/97	19/07/97	moderate	not serious	probable	no	hours	frequent	none	no	yes
		Pain (Side effect intrapleural instillation)	SCHMERZ	19/07/97	.	light	.	.	no	.	.	.	.	.
		chest pain	SCHMERZEN BRUSTKORB	20/07/97	20/07/97	light	not serious	probable	no	hours	frequent	none	no	yes
		Fever	FIEBER	21/07/97	21/07/97	light	not serious	possible	no	hours	occasional	none	na	yes
		pain	SCHMERZ	21/07/97	.	light	.	.	no	.	.	.	.	.
		Fever	FIEBER	22/07/97	22/07/97	light	not serious	possible	no	hours	frequent	none	no	yes
		Pain (Side effect intrapleural Instillation)	SCHMERZ	22/07/97	.	light	.	.	no	.	.	.	.	.
		Dyspnea	DYSPNOE	23/07/97	25/07/97	moderate	death	none	yes	days	permanent	.	na	na
	7	Right chest pain	SCHMERZEN BRUSTKORB	11/09/97	11/09/97	severe	not serious	sure	no	days	unique	suppl. medication	na	na
		Burning (Side effect intrapleural instillation)	BRUSTKORB BRENNSCHMERZ	11/09/97	.	moderate	.	.	no	.	.	.	.	.
		Fever 38 °C (Side effect intrapleural instillation)	FIEBER	11/09/97	.	light	.	.	no	.	.	.	.	.
		Right chest pain	SCHMERZEN BRUSTKORB	18/09/97	18/09/97	severe	not serious	sure	no	hours	unique	suppl. medication	na	na

Group	Pat	symptom	WHO	begin	end	intensity	degree	connection	sae	duration	evolution	measures	cancelling	Re-expo
Doxy-cycline	7	Burning (Side effect intrapleural instillation)	BRUSTKORB BRENNSCHMERZ	18/09/97	.	moderate	.	.	no	.	.	.	.	.
	12	pleuritic chest pain	SCHMERZEN BRUSTKORB	29/07/98	29/07/98	moderate	not serious	none	no	hours	unique	suppl. medication	na	na
		Pain (Side effect intrapleural instillation)	SCHMERZ	31/07/98	.	severe	.	.	no	.	.	.	.	.
	15	pain	SCHMERZ	08/10/98	08/10/98	severe	not serious	sure	no	hours	unknown	suppl. medication	na	na
	16	Chest pain	SCHMERZEN BRUSTKORB	30/09/98	30/09/98	severe	not serious	sure	no	hours	unique	suppl. medication	na	na
	17	Chest pain	SCHMERZEN BRUSTKORB	11/12/98	11/12/98	severe	not serious	sure	no	hours	occasional	suppl. medication	na	na
		Chest pain, right	SCHMERZEN BRUSTKORB	19/12/98	19/12/98	severe	not serious	sure	no	hours	afer each appl.	suppl. medication	na	yes
		Dyspnea (due to general weakness)	DYSPNOE	02/01/99	04/01/99	severe	death	none	yes	days	frequent	none	na	na
	18	Chest pain	SCHMERZEN BRUSTKORB	05/01/99	05/01/99	severe	not serious	sure	no	hours	unique	suppl. medication	na	na
		Chest pain	SCHMERZEN BRUSTKORB	20/01/99	09/02/99	severe	not serious	none	no	days	frequent	hospitalization	na	no
	20	chest pain	SCHMERZEN BRUSTKORB	27/01/99	27/01/99	severe	not serious	sure	no	hours	unique	suppl. medication	na	na
	21	Chest pain	SCHMERZEN BRUSTKORB	29/01/99	29/01/99	severe	not serious	sure	no	hours	unique	suppl. medication	na	na
	23	Dyspnoea	DYSPNOE	01/03/99	05/04/99	severe	death	none	yes	weeks	occasional	hospitalization	na	na
		burning	BRUSTKORB BRENNSCHMERZ	27/03/99	.	severe	.	.	no	.	.	.	.	.
		fever	FIEBER	27/03/99	.	moderate	.	.	no	.	.	.	.	.
		pain	SCHMERZ	27/03/99	.	severe	.	.	no	.	.	.	.	.
	25	Pain	SCHMERZ	06/05/99	06/05/99	severe	not serious	sure	no	minutes	unique	suppl. medication	yes	na
	27	burning sense	BRUSTKORB BRENNSCHMERZ	14/05/99	14/05/99	severe	not serious	sure	no	hours	unique	none	yes	yes
		Fever (Side effect intrapleural instillation)	FIEBER	14/05/99	.	severe	not serious	.	no	.	.	.	.	.
		Pain	SCHMERZ	14/05/99	14/05/99	severe	not serious	sure	no	hours	unique	none	yes	yes
		burning sense	BRUSTKORB BRENNSCHMERZ	21/05/99	21/05/99	severe	not serious	sure	no	hours	unique	suppl. medication	na	na

Group	Pat	symptom	WHO	begin	end	intensity	degree	connection	sae	duration	evolution	measures	cancelling	Re-expo
Doxy-cycline	27	Fever (Side effect intrapleural instillation)	FIEBER	21/05/99	.	severe	not serious	.	no	.	.	.	.	.
		Pain	SCHMERZ	21/05/99	21/05/99	severe	not serious	sure	no	hours	unique	suppl. medication	na	na
	28	Burning (Side effect intrapleural instillation)	BRUSTKORB BRENNSCHMERZ	24/05/99	.	severe	.	.	no	.	.	.	.	.
		Pain	SCHMERZ	24/05/99	24/05/99	severe	not serious	sure	no	hours	unique	suppl. medication	no	no
	30	Dyspnea and weakness	DYSPNOE	04/09/99	18/09/99	severe	death	none	yes	hours	unique	none	no	na
		Foreign body sensation	KOERPERGEFUEHLVERAENDERUNG	09/09/99	09/09/99	light	not serious	sure	no	seconds	unique	none	no	no
	31	Cough (Side effect intrapleural instillation)	HUSTEN	28/08/99	.	.	not serious	.	no	.	.	.	.	.
		pain	SCHMERZ	28/08/99	28/08/99	light	not serious	sure	no	seconds	unique	none	no	no