C O N F I D E N T I A L L Y

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«APPROVE»
Director of the State Enterprise
"Institute of Neurosurgery named after acad.
A.P. Romodanova NAMS of Ukraine"
(stamp and signature) E.G. Pedachenko
«____»_____2020

«ЗАТВЕРДЖУЮ»
Директор Державної установи
«Інститут нейрохірургії ім. акад.
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_____ Є. Г. Педаченко
«____» _____ 2020 р.

REPORT

ABOUT THE CLINICAL STUDY

An open study to study the efficacy and tolerability of Donovit-VS, a tablet produced by Astrapharm LLC, which was used in patients with glioblastoma during chemotherapy in comparison with a group of patients who received only chemotherapy

Phase II

Follow-up code AG-OICH-1/G .2/10.14
Protocol version No. 1 dated 14.03.2015

Sponsor:
LLC SPF "Aksomed LTD"
04210, Kyiv, Heroes of Stalingrad avenue 6, building 4
tel.: (044) 537-78-41

Location of the study:
State Enterprise "Institute of Neurosurgery named after N.N. acad. A.P. Romodanov NAMS of Ukraine,
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CONTENT

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1. GENERAL INFORMATION

Name of the study	An open study on the effectiveness of the drug Donovit-VS, tablets, produced by Astrapharm LLC, which was used in patients with glioblastoma on the background of chemotherapy in comparison with a group of patients who received only chemotherapy
Research sponsor	Aksomed LTD SPF LLC 04210, Kyiv, Geroiv Stalingrad Avenue 6, building 4. tel. (044) 537-78-41
Study code and protocol version number	Research code AF–DN–1/f .2/10.14 Protocol version No. 1 dated 03/14/2015
Development phase	II
The study drug	Donovit-VS, tablets, produced by "Astrapharm" LLC *Composition:* aconite root tuber extract (wrestler) - 1 tablet contains 10 mcg of aconitine alkaloid, excipients - lactose, calcium stearate. *Pharmacotherapy group.* Antitumor drugs. *Physico-chemical properties:* Tablets of light brown color, flat-cylindrical shape with beveled edges or biconvex. *Packaging:* 30 tablets in a blister, 3 blisters in a box. *Manufacturer:* "Astrapharm" LLC. Series: b/n Valid until: 02.2021
Place of research	State University "Institute of Neurosurgery named after Acad. A.P. Romodanova of the National Academy of Sciences of Ukraine". Department of Adjuvant Treatment Methods for CNS Tumors.

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	04050 Kyiv, str. P. Maiborody, 32 tel. (044) 483-92-19 (044) 483-95-73
Clinical trial start date:	07/01/2016 (date of informed consent obtained from the first patient)
End date of the clinical trial:	02/27/2020 (date of the last visit of the last patient)
Date of the final report:	08.12.2020

2. BRIEF CONTENTS OF THE REPORT

Title of the study: An open study on the effectiveness and effectiveness of the drug Donovit-VS, tablets, manufactured by Astrapharm LLC, which was used in patients with glioblastoma on the background of chemotherapy in comparison with a group of patients who received only chemotherapy

Research code: AF–DN–1/f .2/10.14

Protocol version: No. 1 dated 03/14/2015

Study population: Patients of both sexes aged 18 to 65 years with a diagnosis of: glioblastoma, grade IV anaplasia; patients after surgical resection or tumor biopsy and a course of radiation therapy.

Design: open, comparative, randomized, and parallel.

The purpose and objectives of the study:

The purpose of this study was to evaluate the effectiveness of the drug Donovit-VS, tablets, produced by Astrapharm LLC, which was used in patients with glioblastoma on the background of chemotherapy in comparison with a group of patients who received only chemotherapy

The objectives of the study were: to study the effect of the investigated drug, which was used in patients with glioblastoma on the background of chemotherapy, on one-year overall survival and survival without signs of progression, on the degree of toxicity of chemotherapy (according to the CTC-NCIC scale) and on the quality of life of the patient (according to the scale EORTC - QLQ - C 30). And also, a comparison of the results of treatment obtained in the main and control groups, with the aim of establishing the superior effectiveness of treatment in the group of patients who received chemotherapy + Donovit-VS in comparison with the group of patients who received only chemotherapy.

Number of patients.

In the study, 60 patients were randomized, 30 patients - to the group with the prescription of the drug Donovit-VS (the main group) and 30 patients - to the group without the prescription of the drug Donovit-VS (the control group).

The population for the analysis of effectiveness was 28 patients of the main group and 29 patients of the control group. The following patients were not included in the

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efficacy analysis: No. 27 (development of AE with fatal outcome 2 months after Visit 1 – pulmonary embolism), No. 42 (wrong inclusion in the study – the diagnosis of glioblastoma was not confirmed) and No. 60 (development of AR at 3rd day after taking the study drug and which required its withdrawal).

The population for the analysis of safety and portability was 59 patients: 30 patients of the main group and 29 patients of the control group.

Randomization.

A simple randomization method was used. The ratio of patients in the groups: 1:1. Method of randomization: sealed envelope method.

Dose, method of administration, duration of treatment.

Patients of the main and control groups received CT in accordance with international standards for the treatment of glioblastoma according to one of the following schemes:

1. Temozolomide in the form of 6 cycles of adjuvant therapy at a dose of 150-200 mg/m^2 1 time per day for 5 days of a 28-day cycle (5 days - taking temozolomide, 23 days - without taking the drug).
2. Lomustine 130 mg/m^2 per os once every 4-6 weeks. The course is 12 months.
3. PCV scheme: procarbazine + lomustine + vincristine every 4-6 weeks: 1st day - lomustine 130 mg/m^2 per os, 8th, 28th days - vincristine 1.0 mg/m^2 intravenously. From the 8th to the 22nd day inclusive, procarbazine 50 mg 2 times a day per os.

In addition, the patients of the main group received the investigated drug Donovit-VS, tablets produced by Astrapharm LLC, 1 tablet 3 times a day for 12 months. The drug was prescribed immediately after the end of the course of radiation therapy, simultaneously with the appointment of CT.

Concomitant treatment is allowed.

All patients of the main and control groups were prescribed standard symptomatic therapy, which included:

- antiemetics;
- cardioprotectors;
- hepatoprotectors;
- sedative drugs;
- supportive hormonal and anti-edema therapy.

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Patients also took drugs for the treatment of concomitant diseases (except drugs included in the "prohibited" list).

Concomitant treatment is prohibited.

During the study, patients were not allowed to prescribe the following groups of drugs:

- means that have an immunomodulating effect;
- immunosuppressants;
- biostimulants, bioinhibitors, adaptogens.

The duration of the patient's participation in the study and the schedule of visits.

The duration of participation in the study for each patient was 12 months + 3-7 days, of which: 3-7 days of screening, 12 months - treatment and observation.

Participation in the study was lower if the patient died.

As part of the study, 6 visits were planned: before the start of treatment (screening visit), then every 3 months after the start of treatment with the study drug Donovit-VS, regardless of which group the patient was assigned to, the main or control group (without the drug). .

Visit 1 – screening;

Visit 2 – randomization, appointment of treatment;

Visit 3 – the 90th day of the study;

Visit 4 – the 180th day of the study;

Visit 5 – the 270th day of the study;

Visit 6 – the 360th day of the study;

The scheduled visit days could be shifted by ± 7 days for objective reasons.

The total duration of the study was 3 years and 7 months (43 months).

Inclusion criteria:

1. Men and women aged 18 to 65.
2. Diagnosis: glioblastoma, stage IV anaplasia.
3. Patients after surgical resection or tumor biopsy and a course of radiation therapy (total radiation dose 60 Gray).
4. Histological or cytological confirmation of the diagnosis: glioblastoma.
5. Estimated life span of at least 12 weeks (3 months).
6. Functional status of the patient according to the ECOG scale - 0-2 points.

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7. For women of reproductive age - a negative pregnancy test result, as well as the use of reliable contraceptives during the study period.
8. Informed written consent of the patient to participate in the study.

Exclusion criteria:

1. Known hypersensitivity to the components of the studied drug.
2. Pregnancy, lactation.
3. The number of leukocytes < 2.0 x 10^9 cells/l.
4. The number of neutrophils < 1.5 x 10^9 cells/l.
5. The number of platelets < 100 x 10^9 cells/l.
6. Hemoglobin level < 100 g/l.
7. Creatinine exceeds the upper limit of normal by more than 1.25 times.
8. Transaminases (AST, ALT) exceed the upper limit of normal by more than 2.5 times; total bilirubin exceeds the upper limit of normal by more than 1.5 times.
9. Any unstable therapeutic or psychiatric condition that, in the opinion of the investigator, may impair the patient's ability to complete the study or prevent participation in the study.
10. The need to take non-recommended drugs
11. Participation in any other clinical research.

Criteria for early withdrawal from the study:

1. Withdrawal of informed consent (patient's reluctance to continue participating in the study);
2. Occurrence in the patient during the study of severe and/or unexpected AEs/ARs requiring withdrawal of the study drug.
3. The need to prescribe to the patient drugs that are not approved for use within the framework of this study (r. 11.4).
4. Non-compliance by the patient with the treatment regimen.
5. Non-compliance by the patient with the procedures provided for in the protocol.

Performance evaluation.

<u>The main variable</u>

- the overall survival of patients within 12 months from the start of treatment.

<u>Secondary variables</u> :

- progression-free survival within 12 months from the start of treatment;
- median survival rate;

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- degree of chemotherapy toxicity according to the CTC-NCIC scale;
- the patient's quality of life according to the EORTC - QLQ - C30 scale.

Assessment of transferability.

The assessment of transferability was carried out according to the following variables:

- the frequency of cases and the nature of AE/AR, their relationship with the study drug;
- dynamics of vital indicators (blood pressure, heart rate, body t);
- dynamics of ECG data;
- dynamics of laboratory indicators (general blood test, general urine test, biochemical blood test).

General description of the study.

After a preliminary clinical assessment, the relevant candidates were provided with oral and written information about the study drug and the study conditions. All potential patients were given time to consider their participation in the study and an opportunity to ask questions of the researcher. Written informed consent to participate in the study was obtained from potential patients prior to initiation of any screening procedures. Patients who signed the Informed Consent underwent screening procedures (Visit 1) (screening lasted up to 7 days). According to the inclusion/exclusion criteria, the patient was randomized to one of two treatment groups: main or control. The treatment group was randomly selected using a random number generator based on a 1:1 study group ratio. The "sealed envelope" method was used for randomization.

Patients of the main and control groups were prescribed CT in accordance with international standards for the treatment of glioblastoma according to one of the following schemes:

1. Temozolomide in the form of 6 cycles of adjuvant therapy at a dose of 150-200 mg/m^2 1 time per day for 5 days of a 28-day cycle (5 days - taking temozolomide, 23 days - without taking the drug).

2. Lomustine 130 mg/m^2 per os once every 4-6 weeks. The course is 12 months.

3. PCV scheme: procarbazine + lomustine + vincristine every 4-6 weeks: 1st day - lomustine 130 mg/m^2 per os, 8th, 28th days - vincristine 1.0 mg/m^2 intravenously. From the 8th to the 22nd day inclusive, procarbazine 50 mg 2 times a

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day per os.

In addition, the patients of the main group received the investigated drug Donovit-VS, tablets produced by Astrapharm LLC, 1 tablet 3 times a day for 12 months. The drug was prescribed immediately after the end of the course of radiation therapy, simultaneously with the appointment of CT.

During the study, scheduled medical examinations were carried out at the following points: before the start of treatment (screening), on the 90th, 180th, 270th and 360th days after the start of treatment. At each visit, patients underwent a physical examination, recorded subjective complaints, performed a comprehensive blood count, biochemical blood analysis, urinalysis, MRI or CT scan of the brain, ECG, evaluated the toxicity of chemotherapy according to WHO criteria on the CTC NCIC scale, determined functional condition according to the ECOG scale, in addition, patients filled out the EORTC - QLQ - C 30 quality of life questionnaire.

The results of all examinations were recorded in the primary medical documentation and the IRF.

Statistical methods.

In the analysis of research data, methods of descriptive statistics were used (for quantitative variables, indicators were calculated - n, arithmetic mean, median, standard deviation, minimum and maximum, and for categorical variables - frequency and share in %), graphic methods, methods of interval evaluation (construction of confidence intervals for arithmetic means or medians, depending on the agreement of the data with a normal distribution), methods of analysis of covariance (ANCOVA) followed by analysis of contrasts. The Mann-Whitney test or Student's test for independent samples (depending on the normality of the data distribution) was used to assess the significance of differences between two groups, the Wilcoxon signed-rank test or the Student's test for paired samples was used to compare the values of indicators before and after treatment. Survival curves were constructed using the Kaplan-Meier method, and compared using the log-rank test. When performing comparisons, the level of significance was taken equal to 0.05. To analyze the consistency of the data distribution with the normal distribution law, the Shapiro-Wilk test was used at a significance level of 0.01.

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Software.

Data analysis was carried out using built-in statistical analysis tools of Microsoft Excel spreadsheets and the SPSS 23.0 application program package.

Discussion of research results.

This open, single-center, randomized, comparative, parallel study was conducted from July 1, 2016 to February 27, 2020 in the Department of Adjuvant Treatment Methods for CNS Tumors of the State Institution "Institute of Neurosurgery named after Acad. A.P. Romodanova of the National Academy of Sciences of Ukraine". The protocol and materials of the clinical study were approved by the Central Committee of the Ministry of Health of Ukraine and the Ethics Committee of the Institute of Neurosurgery, where the study was conducted. The study was conducted in accordance with the Declaration of Helsinki, the International Principles of Clinical Research (ICH GCP), the current legislation of Ukraine, as well as the approved Research Protocol. All patients gave written informed consent to participate in the study before any screening procedures.

The purpose of this study was to evaluate the effectiveness and tolerability of the drug Donovit-VS, tablets, manufactured by Astrapharm LLC, which was used in patients with glioblastoma on the background of chemotherapy in comparison with a group of patients who received only chemotherapy.

The main efficacy variable was the overall survival of patients within 12 months from the start of treatment.

Secondary variables were: one-year progression-free survival, median survival, degree of toxicity of chemotherapy according to the CTC NCIC scale, quality of life according to the scale of the European Organization for Research and Treatment of Cancer - EORTC - QLQ - C30.

The general research plan included screening - 3-7 days, treatment and observation - 360 days.

The study included patients of both sexes aged 18 to 65 years with a histologically confirmed diagnosis of glioblastoma, grade IV anaplasia. The study included patients after surgical resection or biopsy of the tumor and a course of radiation therapy (total radiation dose 60 Gray). All patients included in the study had a functional status according to the ECOG scale from 0 to 2 points and an expected

life expectancy of at least 12 weeks. Additional criteria included: sufficient bone marrow reserve (leukocyte content ≥ 2.0 x10^9 /l, platelets ≥ 100x10^9/l, hemoglobin ≥ 100 g/l), as well as sufficient liver and kidney function (creatinine does not exceed the upper limit of normal by more than 1.25 times, AST, ALT do not exceed the upper limit of normal by more than 2.5 times; total bilirubin does not exceed the upper limit of normal by more than 1.5 times). Patients were excluded from the study if they had any unstable therapeutic or psychiatric condition that, in the opinion of the investigator, could impair the patient's ability to complete the study or prevent participation in it. Pregnant or lactating women could not participate in the study.

60 patients were randomized into the study, of which: 30 patients - in the group with the prescription of the drug Donovit-VS (main group) and 30 patients - in the group without the prescription of the drug Donovit-VS (control group).

The studied groups were compared in terms of gender and age, clinical symptoms, laboratory data, as well as in all parameters relevant to the assessment of efficacy and safety.

Patients of the main and control groups were prescribed CT in accordance with international standards for the treatment of glioblastoma according to one of the following schemes:

1. Temozolomide in the form of 6 cycles of adjuvant therapy at a dose of 150-200 mg/m^2 once a day for 5 days of a 28-day cycle (5 days - taking temozolomide, 23 days - without taking the drug).
2. Lomustine 130 mg/m^2 per os once every 4-6 weeks. The course is 12 months.
3. PCV scheme: procarbazine + lomustine + vincristine every 4-6 weeks: 1st day - lomustine 130 mg/m^2 orally, 8th, 28th days - vincristine 1.0 mg/m^2 intravenously. From the 8th to the 22nd day inclusive, procarbazine 50 mg 2 times a day per os.

In addition, the patients of the main group received the study drug Donovit-VS, tablets manufactured by Astrapharm LLC, 1 tablet 3 times a day for 12 months. The drug was prescribed immediately after the end of the course of radiation therapy, simultaneously with the appointment of CT.

57 patients were included in the efficiency analysis, of which: 28 patients of the main group and 29 patients of the control group. Patients No. 27 (development of AE with a fatal outcome 2 months after Visit 1 – pulmonary embolism), No. 42 (incorrect inclusion in the study – the diagnosis of glioblastoma was not confirmed)

and No. 60 (development of AR on the 3rd day after taking the study drug, which required its withdrawal).
59 patients were included in the safety and tolerability analysis, including 29 patients of the main group who received the drug Donovit-VS against the background of antitumor chemotherapy and 30 patients of the control group who received only chemotherapy.

Final results of the performance analysis
The results of the study showed that in patients who received the drug Donovit-VS in combination with chemotherapy, a significant increase in overall one-year survival and progression-free survival was achieved.
Analysis of the toxic profile of CT, in general, did not reveal significant differences between groups. Also, no statistically significant difference between the groups was found when analyzing the quality of life according to the QL2 scale of the EORTC QLQ-C30B questionnaire and when analyzing the condition of patients according to the ECOG scale during the study.

Evaluation of efficiency by the main variable.
1. The arithmetic mean of the one-year (365-day) overall survival time (the estimate was limited to the largest censored survival time) was 347.5 days in the main group and 309.45 days in the control group, which indicates the benefit of the exceeding effectiveness of treatment in the main group.
According to the results of the comparison of the curves of the overall one-year (365-day) survival in the groups using the log-rank test, the one-year survival in the main group was statistically significantly higher compared to the control group ($p = 0.030$), which allows us to draw a conclusion about the superior effectiveness of therapy with the use of the drug Donovit-VS in comparison with therapy without the use of this drug.

Evaluation of efficiency by secondary variables:
1. The arithmetic mean of the one-year recurrence-free survival time (the estimate was limited to the largest censored recurrence-free survival time, under the condition of 12-month follow-up) was 11.5 months in the main group and 9.2 months in the control group, which indicates in favor of the superior effectiveness of treatment in the main group.

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2. Median one-year recurrence-free survival in the main group was absent, since relapse during the study developed in less than 50% of patients in the main group, and in the control group, the median recurrence-free survival was 9 months.

3. According to the results of the comparison of the one-year recurrence-free survival curves in the groups using the log-rank test, the one-year recurrence-free survival in the main group was statistically significantly higher compared to the control group ($p < 0.001$), which allows us to draw a conclusion about the superior effectiveness of therapy with the use of the drug Donovit- VS in comparison with therapy without the use of this drug.

4. The overall one-year (365 days) survival of patients in the main group was 78.6%, and in the control group - 51.7%. Formally, the differences between the groups are statistically insignificant ($p = 0.052$). However, the fact that the difference in the percentage of surviving patients [primary – control] is 26.8% indicates the benefit of the superior effectiveness of the therapy with the use of the drug Donovit-VS in comparison with the therapy without the use of this drug.

5. The relapse-free one-year survival of patients in the main group was 75.0%, and in the control group - 34.5%. The difference in proportions [main - control] was 40.5%. The differences between the groups are statistically significant ($p = 0.003$), which allows us to draw a conclusion about the superior effectiveness of therapy with the use of the drug Donovit-VS in comparison with therapy without the use of this drug.

6. On the basis of the statistical analysis of the toxicity data of CT and the safety of the treatment in the groups, the following data were obtained:
1) The analysis of hemodynamic indicators showed the absence of significant changes during the study, in most cases, in both groups. Slight fluctuations in blood pressure, heart rate, and body temperature were noted at different stages of observation, but they were not clinically significant. This indicates the absence of a

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negative effect of the therapy on hemodynamic indicators and body temperature.

2) A decrease in the level of leukocytes and platelets was noted in the patients of both groups during the study. These changes corresponded to the toxicity profile of chemotherapy drugs used and indicated the negative effect of CT on the hematopoietic system.

3) Differences between groups in the presence of leukocytopenia and thrombocytopenia were statistically insignificant at all visits, although there was some tendency at Visit 6 to a lower proportion of patients with leukocytopenia in the main group 7 (35.0%) compared to the control group 5 (55.6%). However, when interpreting these results, it should be taken into account that at the end of the study, 20 patients of the main group and only 9 patients of the control group were included in the analysis.

4) Differences between groups in terms of hematological indicators were statistically insignificant at all visits, which indicates the absence of a negative effect of the studied drug on the hematopoietic system.

5) In patients of both groups, an increase in the levels of ALT, AST and total bilirubin was noted at certain visits, which was the result of the effect of CT on the hepatobiliary system.

6) Statistically significant differences between the groups in terms of laboratory indicators of biochemical blood analysis were not found at any of the visits. The differences that were observed were, as a rule, related to the initial condition of the patients and the CT courses received before the visits.

7) Statistically significant differences between the groups in accordance with laboratory indicators of the biochemical analysis of blood analyzed, the norm and deviation from it, were not found for any of the indicators at any of the visits.

8) The above testifies to the absence of a negative effect of the studied drug on the indicators of biochemical blood analysis.

9) According to the results of the analysis of the laboratory indicators of the general urinalysis, no statistically significant differences between the groups were found for any of the indicators at any of the visits, which indicates the absence of a negative effect of the studied drug on the indicators of the general urinalysis.

10) Differences between groups in the pathology of the cardiovascular system, according to ECG data, were statistically insignificant at each of the corresponding visits (B1, B4, B5 and B6), which indicates the absence of a negative effect of the studied drug on ECG indicators.

11) In the course of treatment, according to ECG data, non-specific pathological

changes were detected in 6 patients (21.4%) of the main group and in 4 (13.8%) patients of the control group, and the differences between the groups were statistically insignificant (p = 0.504) . Heart rhythm disturbances of the 1st-2nd degree of toxicity were observed in 2 (7.7%) patients of the main group and in 4 (16.7%) patients of the control group. Differences between groups were also statistically insignificant (p = 0.670).

12) There were also no statistically significant differences between groups in other parameters of non-hematological toxicity, such as gastrointestinal toxicity (constipation, nausea/vomiting, diarrhea), its manifestations were noted in 20 (71.4%) patients of the main group and in 16 (55.2%) of control patients.

13) Summarizing the above, it can be stated that the overall toxicity profile for the group of patients who received the study drug Donovit-VS on the background of CT was not statistically significantly different from the group that received only CT.

7. The dynamics of quality of life assessments on the QL2 scale of the EORTC QLQ-C30 questionnaire during treatment was insignificant in both groups. Some increase in mean values in the control group at the last visit was due to the fact that in the control group patients with poor quality of life scores dropped out, while in the main group some patients with poor quality of life scores were still present at the last visit (in 20 patients of the main group and only 9 patients of the control group were included in the analysis).

8. As a result of the statistical analysis of the evaluations of the condition of the patients according to the ECOG scale, no statistically significant differences between the groups were found at any of the visits.

The results of the transferability analysis.

During the study, 42 AE/AR were registered in 17 (56.7%) patients of the main group (with the use of Donovit-VS) and 35 AE/AR in 10 (34.5%) patients of the control group (without the use of Donovit-VS).

Of these, in the main group, 10 serious AE/AR were registered in 8 (26.7%) patients and in the control group - 14 serious AE/AR in 3 (10.3%) patients.

In this study, the following AE/AR were most often encountered: leukopenia, thrombocytopenia, increased transaminase levels; from the gastrointestinal tract, such phenomena as constipation and nausea/vomiting. Almost all AE/AR registered during the study were directly related to the course of the underlying disease and

corresponded to the toxicity profile of the chemotherapeutic drugs used.

In the course of the study, no allergic and anaphylactic reactions were recorded in the group of patients taking the studied drug.

On the basis of the conducted statistical analysis, it is possible to draw a conclusion regarding the absence of a negative effect of the studied drug on hemodynamic indicators and body temperature, laboratory indicators of the general blood test, biochemical blood test, general urinalysis and ECG indicators.

Only in one case (patient No. 60, male, 51 years old, main group) was observed an increase in body temperature, probably related to the use of the drug under investigation. The patient was discontinued from the study drug and was withdrawn from the study.

On the basis of the above, it can be assumed that the tolerability of the studied drug Donovit-VS was good in 96.3% of patients.

Conclusions and recommendations.

1. The drug Donovit-VS, tablets produced by Astrapharm LLC, prescribed for 1 tablet 3 times a day for 12 months against the background of CT, is an effective means in the treatment of patients with glioblastoma.

2. Based on the analysis of the data of the clinical study, it was proved that the treatment of glioblastoma was more effective in the group of patients who received the investigated drug Donovit-VS, tablets manufactured by Astrapharm LLC, against the background of antitumor CT, compared to the group of patients who received only CT. This was manifested in terms of overall one-year patient survival and one-year recurrence-free survival. Thus, the arithmetic mean of overall one-year survival was 347.5 days in the main group and 309.45 in the control group, the differences between the groups are statistically significant ($p = 0.030$). The arithmetic mean of one-year recurrence-free survival was 11.5 months in the main group and 9.2 months in the control group, the differences between the groups are statistically significant ($p < 0.001$).

The overall one-year survival of patients in the main group was 78.6%, and in the control group - 51.7%. The difference in the percentage of surviving patients is 26.8%. The relapse-free one-year survival of patients in the main group was 75.0%, and in the control group - 34.5%. The difference in proportions is 40.5%, the differences between groups are statistically significant ($p = 0.003$). The above

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allows us to draw a conclusion about the superior effectiveness of therapy with the use of the drug Donovit-VS in comparison with therapy without the use of this drug in patients with glioblastoma.

3. The overall toxicity profile for the group of patients who received the drug Donovit-VS on the background of CT was not statistically significantly different from the group that received only chemotherapy.

4. There were no statistically significant differences in QL2 scores of the EORTC QLQ-C30 questionnaire and ECOG scores between groups at any of the visits.

5. The data obtained during the research show the safety and good tolerability of the researched drug Donovit-VS, tablets produced by Astrapharm LLC, which is prescribed 1 tablet 3 times a day for 12 months against the background of antitumor CT in patients with glioblastoma.

6. On the basis of the above, the drug Donovit-VS, tablets produced by Astrapharm LLC, can be recommended for medical use in patients with glioblastoma as an accompanying drug during a course of CT. Recommended treatment regimen: 1 tablet 3 times a day for 12 months.

The report contains:

pages – 183; tables – 92; drawings – 15; literary sources – 17

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3. LIST OF ABBREVIATIONS

BP - blood pressure

ALT - alanine aminotransferase

AST - Aspartate aminotransferase

PFS - progression-free survival

UB - upper bound

WHO - World Health Organization

SEC - State expert center of the Ministry of Health of Ukraine

VA - variance analysis

DBP - diastolic blood pressure

CI - confidence interval

OS - overall survival

BMI - body mass index

IRF - Individual registration form

CT - computer tomography

MPE - Medical prophylactic establishment

IU - international units

MTD - maximum tolerated dose

LB - lower bound

AO - abdominal organs

CO - chest organs

AR - adverse reaction

AE - adverse effect

RN - randomization number

SBP - systolic blood pressure

SND - standard normal distribution

ESR - erythrocyte sedimentation rate

Ultrasound - ultrasound examination

CT - chemotherapy

ECG - electrocardiogram

HR- heart rate

CNS - central nervous system

CBER - Central body of executive power

t^{o} - body temperature

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GCP - Good Clinical Practice - Quality clinical practice

ICH - International Conference on Harmonization

EORTC - QLQ - C 30 - European Organization for Research and Treatment of Cancer quality of life questionnaire

CTC NCIC - Common Toxicity Criteria National Cancer Institute - toxicity assessment scale of the National Cancer Institute

4. ETHICAL AND LEGAL ASPECTS OF THE RESEARCH

4.1 Regulatory and legal basis for conducting a clinical trial

This study was conducted in compliance with the following regulatory documents:

1. The Law of Ukraine "On Medicinal Products", 1996, as amended on May 31, 2016 No. 1396-VIII "On Amendments to the Law of Ukraine "On Medicinal Products".

2. The Declaration of Helsinki in its latest version, adopted at the 64th General Assembly of the World Medical Association, Fortaleza, Brazil, October 2013.

3. Order of the Ministry of Health of Ukraine No. 95 dated 16.02.2009, as amended (Order of the Ministry of Health of Ukraine No. 1169 dated 26.09.2017)

4. Order of the Ministry of Health of Ukraine No. 690 dated 23.09.2009 "On approval of the Procedure for conducting a CI and examination of the materials of the CI and the Standard Regulation on ethics commissions" (as amended in accordance with the orders of the Ministry of Health of Ukraine No. 523 dated 12.07.2012, No. 304 dated 06.05. 2014, No. 966 dated 18.12.2014, No. 639 dated 01.10.2015)

4.2 Obtaining approval by the Ethics Committee

The protocol of the clinical study, the documents of the patient's informed consent to participate in the clinical study, the researcher's brochure and other necessary documents were submitted to the Ethics Committee of the State University "Institute of Neurosurgery named after Acad. A.P. Romodanova of the National Academy of Sciences of Ukraine".

The study was started only after receiving the decision of the Central Committee on Clinical Research and receiving the protocol of the Ethics Commission on the approval of the materials of this clinical study.

4.3 Obtaining written informed consent

Written informed consent for participation in the study was obtained from each potential study participant prior to the initiation of any screening procedures.

Patients, potential participants of the study, were verbally informed by the researcher about the nature of the clinical study, the study drug, as well as about the possible risks associated with the use of the drug. In the converSBRion between the researcher and the patient, the following issues were discussed: the purpose and

duration of the study, the scope and nature of the examinations conducted, the treatment scheme, concomitant therapy and restrictions on taking medications, the possibility of side effects, the possibility of providing medical assistance during the study, insurance conditions. Patients were explained their rights and responsibilities related to participation in the study. Information about this clinical study was provided by the researcher in a form accessible to the patient.

Each patient was also provided with written information about the study drug and study conditions contained in the Patient Information. Verbal and written information was provided to the patient at his request - in Russian or Ukrainian.

Patients were informed that they could refuse to participate in the study at any time, without prejudice to further treatment.

Patients were also informed about the conditions of confidentiality and use of their personal data, including the need for access to them by authorized persons (in case of audit, inspection, etc.).

Each patient was given a sufficient amount of time to consider the possibility of his participation in the study and to ask the researcher what questions he was interested in. The researcher did not put pressure on the patient in order to influence his decision.

If the patient made a decision to participate in the study, he filled out and signed the Informed Consent Form in his own hand, in 2 copies, one copy of which was given to the patient with information about participation in the clinical study, as well as information about the contract of mandatory insurance of his life and health, as a participant in a clinical study. The 2nd copy of this form remained in the research center for further storage for 15 years.

The fact of the discussion of the informed consent was recorded in the primary medical documentation and in the IRF with an indication of the date of signing

4.4 Insurance

The subjects of this clinical study were insured by the sponsor of the study Astrapharm LLC in accordance with the current legislation of Ukraine. All patients who signed the Informed Consent Form were covered by insurance.

4.5 Confidentiality and protection of personal data

All documentation of the study was conducted in compliance with the conditions of strict confidentiality. The researcher and the Sponsor ensured the protection of personal data of patients participating in the study in accordance with the Law of Ukraine "On the Protection of Personal Data". The necessary personal data of the research participants were used exclusively to achieve the research goals.

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5. RESEARCHERS AND ADMINISTRATIVE STRUCTURE OF RESEARCH

The name of the study: An open study to study the effectiveness and tolerability of the drug Donovit-VS, tablets, manufactured by Astrapharm LLC, which was used in patients with glioblastoma on the background of chemotherapy in comparison with a group of patients who received only chemotherapy. **Research code: AF–DN–1/f .2/10.14** **Protocol version No. 1 dated 03/14/2015**
Research sponsor Aksomed LTD SPF LLC 04210, Kyiv, Heroiv Stalingrad Avenue 6, building 4. tel. (044) 537-78-41

Director of NVF LLC "Aksomed LTD"	Cand. tech. Sciences, Associate Professor, Aksonov G.N.
Scientific consultant	Dr med. Sciences, Honored Doctor of Ukraine, Sobetsky V.V.

Place of research State University "Institute of Neurosurgery named after Acad. A.P. Romodanova National Academy of Sciences of Ukraine". Department of Adjuvant Treatment Methods for CNS Tumors. 04050 Kyiv, str. P. Maiborody, 32 tel. (044) 483-92-19 (044) 483-95-73

Responsible researcher	Oleksandr Yakovych Hlavatskyi - head of the department of adjuvant treatment methods for tumors of the central nervous system, MD. Sciences, professor.
Co-researcher	Khmelnytskyi Gennadiy Vladyslavovich - neurosurgeon of the department of adjuvant treatment methods for tumors of the central nervous system, Candidate of Medical Sciences
Co-researcher	Iryna Mykolaivna Shuba is a senior researcher at the Department of Neurobiochemistry

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6. INTRODUCTION

6.1. Description of the studied drug

The studied drug Donovit-VS, tablets produced by Astrapharm LLC, is an original development of the research and production company Aksomed LTD, proposed for clinical study in order to resolve the issue of the possibility of registering the drug in Ukraine as a medicinal product.

The drug Donovit-VS belongs to anticancer drugs. The composition of the drug includes an extract of the rhizome of aconite (wrestler) - 1 tablet contains 10 μg of alkaloid aconitine, excipients - lactose, calcium stearate.

Pharmacological action.

According to preclinical studies, Donovit-VS exhibits antitumor activity against solid tumors with angiogenesis-dependent growth. The drug also significantly suppresses the metastasis process, reducing the number of metastases and their volume. The antitumor and antimetastatic effect is dose-dependent and due to the implementation of two mechanisms: antivascular (at total doses of the order of MTD/2) and antiangiogenic (at total doses less than MTD/20). The antiangiogenic mechanism of action determines the anti-tumor and anti-metastatic effect only for malignant neoplasms with angiogenesis-dependent growth.

Intended indications for use.

The drug is intended to be used in the treatment of oncological diseases as an "accompanying" therapy to the main treatment: for the treatment of toxic effects of chemotherapy and radiation reactions; as supportive (symptomatic) therapy of late complications of tumor processes. The drug is intended to be used for:

- brain tumors (astrocytomas, glioblastomas, medulloblastomas, melanoma metastases to the brain);
- breast tumors;
- colorectal cancer.

Contraindications are possible.

Hypersensitivity to the components of the drug.

Special warnings.

Patients with severe kidney and/or liver dysfunction should reduce the daily dose by two times. The drug contains lactose, so it should not be prescribed to patients with rare hereditary forms of galactose intolerance and lactase deficiency.

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Method of application and dosage.

Possible schemes for prescribing the studied drug will be specified in the course of clinical trials.

Adverse reactions.

A hypersensitivity reaction in the form of rashes, urticaria, a feeling of heaviness in the epigastric area is possible. The nature of adverse reactions will be clarified during clinical trials.

Overdose.

The use of very high doses of the drug leads to the appearance of nausea, shortness of breath, headache, facial hyperemia. One of the first signs of an overdose is numbness of the tip of the tongue and lips, sometimes a feeling of numbness of the scalp.

Features of application.

The drug should not be used at night, as it can cause insomnia in some patients.

Use during pregnancy and lactation. There are no data.

Interaction with other medicinal products. There are no data.

6.2 Preclinical studies of the drug Donovit-VS

Preclinical studies of the drug "Donovit-VS" (test-agent VS-1), conducted by the Institute of Experimental Pathology, Oncology and Radiobiology named after R.E. Kavetskyi, National Academy of Sciences of Ukraine. Research was conducted on three types of animals: mice, rats and pigs of the "Vietnamese pot-bellied" breed. As a result of the conducted research, the following reports were prepared:

1. "Investigation of the specific antitumor activity of the VS-1 agent (the name of the drug Donovit-VS at the preclinical stage) in relation to Lewis lung carcinoma with low metastatic potential (LLC/R9)".
2. "Comparative study of the specific antitumor activity of the VS-1 agent in relation to variants of Lewis carcinoma LLC and LLC/R9 with different dependence on angiogenesis."
3. "Investigation of the specific pharmacological activity of the drug VS-1 in relation to melanoma B16".

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4. "Investigation of the specific antitumor activity of the VS-1 agent in relation to variants of Geren's carcinoma of rats with high and low rates of tumor growth."
5. "Investigation of antitumor and antimetastatic activity of VS-1 in relation to tumor models: Lewis lung carcinoma LLC/R9, sarcoma (S 180) and lymphoid leukemia L1210".
6. "Investigation of the specific antitumor activity of the VS-1 agent in relation to rat brain glioma".
7. "The effect of VS-1 on the life span of mice with Lewis carcinoma".
8. "Comparative study of the antitumor activity of VS-1 in relation to ascites and solid forms of Ehrlich's sarcoma".
9. "Determination of the maximum tolerated dose (MTD) and analysis of the acute toxicity of the VS-1 agent in mice and rats."
10. "Investigation of the cumulative properties and chronic toxicity of the VS-1 agent on mice."
11. "Study of immunotoxicity of VS-1 in mice".
12. "Study of the cumulative properties and chronic toxicity of the agent VS-1 on pigs of the "Vietnamese flat-bellied" breed

The conducted research made it possible to draw the following conclusions:

A) VS-1 has a pronounced antitumor effect on malignant neoplasms with angiogenesis-dependent growth and is ineffective against tumors with an unexpressed vascular network. This indicates the antiangiogenic mechanism of the antitumor effect of this agent.

B) VS-1 has an antitumor effect on malignant brain neoplasms (for example, rat glioma), which is expressed in an increase in life expectancy by more than 19%.

C) VS-1 has no antitumor effect on the ascites form of Ehrlich's carcinoma. At the same time, the solid form of this tumor model is sensitive to the action of VS-1, which is manifested in the pronounced stabilization of tumor growth, which provides inhibition of tumor growth by more than 77%.

D) Metronomic administration of VS-1 in a total dose of MTD/2 leads to a 73% increase in the lifespan of mice with Lewis carcinoma.

E) VS-1 has a pronounced antimetastatic effect against LLC/R9 tumor cells in passive and spontaneous metastasis. As a result of the experiment, it was established that VS-1 has a pronounced antimetastatic effect in relation to Lewis carcinoma

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resistant to cis-DDP. The percentage of inhibition of metastasis, estimated by the average number of metastases in the group, was 92.2%.

F) The hypothesis that VS-1 has a high antitumor effect against fast-growing tumors was confirmed in studies on two variants of Geren's carcinoma.

G) The use of the test agent VS-1 at a dose of MTD/2 was ineffective on the L1210 tumor model of lymphoid origin.

H) VS-1 at a dose of MTD/2 showed antitumor activity against S 180 sarcoma, which was expressed in inhibition of tumor growth by 60% on the 19th day, after resection of the tumor.

I) The tested test agent at a dose of MTD/2 showed antitumor and antimetastatic activity against Lewis LLC lung carcinoma, which was expressed in the treatment of 40% of animals and in the absence of metastases in 37% of the animals of the experimental group.

The results of preclinical studies are published in the article: ANTICANCER ACTIVITY OF ACONITINE-CONTAINING HERBAL EXTRACT BC1. Exp Oncol 2004 26,4, 307-311.

In 2003, the drug Donovit-VS was registered in Ukraine as a biologically active dietary supplement. For a number of years, in the Main Military Clinical Hospital of the Ministry of Defense of Ukraine, the Kyiv City Oncology Clinic and the "Medicom" clinic, Donovit-VS was used as part of the complex therapy of immunodeficiency states, persistent viral infections, as well as tumor diseases of the III-IV clinical stage after PCT and radiation therapy tumors of various genesis as monotherapy and accompanying therapy.

In the treatment of oncological diseases of the IV clinical stage, Donovit-VS was included in treatment schemes as a therapy "accompanying" the main treatment; treatment of toxic effects and radiation reactions, supportive (symptomatic) therapy of late complications of tumor processes. The term of treatment ranged from 2 months to 2.5 years. The improvement was determined by the general well-being of patients, stabilization of hemodynamic indicators, reduction of manifestations of compressive, edematous and dyspeptic syndromes. The period of onset of primary effects is from 2 weeks to 1 month. Treatment courses were continuous with periodic consolidation of the effect. A particularly pronounced effect, with prolongation of survival, was observed in patients with brain and lung tumors. Thus, the number of positive reactions to treatment was 70%,

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The use of dietary supplements Donovit-VS in COPD, bronchial asthma, osteochondrosis, depressive syndromes increased the effect of Main drugs, their dose was reduced, which allowed to achieve a clinical effect in a shorter time.

Adverse effects when using dietary supplements Donovit-VS were not noted in any case. Withdrawal from treatment was not accompanied by a withdrawal syndrome. More detailed information on clinical observations of dietary supplements Donovit-VS are presented on the website of the SPF "Aksomed": aksomed.kiev.ua and donovit.com

6.3 Results of the first phase of the clinical study of the drug Donovit-VS

The first phase of the clinical study of the drug Donovit-VS, tablets produced by Astrapharm LLC, was conducted on the basis of the Rivne Regional Oncology Dispensary. 20 male and female patients aged 18 to 65 years with a diagnosis of colorectal cancer, T2-4 N0-2 M0 after surgical resection of the tumor and 4 courses of polychemotherapy were included in the study. All included patients, by the method of simple randomization, were divided in a ratio of 1:1 into 2 groups of 10 people each. Patients in each of the groups received the study drug according to different schemes: I group - 1 tablet 2 times a day for 28 days; II group - 1 tablet 3 times a day for 28 days. The tasks of the research were:

The data obtained in the study made it possible to draw a conclusion about the good tolerability of the studied drug in all studied treatment schemes. The drug did not have a negative impact on the results of objective clinical and laboratory studies, which made it possible to express a generalized assessment of the tolerability of the treatment as "good" in both compared groups.

7. PURPOSE AND OBJECTIVES OF THE RESEARCH

The purpose of this study was to evaluate the effectiveness and tolerability of the drug Donovit-VS, tablets, manufactured by Astrapharm LLC, which was used in patients with glioblastoma on the background of chemotherapy in comparison with a group of patients who received only chemotherapy.

The objectives of the study were : to study the effect of the study drug, which was used in patients with glioblastoma on the background of chemotherapy, on one-

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year overall survival and survival without signs of progression; on the degree of toxicity of chemotherapy (according to the CTC-NCIC scale) and on the patient's quality of life (according to the EORTC - QLQ - C 30 scale). And also, a comparison of the results of treatment obtained in the main and control groups, with the aim of establishing the superior effectiveness of treatment in the group of patients who received chemotherapy + Donovit-VS in comparison with the group of patients who received only chemotherapy.

8. DESCRIPTION OF THE RESEARCH PLAN

8.1 Research design

This study was conducted as an open comparative randomized in parallel groups.

8.2 The analyzed number of patients

In the study, 60 patients were randomized, 30 patients - in group c with the appointment of the drug Donovit-VS (main group) and 30 patients - in the group without the appointment of the drug Donovit-VS (control group).

The population for the effectiveness analysis was 57 patients, of which: 28 patients of the main group and 29 patients of the control group. The following patients were not included in the efficacy analysis: No. 27 (development of AE with fatal outcome 2 months after Visit 1 – pulmonary embolism), No. 42 (wrong inclusion in the study – the diagnosis of glioblastoma was not confirmed) and No. 60 (development of AR at 3rd day after taking the study drug, which required its withdrawal).

The population for the analysis of safety and portability was 59 patients, of which: 30 patients of the main group and 29 patients of the control group (patient No. 42 was not included due to erroneous inclusion in the study).

8.3 The duration of the patient's participation in the study and the schedule of visits

The duration of participation in the study for each patient was 12 months, of which: 3-7 days of screening, 12 months - treatment and observation.

Study participation was lower if the patient died.

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As part of the study, 6 visits were planned: before the start of treatment (screening visit), then every 3 months from the start of treatment with the study drug Donovit-VS, regardless of which group the patient was assigned to, the main or control group (without the drug).

Visit 1 – screening;

Visit 2 – randomization, appointment of treatment;

Visit 3 – the 90th day of the study;

Visit 4 – the 180th day of the study;

Visit 5 – the 270th day of the study;

Visit 6 – the 360th day of the study;

The scheduled visit days could be shifted by ± 7 days for objective reasons.

The total duration of the study was 3 years and 7 months (43 months).

8.4 General description of the study

After a preliminary clinical assessment, the relevant candidates were given verbal and written information about the study drug and the study conditions. All potential patients were given time to consider their participation in the study and an opportunity to ask questions of the researcher. Written informed consent to participate in the study was obtained from potential patients prior to initiation of any screening procedures. Patients who signed the informed consent form underwent screening procedures (Visit 1) (screening lasted up to 7 days). The study included patients of both sexes aged 18 to 65 years with a histologically confirmed diagnosis of glioblastoma, grade IV anaplasia, after surgical removal of the tumor and a course of radiation therapy.

According to the inclusion/exclusion criteria, the patient was randomized to one of two treatment groups: main or control. The treatment group was randomly selected using a random number generator based on a 1:1 study group ratio. The "sealed envelope" method was used for randomization.

Patients of the main and control groups were prescribed chemotherapy in accordance with international standards for the treatment of glioblastoma according to one of the following schemes:

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1. Temozolomide in the form of 6 cycles of adjuvant therapy at a dose of 150-200 mg/m^2 once a day for 5 days of a 28-day cycle (5 days - taking temozolomide, 23 days - without taking the drug).
2. Lomustine 130 mg/m^2 per os once every 4-6 weeks. The course is 12 months.
3. PCV scheme: procarbazine + lomustine + vincristine every 4-6 weeks: 1st day - lomustine 130 mg/m^2 per os, 8th, 28th days - vincristine 1.0 mg/m^2 intravenously. From the 8th to the 22nd day inclusive, procarbazine 50 mg 2 times a day per os.

In addition, the patients of the main group received the investigated drug Donovit-VS, tablets produced by Astrapharm LLC, 1 tablet 3 times a day for 12 months. The drug was prescribed simultaneously with the appointment of CT.

During the study, scheduled medical examinations were carried out at the following points: before the start of treatment (screening), on the 90th, 180th, 270th and 360th days after the start of treatment.

At each visit, patients underwent a physical examination, measured heart rate, blood pressure, and body temperature, recorded subjective complaints, performed a comprehensive blood count, biochemical blood analysis, urinalysis, brain MRI or CT scan, ECG, and evaluated the toxicity of chemotherapy according to the CTC scale NCIC, functional status was determined according to the ECOG scale, in addition, patients filled out the EORTC - QLQ - C 30 quality of life questionnaire.

The results of all examinations were recorded in the primary medical documentation and the IRF.

Periodicity of examination of patients and registration of the received data was carried out in accordance with the following schedule, given in the table. 8.4.1.

Table 8.4.1 Schedule of research procedures

	Screening	**Treatment, observation**				
Study days [1]	**-7-0**	**1**	**90(±7)**	**180(±7)**	**270(±7)**	**360(±7)**
Visits	**1**	**2**	**3**	**4**	**5**	**6**
Obtaining written informed consent	*					
Anamnesis	*					
Pregnancy Test	*					
MRI or CT scan of the brain	* [2]			*		*
Ultrasound of the AO and R-graphy of the CO	* [2]					

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EKG	*			*		*
Objective examination	*		*	*	*	*
Measurement of heart rate, blood pressure and body t	*		*	*	*	*
General blood test General analysis of urine Biochemical analysis of blood	*		*	*	*	*
Evaluation of the functional state of the patient according to the ECOG scale	*		*	*	*	*
Evaluation of the degree of toxicity of therapy according to the CTC NCIC scale	*		*	*	*	*
Evaluation of the quality of life according to the EORTC - QLQ - C 30 scale	*		*	*	*	*
Assessment of patient compliance with inclusion/exclusion criteria		*				
Randomization, treatment assignment		*				
Dispensing / accounting for the researched drug		*	*	*	*	*
Identification and registration of possible AE/AR			*	*	*	*

[1] *It was assumed that the date of the visit could be shifted by 1-7 days from that indicated in the table.*

[2] *If MRI or CT of the brain, AO (abdominal organs) ultrasound, and R-graph of the CO(chest organs) were performed no earlier than 4 weeks before the patient was included in the screening and the patient did not receive antitumor therapy during this period, a repeat examination of this patient during the screening process was not performed.*

8.5 Plan of visits

Periodicity of examination of patients and registration of received data was carried out at Visits according to the following plan:

Visit 1 (screening)

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- registration of demographic and physical data (age, height, body weight);
- collection of anamnesis (including information about concomitant diseases and taking concomitant medications);
- pregnancy test (for women of reproductive age);
- objective examination;
- measurement of blood pressure, heart rate, body t;
- MRI or CT scan of the brain;
- Ultrasound of abdominal organs;
- R-graphy of chest organs;
- ECG at rest;
- evaluation of the degree of toxicity of therapy according to the CTC NCIC scale;
- assessment of the functional state of the patient using the ECOG scale;
- assessment of the patient's quality of life according to the EORTC-QL-C30 scale;
- general blood test;
- general analysis of urine;
- biochemical blood analysis.

Visit 2 (randomization, treatment appointment)

- assessment of the patient's compliance with inclusion/exclusion criteria;
- randomization;
- objective examination;
- measurement of blood pressure, heart rate, body t;
- appointment of treatment;
- dispensing of the researched drug.

Visit 3 (day 90 ± 7)

- objective examination;
- measurement of blood pressure, heart rate, body t;
- registration of performed therapy, including concomitant therapy;
- assessment of the degree of toxicity of CT according to the CTC NCIC scale;
- assessment of the functional state of the patient according to the ECOG scale;
- assessment of the patient's quality of life according to the EORTC-QLQ-C30 scale;
- general blood test;
- general analysis of urine;
- biochemical blood analysis;
- registration of AE/AR;
- issuance/accounting of the researched drug.

Visit 4 (day 180 ± 7)

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- objective examination;
- measurement of blood pressure, heart rate, body t;
- registration of performed therapy, including concomitant therapy;
- MRI or CT scan of the brain;
- ECG at rest;
- assessment of the degree of toxicity of CT according to the CTC NCIC scale;
- assessment of the functional state of the patient according to the ECOG scale;
- assessment of the patient's quality of life according to the EORTC-QLQ-C30 scale;
- general blood test;
- general analysis of urine;
- biochemical blood analysis;
- registration of AE/AR;
- issuance/accounting of the researched drug.

Visit 5 (day 270 ± 7)

- objective examination;
- measurement of blood pressure, heart rate, body t;
- registration of performed therapy, including concomitant therapy;
- assessment of the degree of toxicity of CT according to the CTC NCIC scale;
- assessment of the functional state of the patient according to the ECOG scale;
- assessment of the patient's quality of life according to the EORTC - QLQ - C 30 scale;
- general blood test;
- general analysis of urine;
- biochemical blood analysis;
- registration of AE/AR;
- issuance/accounting of the researched drug.

Visit 6 (day 360 ± 7)

- objective examination;
- measurement of blood pressure, heart rate, body t;
- registration of performed therapy, including concomitant therapy;
- MRI or CT scan of the brain;
- ECG at rest;
- assessment of the functional state of the patient according to the ECOG scale;
- assessment of the degree of toxicity of CT according to the CTC NCIC scale;
- assessment of the patient's quality of life according to the EORTC-QLQ-C30 scale;
- general blood test;
- general analysis of urine;

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- biochemical blood analysis;
- registration of AE/AR.

8.6 Description of research procedures

1) Obtaining informed consent.

Written informed consent to participate in the study was obtained from all potential trial participants prior to the initiation of any diagnostic and treatment procedures related to this study. Each patient personally filled out and signed the Informed Consent Form in 2 copies, one copy of which was given to the patient, the other remained in the research center for further storage for 15 years.

The fact of discussing the informed consent should have been recorded in the medical history and IRF with an indication of the date of signing.

2) History collection.

Life and disease anamnesis was conducted according to generally accepted methods and included: characteristics of the tumor, stage of the disease, type and extent of surgery, results of CT scan or MRI before surgery, concomitant diseases, and therapy that the patient received during the last 3 months. The anamnesis of the patient's life and illness was reflected in the primary documentation and IRF.

3). Pregnancy Test.

It was carried out in the urine of women of reproductive age, using test strips. Women of reproductive age, at the time of inclusion in the study, used adequate methods of contraception and agreed to continue their use throughout the study and 30 days after the last intake of the study drug. Acceptable methods of contraception were: intrauterine spiral, barrier method (condom, contraceptive cap, cervical cap or spermicide), hormonal contraception, previously performed surgical sterilization.

4). Objective review.

It included an assessment of the patient's general condition, an examination of organs and systems. In the primary documentation and IRF, the result of the examination of each system at the first visit was noted. At subsequent visits, data on the changes recorded during the inspection were entered into the primary documentation and IRF. Identified changes were given a short assessment for their compliance with the AE/AR.

5). Measurement of heart rate, blood pressure and body temperature.

Heart rate, blood pressure, and body temperature were measured at each visit during the study. Blood pressure was measured according to the standard method,

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after the patient had rested for 15 minutes, three times with breaks between measurements of at least 10 minutes. Heart rate was measured once.

Body temperature was measured in the armpit with a mercury thermometer.

6). Registration of concomitant therapy.

At each visit, the drugs the patient took during the study were recorded. The trade name of the drug, single and daily dose, duration of administration were recorded in the primary documentation and IRF.

7). MRI or CT scan of the brain.

It was conducted before the start of treatment, then after 3, 6, 9 and 12 months, in order to detect relapses.

8). ECG, R-graphy of the CO, ultrasound of the AO.

Were performed according to the schedule of research procedures.

9). The assessment of the patient's functional state was carried out according to the ECOG scale, designed to determine the working capacity of oncology patients according to degrees from 0 to 4, where 0 - the patient maintains full activity; 4 - cannot perform self-service:

Points	Sign
0	No symptoms
1	There are symptoms, but daily activities are preserved
2	Spends less than half of the day in bed
3	Spends half of the day or more in bed
4	Does not get up, requires care

10). Chemotherapy toxicity was assessed using the Common Toxicity Criteria NCIC (CTC NCIC) scale (Appendix B).

11). Quality of life was assessed using the questionnaire of the European Organization for Research and Treatment of Cancer EORTC - QLQ - C 30 (Appendix B).

12). Laboratory studies were carried out according to the following indicators:

- general blood analysis (hemoglobin, erythrocytes, hematocrit, platelets, leukocytes, leukocyte formula, ESR);
- general analysis of urine (pH, specific gravity, protein, sugar, leukocytes, erythrocytes, epithelial cells, salts);
- biochemical blood analysis (ALT, AST, total bilirubin, creatinine, glucose).

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9. PATIENT SELECTION CRITERIA

9.1 Inclusion criteria

1. Men and women aged 18 to 65.
2. Diagnosis: glioblastoma, stage IV anaplasia.
3. Patients after surgical resection or tumor biopsy and a course of radiation therapy (total radiation dose 60 Gray).
4. Histological or cytological confirmation of the diagnosis: glioblastoma.
5. Estimated lifespan is at least 12 weeks (3 months).
6. Functional status of the patient according to the ECOG scale - 0-2 points.
7. For women of reproductive age - a negative pregnancy test result, as well as the use of reliable contraceptives during the study period.
8. Informed written consent of the patient to participate in the study.

9.2 Exclusion criteria

1. Hypersensitivity to the components of the studied drug is known.
2. Pregnancy, lactation.
3. The number of leukocytes < 2.0 x 10^9 cells/l.
4. The number of neutrophils < 1.5 x 10^9 cells/l.
5. The number of platelets < 100 x 10^9 cells/l.
6. Hemoglobin level < 100 g/l.
7. Creatinine exceeds the upper limit of normal by more than 1.25 times.
8. Transaminases (AST, ALT) exceed the upper limit of normal by more than 2.5 times; total bilirubin exceeds the upper limit of normal by more than 1.5 times.
9. Any unstable therapeutic or psychiatric condition that, in the opinion of the investigator, may impair the patient's ability to complete the study or prevent participation in the study.
10. The need to take non-recommended drugs (p. 11.4).
11. Participation in any other clinical trial.

9.3 Criteria for early withdrawal of a patient from the study

Any patient had the right to withdraw from the study at any time and for any reason. In addition, the patient should be removed from the study immediately if any of the following situations occur:

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1. False inclusion of a patient in the study (not meeting inclusion/non-inclusion criteria).
2. Occurrence in the patient during the study of severe and/or unexpected AE/AR requiring withdrawal of the drug.
3. Necessity of prescription of prohibited concomitant therapy.
4. Non-compliance by the patient with the treatment regimen.
5. Non-compliance by the patient with the procedures provided for in the protocol.
6. Termination of Study by Sponsor or Regulatory Authorities.

In case of early termination of participation in the study, the patient should, if possible, have a visit corresponding to the scope of the examination of Visit 6.

9.4 Early termination or suspension of the entire study

The clinical study had to be stopped at the initiative of the responsible researcher of the clinical base in the event of a risk to the health or life of the patients, in connection with taking the study drug. The researcher had to notify the Sponsor, the SEC of the Ministry of Health of Ukraine and the Commission on Ethics at the MPE about the termination of the trial.

The sponsor had the right to stop the study at any time, temporarily or completely, if it had data indicating an increased risk to the health or life of patients in connection with taking the study drug, as well as in case violations of protocol requirements or ethical norms of clinical research. The sponsor had to inform the Health and Safety Committee of the Ministry of Health of Ukraine and the Ethics Committee at the Medical Center about the suspension of the study.

The SEC of the Ministry of Health of Ukraine had the right to temporarily or completely stop the study in case of violations of the terms of the protocol, ethical norms of conducting a clinical trial or the presence of data that question the safety of study participants. The SEC of the Ministry of Health of Ukraine had to inform the Sponsor, the Commission on Ethics at the MPE and the responsible researcher about its decision and the reasons for its adoption.

10. DRUG UNDER RESEARCH

10.1 Name and description of drug under study.

Name: Donovit-VS.

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Pharmaceutical form: tablets.

Composition: root tuber extract of aconite - 1 tablet contains 10 mcg of alkaloid aconitine, excipients - lactose, calcium stearate.

Pharmacotherapeutic group. Antitumor drugs.

Physico-chemical properties: Tablets of light brown color, flat-cylindrical shape with beveled edges or biconvex.

Packaging: 30 tablets in a blister, 3 blisters in a box.

Manufacturer: "Astrapharm" LLC.

Series number: b/n

Expiry date: 02.2021

10.2 Packaging and labeling

The studied drug Donovit-VS, tablets, produced by Astrapharm LLC, was sent to the research center in the following packaging: 30 tablets in a blister, 3 blisters in a box.

The label on the package with the study drug had the following information: clinical trial code; name of the manufacturer, address; name of the drug; storage; release form; serial number; storage conditions; issue date, expiration date (date, month, year); designation: "Keep out of the reach of children"; designation: "For clinical research."

10.3 Terms of transfer, accounting and return of the researched drug

The drug under investigation was provided to the clinical base by the Sponsor (LLS SPF "AKSOMED LTD"). The transfer of the drug was confirmed by the act of transfer. The act indicated the amount of the researched drug, the batch and the date of transfer.

The studied drug was used only for the purpose of conducting this clinical study in strict accordance with the protocol.

The studied drug was given to the patient according to the randomization scheme at 2, 3, 4 and 5 visits in the amount necessary for treatment for 3 months. Patients brought all used and unused packaging materials, as well as unused tablets, to the clinic at each subsequent visit.

The investigator kept a log of dispensing/returning the study drug. The journal indicated the amount of drug dispensed/returned, the date of issue/return, the patient's randomization number and initials, as well as the name of the person who dispensed the drug.

The count of the study drug was documented throughout the study. Upon completion of the study, the investigator provided the Sponsor with a report on the use of the investigational drug.

10.4 Storage conditions

The drug under study was stored in a place protected from light, at a temperature not higher than 25°C, in a room to which only the responsible researcher and a person authorized by him had access.

Patients who received the studied drug were instructed about its storage conditions.

11. TREATMENT

11.1 **Preliminary treatment**

At the first stage of treatment (before inclusion in the study), patients underwent surgical treatment in the amount of total, subtotal, or partial removal of the tumor. After surgical treatment, remote radiation therapy was prescribed to the patients in the standard mode. The total radiation dose was 60 Gr. At the same time, patients were prescribed chemotherapy with temozolomide, starting from the first day of radiation therapy, at a dose of 120-160 mg/m^2.

11.2 Scheme of treatment during the study

Patients of the main and control groups were prescribed chemotherapy in accordance with international standards for the treatment of glioblastoma according to one of the following schemes:

1. Temozolomide in the form of 6 cycles of adjuvant therapy at a dose of 150-200 mg/m^2 once a day for 5 days of a 28-day cycle (5 days - taking temozolomide, 23 days - without taking the drug).
2. Lomustine 130 mg/m^2 per os once every 4-6 weeks. The course is 12 months.

3. PCV scheme: procarbazine + lomustine + vincristine every 4-6 weeks: 1st day - lomustine 130 mg/m^2 per os, 8th, 28th days - vincristine 1.0 mg/m^2 intravenously. From the 8th to the 22nd day inclusive, procarbazine 50 mg 2 times a day per os.

The treatment scheme was chosen on the basis of a molecular genetic study on sensitivity to temozolomide.

In addition, the patients of the main group were prescribed the study drug Donovit-VS, tablets produced by Astrapharm LLC, 1 tablet 3 times a day for 12 months. The drug was prescribed simultaneously with the appointment of CT.

11.3 Concomitant therapy

In order to prevent nausea and vomiting, patients were premedicated with antiemetic drugs, in particular 5-HT3 blockers, such as ondansetron. According to indications, hepatoprotectors, cardioprotectors, sedatives and analgesics, supportive hormonal and anti-edema therapy, as well as drugs for the treatment of concomitant diseases were prescribed.

11.4 Prohibited concomitant treatment

During the study, patients were not allowed to use the following groups of drugs:

- means that have an immunomodulating effect;
- immunosuppressants;
- biostimulants, bioinhibitors, adaptogens.

If it is necessary to prescribe "forbidden" drugs, the researcher was obliged to exclude the patient from the study.

12. EVALUATION OF EFFICIENCY

The main variable

- overall survival of patients within 12 months from the start of treatment.

Secondary variables :

- progression-free survival within 12 months from the start of treatment;
- median survival;
- the degree of toxicity of chemotherapy according to the CTC-NCIC scale;
- the patient's quality of life according to the EORTC - QLQ - C30 scale.

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Chemotherapy toxicity was assessed using the Common Toxicity Criteria NCIC (CTC NCIC) scale (Appendix B).

The scale shows the objective and subjective manifestations of various types of toxicity of chemotherapy with an assessment on a 5-point scale:

Points	Degree of toxicity	
0 points	0	no toxicity
1 point	I	slight toxicity
2 points	II	medium toxicity
3 points	III	severe toxicity
4 points	IV	life-threatening toxicity

Chemotherapy toxicity was assessed starting from Visit 3, according to clinical and laboratory parameters relevant to the chemotherapy used, such as: anemia, leukopenia, thrombocytopenia, liver dysfunction, diarrhea, nausea, vomiting, etc.

Quality of life was assessed using the questionnaire of the European Organization for Research and Treatment of Cancer EORTC- QLQ-C30 (Appendix B).

13. EVALUATION

13.1. List of transferability indicators

The transferability assessment was carried out according to the following variables:

- the frequency of cases and the nature of AE/AR, their relationship with the study drug;
- dynamics of vital indicators (blood pressure, heart rate, body t);
- dynamics of ECG data;
- dynamics of laboratory indicators (general blood test, general urine test, biochemical blood test).

13.2. Methods and timing for assessing indicators of tolerance

During the period of the study, the researcher conducted a survey and recorded information on cases of AE/AR, according to the definitions given in the research protocol.

Information on any AE/AR observed from screening to the end of the patient's participation in the study was recorded according to the definitions given in the study protocol.

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13.3 Adverse events/reactions (AE/AR)

13.3.1 Definition of the concept, types of AE/AR

Adverse reaction (AR) - all negative or unpredictable reactions associated with the administration of any dose of a medicinal product (drug), provided that there is at least a minimal probability of a causal relationship between the drug and the adverse reaction, i.e. a relationship connection cannot be ruled out.

Adverse event (AE) is any unwanted medical manifestation in a subject under observation, which does not necessarily have a causal relationship with the use of a medicinal product (changes in laboratory data, a symptom or disease that coincides in time with using the drug under study).

Types of AE/AR:

Serious adverse reaction or serious adverse event - any adverse medical manifestation when using a medicinal product (regardless of dosage) that leads to death; poses a threat to life; requires hospitalization or extension of the existing hospitalization; leads to long-term or significant incapacity for work or disability, to congenital anomalies or malformations;

A minor adverse reaction is an unwanted reaction that does not fall under the category of serious.

An unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with the available information about the drug.

13.3.2 Assessment of the degree of severity of AE/AR

- **light** - phenomena are transient, do not affect the patient's daily activity;
- **average** - phenomena cause some inconvenience to the patient and may affect his daily activity;
- **expressed** - phenomena cause discomfort to the patient and interfere with the performance of everyday activities.

13.3.3 Connection of AE/AR with the drug under study

Assessment of the cause-and-effect relationship of AE/AR with the drug under investigation was carried out according to the following scale:

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- **cannot be assessed** - it is impossible to give an assessment due to the insufficiency or contradiction of the available data, as well as in those cases when they cannot be verified or supplemented;
- **absent** - an undesirable clinical phenomenon or changes in laboratory indicators are not related to the use of the medicinal product;
- **possible** - there is a certain temporal relationship with taking the drug, but the development of AE/AR can also be explained by a concomitant disease and/or taking other drugs;
- **probable** - there is a certain temporal relationship with taking the medicine, but the probability that the development of AE/AR is due to a concomitant disease and/or taking other medicines is low;
- **Undoubted** - AE/AR occurs after a certain period of time after taking the drug, the reaction subsides after the withdrawal of the drug, symptoms reappear after re-taking the drug

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13.3.4 Result of AE / AR

- **recovery without consequences** - AE/AR has passed (symptoms are absent and the patient is not treated to eliminate this AE/AR);
- **recovery with consequences** - AE/AR has passed, but its consequences remain;
- **no changes** - AE/AR did not go away, symptoms persisted, despite medical measures taken to eliminate it;
- **deterioration** - there was an increase in the symptoms of AE/AR;
- **fatal outcome** - the patient died as a result of this AE/AR.
- **no data** - communication with the patient has been lost, as a result of which it is impossible to obtain reliable data about the patient's condition.

13.3.5 Measures taken in case of AE/AR

In the event of an AE/AR, the researcher provides (if necessary) appropriate qualified medical care to the patient, including conducting laboratory and instrumental studies and observes the patient until the AE/AR is completely resolved.

13.3.6 Notification of unforeseen and/or serious AE/AR

In the event of an unforeseen and/or serious AE/AR, the researcher informs the Research Sponsor about it within 24 hours (by phone and e-mail). The full report is

provided within 5 days to the Sponsor and within 15 days to the Commission on Ethics at the MPE. In the event of the death of the subject, the information is provided to the Sponsor and within 7 calendar days to the Commission on Ethics at the MPE.

14. METHODS OF STATISTICAL DATA ANALYSIS

14.1 Justification of the number of subjects

This study is parallel, two-group, with the same number of patients in the groups, and was conducted to prove the superior effectiveness of therapy that includes chemotherapy + Donovit-VS compared to the group of patients receiving only chemotherapy.

The planned power of the test is 80% (the probability of making a type 2 error is 0.2), the two-sided probability of making a type 1 error is 0.05.

The main variable in this study is the overall survival of patients within 12 months from the start of treatment, which in turn leads to the analysis of time-dependent events. The critical event in this study is death. Survival in two groups was compared using the log-rank test to compare survival curves constructed using the Kaplan-Meier method.

The duration of observation of patients in this study (T) is 12 months (365 days). It was assumed that patients will be recruited in 6 months (time of recruitment of patients, denoted as T_0).

When evaluating the results of this study, it was planned to test the following statistical hypotheses:

$$H_0: \varepsilon \leq \delta \quad \text{against } Ha: \varepsilon > \delta, \qquad (1)$$

where: $\varepsilon = \lambda_1 - \lambda_2$; λ_1 - the intensity of risk in the control group, λ_2 - the intensity of risk in the main group, $\delta > 0$ - the value of clinically significant differences.

However, in this study we can take δ equal to 0, as this would mean that there are statistically significant differences between the compared groups. That is, the statistical hypothesis will be tested:

$$H_0: \varepsilon \leq 0 \text{ against } Ha: \varepsilon > 0, \qquad (2)$$

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The sample size can be estimated using the formula:

$$n_{\text{groups}} = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{(\varepsilon - \delta)^2} \cdot \left[\frac{\sigma^2(\lambda_1)}{k} + \sigma^2(\lambda_2) \right]^1, \qquad (3)$$

where: α is the marginal probability of making an error of the 1st kind (significance level);

β - the probability of making a type 2 error (the determining power of the study, which is calculated as 1-β); $z_{1-\alpha/2}$ and $z_{1-\beta}$ are the corresponding percentage points of the standard normal distribution.

The results of the calculations are shown in the table below:

Statistical indicator	**Value**
Group size ratio	1
Duration of observation T, months.	12
Duration of recruitment of patients T_0, months.	6
Risk intensity in the control group λ_1	0.7
Risk intensity in the main group λ_2	0.21
The value of clinically significant differences δ	0
Dispersion for the control group $\sigma^2(\lambda_1)$	0.490
Dispersion for the main group $\sigma^2(\lambda_2)$	0.042
The amount of error 1 of the kind α (two-sided)	0.05
The magnitude of the error of the 2nd kind β	0.2
Percentage point SND for α	1.96
Percentage point SND for β	0.84
Number of patients	30

Based on previous clinical trial experience, up to 3 patients from each group may drop out of such a study. Therefore, in order to ensure the required 80% power of this study, it is necessary to increase each group by 3 patients. Thus, the final number of subjects in each group should be 30 patients, a total of 60 patients in the study.

14.2 Statistical analysis plan

Statistical analysis included:

- description of patients included in the study;
- the number of subjects who dropped out;
- number of AE/AR;
- analysis of initial homogeneity of groups;

[1] S.C. Chow, J. Shao, H.Wang. Sample Size Calculations in Clinical Research. — London: Taylor&Francis, 2003. — 358 p.

- analysis of effectiveness in groups;
- comparison of efficiency between groups;
- proof of exceeding efficiency;
- statistical conclusions.

14.3 Analysis of initial homogeneity of groups

An analysis of the homogeneity of groups was made according to clinical and demographic indicators, indicators of efficiency and safety. For this:

Methods of descriptive statistics were used to describe the initial state of the groups (for quantitative indicators - n, arithmetic mean, median, standard deviation, minimum and maximum value; for qualitative indicators - frequency and share in %).

For quantitative indicators, the normality of data distribution in groups was checked using the Shapiro-Wilk test. If the data in the groups according to certain indicators are normally distributed, then the groups were compared according to these indicators using the Student's test for independent samples (having previously checked the homogeneity of variances in the groups using the Levene's test in order to choose the Student's test). In another case (the data are not normally distributed), the comparison of groups was performed using the Mann-Whitney test.

For categorical indicators, groups were compared using the Pearson chi-square test. If the prerequisites for applying this criterion were not met, Fisher's exact test was used for comparison.

Statistical conclusions were made regarding the initial homogeneity of the groups according to the specified variables.

14.4 Analysis of efficacy in each Group

For time-dependent events, survival curves were constructed using the Kaplan-Meier method, and mean time to event and median survival were estimated. In addition, the proportion of events in each group at the end of the study was estimated.

For quantitative performance indicators (secondary variables measured quantitatively), descriptive statistics were evaluated for each visit. To assess the dynamics of these indicators, a variance analysis (VA) was performed using a mixed two-factor model (the dependent variable is the value of the analyzed indicator, the

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"visit" factor is fixed), the "subjects" factor is random. Values at visits starting at Visit 3 were compared with Visit 1 using a contrast analysis (simple contrasts were used). The normality of the distribution of DA residues was checked. If the residuals were not normally distributed, then the corresponding indicator was converted into ranks and analysis was performed in ranks.

The number and proportion of patients who did not experience a critical event within 12 months were assessed in each group.

14.5 Comparison of efficacy between groups

For the primary variable and other variables assessed by time-dependent events:

– If in the initial state the groups did not differ statistically significantly, then the survival curves in the groups were compared using the log-rank test.

–If in the initial state the groups differed by any indicators, then Cox regression was performed using the stepwise formation of the regression equation. As a covariate, those variables were included in the regression equation for which statistically significant differences between groups were observed at baseline, and the significance of the influence of the "group" effect and the relative risk were assessed.

For quantitative indicators of efficiency (secondary variables, measured quantitatively), the groups were compared according to dTvizit i = Tvizit i – Tvizit 1.

Individual differences dTvisit i were calculated for each subject and for each parameter.

– If the groups in the initial state did not differ statistically significantly, then the comparison of groups by dTvisit i was performed using the Student's test for independent samples or the Mann-Whitney test, depending on the normality of the distribution of the compared data sets.

– If the groups in the initial state were statistically significantly different, then to compare the groups by dTvisit i, taking into account the possible initial differences between the groups, a covariance analysis was performed at each time point Ti according to the scheme: dependent variable - dTi for the corresponding parameter, factor "Group" - fixed (levels: main and control), covariate - the value of this parameter at the time of Tvizit 2. A contrast analysis was performed using simple contrasts between the levels of the "Group" factor. The normality of the distribution

of the residuals of the covariance analysis was checked using the Shapiro-Wilkie test. If the residuals were not normally distributed, then the specified rank analysis was performed. Conclusions were drawn regarding differences between groups.

The proportion of patients in the groups who did not experience a critical event during the follow-up period (12 months) was compared using Fisher's exact test.

14.6 Analysis of tolerance

Results of laboratory studies (indicators of general blood analysis, general urine analysis, biochemical blood analysis).

Indicators of descriptive statistics (n, arithmetic mean, median, standard deviation, minimum and maximum value) for each group and visit according to the patient examination scheme.

Each indicator was transformed into a categorical variable with categories: "normal", "outside the norm". For the transformed variables in each group and for each visit according to the patient examination scheme, the frequency and share in percentages were calculated and their dynamics in each group were evaluated.

Results of measurement of heart rate, blood pressure, body temperature.

Indicators of descriptive statistics (n, arithmetic mean, median, standard deviation, minimum and maximum value) for each group and visit according to the patient examination scheme.

Data on AE/ AR.

Indicators of descriptive statistics (frequency and percentage share for each group).

The variable of the total transfer area **.**

Indicators of descriptive statistics (frequency and percentage share for each group).

14.7 Significance levels and power

The significance level for the Shapiro-Wilkie test was set at 0.01, and for the other tests at 0.05.

14.8 Conclusion of superior efficacy

The conclusion of superior efficacy of therapy including chemotherapy + Donovit-VS compared to the group of patients who received only chemotherapy was

made on the basis of statistically significant differences when comparing survival curves using the log-rank test, or the results of evaluating the significance of the effect groups based on the results of the Cox regression

14.9 Working with data

Work with data was carried out in accordance with the Main principles of data management, in order to ensure their integrity and validity. For this, the data was entered into pre-designed EXCEL spreadsheets, using the principle of "double entry" and subsequent cross-validation.

14.10 Software

Statistical processing of the results was performed using the built-in module for statistical data analysis of Microsoft Excel and using the SPSS 23.0 software package.

15. RESULTS OF THE RESEARCH AND THEIR DISCUSSION

15.1 Description of the patients included in the study

60 patients were randomized into the study, of which: 30 patients in the main group and 30 patients in the control group. The randomization scheme is given in Appendix A, table. A.1. Patients in the main group were prescribed the study drug Donovit-VS, tablets produced by Astrapharm LLC against the background of Main CT. Control group patients received only CT. One patient was randomized by mistake (No. 042), so he was immediately excluded from the study and, in the future, he is not taken into account anywhere.

When consulting a doctor, the majority of patients had brain-wide clinical symptoms in the form of: headache, dizziness, symptomatic epilepsy, etc. The duration of the disease before diagnosis was from 2 weeks to 21 months.

The study included patients with a histologically confirmed diagnosis: glioblastoma, stage IV anaplasia, after surgical removal of the tumor and a course of radiation therapy. Tumors were mainly localized in temporal – 26 (45.6%), frontal – 20 (35.1%) and parietal – 11 (19.3%) areas. Tumors were found in 27 (47.4%) cases in the left hemisphere, in 30 (52.6%) cases in the right hemisphere. In the vast majority of patients, tumors spread to adjacent parts of the brain.

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All patients included in the study had a functional status according to the ECOG scale from 0 to 2 points and an expected life expectancy of at least 12 weeks.

Patients aged 18 to 65 years (Me = 54 years) with BMI from 18.73 to 38.67 kg/m^2 (M = 26.74, St = 3.69) were included in the study. 28 (47.5%) men and 31 (52.5%) women were included in the study. The results of the descriptive analysis of the patients who participated in the study, according to clinical and demographic indicators, are shown in the table. 15.1.1.

Table 15.1.1 Characteristics of patients by age and body weight

Parameter	n	M	Me	St	MIN	MAX
Age, years	59	52.41	54	10.41	18	65
Body weight, kg	59	77.80	79	13.72	45	108
BMI, kg/m ^{2}	59	26.74	26.3	3.69	18.73	38.67
ECOG, points	59	0.88	1	0.53	0	2
Leukocytes, x 10 ^{9} cells/l	59	6.58	6.5	2.44	2.4	14
Neutrophils, %	59	71.00	69.6	10.68	47.7	89.8
Platelets, x 10 ^{9} cells/l	59	197.41	183	56,27	112	333
Hemoglobin, g/l	59	134.58	135	14.79	100	169
ALT, units/l	59	30,35	29.7	13,13	6.1	57.5
AST, Od, l	59	23.88	21.2	11,10	9.1	60
Total bilirubin, mlmol/l	59	12,18	11.02	5.36	4.47	26,26
Creatinine, μmol/l	59	71.04	68.7	14.94	41,51	110.12

The results of the analysis of the normality of the data distribution are given in Appendix D, table. G.1.

15.2 Number of analyzed patients

Patients for whom the end of observation or the date of death were known were included in the efficacy analysis. Patients who died from causes unrelated to the underlying disease, as well as patients who dropped out of the study for any other reason, were considered dropouts.

57 patients were included in the efficiency analysis, of which: 28 patients of the main group and 29 patients of the control group. Patients No. 027 (fatal pulmonary embolism), No. 042 (erroneous inclusion in the study) and No. 060 (AR that required discontinuation of the study drug) were not included in the efficacy analysis.

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The population for the analysis of safety and portability was 59 patients, of which: 30 patients of the main group and 29 patients of the control group. The patient of the control group No. 042 was not included in the analysis (erroneous inclusion in the study).

Table 15.2.1 List of patients who dropped out

Randomization number	Group	Reason for elimination from research
027	The main one	Fatal pulmonary embolism 2 months after Visit 1
042	Control	False inclusion in the study - the diagnosis of "glioblastoma" was not confirmed
060	The main one	The development of AR on the 3rd day after taking the study drug, which required its withdrawal

15.3 Analysis of baseline homogeneity of groups

Analysis of baseline homogeneity of groups was performed for patients who were included in the efficacy analysis, as the purpose of this analysis is to demonstrate that the groups are comparable and their differences will not lead to significant biases in the efficacy estimates.

15.3.1 Analysis of baseline homogeneity of groups by demographic parameters

The results of the analysis of the homogeneity of groups by gender using the methods of descriptive statistics (frequency and percentage in%) are given in Table. 15.3.1.1. This table also presents the result of comparing groups by sex using Fisher's exact test.

Table 15.3.1.1 Distribution of patients in groups by gender and results of group comparison

Sex	**Main group n=28**		**Control group n=29**		**p-value***
	n	**%**	**n**	**%**	
Men	15	53.6	12	41.4	0.431
Women	13	46.4	17	58.6	
In total	28	100.0	29	100.0	
** Calculated using Fisher's exact test.*					

Conclusion. Based on the results of the statistical analysis (Table 15.3.1.1), it can be stated that the groups in the initial state were homogeneous in terms of gender ($p = 0.431$).

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The results of the analysis of the comparison of groups by indicators: age, height, body weight and BMI, using the methods of descriptive statistics, are given in table. 15.3.1.2.

Table 15.3.1.2 Results of the analysis of the comparison of groups by age, height, body weight and BMI using descriptive statistics methods

Indicator	Group	Statistical indicators					
		n	M	Me	St	MIN	MAX
Age, years	main	28	54,25	56	9.39	23	65
	control	29	51.24	53	11,17	18	65
Height, see	main	28	170.64	169	7.69	155	187
	control	29	170.03	167	9.85	155	190
Body weight, kg	main	28	77.07	77	14.57	45	108
	control	29	79.48	80	12.90	52	104
BMI, kg/m^2	main	28	26,29	26,085	3.62	18.73	33,33
	control	29	27.44	26.9	3.69	20,31	38.67

In order to select a criterion for checking the homogeneity of groups by age and body weight, a check of the normality of the distribution of the analyzed data was performed (Appendix D, table D.2). According to the obtained results, the Student's test for independent samples was used to assess the homogeneity of the groups by height, body weight, and BMI (Table 15.3.1.2), and the Mann-Whitney test was used to compare by age (Table 15.3.1.3, Appendix D, table G. 3).

Table 5.3.1.2 Results of the analysis of homogeneity of groups by some anthropometric parameters using the Student's test for independent samples

Changeable	t-statistics	Number of degrees of freedom	p-value (two pages)	Difference of mean	Conclusion on homogeneity of groups*
Height	0.259	55	0.796	0.608	Homogeneous
Body weight	-0.662	55	0.511	-2.411	Homogeneous
BMI	-1.187	55	0.240	-1.151	Homogeneous
** The conclusion is made at a significance level of 0.05.*					

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Table 15.3.1.3 Results of the analysis of homogeneity of groups by age using the Mann-Whitney test

Changeable	Mann-Whitney U	Wilcoxon W	Z	p-value	Conclusion on homogeneity of groups*
Age	335.5	770.5	-1.127	0.260	Homogeneous
** The conclusion is made at a significance level of 0.05.*					

Thus, the main group included patients aged from 23 to 65 years (Me = 56 years), with BMI from 18.73 kg/m ^{2} to 33.33 kg/m ^{2} (M = 26.29 kg/m ^{2}; St = 3.62 kg/m^2).

The control group included patients aged 18 to 65 years (M = 51.24; St = 11.17), with BMI from 20.31 kg/m ^{2} to 38.67 kg/m ^{2} (M = 27.44 kg/m ^{2} ; St = 3.69 kg/m^2).

Conclusion. Based on the results of the statistical analysis (tables 15.3.1.1 - 15.3.1.3), it can be stated that the groups in the initial state were homogeneous in terms of gender (p = 0.431), age (p = 0.260) and BMI (p = 0.240).

15.3.2 Analysis of homogeneity of groups according to accompanying pathology

The results of the analysis of the homogeneity of the groups, according to the accompanying pathology, are given in the table. 15.3.2.1.

Table 15.3.2.1 Results of comparative analysis of groups by concomitant pathology

Type of pathology	Main group (n = 28)		Control group (n=29)		P-value*
	n	%	n	%	
Symptomatic arterial hypertension	1	3.57	1	3.45	1,000
Hypertensive disease	4	14,29	3	10.34	0.706
Coronary heart disease	1	3.57	1	3.45	1,000
Episyndrome	5	17.86	5	17,24	1,000
Vegeto-vascular dystonia of the hypertensive type	1	3.57	1	3.45	1,000
Vegeto-vascular dystonia of the hypotonic type	1	3.57	2	6.90	1,000
Varicose veins of the lower	3	10.71	3	10.34	1,000

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extremities					
Bronchial asthma	1	3.57	0	0.00	0.491
Pneumonia	1	3.57	1	3.45	1,000
Chronic obstructive pulmonary disease	0	0.00	1	3.45	1,000
Chronic cholecystitis	2	7,14	1	3.45	0.611
Chronic pancreatitis	0	0.00	1	3.45	1,000
Chronic gastroduodenitis	3	10.71	2	6.90	0.670
Ulcer disease of the stomach and/or duodenum	3	10.71	2	6.90	0.670
Calculous cholecystitis	0	0.00	1	3.45	1,000
Urinary diathesis	4	14,29	3	10.34	0.706
Diabetes	0	0.00	1	3.45	1,000
Adiposity	5	17.86	3	10.34	0.470
Pulmonary embolism	1	3.57	0	0.00	0.491
** Calculated using Fisher's exact test.*					

Conclusion. As can be seen from the table. 15.3.2.1 statistically significant differences between the groups in terms of concomitant pathology were not found.

15.3.3 Analysis of the initial homogeneity of the groups according to the volume of surgical intervention, localization and side of the lesion, patients status according to the ECOG scale

At the first stage of treatment (before inclusion in the study), all patients underwent resection of the tumor in the maximum possible volume.

The following conditional criteria were used to assess the degree of radical surgical intervention: total removal - removal of more than 95% of the tumor, subtotal removal - removal of 80-94% of the tumor, partial removal - removal of 50-79% of the tumor, biopsy - removal of less than 50% of the tumor.

The predominant amount of surgical intervention in patients of both groups was "total" removal of the tumor: the main group - 21 (75%) patients, the control group - 22 (75.9%) patients.

The results of the analysis of the homogeneity of the groups by the volume of surgical intervention are shown in the table. 15.3.3.1.

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Table 15.3.3.1 Results of the comparative analysis of groups by the volume of surgical intervention

The volume of surgical intervention	Main group n=28		Control group n=29		P-value*
	n	%	n	%	
"Total" tumor removal	21	75.0	22	75.9	1,000
Subtotal removal of the tumor	6	21.4	5	17.2	
Partial tumor removal	1	3.6	1	3.4	
Biopsy	0	0.0	1	3.4	
In total	28	100.0	29	100.0	
** Calculated using Fisher's exact test.*					

Conclusion. According to the results of the statistical analysis of the data given in the table. 15.3.3.1, it can be stated that the groups did not differ statistically significantly in the volume of surgical intervention (p = 1,000).

Tumors were mainly localized in temporal – 26 (45.6%), frontal – 20 (35.1%) and parietal – 11 (19.3%) areas. In the left hemisphere, tumors were found in 27 (47.4%) cases, in the right - in 30 (52.6%).

Table 15.3.3.2 Results of comparative analysis of groups by localization and side of lesion

Localization variable	Localization and side of the lesion	Main group n=28		Control group n=29		P-value*
		n	%	n	%	
Area of the brain	Temporal area	13	46.4	13	44.8	0.654
	Frontal area	11	39.3	9	31.0	
	Parietal area	4	14.3	7	24.1	
Hemisphere of the brain	Left hemisphere	13	46.4%	17	58.6%	0.431
	Right hemisphere	15	53.6%	12	41.4%	
** Calculated using Fisher's exact test.*						

Conclusion. According to the results of the statistical analysis of the data given in the table. 15.3.3.2, it can be stated that the groups did not differ statistically significantly in tumor localization and the side of the lesion.

The general condition of patients before treatment corresponded to 0-2 points on the ECOG scale. The results of the comparative analysis of groups according to the ECOG scale using descriptive statistics are shown in table. 15.3.3.3.

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Table 15.3.3.3 Results of comparative analysis of groups on the ECOG scale using descriptive statistics methods

Indicator	Group	Statistical indicators					
		n	M	Me	St	MIN	MAX
ECOG, points	main	28	0.96	1	0.33	0	2
	control	29	0.79	1	0.62	0	2

Since the data in the groups were not distributed normally (Appendix D, table D.2), the Mann-Whitney test was used to compare the groups (table 15.3.3.4 and Appendix D, table D.3).

Table 15.3.3.4 The results of the analysis of homogeneity of groups in the initial state according to the ECOG scale using the Mann-Whitney test

Changeable	Mann-Whitney U	Wilcoxon W	Z	p-value	Conclusion on homogeneity of groups*
ECOG	338	773	-1.41	0.159	Homogeneous
** The conclusion is made at a significance level of 0.05.*					

We also analyzed the initial homogeneity of the groups according to the distribution of patients according to individual scores of the ECOG scale. The results of this comparative analysis are shown in table. 15.3.3.5.

Table 15.3.3.5 Results of comparison of groups according to assessments of the general condition of patients at the time of inclusion in the study using the ECOG scale

Changeable	Points	Main group n=28		Control group n=29		P-value*
		n	%	n	%	
ECOG	0 points	2	7.1	9	31.0	0.051
	1 point	25	89.3	17	58.6	
	2 points	1	3.6	3	10.3	
** Calculated using Fisher's exact test.*						

Conclusion. According to the results of the statistical analysis of the data given in the table. 15.3.3.4 and table. 15.3.3.5, it can be stated that the groups, in the initial state, did not differ statistically significantly in terms of the general state, assessed by the ECOG scale.

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15.3.4 Analysis of the initial homogeneity of groups according to the scheme of chemotherapy used

Patients of the main and control groups received chemotherapy in accordance with international standards for the treatment of glioblastoma according to one of the following schemes:

1. Temozolomide in the form of 6 cycles of adjuvant therapy at a dose of 150-200 mg/m ^{2} 1 time per day for 5 days of a 28-day cycle (5 days - taking temozolomide, 23 days - without taking the drug).
2. Lomustine 130 mg/m ^{2} per os once every 4-6 weeks. The course is 12 months.
3. PCV scheme: procarbazine + lomustine + vincristine every 4-6 weeks: 1st day - lomustine 130 mg/m^2 per os, 8th, 28th days - vincristine 1.0 mg/m ^{2} intravenously. From the 8th to the 22nd day inclusive, procarbazine 50 mg 2 times a day per os.

The treatment scheme was chosen on the basis of a molecular genetic study of patients for sensitivity to temozolomide.

The results of a comparative analysis of the homogeneity of the groups according to the scheme of chemotherapy used are shown in the table. 15.3.4.1.

Table 15.3.4.1 Results of the analysis of the comparison of groups according to the scheme of chemotherapy used

Changeable	**Categories**	**Main group n=28**		**Control group n=29**		**P-value***
		n	**%**	**n**	**%**	
Scheme of CT	Temozolomide	19	67.9	22	75.9	0.266
	Lomustine	6	21.4	2	6.9	
	PCV	3	10.7	5	17.2	
** Calculated using Fisher's exact test.*						

As can be seen from the table. 15.3.4.1, the groups did not differ statistically significantly according to the CT schemes (p = 0.266).

The total number of CT courses received by patients in the course of this study in groups is shown in the table. 15.3.4.2.

Table 15.3.4.2 Total number of CT courses received by patients during this study

Scheme of CT	**Main group (n = 28)**	**Control group (n = 29)**
Temozolomide	130	162

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Lomustine	33	9
PCV	15	12
In total	178	183

The results of the comparison of groups by the number of CT courses are shown in the table. 15.3.4.3. Since the data in the groups were distributed normally (Appendix D, Table D.2), the Student's test for independent samples was used to compare the groups (Table 15.3.4.4).

Table 15.3.4.3 Results of comparison of groups by the number of CT courses using descriptive statistics methods

Indicator	**Group**	**Statistical indicators**					
		n	**M**	**Me**	**St**	**MIN**	**MAX**
Number of CT courses	main	28	7.25	7.00	3,395	1	13
	control	29	5.86	5.00	3,573	1	14

Table 5.3.4.4 Comparison of groups by the number of CT courses using the Student's test for independent samples

Changeable	**t-statistics**	**Number of degrees of freedom**	**p-value (two pages)**	**Difference of mean**	**Conclusion on homogeneity of groups***
Number of CT courses	1,502	55	0.139	1,388	Homogeneous
** The conclusion is made at a significance level of 0.05.*					

Conclusion. According to the results of the statistical analysis of the data given in the table. 5.3.4.2 - 5.3.4.4, it can be stated that the groups did not differ statistically significantly in terms of chemotherapy regimens used and the number of CT courses received by patients during this study.

15.3.5 Analysis of the initial homogeneity of groups according to vital signs

During the objective examination of the patients at the screening stage, in no case were decompenSBRed pathological conditions that should have prevented the patient's participation in the study found SBP, DBP, heart rate and body temperature were evaluated as the main physiological parameters.

The results of the comparative descriptive statistical analysis of the groups according to these parameters are shown in the table. 15.3.5.1.

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Table 15.3.5.1 Results of comparative analysis of groups by vital signs using descriptive statistics methods

Indicator	Group	n	M	Me	St	MIN	MAX
SBP, mm Hg Art.	The main one	28	123.86	124	13.74	100	170
	Control	29	123.45	120	14,21	85	160
DAT, mm Hg Art.	The main one	28	79.93	80	7.83	60	100
	Control	29	80.34	80	9.54	60	100
Heart rate, beats/Min.	The main one	28	73.93	72	12.65	50	100
	Control	29	75.97	72	12.37	57	110
t body (°C)	The main one	28	36.55	36.6	0.18	36.2	37.2
	Control	29	36,56	36.6	0.35	35.5	38

Since the data in one or another group for the analyzed parameters were not distributed normally (Appendix D, Table D.2), the Mann-Whitney test was used to compare groups (Table 15.3.5.2; additional statistics in the Appendix D, table D.3).

Table 15.3.5.2 Results of homogeneity analysis of groups with SBP and DBP, heart rate and body temperature using the Mann-Whitney test

Changeable	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)	Conclusion on homogeneity of groups*
SBR	404	810	-0.033	0.974	Homogeneous
DATE	376	782	-0.503	0.615	Homogeneous
heart rate	394	800	-0.194	0.846	Homogeneous
Body temperature	396	802	-0.194	0.846	Homogeneous
** The conclusion is made at a significance level of 0.05.*					

Conclusion. Based on the results of the statistical analysis given in the table. 15.3.5.2, it can be stated that in the initial state the groups did not differ statistically significantly in vital indicators (SBP, DBP, heart rate and body temperature).

15.3.6 Analysis of initial homogeneity of groups based on ECG and ultrasound of abdominal organs

According to the protocol, all patients underwent a standard 12-lead resting ECG. In the majority of patients, according to the ECG, clinically insignificant changes were observed, such as: diffuse-dystrophic changes in the myocardium,

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moderate hypertrophy of the left ventricle, incomplete blockade of the bundle of His, impaired intraventricular conduction, reduced voltage of the T wave, shortening of the PQ interval, etc. The doctor-researcher evaluated these changes and made a conclusion in the categories of "norm" or "deviation from the norm". Deviations from the norm of some indicators were not clinically significant and did not prevent the patient from participating in the study.

The results of the comparison of groups according to the presence of cardiovascular pathology in patients according to ECG data are shown in table. 15.3.6.1.

Table 15.3.6.1 Results of comparison of groups according to ECG data in the initial state (B1)

Presence of pathology	**Main group (n = 28)**		**Control group (n = 29)**		**p-value***
	n	**%**	**n**	**%**	
Norm	5	17.9	6	20.7	1,000
Deviation from the norm	23	82.1	23	79.3	
In total	28	100.0	29	100.0	
**Estimated using Fisher's exact test*					

Conclusion. Based on the results of the statistical analysis given in the table. 15.3.6.1, it can be stated that according to ECG data, in the initial state, the groups did not differ statistically significantly in the presence and severity of cardiovascular pathology.

According to the protocol, all patients underwent abdominal ultrasound (AO). In the majority of patients, according to ultrasound, diffuse changes in the liver and pancreas, uric acid diathesis, etc. were observed. The doctor-researcher evaluated these changes and made a conclusion in the categories of "norm" or "deviation from the norm". Deviations from the norm of the detected changes were not clinically significant and did not prevent the patient from participating in the study.

The results of the comparison of groups according to the presence of AO pathology according to ultrasound data are shown in the table. 15.3.6.2.

Table 15.3.6.2 Results of comparison of groups according to the ultrasound data of OCP in the initial state

Presence of pathology	**Main group (n = 28)**		**Control group (n = 29)**		**p-value***
	n	**%**	**n**	**%**	
Norm	2	7.1	4	13.8	

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Deviation from the norm	26	92.9	25	86.2	0.670
In total	28	100.0	29	100.0	
**Estimated using Fisher's exact test*					

Conclusion. Based on the results of the statistical analysis given in the table. 15.3.6.2, it can be stated that according to the ultrasound of the AO, in the initial state, the groups did not differ statistically significantly in the presence and severity of pathological changes.

15.3.7 Analysis of initial homogeneity of the groups according to laboratory indicators of general blood test

In the initial state, the patients underwent a general blood test according to the following indicators: leukocytes, erythrocytes, hematocrit, hemoglobin, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils and ESR. In most patients, these parameters were within the normal range. Deviations from the norm of some indicators, in some patients, were due to the previous use of radiation therapy and CT and were clinically insignificant.

The results of the comparative analysis of the groups according to the analyzed parameters of the general blood test, using the methods of descriptive statistics, are given in the table. 15.3.7.1.

Table 15.3.7.1 Results of a comparative analysis of groups according to indicators of a general blood analysis

Indicator	Group	n	M	Me	St	MIN	MAX
Leukocytes, x 10^{9} /l	The main one	28	6.31	6.6	2.48	2.4	14
	Control	29	6.68	6.4	2.43	2.7	12.2
Erythrocytes, x 10^{12} /l	The main one	28	4.54	4.57	0.43	3.74	5.38
	Control	29	4.57	4.54	0.51	3.77	5.85
Hematocrit, %	The main one	28	38.66	38.7	7.28	4.5	45.3
	Control	29	40.97	41.2	4.15	33.2	50
Hemoglobin, g/l	The main one	28	133.96	131	13.61	107	160
	Control	29	135.86	137	15.98	100	169
Platelets, x 10^{9} /l	The main one	28	209.25	193	52.80	137	312
	Control	29	186.48	177	56,48	112	333
Neutrophils, %	The main one	28	70.18	69.55	10.86	47.7	86.3
	Control	29	71.29	69.7	10.55	52.9	89.8
Lymphocytes, %	The main one	28	22.20	19.6	9.23	8	42
	Control	29	22.47	23	9.56	8	40.2

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Monocytes, %	The main one	28	6.07	5	3.09	2	14
	Control	29	6.34	5	2.76	3	12
Eosinophils, %	The main one	28	1.82	1	1.85	0	8
	Control	29	1.97	1	4.66	0	25
Basophils, %	The main one	28	0.18	0	0.48	0	2
	Control	29	0.14	0	0.35	0	1
ESR, mm/h	The main one	28	14.79	12.5	11.63	1	61
	Control	29	15.38	10	13.98	1	63

In order to select a criterion for checking the homogeneity of the groups based on the laboratory parameters of the general blood analysis, a check of the normality of the distribution of the analyzed data was performed (Appendix D, table D.2). Depending on the results of testing the normality of data distribution, the Student's test for independent samples (Table 15.3.7.2) or the Mann-Whitney test (Table 15.3.7.3, Appendix D, Table D.3) was applied.

Table 15.3.7.2 Results of the analysis of the initial homogeneity of the groups according to some laboratory parameters of the general blood analysis using the Student's test for independent samples

Changeable	t-statistics	Number of degrees of freedom	p-value (two pages)	Difference of mean	Conclusion on homogeneity of groups*
Leukocytes	-0.567	55	0.573	-0.369	Homogeneous
Erythrocytes	-0.183	55	0.856	-0.023	Homogeneous
Hemoglobin	-0.482	55	0.632	-1.898	Homogeneous
Neutrophils	-0.392	55	0.697	-1.111	Homogeneous
Lymphocytes	-0.105	55	0.917	-0.262	Homogeneous

** The conclusion is made at a significance level of 0.05.*

Table 15.3.7.3 Results of the analysis of the initial homogeneity of the groups according to some laboratory parameters of the general blood analysis using the Mann-Whitney test

Changeable	Mann-Whitney U	Wilcoxon W	Z	p-value	Conclusion on homogeneity of groups*
Hematocrit	320	726	-1.373	0.170	Homogeneous
Platelets	288.5	723.5	-1.876	0.061	Homogeneous
Monocytes	367.5	773.5	-0.621	0.534	Homogeneous
Eosinophils	320.5	755.5	-1,418	0.156	Homogeneous

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Changeable	Mann-Whitney U	Wilcoxon W	Z	p-value	Conclusion on homogeneity of groups*
Basophils	402	837	-0.106	0.916	Homogeneous
ESR	379.5	814.5	-0.424	0.672	Homogeneous
* *The conclusion is made at a significance level of 0.05.*					

Conclusion. Based on the results of the statistical analysis given in the table. 15.3.7.2 – 15.3.7.3, it can be stated that in the initial state the groups did not differ statistically significantly in terms of the parameters of the studied general blood analysis (leukocytes, erythrocytes, hematocrit, hemoglobin, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils and ESR).

According to the study protocol, a comparison of the groups was performed in the initial state according to the compliance with the normal values of the laboratory parameters of the general blood analysis (Table 15.3.7.4). Differences between groups were assessed using Fisher's exact test (Table 15.3.7.4).

Table 15.3.7.4 Results of comparative analysis of groups in the initial state according to compliance with normal values of laboratory indicators of general blood analysis

Changeable	Visit	Compliance with the norm / statistical indicator	The main one		Control		p-value [a)]
			n	%	n	%	
Leukocytes	B1	Norm	20	71,4	23	79.3	0.550
		Wedge insignificant departure from the norm	8	28.6	6	20.7	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
Erythrocytes	B1	Norm	22	78.6	20	69.0	0.550
		Wedge insignificant departure from the norm	6	21.4	9	31.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Hematocrit	B1	Norm	27	96.4	29	100.0	0.491
		Wedge insignificant departure from the norm	1	3.6	0	0.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Hemoglobin	B1	Norm	23	82.1	22	75.9	0.747
		Wedge insignificant departure from the norm	5	17.9	7	24.1	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Platelets	B1	Norm	18	64.3	12	41.4	0.113
		Wedge insignificant departure from the norm	10	35.7	17	58.6	

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		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Neutrophils	B1	Norm	17	60.7	16	55.2	1,000
		Wedge insignificant departure from the norm	11	39.3	12	41.4	
		Wedge significant departure departure norms	0	0.0	1	3,4	
		In total	28	100.0	29	100.0	
Lymphocytes	B1	Norm	12	42.9	18	62.1	0.298
		Wedge insignificant departure from the norm	15	53.6	10	34.5	
		Wedge significant departure from the norm	1	3.6	1	3,4	
		In total	28	100.0	29	100.0	
Monocytes	B1	Norm	25	89.3	27	93.1	0.670
		Wedge insignificant departure from the norm	3	10.7	2	6.9	
		Wedge significant departure departure norms	0	0	0	0	
		In total	28	100	29	100	
Eosinophils	B1	Norm	27	96.4	27	93.1	1,000
		Wedge insignificant departure from the norm	1	3.6	1	3,4	
		Wedge significant departure from the norm	0	0.0	1	3,4	
		In total	28	100.0	29	100.0	
Eosinophils	B3	Norm	26	92.9	28	96.6	0.362
		Wedge insignificant departure from the norm	2	7.1	0	0.0	
		Wedge significant departure from the norm	0	0.0	1	3,4	
		In total	28	100.0	29	100.0	
Basophils	B1	Norm	27	96.4	29	100.0	0.491
		Wedge insignificant departure from the norm	1	3.6	0	0.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
SOE	B1	Norm	14	50.0	17	58.6	0.339
		Wedge insignificant departure from the norm	12	42.9	8	27.6	
		Wedge significant departure from the norm	2	7.1	4	13.8	
		In total	28	100.0	29	100.0	
[a] *Calculated using Fisher's exact test.*							

Conclusion . Based on the results of the statistical analysis given in the table. 15.3.7.4, it can be concluded that in the initial state the groups did not differ statistically significantly in accordance with the normal values of the laboratory parameters of the general blood analysis.

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15.3.8 Analysis of initial homogeneity of groups according to laboratory indicators of biochemical blood analysis

In the initial state, patients underwent biochemical blood analysis according to the following indicators: AST, ALT, total bilirubin, creatinine, glucose.

In most patients, these parameters were within the normal range. Deviations from the norm of some indicators, in some patients, were due to the previous use of radiation therapy and CT and were clinically insignificant.

The results of the analysis of the homogeneity of the groups according to the analyzed indicators of the biochemical analysis of blood by the methods of descriptive statistics are given in the table. 15.3.8.1.

Table 15.3.8.1 Results of comparative analysis of groups according to laboratory indicators of biochemical blood analysis

Indicator	Group	n	M	Me	St	MIN	MAX
AST, unit/l	The main one	28	23.20	22	9,11	10.7	48.2
	Control	29	23.46	20.4	11,28	9.1	54.7
ALT, unit/l	The main one	28	28.74	26.4	12.89	6.1	57.5
	Control	29	31.90	31.5	12.94	13	56.2
Total bilirubin, μmol/l	The main one	28	10.72	10.945	4.64	4.47	24.78
	Control	29	13.76	13.12	5.78	5.39	26.26
Creatinine, μmol/l	The main one	28	73,24	71,19	14.61	41,51	107.93
	Control	29	69.95	65.65	14.99	43.04	110.12
Glucose, mmol/l	The main one	28	5.77	5.5	1.61	3.8	11.1
	Control	29	5.50	5.7	0.85	4	7.4

In order to select a criterion for checking the homogeneity of groups according to the laboratory indicators of biochemical blood analysis, a check of the normality of the distribution of the analyzed data was performed (Appendix D, table D. 2). Depending on the results of testing the normality of the data distribution, the Student's test for independent samples (Table 15.3.8.2) or the Mann-Whitney test (Table 15.3.8.3, Appendix D, Table D.3) was applied.

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Table 15.3.8.2 Results of the analysis of the initial homogeneity of groups according to some laboratory indicators of biochemical blood analysis using the Student's test for independent samples

Changeable	t-statistics	Number of degrees of freedom	p-value (two pages)	Difference of mean	Conclusion on homogeneity of groups*
ALT	-0.925	55	0.359	-3,164	Homogeneous
Total bilirubin	-2,188	55	0.053	-3.043	Homogeneous
Creatinine	0.840	55	0.405	3,294	Homogeneous
** The conclusion is made at a significance level of 0.05.*					

Table 15.3.8.3 Results of the analysis of the initial homogeneity of the groups according to some laboratory indicators of biochemical blood analysis using the Mann-Whitney test

Changeable	Mann-Whitney U	Wilcoxon W	Z	p-value	Conclusion on homogeneity of groups*
AST	388.5	823.5	-0.279	0.780	Homogeneous
Glucose	396.5	831.5	-0.152	0.879	Homogeneous
** The conclusion is made at a significance level of 0.05.*					

Conclusion. Based on the results of the statistical analysis given in the table. 15.3.8.2-15.3.8.3, it can be stated that in the initial state the groups did not differ statistically significantly in terms of laboratory parameters of biochemical blood analysis that were studied (AST, ALT, total bilirubin, creatinine, glucose).

According to the Research Protocol, the groups were compared in the initial state according to the normal values of laboratory indicators of biochemical blood analysis (Table 15.3.8.4). Differences between groups were assessed using Fisher's exact test.

Table 15.3.8.4 – Results of comparative analysis of groups in the initial state according to compliance with normal values of laboratory indicators of biochemical blood analysis

Changeable	Visit	Compliance with the norm / statistical indicator	The main one		Control		p-value [a)]
			n	%	n	%	
AST	V1	Norm	26	92.9	26	89.7	1,000
		Wedge insignificant departure from the norm	2	7.1	3	10.3	
		Wedge significant departure from the	0	0	0	0	

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		norm					
		In total	28	100	29	100	
ALT	V1	Norm	23	82.1	25	86.2	0.730
		Wedge insignificant departure from the norm	5	17.9	4	13.8	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Total bilirubin	V1	Norm	27	96.4	25	86.2	0.352
		Wedge insignificant departure from the norm	1	3.6	4	13.8	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Creatinine	V1	Norm	27	96.4	28	96.6	1,000
		Wedge insignificant departure from the norm	1	3.6	1	3,4	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Glucose	V1	Norm	22	78.6	25	86.2	0.504
		Wedge insignificant departure from the norm	6	21.4	4	13.8	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
[a)] *Calculated using Fisher's exact test.*							

Conclusion . Based on the results of the statistical analysis given in the table. 15.3.8.4, it can be stated that in the initial state the groups did not differ statistically significantly in accordance with the normal values of the laboratory indicators of biochemical blood analysis.

15.3.9 Analysis of initial homogeneity of groups according to laboratory indicators of general urine analysis

In the initial state, patients underwent a general urine analysis according to the following indicators: specific gravity, pH, protein, glucose, leukocytes, erythrocytes, cylinders, salts. In most patients, these indicators were within the normal range. Deviations from the norm of some indicators, in some patients, were clinically insignificant.

The results of the comparative analysis of the groups according to the indicators of the general analysis of urine, using the methods of descriptive statistics, are given in the table. 15.3.9.1 for quantitative variables and in the table. 15.3.9.2 for categorical variables (presence of salt).

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Table 15.3.9.1 Results of comparative analysis of groups according to laboratory parameters of general urine analysis

Indicator	Group	n	M	Me	St	MIN	MAX
Specific weight	The main one	28	1014.50	1014	9.36	1002	1050
	Control	29	1013.48	1013	5.62	1002	1024
pH	The main one	28	6.04	6	0.19	6	7
	Control	29	6.52	6	0.87	6	8
Protein, g/l	The main one	28	0.00	0	0.01	0	0.033
	Control	29	0.00	0	0.01	0	0.033
Glucose, mmol/l	The main one	28	0	0	N/A	0	0
	Control	29	0	0	N/A	0	0
leukocytes, cells in sight	The main one	28	4.29	4	3.32	0	15
	Control	29	6.72	3	13.01	1	70
erythrocytes, cells in sight	The main one	28	0.54	0	1.00	0	3
	Control	29	0.76	0	1.48	0	5
cylinders, cells in sight	The main one	28	0.04	0	0.19	0	1
	Control	29	0.07	0	0.37	0	2

Table 15.3.9.2 Results of comparison of groups according to the presence of salt in urine

Changeable	Variable category	Main group n=30		Control group n=30		p-value*
		n	%	n	%	
Salts in the urine	So	20	71.4	21	72.4	1,000
	No	8	28.6	8	27.6	
	In total	28	100.0	29	100.0	
** Calculated using Fisher's exact test.*						

As can be seen from the table. 15.3.9.1 glucose in the urine was absent in all patients in both groups. Therefore, the groups according to this indicator were homogeneous and no further comparison of the groups according to it was carried out.

In order to select a criterion for checking the homogeneity of groups according to the laboratory parameters of the general analysis of urine, a check of the normality of the distribution of the analyzed data was performed (Appendix D, table D.2). Since the data in the groups (at least in one) were not distributed normally, the Mann-Whitney test was used to compare them (Table 15.3.9.3, Appendix D, Table D.3).

Table 15.3.9.3 Results of the analysis of the initial homogeneity of the groups according to some laboratory parameters of the general urine analysis using the Mann-Whitney test

Changeable	Mann-Whitney U	Wilcoxon W	Z	p-value	Conclusion on homogeneity of groups*
Specific weight	406	841	0.000	1,000	Homogeneous
pH	305	711	-2.546	0.051	Homogeneous

Protein in the urine	364.5	770.5	-1.352	0.176	Homogeneous
Leukocytes in the urine	394	829	-0.194	0.846	Homogeneous
Erythrocytes in the urine	400	806	-0.121	0.904	Homogeneous
Cylinders	406	841	0.000	1,000	Homogeneous
** The conclusion is made at a significance level of 0.05.*					

Conclusion. Based on the results of the statistical analysis given in the table. 15.3.9.2 - 15.3.9.3, it can be stated that in the initial state, the groups did not differ statistically significantly in terms of the laboratory parameters of the studied general urine analysis.

According to the study protocol, a comparison of groups was performed in the initial state according to the correspondence of normal values of the laboratory parameters of the general urine analysis (Table 15.3.9.4). Differences between groups were assessed using Fisher's exact test.

Table 15.3.9.4 Results of comparative analysis of groups in the initial state according to compliance with normal values of laboratory indicators of general urine analysis

Changeable	**Visit**	**Compliance with the norm / statistical indicator**	**The main one**		**Control**		**p-value a)**
			n	**%**	**n**	**%**	
Specific weight	V1	Norm	18	64.3	18	62.1	1,000
		Wedge insignificant departure from the norm	10	35.7	11	37.9	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
pH	V1	Norm	28	100.0	25	86.2	0.112
		Wedge insignificant departure from the norm	0	0.0	4	13.8	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
Protein in the urine	V1	Norm	27	96.4	25	86.2	0.352
		Wedge insignificant departure from the norm	1	3.6	4	13.8	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
Leukocytes in the urine	V1	Norm	22	78.6	22	75.9	0.793
		Wedge insignificant departure from the norm	5	17.9	4	13.8	
		Wedge significant departure from the norm	1	3.6	3	10.3	
		In total	28	100.0	29	100.0	

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Erythrocytes in the urine	V1	Norm	22	78.6	25	86.2	0.504
		Wedge insignificant departure from the norm	6	21.4	4	13.8	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
Cylinders	V1	Norm	28	100.0	28	96.6	1,000
		Wedge insignificant departure from the norm	0	0.0	1	3,4	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
Salt	V1	Norm	23	82.1	25	86.2	0.730
		Wedge insignificant departure from the norm	5	17.9	4	13.8	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
[a)] Calculated using Fisher's exact test.							

Conclusion . Based on the results of the statistical analysis given in the table. 15.3.9.4, it can be stated that in the initial state the groups did not differ statistically significantly in accordance with the normal values of the laboratory parameters of the general urine analysis.

15.3.10 Analysis of homogeneity of groups according to QL2 quality of life assessments of the EORT QLQ-C30 questionnaire

We analyzed the QL2 quality of life scale, which is formed on the basis of two scales (the "quality of life" scale and the "general health status" scale) of the EORTC questionnaire QLQ-C30.

The results of a comparative analysis of groups based on quality of life assessments on the QL2 scale of the EORTC QLQ-C30 questionnaire, using descriptive statistics methods, are shown in table. 15.3.10.1.

Table 15.3.10.1 Results of the comparative analysis of the groups according to the QL2 scale of the EORTC QLQ-C30 questionnaire

Parameter	Group	N	M	Me	St	MIN	MAX
QL2, points	The main one	28	59.82	62.50	13.62	33,33	100.00
	Control	29	66,67	66,67	16.67	33,33	100.00

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In order to select a criterion for checking the homogeneity of the groups, a check of the normality of the distribution of the analyzed data was performed (Appendix D, table D.2). Since the data in the groups were not distributed normally, the Mann-Whitney test was used to compare them (Table 15.3.10.2, Appendix D, Table D.3).

Table 15.3.10.2 - Results of the analysis of the initial homogeneity of the groups according to the QL2 scale of the EORTC QLQ-C30 questionnaire using the Mann-Whitney test

Changeable	Mann-Whitney U	Wilcoxon W	Z	p-value	Conclusion on homogeneity of groups*
QL2	310.5	716.5	-1,618	0.106	Homogeneous
* *The conclusion is made at a significance level of 0.05.*					

Conclusion . Based on the results of the statistical analysis given in the table. 15.3.10.1 – 15.3.10.2, it can be stated that, in the initial state, the groups did not differ statistically significantly in quality of life assessments according to the QL2 scale of the EORTC QLQ-C30 questionnaire.

15.3.11. Summary results of analysis of initial homogeneity of groups

Thus, the formed groups were homogeneous in terms of nosology, demographic and anthropometric parameters, concomitant pathology, volume of surgical intervention, localization and side of the lesion, general condition according to the ECOG scale, chemotherapy regimens and the average number of received CT courses. laboratory and vital signs.

15.4 Evaluation of treatment effectiveness

15.4.1 Evaluation of efficacy by the main variable

The main variable in this study was one-year (365 days) overall survival of patients from the moment of inclusion in this study (the date of signing the Informed Consent).

57 patients were included in the analysis of one-year survival, of which: 28 patients of the main group and 29 patients of the control group.

To analyze the survival time for 365 days, survival analysis methods were used, namely, the construction of survival curves using the Kaplan-Meier method (Fig. 15.4.1.1),

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the estimation of the survival median and the comparison of survival curves using the Log Rank test (Table 15.4. 1.2).

During the specified time (365 days), the median survival (the time when a critical event occurs in 50% of patients) was not reached in any of the groups. Therefore, only the average values of the survival time in the groups for this period, which are listed in the table, were estimated. 15.4.1.1.

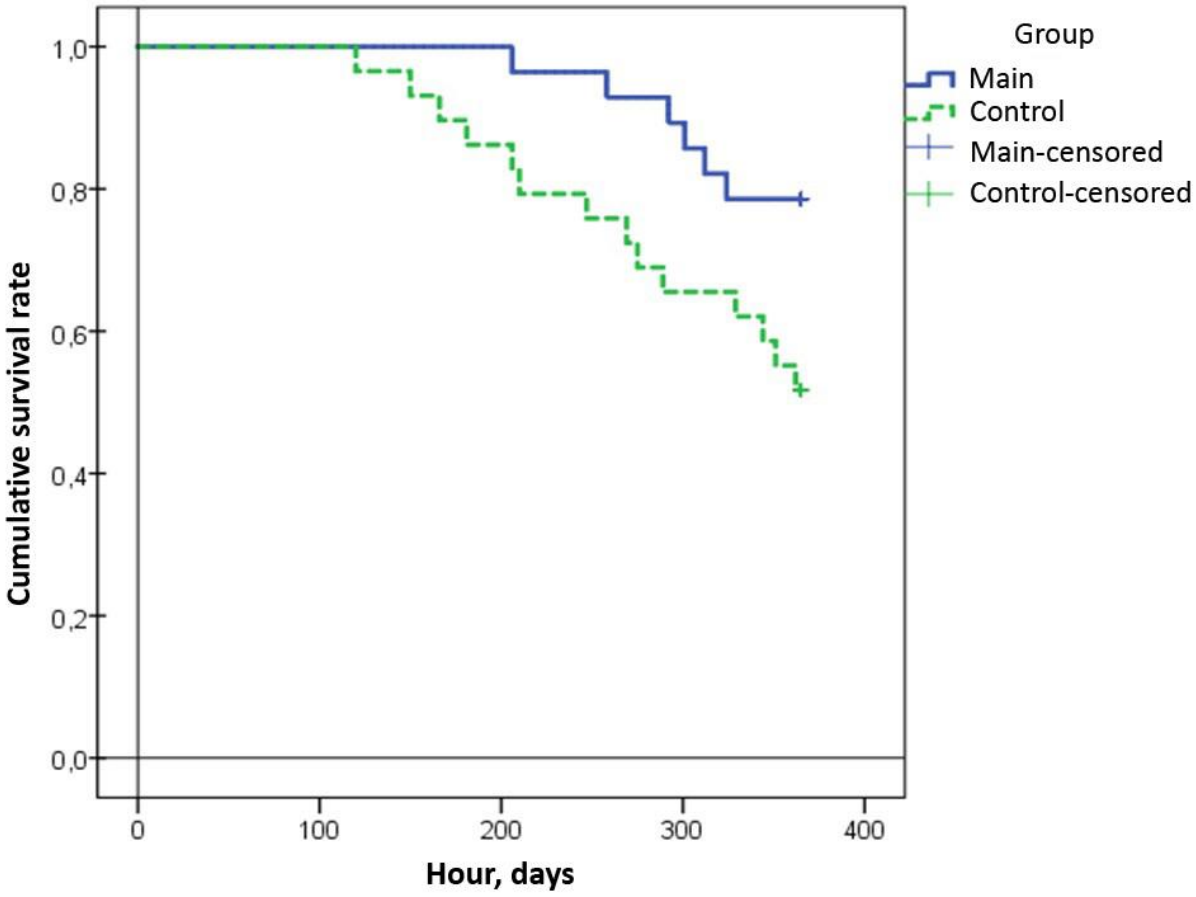

Fig. 15.4.1.1 Overall survival curves in groups constructed using the Kaplan-Meier method

Table 15.4.1.1 Estimates of mean values of survival time in groups, taking into account that the data are censored to the right, since the duration of the observation period was 365 days

Group	Arithmetic average *			
	Rating	Standard error	95% CI	
			NG	VG
main	347.25	7.30	332.93	361.57
control	309.45	14.57	280.90	338.00
united	328.02	8.61	311.15	344.89
** Estimate limited to longest survival time if censored.*				

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Table 15.4.1.2 Results of comparison of survival curves in groups using the log-rank test

Statistical criterion	χ^2 (chi-square)	df	p-value
Log Rank (Mantel-Cox)*	4,733	1	0.030
**Criterion for testing the uniformity of survival time distributions for different levels of the "group" factor.*			

Conclusions

1. The arithmetic mean of one-year (365-day) overall survival time (the estimate was limited to the largest censored survival time) was 347.5 days in the main group and 309.45 days in the control group, which indicates in favor of the excess effectiveness of treatment in the main group.
2. Median survival (when the studied event occurs in 50% of patients) was not reached in any of the groups.
3. According to the results of the comparison of the curves of the overall one-year (365-day) survival in the groups using the log-rank test, the one-year survival in the main group was statistically significantly higher compared to the control group (p = 0.030), which allows us to draw a conclusion about the superior effectiveness of therapy with the use of the drug Donovit-VS in comparison with therapy without the use of this drug.

15.4.2 Efficacy assessment of one-year overall survival with survival/non-survival categories

Overall survival at 365 days from study entry was also assessed, using a categorical variable with the categories of "survivor"/"non-survivor". The results of the analysis of this variable in groups and the results of the comparison of groups using Fisher's exact test are given in the table. 15.4.2.1. The graphic interpretation is shown in fig. 15.4.2.1.

Table 15.4.2.1 Results of the assessment of overall one-year survival in groups by categorical variable with the categories "survived"/"did not survive"

Survival for 365 days	Main group n=28		Control group n=29		p-value*
	n	%	n	%	
Survived	22	78.6	15	51.7	0.052
Died	6	21.4	14	48.3	
In total	28	100.0	29	100.0	
** Calculated using Fisher's exact test.*					

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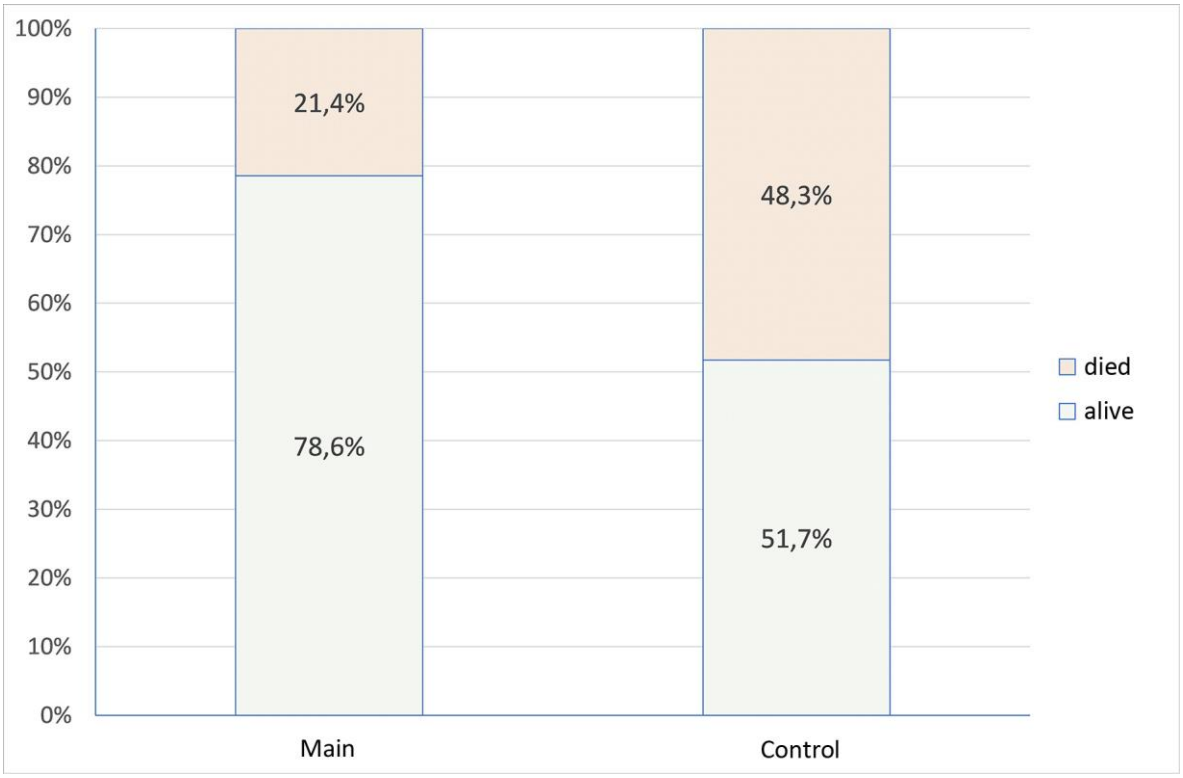

Fig. 15.4.2.1 - Graphical interpretation of one-year overall survival in groups

Conclusion . The overall one-year (365 days) survival of patients in the main group was 78.6%, and in the control group - 51.7%. Formally, the differences between the groups are statistically insignificant (p = 0.052). However, the fact that the difference in the percentage of surviving patients [primary – control] is 26.9% indicates the benefit of the superior effectiveness of the therapy with the use of the drug Donovit-VS in comparison with the therapy without the use of this drug.

15.4.3. Efficacy assessment by one-year (12-month) recurrence-free survival

Relapse-free survival is an important secondary efficacy endpoint. 57 patients were included in her analysis, of which: 28 patients of the main group and 29 patients of the control group.

Survival analysis methods were used as a statistical tool, namely, construction of survival curves using the Kaplan-Meier method (Fig. 15.4.3.1), median survival estimation and comparison of survival curves using the Log Rank test (Table 15.4.3.2).

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Median recurrence-free survival (the time at which a critical event occurs in 50% of patients) in the main group was not reached during the specified time (12 months). Therefore, only the average values of recurrence-free survival in both groups during this period were estimated, which are listed in the table. 15.4.1.1, and median survival was estimated only for the control group.

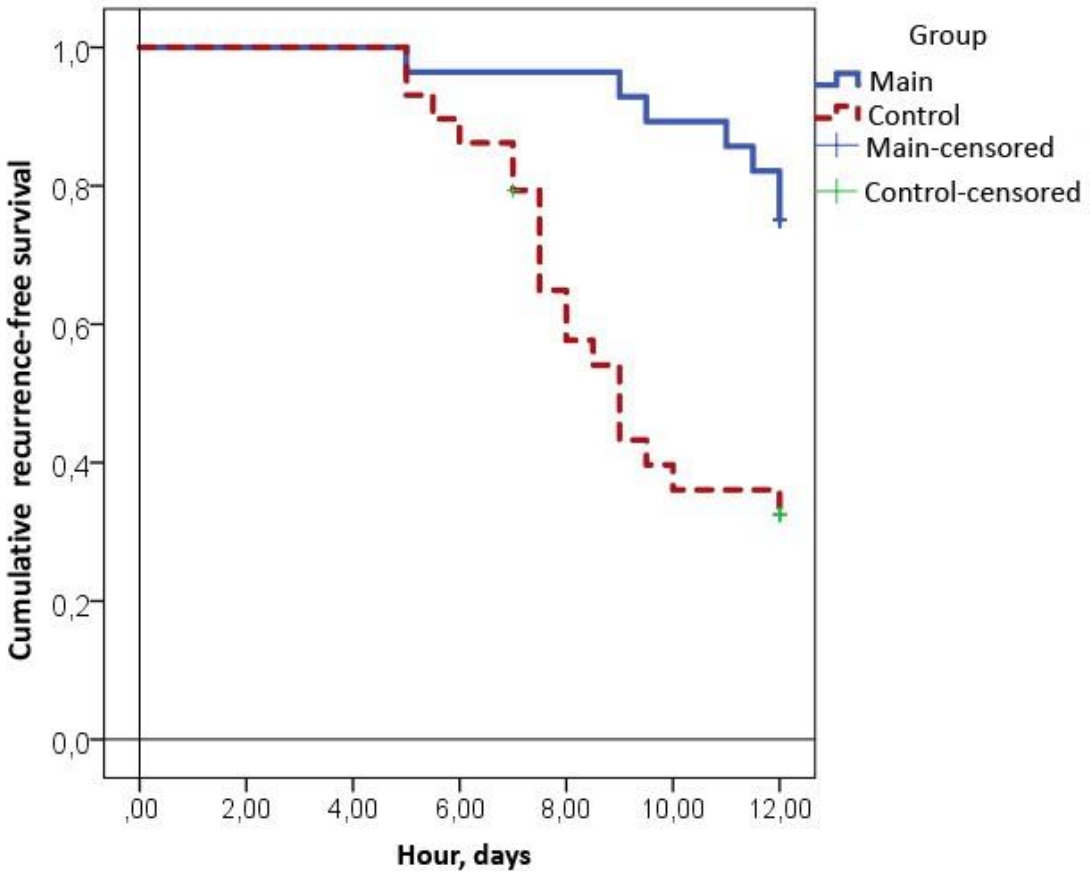

Fig. 15.4.3.1 Curves of recurrence-free survival in groups, constructed using the Kaplan-Meier method

Table 15.4.3.1 Estimates of the mean values of the time of relapse-free survival in the groups, taking into account that the data are censored to the right, since the duration of the observation period was 12 months

Group	Arithmetic average *				Median survival			
	Rating	Std. error	95% CI		Rating	Std. error	95% CI	
			NG	VG			NG	VG
main	11.5	0.3	10.9	12.1	-	-	-	-
control	9.2	0.5	8.3	10.1	9.0	0.6	7.7	10.3
united	10.3	0.3	9.7	11.0	-	-	-	-

** Estimate limited to longest survival time if censored.*

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Table 15.4.3.2 Results of comparison of one-year recurrence-free survival curves in groups using the Log Rank test

Statistical criterion	χ - square	df	p-value
Log Rank (Mantel-Cox)	12,974	1	<0.001

Conclusions .

1. The arithmetic mean of the one-year recurrence-free survival time of patients (the assessment was limited to the largest censored time of recurrence-free survival of patients, under the condition of 12-month follow-up) was 11.5 months in the main group and 9.2 months in the control group, which indicates the benefit of the exceeding effectiveness of treatment in the main group.
2. Median one-year recurrence-free survival in the main group was not available, since less than 50% of patients in the main group relapsed during the study, and in the control group, the median recurrence-free survival was 9 months.
3. According to the results of comparing the one-year recurrence-free survival curves in the groups using the Log Rank test, the one-year recurrence-free survival in the main group was statistically significantly higher compared to the control group ($p < 0.001$), which allows us to draw a conclusion about the superior effectiveness of therapy with the use of Donovit-VS in the preparation compared with therapy without the use of this drug.

The results of a comparative analysis of one-year recurrence-free survival using a categorical variable with the categories "No recurrence"/"There is a recurrence" are shown in table. 15.4.3.3, and the graphic interpretation is in fig. 15.4.3.1.

Table 15.4.3.3 Results of analysis of 12-month recurrence-free survival

Relapse within 12 months of follow-up	Main group n=28		Control group n=29		p-value*
	n	%	n	%	
No relapse	21	75.0	10	34.5	0.003
There is a relapse	7	25.0	19	65.5	
In total	28	100.0	29	100.0	

** Calculated using Fisher's exact test.*

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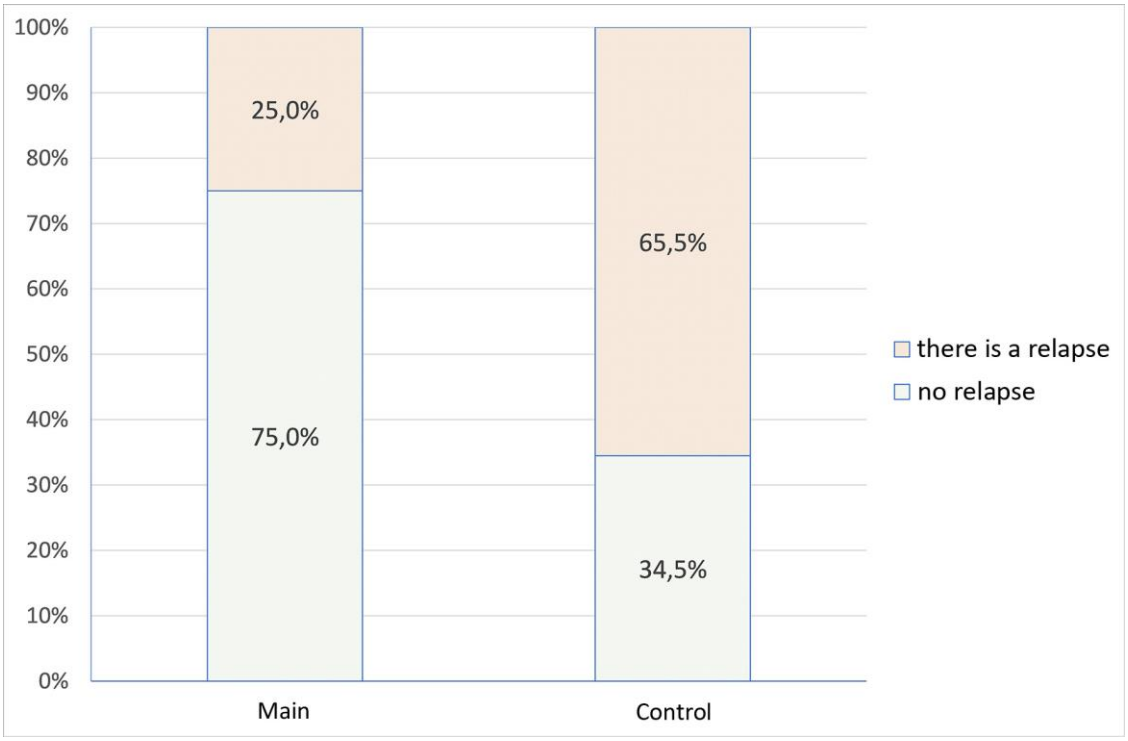

Fig. 15.4.3.1 – Graphical interpretation of 12-month recurrence-free survival

Conclusion . The relapse-free one-year survival of patients in the main group was 75.0%, and in the control group - 34.5%. The difference in proportions [main - control] was 40.5%. The differences between the groups are statistically significant (p = 0.003), which allows us to draw a conclusion about the superior effectiveness of therapy with the use of the drug Donovit-VS in comparison with therapy without the use of this drug.

15.4.4 Evaluation of effectiveness by the degree of toxicity of chemotherapy

One of the secondary variables in this study was the degree of manifestation of toxicity of chemotherapy in the course of treatment. It was assumed that the use of the investigated drug Donovit-VS, against the background of chemotherapy, will reduce the frequency and severity of toxic reactions caused by the use of chemotherapeutic drugs.

15.4.4.1 Analysis of blood pressure, heart rate and body temperature data in

Hemodynamic indicators, during treatment, were within normal values or slightly deviated from the norm in patients of both groups. Body temperature also did not exceed 37.0°C in most patients of both groups during the entire study, except for

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an increase in body temperature in two patients of the main group (No 013 and No 032). However, this temperature increase was subfebrile and was judged by the investigator to be clinically insignificant.

The results of a descriptive analysis of the dynamics of these parameters in the research process are given in table. 15.4.4.1.1 for the main group and in the table. 15.4.4.1.2 for the control room.

Table 15.4.4.1.1 Results of the analysis of the dynamics of hemodynamic indicators and body temperature in the main group

Indicator	Visit	n	M	Me	St	MIN	MAX
SBR, mmHg	Visit 1 (screening)	28	123.86	124	13.74	100	170
	Visit 3 (day 90)	28	122.25	122.5	12.67	100	150
	Visit 4 (day 180)	25	121.60	120	14.34	95	150
	Visit 5 (day 270)	24	117.96	115.5	16.47	95	160
	Visit 6 (day 360)	19	117.89	120	16.78	90	170
DBR, mmHg	Visit 1 (screening)	28	79.93	80	7.83	60	100
	Visit 3 (day 90)	28	80.46	80	8.98	60	100
	Visit 4 (day 180)	25	78.00	80	9.68	60	100
	Visit 5 (day 270)	24	77.50	80	9.56	60	90
	Visit 6 (day 360)	19	78.95	80	10.49	60	110
Heart rate, beats/Min.	Visit 1 (screening)	28	73.93	72	12.65	50	100
	Visit 3 (day 90)	28	76,57	76	8.30	62	98
	Visit 4 (day 180)	25	70.04	72	10,10	50	88
	Visit 5 (day 270)	24	70.46	72	11.58	45	95
	Visit 6 (day 360)	19	73.32	75	9.56	52	90
Body temperature, °C	Visit 1 (screening)	28	36.55	36.6	0.18	36.2	37.2
	Visit 3 (day 90)	28	36.63	36.6	0.21	36.2	37.6
	Visit 4 (day 180)	25	36,56	36.6	0.11	36.2	36.6
	Visit 5 (day 270)	24	36.62	36.6	0.24	36.3	37.7
	Visit 6 (day 360)	19	36,57	36.6	0.09	36.2	36.6

Table 15.4.4.1.1 Results of the analysis of the dynamics of hemodynamic parameters and body temperature in the control group

Indicator	Visit	n	M	Me	St	MIN	MAX
SBR, mmHg	Visit 1 (screening)	29	123.45	120	14,21	85	160
	Visit 3 (day 90)	29	122.93	120	10,22	100	150
	Visit 4 (day 180)	21	116.67	120	13.35	80	140
	Visit 5 (day 270)	12	111.67	110	16.00	90	150
	Visit 6 (day 360)	6	105.83	102.5	9.70	95	120

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Indicator	Visit	n	M	Me	St	MIN	MAX
DBR, mmHg	Visit 1 (screening)	29	80.34	80	9.54	60	100
	Visit 3 (day 90)	29	80.17	80	6.88	60	90
	Visit 4 (day 180)	21	77,38	80	7.68	60	90
	Visit 5 (day 270)	12	73.75	75	9.32	60	90
	Visit 6 (day 360)	6	69.17	70	8.01	60	80
Heart rate, beats/Min.	Visit 1 (screening)	29	75.97	72	12.37	57	110
	Visit 3 (day 90)	29	76.52	76	9.45	58	96
	Visit 4 (day 180)	21	69.52	70	9.66	50	90
	Visit 5 (day 270)	12	70.92	72	5.16	60	80
	Visit 6 (day 360)	6	72,83	72	2.04	72	77
Body temperature, °C	Visit 1 (screening)	29	36,56	36.6	0.35	35.5	38.0
	Visit 3 (day 90)	29	36.54	36.6	0.15	36.0	36.6
	Visit 4 (day 180)	21	36,56	36.6	0.10	36.3	36.6
	Visit 5 (day 270)	12	36.60	36.6	0.09	36.4	36.8
	Visit 6 (day 360)	6	36.60	36.6	N/A	36.6	36.6

Conclusion. As can be seen from the analysis, hemodynamic indicators in most cases did not change during the observation process in both studied groups of patients. Slight fluctuations in blood pressure, heart rate, and body temperature were noted at different stages of observation, but they were not clinically significant. This indicates the absence of a negative effect of the therapy on hemodynamic indicators and body temperature.

15.4.4.2 Analysis of dynamics of general blood analysis indicators

The results of the analysis of the dynamics of the indicators of the general blood test are shown in the table. 15.4.4.2.1 for patients of the main group and in table 15.4.4.2.2 for patients of the control group.

Table 15.4.4.2.1 Dynamics of indicators of general blood analysis during the study in patients of the main group

Indicator	Visit	n	M	Me	St	MIN	MAX
Leukocytes, $\times 10^9$ cells/l	Visit 1 (screening)	28	6.31	6.6	2.48	2.4	14
	Visit 3 (day 90)	28	4.93	4.65	2.34	2.5	13,27
	Visit 4 (day 180)	26	5.15	4.1	3.55	2	18.6
	Visit 5 (day 270)	24	5.17	4.6	2.46	2.5	11.6
	Visit 6 (day 360)	20	5.11	4.5	2.37	1.7	9.3

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Indicator	Visit	n	M	Me	St	MIN	MAX
Erythrocytes, $\times 10^{12}$ cells/l	Visit 1 (screening)	28	4.54	4.57	0.43	3.74	5.38
	Visit 3 (day 90)	28	4.28	4.28	0.54	3.16	5.22
	Visit 4 (day 180)	26	4.14	4.17	0.59	2.49	5.48
	Visit 5 (day 270)	24	4.18	4.1	0.75	2.63	5.5
	Visit 6 (day 360)	20	4.25	4.32	0.72	2.96	5.87
Hematocrit, %	Visit 1 (screening)	28	38.66	38.7	7.28	4.5	45.3
	Visit 3 (day 90)	28	39.65	39.9	4.64	30.5	47.6
	Visit 4 (day 180)	26	38.99	39.05	4.96	26	49.3
	Visit 5 (day 270)	24	39.50	38.55	6.29	28.2	49.6
	Visit 6 (day 360)	20	39.00	39.55	5.55	30.6	51.5
Hemoglobin, g/l	Visit 1 (screening)	28	133.96	131	13.61	107	160
	Visit 3 (day 90)	28	133.46	132.5	13,13	112	156
	Visit 4 (day 180)	26	128.38	129.5	15.32	89	156
	Visit 5 (day 270)	24	129.33	129.5	22.10	86	177
	Visit 6 (day 360)	20	127.25	123.5	20,34	89	158
Platelets, x 10^{9} /l	Visit 1 (screening)	28	209.25	193	52.80	137	312
	Visit 3 (day 90)	28	170.32	176	65.10	46	292
	Visit 4 (day 180)	26	156.96	159	56,63	51	259
	Visit 5 (day 270)	24	184.50	171.5	61.30	95	352
	Visit 6 (day 360)	20	197.70	198.5	75.97	90	430
Neutrophils, %	Visit 1 (screening)	28	70.18	69.55	10.86	47.7	86.3
	Visit 3 (day 90)	28	69.05	68.9	8.72	54.9	91.4
	Visit 4 (day 180)	26	66.07	63.9	10.06	49.9	90.8
	Visit 5 (day 270)	24	69.97	71.85	14.83	39.2	89.8
	Visit 6 (day 360)	20	68.74	67.2	12.45	48.3	94.3
Lymphocytes, %	Visit 1 (screening)	28	22.20	19.6	9.23	8	42
	Visit 3 (day 90)	28	23.20	24.2	8.35	5	37.8
	Visit 4 (day 180)	26	26.08	27.65	10.02	5	45
	Visit 5 (day 270)	24	21.05	20.5	11,12	5	46
	Visit 6 (day 360)	20	23,17	22.5	9.91	6	45
Monocytes, %	Visit 1 (screening)	28	6.07	5	3.09	2	14
	Visit 3 (day 90)	28	6.43	6	2.43	2	11
	Visit 4 (day 180)	26	7.30	6.5	2.78	3	16
	Visit 5 (day 270)	24	6.17	6	2.65	2	12
	Visit 6 (day 360)	20	6.40	7	2.11	2	10
Eosinophils, %	Visit 1 (screening)	28	1.82	1	1.85	0	8
	Visit 3 (day 90)	28	1.86	1	1.90	0	6

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Indicator	Visit	n	M	Me	St	MIN	MAX
	Visit 4 (day 180)	26	1.95	1.5	2.06	0	10
	Visit 5 (day 270)	24	1.29	1	1.40	0	5
	Visit 6 (day 360)	20	1.40	1	1.19	0	4
Basophils, %	Visit 1 (screening)	28	0.18	0	0.48	0	2
	Visit 3 (day 90)	28	0.21	0	0.50	0	2
	Visit 4 (day 180)	26	0.12	0	0.33	0	1
	Visit 5 (day 270)	24	0.08	0	0.28	0	1
	Visit 6 (day 360)	20	0.00	0	ND	0	0
ESR, mm/h	Visit 1 (screening)	28	14.79	12.5	11.63	1	61
	Visit 3 (day 90)	28	13,21	11.5	10.44	2	49
	Visit 4 (day 180)	26	12.62	10	8.92	2	45
	Visit 5 (day 270)	24	16.92	12.5	19,16	2	75
	Visit 6 (day 360)	20	13.60	7	15.72	1	65

Table 15.4.4.2.2 Dynamics of indicators of general blood analysis during the study in patients of the control group

Indicator	Visit	n	M	Me	St	MIN	MAX
Leukocytes, $\times 10^9$ cells/l	Visit 1 (screening)	29	6.68	6.4	2.43	2.7	12.2
	Visit 3 (day 90)	29	4.96	4.2	2.35	2,2	12.6
	Visit 4 (day 180)	21	5.18	4.3	2.50	1.6	10.8
	Visit 5 (day 270)	12	5.32	5.2	2.42	2,2	10.3
	Visit 6 (day 360)	9	4.00	3.9	1.21	2,3	6.2
Erythrocytes, $\times 10^{12}$ cells/l	Visit 1 (screening)	29	4.57	4.54	0.51	3.77	5.85
	Visit 3 (day 90)	29	4.46	4.43	0.56	3.48	5.87
	Visit 4 (day 180)	21	4.39	4.48	0.76	2.66	5.65
	Visit 5 (day 270)	12	4.36	4.34	0.69	3.37	5.65
	Visit 6 (day 360)	9	4.18	4.3	0.86	2.67	5.38
Hematocrit, %	Visit 1 (screening)	29	40.97	41.2	4.15	33.2	50
	Visit 3 (day 90)	29	40.12	39.7	4.54	33.2	51.7
	Visit 4 (day 180)	21	40,26	40.6	6.65	25.5	51.6
	Visit 5 (day 270)	12	40,28	40.85	4.69	31.8	50.5
	Visit 6 (day 360)	9	38.90	40.9	6.43	26.7	47.6
Hemoglobin, g/l	Visit 1 (screening)	29	135.86	137	15.98	100	169
	Visit 3 (day 90)	29	136.28	134	16.06	109	171
	Visit 4 (day 180)	21	135.86	139	20.56	95	173
	Visit 5 (day 270)	12	135.25	138	18.48	103	169
	Visit 6 (day 360)	9	129.22	136	18.44	95	153
Platelets, x 10^9 /l	Visit 1 (screening)	29	186.48	177	56,48	112	333
	Visit 3 (day 90)	29	174.59	170	58.08	35	325
	Visit 4 (day 180)	21	163.86	164	50,59	47	248

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Indicator	Visit	n	M	Me	St	MIN	MAX
	Visit 5 (day 270)	12	136.42	139.5	46,46	70	225
	Visit 6 (day 360)	9	162.00	163	42.80	103	222
Neutrophils, %	Visit 1 (screening)	29	71.29	69.7	10.55	52.9	89.8
	Visit 3 (day 90)	29	64.20	64.4	10.89	38.9	85.3
	Visit 4 (day 180)	21	66.99	65.2	9.25	48.8	83.9
	Visit 5 (day 270)	12	65.87	70.65	12.39	35.9	77.6
	Visit 6 (day 360)	9	62,23	66.1	13.76	36.6	77.9
Lymphocytes, %	Visit 1 (screening)	29	22.47	23	9.56	8	40.2
	Visit 3 (day 90)	29	27,41	25	10.00	10	53.8
	Visit 4 (day 180)	21	24.04	24	8.83	7	38.5
	Visit 5 (day 270)	12	26,18	24	9.81	15.7	47
	Visit 6 (day 360)	9	29.08	23	11.57	19	52
Monocytes, %	Visit 1 (screening)	29	6.34	5	2.76	3	12
	Visit 3 (day 90)	29	6.79	7	3.13	2	16
	Visit 4 (day 180)	21	6.19	6	2.32	1	9
	Visit 5 (day 270)	12	5.50	5	3.29	1	13
	Visit 6 (day 360)	9	7.44	7	2.19	5	12
Eosinophils, %	Visit 1 (screening)	29	1.97	1	4.66	0	25
	Visit 3 (day 90)	29	2.00	2	2.04	0	11
	Visit 4 (day 180)	21	1.48	1	1.36	0	6
	Visit 5 (day 270)	12	1.67	1	1.56	0	5
	Visit 6 (day 360)	9	1.89	2	1.54	0	5
Basophils, %	Visit 1 (screening)	29	0.14	0	0.35	0	1
	Visit 3 (day 90)	29	0.20	0	0.48	0	2
	Visit 4 (day 180)	21	0.19	0	0.51	0	2
	Visit 5 (day 270)	12	0.08	0	0.29	0	1
	Visit 6 (day 360)	9	0.11	0	0.33	0	1
ESR, mm/h	Visit 1 (screening)	29	15.38	10	13.98	1	63
	Visit 3 (day 90)	29	9.55	9	6.68	2	26
	Visit 4 (day 180)	21	11.86	7	13.93	2	55
	Visit 5 (day 270)	12	9.08	6	6.84	3	23
	Visit 6 (day 360)	9	14.89	13	11.01	5	40

Taking into account the importance of the levels of leukocytes, erythrocytes, hemoglobin, platelets and other indicators of the general blood analysis, in connection with the influence of CT, in fig. 15.4.4.2.1 – 15.4.4.2.4 provides a graphical interpretation of the dynamics of the average values of some indicators. However, it should be noted that due to the dropout of patients during the study, the graphs shown are slightly skewed due to incomplete data at the last visits.

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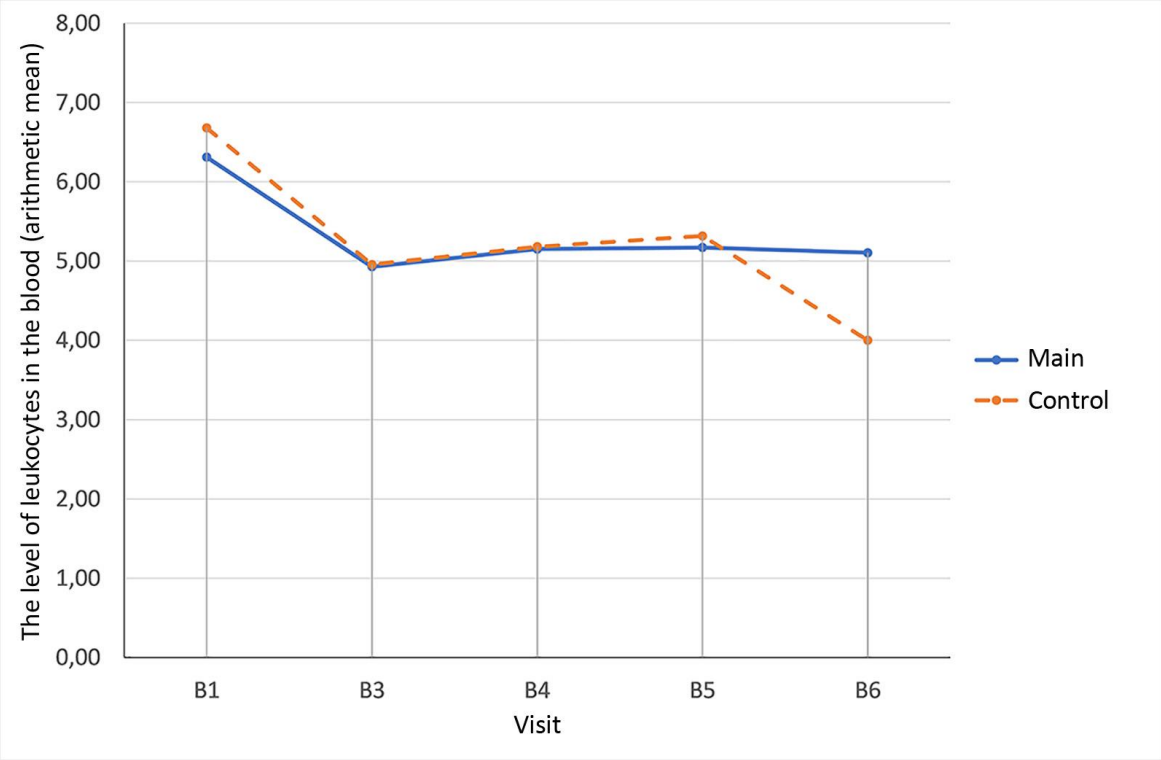

Fig. 15.4.4.2.1 - Leukocyte level dynamics in groups

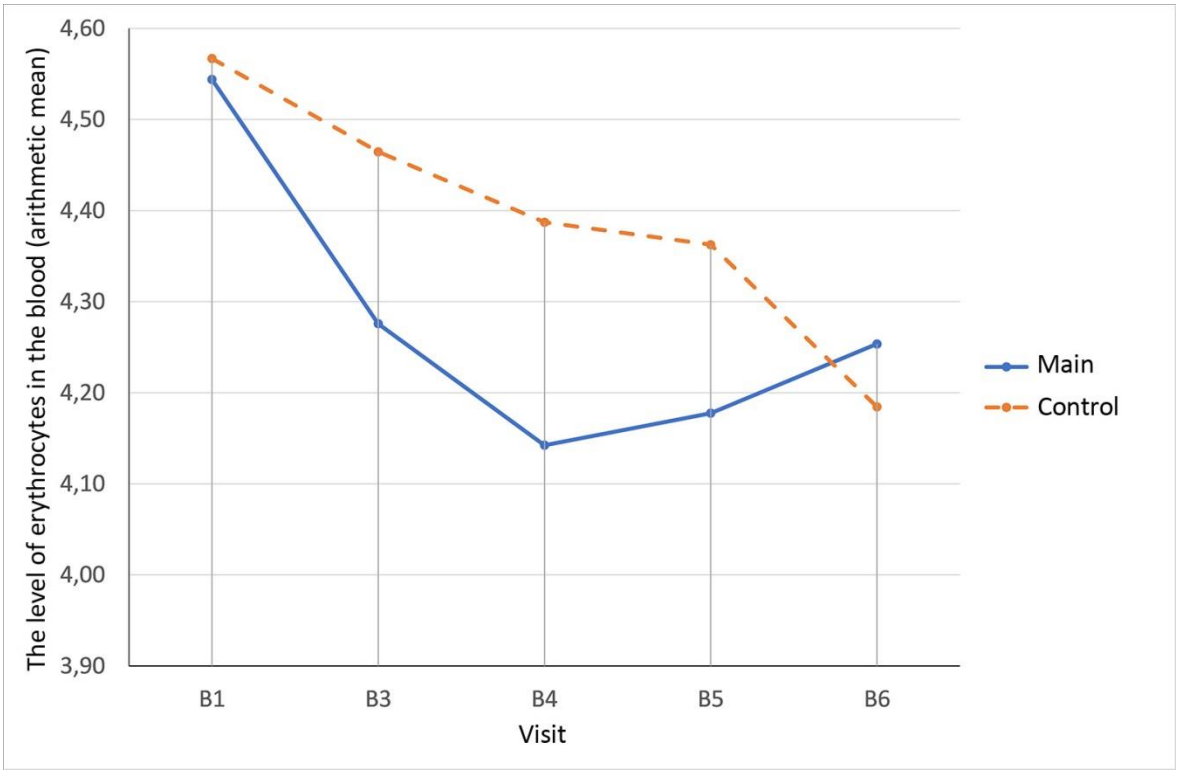

Fig. 15.4.4.2.2 - Dynamics of the level of erythrocytes in groups

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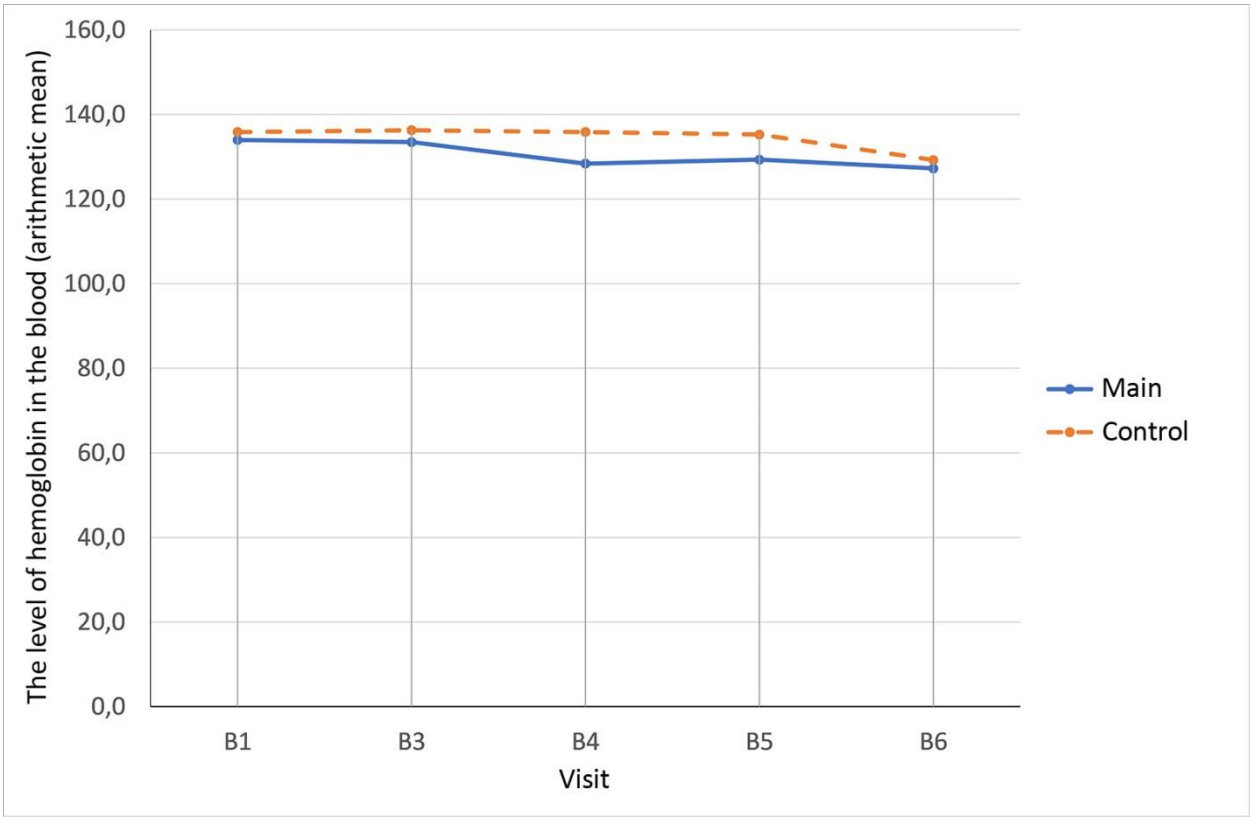

Fig. 15.4.4.2.3 - Dynamics of hemoglobin level in groups

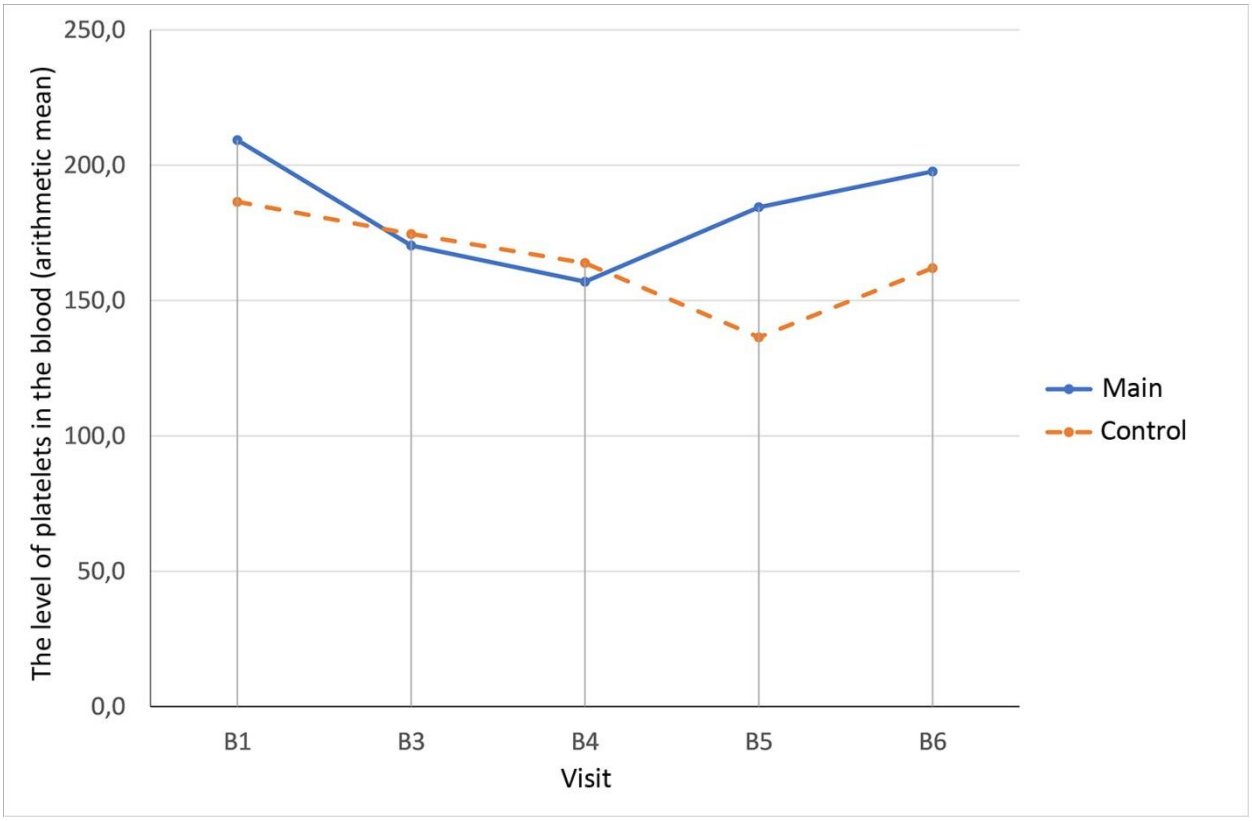

Fig. 15.4.4.2.4 - Dynamics of the level of platelets in groups

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As can be seen from the figures, patients of both groups had a slight decrease in the level of leukocytes, erythrocytes, and platelets. These changes corresponded to the toxicity profile of the chemotherapy drugs used and indicated the negative effect of chemotherapy drugs on the hematopoietic system.

To assess differences between groups at visits B3, B4, B5, and B6, group comparisons were performed using analysis of covariance (ANCOVA). This is due to the fact that the initial homogeneity of the groups could be disturbed due to the elimination of patients during the study and, by entering the covariance analysis model of the initial values as a covariate, an informational correction of the initial heterogeneity took place.

The covariance analysis model was as follows: the dependent variable is the value of the analyzed indicator at the corresponding visit (B3 - B6); factor "group" - fixed {levels: "main" and "control"}; covariate - the value of the corresponding indicator at the time of inclusion in the study, followed by the use of contrast analysis to compare groups (simple contrasts; "control" level = reference). The results of the analysis are given in Appendix D, table. D.4. The results of checking the normality of the distribution of ANCOVA residuals are given in Appendix D, table. G.5. For those dependent variables whose residuals were not normally distributed, ANCOVA on ranks was conducted (Appendix D, Table D.6). The results of the contrast analysis of some indicators of the general blood test are given in the table. 15.4.4.2.3.

Table 15.4.4.2.3 Results of comparison of groups according to indicators of general blood analysis at visits B3, B4, B5 and B6 using simple contrasts

Parameter	Contrasts	Contrast assessment	Hypothetical value	Difference (estimated - hypothesis)	Std. error	p-value
Ranks "Leukocytes for B3"	"primary" relative to "control"	0.471	0	0.471	4,121	0.910
Ranks "Leukocytes for B4"	"primary" relative to "control"	-1.915	0	-1.915	4,039	0.638
Ranks "Leukocytes for B5"	"primary" relative to "control"	-1,211	0	-1,211	3,838	0.754
Ranks "Leukocytes" for	"primary" relative to	1,179	0	1,179	0.856	0.180

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Parameter	Contrasts	Contrast assessment	Hypothetical value	Difference (estimated - hypothesis)	Std. error	p-value
B6	"control"					
Hemoglobin ranks for B3	"primary" relative to "control"	-2.065	0	-2.065	3,613	0.570
Hemoglobin ranks for B4	"primary" relative to "control"	-4,425	0	-4,425	4,544	0.335
Hemoglobin ranks for B5	"primary" relative to "control"	-1.832	0	-1.832	5,966	0.761
Hemoglobin ranks for B6	"primary" relative to "control"	-0.968	0	-0.968	7,560	0.899
Platelets ranks for B3	"primary" relative to "control"	-9,676	0	-9,676	16,464	0.559
Platelets ranks for B4	"primary" relative to "control"	-13,229	0	-13,229	15,733	0.405
Platelets ranks for B5	"primary" relative to "control"	32,415	0	32,415	17,266	0.069
Platelets ranks for B6	"primary" relative to "control"	18,709	0	18,709	27,622	0.504
Ranks "Erythrocytes" for B3	"primary" relative to "control"	-0.175	0	-0.175	0.128	0.176
Ranks "Erythrocytes" for B4	"primary" relative to "control"	-6,835	0	-6,835	3,492	0.057
Ranks "Erythrocytes" for B5	"primary" relative to "control"	-0.157	0	-0.157	0.230	0.499
Ranks "Erythrocytes" for B6	"primary" relative to "control"	0.000	0	0.000	0.272	0.999

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Parameter	Contrasts	Contrast assessment	Hypothetical value	Difference (estimated - hypothesis)	Std. error	p-value
"Neutrophil" ranks for B3	"primary" relative to "control"	5.319*	0	5,319	2,359	0.028
"Neutrophils for B4" ranks	"primary" relative to "control"	-2,161	0	-2,161	3,790	0.571
"Neutrophil" ranks for B5	"primary" relative to "control"	4,711	0	4,711	4,839	0.337
"Neutrophil" ranks for B6	"primary" relative to "control"	7,614	0	7,614	5,379	0.169
Ranks "Lymphocytes" for B3	"primary" relative to "control"	-4,064	0	-4,064	2,030	0.050
Ranks "Lymphocytes" for B4	"primary" relative to "control"	2,488	0	2,488	2,693	0.360
Ranks "Lymphocytes" for B5	"primary" relative to "control"	-5,176	0	-5,176	3,716	0.173
Ranks "Lymphocytes" for B6	"primary" relative to "control"	-7,031	0	-7,031	4,247	0.110
"SOE for B3" ranks	"primary" relative to "control"	3,853	0	3,853	2,056	0.066
"SOE for B4" ranks	"primary" relative to "control"	6,451	0	6,451	3,734	0.091
"SOE for B5" ranks	"primary" relative to "control"	3,992	0	3,992	3,686	0.287
"SOE for B6" ranks	"primary" relative to "control"	-2.867	0	-2.867	3,433	0.411

** This contrast is statistically significant at the 0.05 significance level.*

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According to the research protocol, a comparison of groups was performed at the visits according to the conformity of the laboratory parameters of the general blood test with normal values. The results are given in the table. 15.4.4.2.4.

Table 15.4.4.2.4 - Comparison of groups according to compliance with normal values of laboratory indicators of general blood analysis at each visit

Changeable	Visit	Compliance with the norm/statistical indicator	The main one		Control		p-value [a)]
			n	%	n	%	
Leukocytes	B1	Norm	20	71.4	23	79.3	0.550
		Wedge insignificant departure from the norm	8	28.6	6	20.7	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
Leukocytes	B3	Norm	15	53.6	19	65.5	0.701
		Wedge insignificant departure from the norm	12	42.9	9	31.0	
		Wedge significant departure from the norm	1	3.6	1	3,4	
		In total	28	100.0	29	100.0	
Leukocytes	B4	Norm	15	57.7	13	61.9	0.644
		Wedge insignificant departure from the norm	10	38.5	6	28.6	
		Wedge significant departure from the norm	1	3.8	2	9.5	
		In total	26	100.0	21	100.0	
Leukocytes	B5	Norm	14	58.3	8	66.7	0.096
		Wedge insignificant departure from the norm	10	41.7	2	16.7	
		Wedge significant departure from the norm	0	0.0	2	16.7	
		In total	24	100.0	12	100.0	
Leukocytes	B6	Norm	12	60.0	5	55.6	0.369
		Wedge insignificant departure from the norm	7	35.0	2	22.2	
		Wedge significant departure from the norm	1	5.0	2	22.2	
		In total	20	100.0	9	100.0	
Erythrocytes	B1	Norm	22	78.6	20	69.0	0.550
		Wedge insignificant departure from the norm	6	21.4	9	31.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Erythrocytes	B3	Norm	19	67.9	20	69.0	1,000
		Wedge insignificant departure from the norm	9	32.1	9	31.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Erythrocytes	B4	Norm	18	69.2	13	61.9	0.758
		Wedge insignificant departure from the norm	8	30.8	8	38.1	
		Wedge significant departure from the norm	0	0	0	0	
		In total	26	100.0	21	100.0	
Erythrocytes	B5	Norm	thirteen	54.2	8	66.7	0.721

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Changeable	Visit	Compliance with the norm/statistical indicator	The main one		Control		p-value [a)]
			n	%	n	%	
		Wedge insignificant departure from the norm	11	45.8	4	33.3	
		Wedge significant departure from the norm	0	0	0	0	
		In total	24	100.0	12	100.0	
Erythrocytes	B6	Norm	13	65.0	5	55.6	0.694
		Wedge insignificant departure from the norm	7	35.0	4	44.4	
		Wedge significant departure from the norm	0	0	0	0	
		In total	20	100	9	100	
Hematocrit	B1	Norm	27	96.4	29	100.0	0.491
		Wedge insignificant departure from the norm	1	3.6	0	0.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Hematocrit	B3	Norm	25	89.3	27	93.1	0.670
		Wedge insignificant departure from the norm	3	10.7	2	6.9	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Hematocrit	B4	Norm	23	88.5	17	81.0	0.684
		Wedge insignificant departure from the norm	3	11.5	4	19.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	26	100	21	100	
Hematocrit	B5	Norm	20	83.3	9	75.0	0.664
		Wedge insignificant departure from the norm	4	16.7	3	25.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	24	100	12	100	
Hematocrit	B6	Norm	15	75.0	7	77.8	1,000
		Wedge insignificant departure from the norm	5	25.0	2	22.2	
		Wedge significant departure from the norm	0	0	0	0	
		In total	20	100	9	100	
Hemoglobin	B1	Norm	23	82.1	22	75.9	0.747
		Wedge insignificant departure from the norm	5	17.9	7	24.1	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Hemoglobin	B3	Norm	21	75.0	17	58.6	0.263
		Wedge insignificant departure from the norm	7	25.0	12	41.4	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Hemoglobin	B4	Norm	17	65.4	14	66.7	0.378
		Wedge insignificant departure from the norm	8	30.8	4	19.0	
		Wedge significant departure from the norm	1	3.8	3	14.3	
		In total	26	100.0	21	100.0	

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Changeable	Visit	Compliance with the norm/statistical indicator	The main one		Control		p-value [a)]
			n	%	n	%	
Hemoglobin	B5	Norm	11	45.8	7	58.3	0.659
		Wedge insignificant departure from the norm	10	41.7	5	41.7	
		Wedge significant departure from the norm	3	12.5	0	0.0	
		In total	24	100.0	12	100.0	
Hemoglobin	B6	Norm	11	55.0	6	66.7	0.844
		Wedge insignificant departure from the norm	7	35.0	2	22.2	
		Wedge significant departure from the norm	2	10.0	1	11.1	
		In total	20	100.0	9	100.0	
Platelets	B1	Norm	18	64.3	12	41.4	0.113
		Wedge insignificant departure from the norm	10	35.7	17	58.6	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Platelets	B3	Norm	12	42.9	14	48.3	0.839
		Wedge insignificant departure from the norm	14	50.0	14	48.3	
		Wedge significant departure from the norm	2	7.1	1	3,4	
		In total	28	100.0	29	100.0	
Platelets	B4	Norm	9	34.6	9	42.9	0.586
		Wedge insignificant departure from the norm	13	50.0	11	52.4	
		Wedge significant departure from the norm	4	15.4	1	4.8	
		In total	26	100.0	21	100.0	
Platelets	B5	Norm	11	45.8	2	16.7	0.066
		Wedge insignificant departure from the norm	12	50.0	7	58.3	
		Wedge significant departure from the norm	1	4.2	3	25.0	
		In total	24	100.0	12	100.0	
Platelets	B6	Norm	10	50.0	3	33.3	0.378
		Wedge insignificant departure from the norm	8	40.0	6	66.7	
		Wedge significant departure from the norm	2	10.0	0	0.0	
		In total	20	100.0	9	100.0	
Neutrophils	B1	Norm	17	60.7	16	55.2	1,000
		Wedge insignificant departure from the norm	11	39.3	12	41.4	
		Wedge significant departure from the norm	0	0.0	1	3,4	
		In total	28	100.0	29	100.0	
Neutrophils	B3	Norm	18	64.3	18	62.1	1,000
		Wedge insignificant departure from the norm	9	32.1	10	34.5	
		Wedge significant departure from the norm	1	3.6	1	3,4	
		In total	28	100.0	29	100.0	
Neutrophils	B4	Norm	21	80.8	14	66.7	0.300
		Wedge insignificant departure from the norm	4	15.4	7	33.3	
		Wedge significant departure from the norm	1	3.8	0	0.0	

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Changeable	Visit	Compliance with the norm/statistical indicator	The main one		Control		p-value [a)]
			n	%	n	%	
		In total	26	100.0	21	100.0	
Neutrophils	B5	Norm	9	37.5	5	41.7	1,000
		Wedge insignificant departure from the norm	15	62.5	7	58.3	
		Wedge significant departure from the norm	0	0	0	0	
		In total	24	100	12	100	
Neutrophils	B6	Norm	13	65.0	4	44.4	0.592
		Wedge insignificant departure from the norm	6	30.0	5	55.6	
		Wedge significant departure from the norm	1	5.0	0	0.0	
		In total	20	100.0	9	100.0	
Lymphocytes	B1	Norm	12	42.9	18	62.1	0.298
		Wedge insignificant departure from the norm	15	53.6	10	34.5	
		Wedge significant departure from the norm	1	3.6	1	3,4	
		In total	28	100.0	29	100.0	
Lymphocytes	B3	Norm	19	67.9	18	62.1	0.576
		Wedge insignificant departure from the norm	8	28.6	11	37.9	
		Wedge significant departure from the norm	1	3.6	0	0.0	
		In total	28	100.0	29	100.0	
Lymphocytes	B4	Norm	18	69.2	15	71.4	1,000
		Wedge insignificant departure from the norm	6	23.1	5	23.8	
		Wedge significant departure from the norm	2	7.7	1	4.8	
		In total	26	100.0	21	100.0	
Lymphocytes	B5	Norm	12	50.0	7	58.3	0.870
		Wedge insignificant departure from the norm	10	41.7	5	41.7	
		Wedge significant departure from the norm	2	8.3	0	0.0	
		In total	24	100.0	12	100.0	
Lymphocytes	B6	Norm	11	55.0	7	77.8	0.598
		Wedge insignificant departure from the norm	8	40.0	2	22.2	
		Wedge significant departure from the norm	1	5.0	0	0.0	
		In total	20	100.0	9	100.0	
Monocytes	B1	Norm	25	89.3	27	93.1	0.670
		Wedge insignificant departure from the norm	3	10.7	2	6.9	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Monocytes	B3	Norm	28	100.0	26	89.7	0.237
		Wedge insignificant departure from the norm	0	0.0	3	10.3	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Monocytes	B4	Norm	24	92.3	20	95.2	1,000
		Wedge insignificant departure from the norm	2	7.7	1	4.8	

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Changeable	Visit	Compliance with the norm/statistical indicator	The main one		Control		p-value [a)]
			n	%	n	%	
		Wedge significant departure from the norm	0	0	0	0	
		In total	26	100	21	100	
Monocytes	B5	Norm	22	91.7	11	91.7	1,000
		Wedge insignificant departure from the norm	2	8.3	1	8.3	
		Wedge significant departure from the norm	0	0	0	0	
		In total	24	100	12	100	
Monocytes	B6	Norm	19	95.0	8	88.9	0.532
		Wedge insignificant departure from the norm	1	5.0	1	11.1	
		Wedge significant departure from the norm	0	0	0	0	
		In total	20	100	9	100	
Eosinophils	B1	Norm	27	96.4	27	93.1	1,000
		Wedge insignificant departure from the norm	1	3.6	1	3,4	
		Wedge significant departure from the norm	0	0.0	1	3,4	
		In total	28	100.0	29	100.0	
Eosinophils	B3	Norm	26	92.9	28	96.6	0.362
		Wedge insignificant departure from the norm	2	7.1	0	0.0	
		Wedge significant departure from the norm	0	0.0	1	3,4	
		In total	28	100.0	29	100.0	
Eosinophils	B4	Norm	25	96.2	20	95.2	1,000
		Wedge insignificant departure from the norm	1	3.8	1	4.8	
		Wedge significant departure from the norm	0	0	0	0	
		In total	26	100	21	100	
Eosinophils	B5	Norm	24	100	12	100	N/A
		Wedge insignificant departure from the norm	0	0	0	0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	24	100	12	100	
Eosinophils	B6	Norm	20	100	9	100	N/A
		Wedge insignificant departure from the norm	0	0	0	0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	20	100	9	100	
Basophils	B1	Norm	27	96.4	29	100.0	0.491
		Wedge insignificant departure from the norm	1	3.6	0	0.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Basophils	B3	Norm	27	96.4	28	96.6	1,000
		Wedge insignificant departure from the norm	1	3.6	1	3,4	

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Changeable	Visit	Compliance with the norm/statistical indicator	The main one		Control		p-value [a)]
			n	%	n	%	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Basophils	B4	Norm	26	100.0	20	95.2	0.447
		Wedge insignificant departure from the norm	0	0.0	1	4.8	
		Wedge significant departure from the norm	0	0	0	0	
		In total	26	100	21	100	
Basophils	B5	Norm	24	100	12	100	N/A
		Wedge insignificant departure from the norm	0	0	0	0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	24	100	12	100	
Basophils	B6	Norm	20	100	9	100	N/A
		Wedge insignificant departure from the norm	0	0	0	0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	20	100	9	100	
SOE	B1	Norm	14	50.0	17	58.6	0.339
		Wedge insignificant departure from the norm	12	42.9	8	27.6	
		Wedge significant departure from the norm	2	7.1	4	13.8	
		In total	28	100.0	29	100.0	
SOE	B3	Norm	19	67.9	24	82.8	0.257
		Wedge insignificant departure from the norm	7	25.0	5	17.2	
		Wedge significant departure from the norm	2	7.1	0	0.0	
		In total	28	100.0	29	100.0	
SOE	B4	Norm	18	69.2	15	75.0	0.402
		Wedge insignificant departure from the norm	6	23.1	2	10.0	
		Wedge significant departure from the norm	2	7.7	3	15.0	
		In total	26	100.0	20	100.0	
SOE	B5	Norm	15	62.5	9	75.0	0.482
		Wedge insignificant departure from the norm	5	20.8	3	25.0	
		Wedge significant departure from the norm	4	16.7	0	0.0	
		In total	24	100.0	12	100.0	
SOE	B6	Norm	14	70.0	4	44.4	0.360
		Wedge insignificant departure from the norm	4	20.0	4	44.4	
		Wedge significant departure from the norm	2	10.0	1	11.1	
		In total	20	100.0	9	100.0	

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In addition, the presence of leukocytopenia and thrombocytopenia was analyzed. Leukocytopenia was defined as the number of leukocytes in the blood < 4.0x10 ^{9} cells/l. Thrombocytopenia was determined if the number of platelets in the blood was < 100x10 ^{9} cells/l. The results of a comparative analysis of the presence of leukocytopenia and thrombocytopenia are shown in the table. 15.4.4.2.5.

Table 15.4.4.2.5 – Comparative analysis of the presence of leukocytopenia and thrombocytopenia in groups by visits

Changeable	**Visit**	**Compliance with the norm / statistical indicator**	**The main one**		**Control**		**p-value [a)]**
			n	**%**	**n**	**%**	
Leukocytopenia	B1	Leukocytopenia	7	25.0	2	6.9	0.079
		There is no leukocytopenia	21	75.0	27	93.1	
		In total	28	100.0	29	100.0	
Leukocytopenia	B3	Leukocytopenia	13	46.4	12	41.4	0.792
		There is no leukocytopenia	15	53.6	17	58.6	
		In total	28	100.0	29	100.0	
Leukocytopenia	B4	Leukocytopenia	12	46.2	7	33.3	0.551
		There is no leukocytopenia	14	53.8	14	66.7	
		In total	26	100.0	21	100.0	
Leukocytopenia	B5	Leukocytopenia	8	33.3	4	33.3	1,000
		There is no leukocytopenia	16	66.7	8	66.7	
		In total	24	100.0	12	100.0	
Leukocytopenia	B6	Leukocytopenia	7	35.0	5	55.6	0.422
		There is no leukocytopenia	13	65.0	4	44.4	
		In total	20	100.0	9	100.0	
Thrombocytopenia	B1	Thrombocytopenia	0	0	0	0	N/A
		No thrombocytopenia	28	100	29	100	
		In total	28	100	29	100	
Thrombocytopenia	B3	Thrombocytopenia	3	10.7	1	3,4	0.352
		No thrombocytopenia	25	89.3	28	96.6	
		In total	28	100.0	29	100.0	
Thrombocytopenia	B4	Thrombocytopenia	4	15.4	1	4.8	0.362
		No thrombocytopenia	22	84.6	20	95.2	
		In total	26	100.0	21	100.0	
Thrombocytopenia	B5	Thrombocytopenia	1	4.2	3	25.0	0.098
		No thrombocytopenia	23	95.8	9	75.0	
		In total	24	100.0	12	100.0	
Thrombocytopenia	B6	Thrombocytopenia	2	10.0	0	0.0	1,000
		No thrombocytopenia	18	90.0	9	100.0	
		In total	20	100.0	9	100.0	

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As can be seen from the results of the analysis given in the table. 15.4.4.2.5, there were no statistically significant differences between the groups in the presence of leukocytopenia. The graphic interpretation of the comparative analysis of the presence of leukocytopenia in the groups is shown in fig. 15.4.4.2.8.

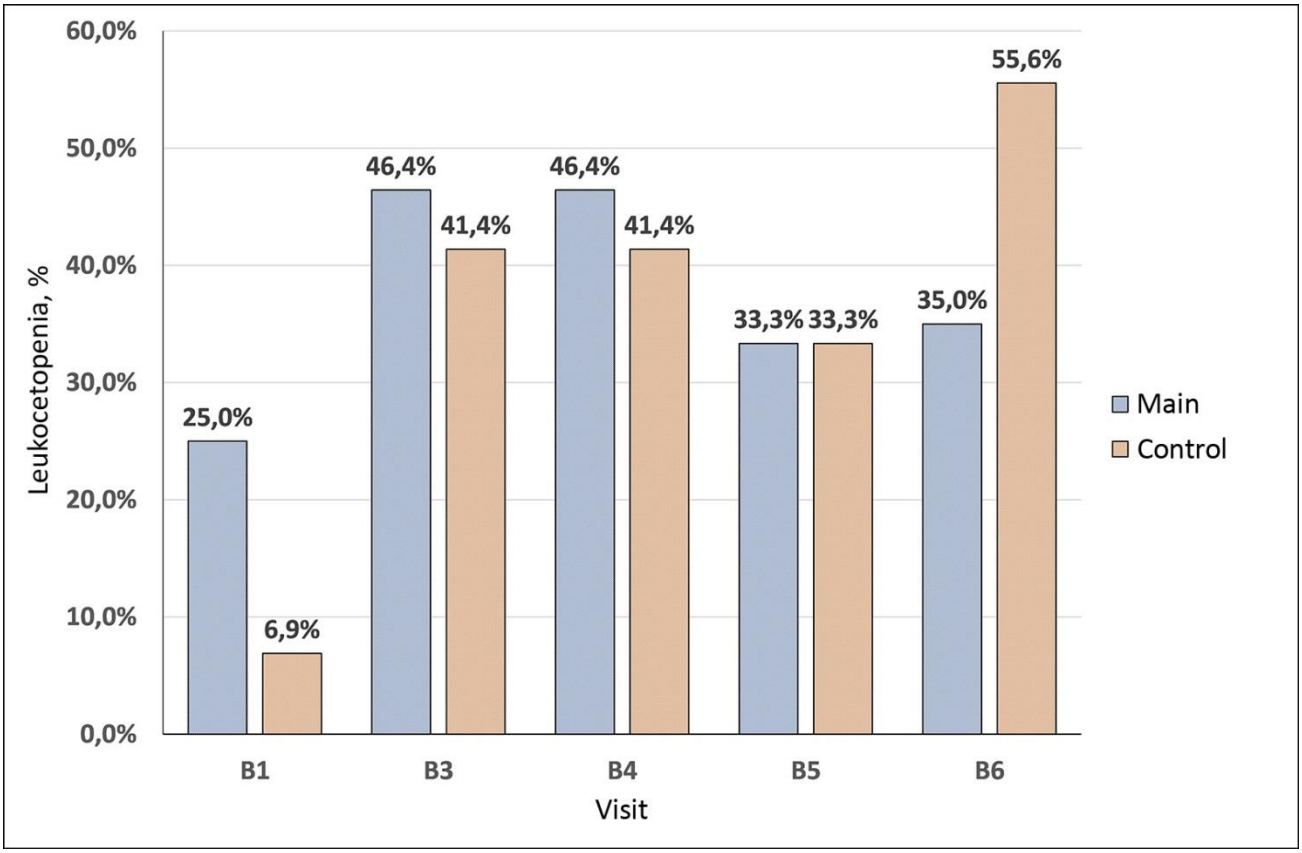

Fig. 15.4.4.2.8 – Graphical interpretation of the dynamics of the presence of leukocytopenia in groups by visit

As can be seen from the table. 15.4.4.2.5 and fig. 15.4.4.2.8 leukocytopenia was slightly higher at the beginning of the study in the main group compared to the control group. Thus, in the main group there were 7 (25.0%) patients with leukocytopenia on B1 and in the control group 3 (6.9%) patients. At the end of the study (B6), 7 (35.0%) patients of the main group and 5 (55.6%) patients of the control group had leukocytopenia. Differences between groups were not statistically significant at all visits, although the proportion of patients with leukocytopenia was greater in the control group at the end of the study.

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As for thrombocytopenia, on B1 it was not present in any patient of the main and control groups. During the study, thrombocytopenia was observed in individual patients in groups. At the end of the study, thrombocytopenia was present in 2 (10.0%) patients of the main group and in no patient of the control group. However, at the same time, it should be taken into account that 20 patients were included in the analysis in the main group, and only 9 patients in the control group. Differences between groups in the presence of thrombocytopenia were statistically insignificant at each of the visits.

Conclusions.

Based on the results of the analysis of the dynamics of hematological indicators, the following conclusions can be drawn.

1. In patients of both groups, a decrease in the level of leukocytes and platelets was noted during the study. These changes corresponded to the toxicity profile of the chemotherapy drugs used and indicated the negative effect of chemotherapy drugs on the hematopoietic system.
2. Differences between groups in the presence of leukocytopenia and thrombocytopenia were not statistically significant at all visits, although at Visit 6 there was some trend toward a lower proportion of patients with leukocytopenia in primary group 7 (35.0%) compared with control group 5 (55.6%). However, when interpreting these results, it should be taken into account that at the end of the study, 20 patients of the main group were included in the analysis, and only 9 patients in the control group.
3. Differences between groups in hematological indicators were statistically insignificant at all visits, which indicates the absence of a negative effect of the studied drug on the hematopoietic system.

15.4.4.3 Analysis of dynamics of indicators of biochemical blood analysis

Biochemical blood analysis was performed during screening (B1), and then at visits: B3, B4, B5 and B6.

The results of the analysis of the dynamics of laboratory indicators of biochemical blood analysis by descriptive statistics methods are shown in table. 15.4.4.3.1 for patients of the main group and in table 15.4.4.3.2 for patients of the control group.

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Table 15.4.4.3.1 Dynamics of laboratory indicators of biochemical blood analysis during the study in patients of the main group

Indicator	Visit	n	M	Me	St	MIN	MAX
AST, unit/l	Visit 1 (screening)	28	23.20	22	9,11	10.7	48.2
	Visit 3 (day 90)	28	23,33	21.7	7.57	11.1	40.6
	Visit 4 (day 180)	26	27.70	25.15	12.64	7	58.5
	Visit 5 (day 270)	24	28.61	24.4	18.42	7.6	100.1
	Visit 6 (day 360)	19	24.68	22.7	8.79	12.7	39.6
ALT, unit/l	Visit 1 (screening)	28	28.74	26.4	12.89	6.1	57.5
	Visit 3 (day 90)	28	29.86	23.15	17.72	6.9	77.4
	Visit 4 (day 180)	26	35,14	23.5	36.60	6.3	165
	Visit 5 (day 270)	24	54,54	25.15	98.66	5.9	481.7
	Visit 6 (day 360)	19	35,22	31.9	19.67	8,9	82.6
Total bilirubin, mmol/l	Visit 1 (screening)	28	10.72	10,945	4.64	4.47	24.78
	Visit 3 (day 90)	28	14.70	13.95	6.37	2.06	29.3
	Visit 4 (day 180)	26	13,26	12,425	5.61	3.13	25.5
	Visit 5 (day 270)	24	12.71	11,165	6.56	4.45	33.83
	Visit 6 (day 360)	19	11.87	10,17	5.18	2.29	21.6
Creatinine, μmol/l	Visit 1 (screening)	28	73,24	71,19	14.61	41,51	107.93
	Visit 3 (day 90)	28	72.92	71,995	12.55	52.68	109.75
	Visit 4 (day 180)	26	72,93	67.74	19.69	35,28	124.1
	Visit 5 (day 270)	24	74,79	69,795	23.86	41,49	157
	Visit 6 (day 360)	19	77,76	73.03	25.63	45.5	162.88
Glucose, mmol/l	Visit 1 (screening)	28	5.77	5.5	1.61	3.8	11.1
	Visit 3 (day 90)	28	5.89	5.45	1.93	4	14.5
	Visit 4 (day 180)	26	5.53	5,085	1.50	3.2	10.8
	Visit 5 (day 270)	24	6.76	6	2.93	4.5	16.3
	Visit 6 (day 360)	19	5.62	5.3	1.27	3.8	9.4

Table 15.4.4.3.2 Dynamics of laboratory indicators of biochemical blood analysis during the study in patients of the control group

Indicator	Visit	n	M	Me	St	MIN	MAX
AST, unit/l	Visit 1 (screening)	29	23.46	20.4	11,28	9.1	54.7
	Visit 3 (day 90)	29	29.73	26.5	17.54	11.4	103.6
	Visit 4 (day 180)	21	25.95	18.6	19.40	11.3	80.1
	Visit 5 (day 270)	12	24.88	18.9	15.93	11.6	66.8
	Visit 6 (day 360)	9	39.92	23.7	38.99	10.1	132.6
ALT, unit/l	Visit 1 (screening)	29	31.90	31.5	12.94	13	56.2
	Visit 3 (day 90)	29	34,43	28.4	19.74	7,8	92.3
	Visit 4 (day 180)	21	32.85	28.7	24.77	8.3	101
	Visit 5 (day 270)	12	38,19	22.65	42.27	5.9	155.1
	Visit 6 (day 360)	9	39.79	24.4	36,41	9.1	127.7

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Indicator	Visit	n	M	Me	St	MIN	MAX
Total bilirubin, mmol/l	Visit 1 (screening)	29	13.76	13,12	5.78	5.39	26,26
	Visit 3 (day 90)	29	16,18	12.53	12.40	7.16	72.56
	Visit 4 (day 180)	21	13.25	12,18	8,14	5.76	44.6
	Visit 5 (day 270)	12	15.81	16,125	10.46	3.63	43.13
	Visit 6 (day 360)	9	13.73	13.05	5.04	6.64	24.5
Creatinine, µmol/l	Visit 1 (screening)	29	69.95	65.65	14.99	43.04	110.12
	Visit 3 (day 90)	29	73.56	70.57	12.52	52.24	102.36
	Visit 4 (day 180)	21	76.10	72.89	13.07	55.06	106.53
	Visit 5 (day 270)	12	68.72	66,325	18.69	25,14	109.7
	Visit 6 (day 360)	9	76.45	71.73	17,12	60.49	113.61
Glucose, mmol/l	Visit 1 (screening)	29	5.50	5.7	0.85	4	7.4
	Visit 3 (day 90)	29	5.60	5,6	0.68	4.7	7.9
	Visit 4 (day 180)	21	5.36	5.3	0.84	3.8	7
	Visit 5 (day 270)	12	5.59	5.55	1.01	3.9	7.4
	Visit 6 (day 360)	9	5.42	5.5	0.83	4.1	6.4

Graphically, the dynamics of the average values of biochemical blood analysis indicators are shown in fig. 15.4.4.3.1 - fig. 15.4.4.3.5.

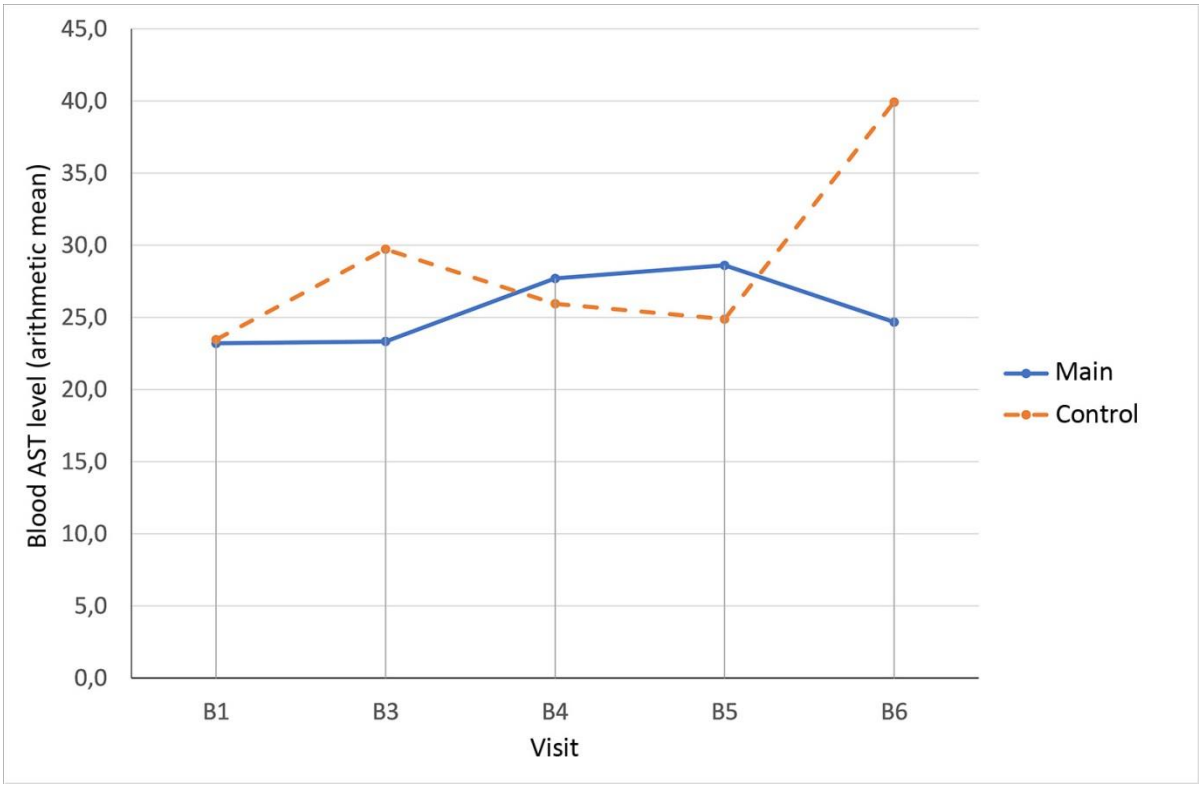

Fig. 15.4.4.3.1 - Dynamics of average AST values in groups

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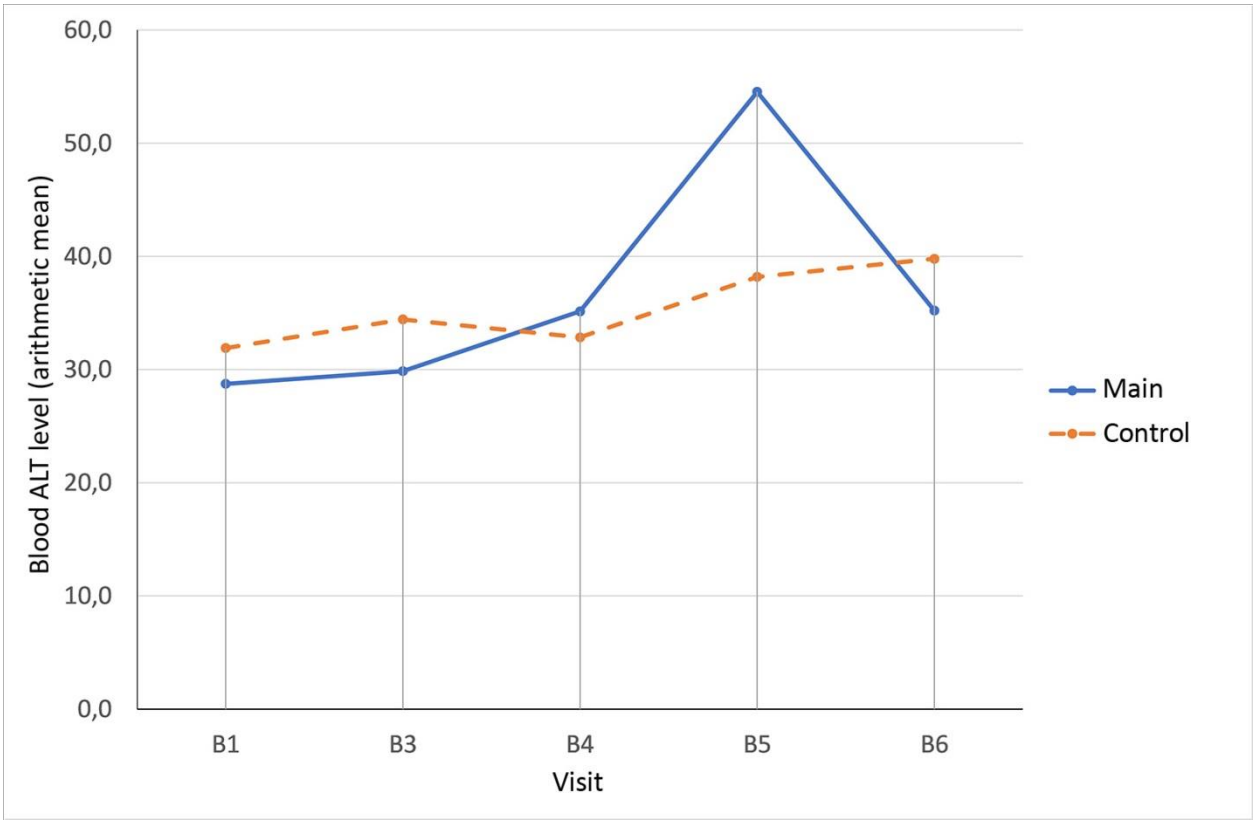

Fig. 15.4.4.3.2 - Dynamics of average ALT values in groups

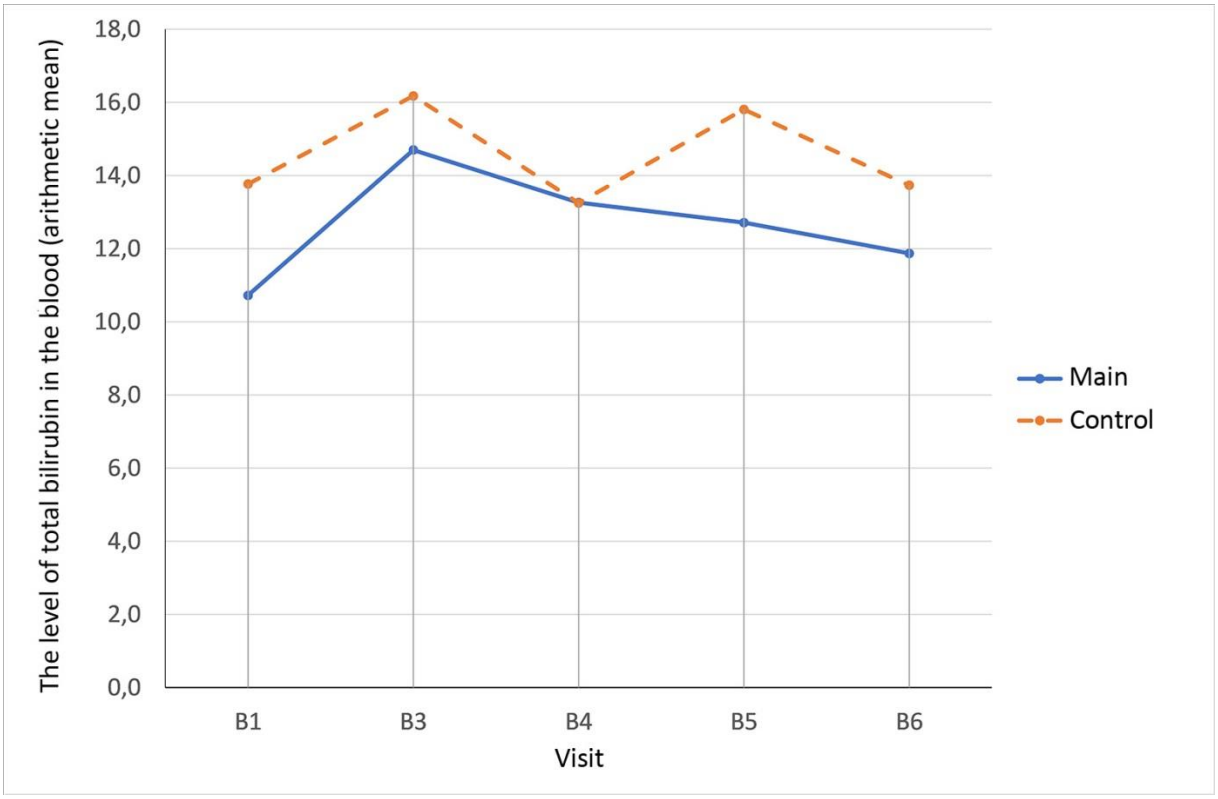

Fig. 15.4.4.3.3 - Dynamics of average values of total bilirubin in groups

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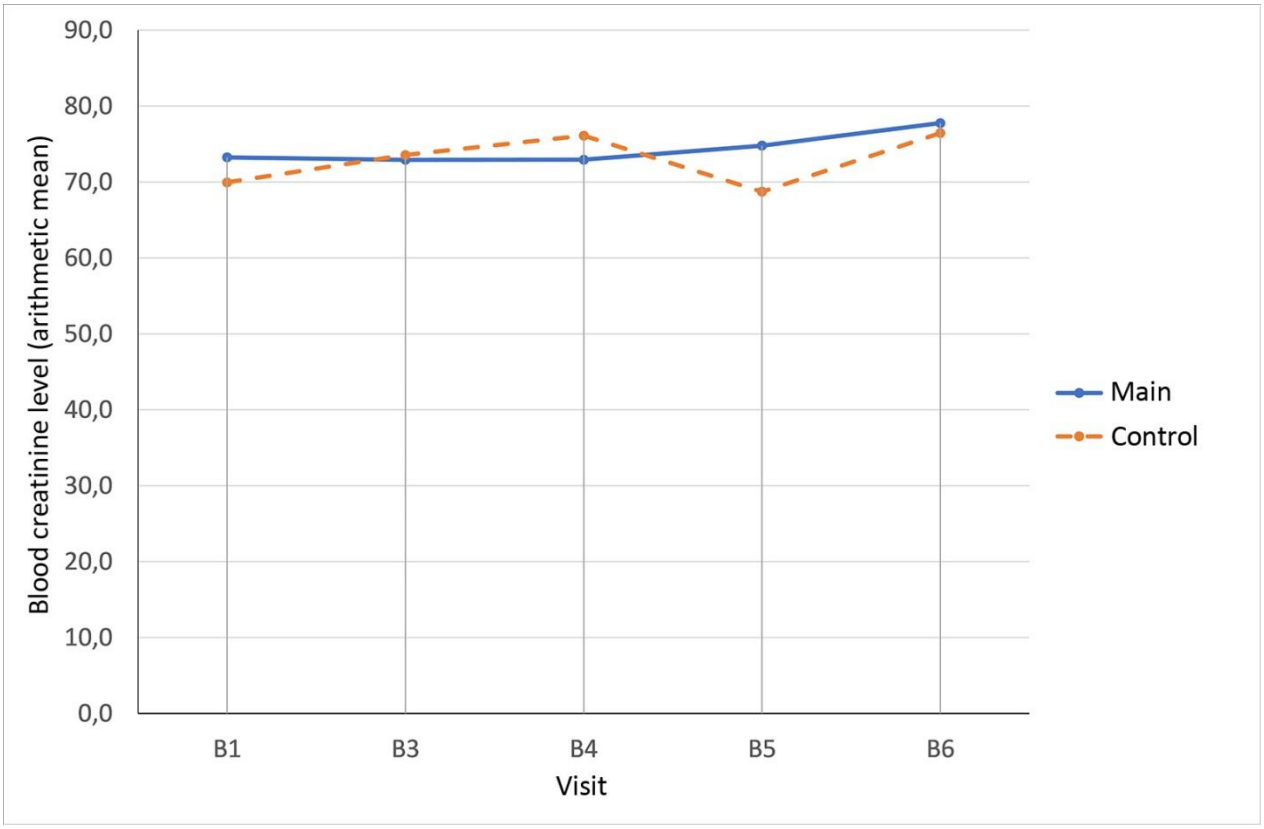

Fig. 15.4.4.3.4 - Dynamics of average creatinine values in groups

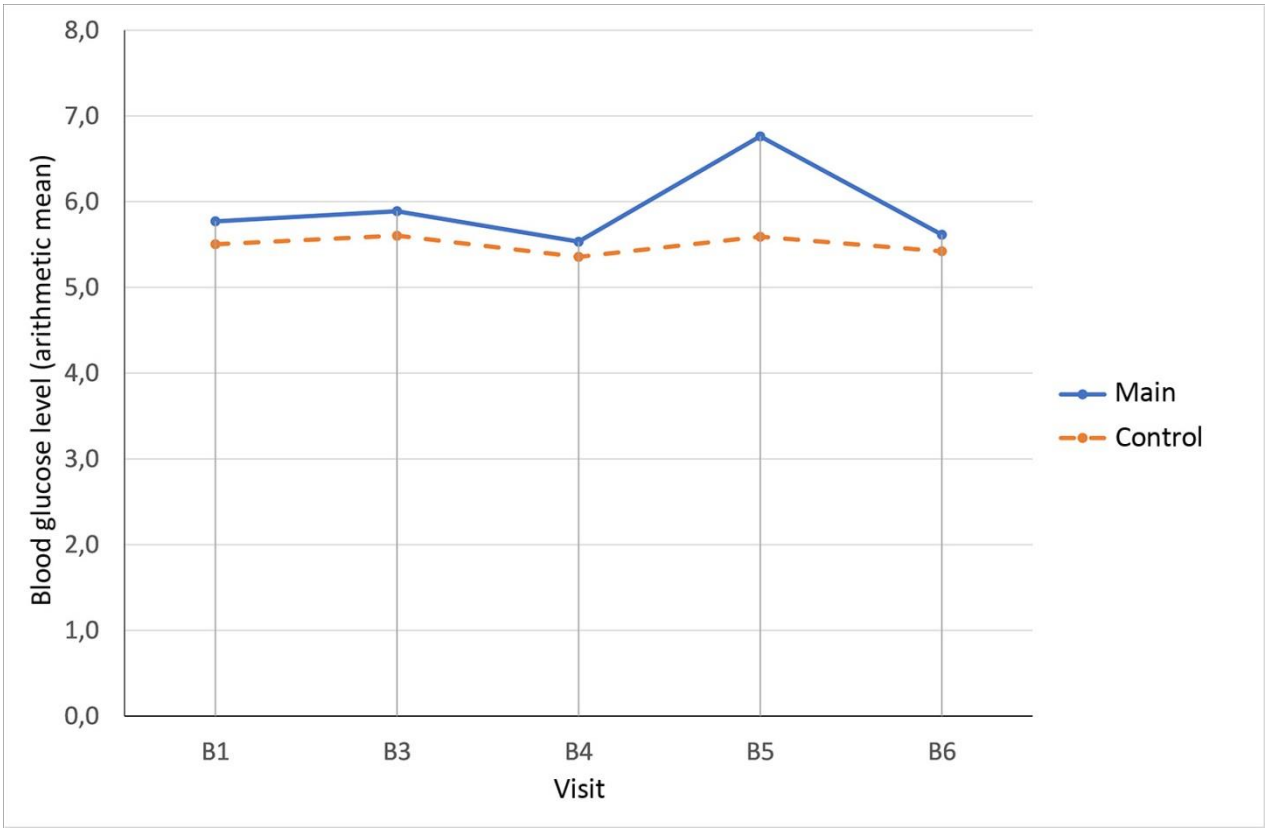

Fig. 15.4.4.3.5 - Dynamics of average blood glucose values in groups

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However, when evaluating the dynamics of laboratory indicators of biochemical blood analysis, it is necessary to take into account the fact that, firstly, not all data at certain visits were distributed normally (Appendix D, table D.11), and secondly, these indicators were influenced by courses CT, the number of which was different for different patients, and, thirdly, the number of patients at visits also constantly changed, and more patients dropped out in the control group than in the main one. Therefore, estimates of dynamics are approximate.

To assess differences between groups at visits B3, B4, B5, and B6, group comparisons were performed using analysis of covariance (ANCOVA). This is due to the fact that the initial homogeneity of the groups could be disturbed due to the elimination of patients during the study and, by entering the covariance analysis model of the initial values as a covariate, an informational correction of the initial heterogeneity took place.

The covariance analysis model was as follows: the dependent variable is the value of the analyzed indicator at the corresponding visit (B3 - B6); factor "group" - fixed {levels: "main" and "control"}; covariate - the value of the corresponding indicator at the time of inclusion in the study, followed by the use of contrast analysis to compare groups (simple contrasts; "control" level = reference). The results of the analysis are given in Appendix D, table. D.4. The results of checking the normality of the distribution of ANCOVA residuals are given in Appendix D, table. G.5. For those dependent variables whose residuals were not normally distributed, ANCOVA on ranks was conducted (Appendix D, Table D.6). The results of the contrast analysis of the comparison of the groups according to the laboratory parameters of the biochemical blood analysis are given in the table. 15.4.4.3.3.

Table 15.4.4.3.3 Results of comparison of groups according to laboratory indicators of biochemical blood analysis at visits B3, B4, B5 and B6 using simple contrasts

Parameter	Contrasts	Contrast assessment	Hypothetical value	Difference (estimated - hypothesis)	Std. error	p-value
Ranks "AST for B3"	"primary" relative to "control"	-6,406	0	-6,406	4,286	0.141
Ranks "AST for B4"	"primary" relative to	6,855	0	6,855	3,943	0.089

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Parameter	Contrasts	Contrast assessment	Hypothetical value	Difference (estimated - hypothesis)	Std. error	p-value
	"control"					
Ranks "AST for B5"	"primary" relative to "control"	4,545	0	4,545	3,679	0.225
"AST for B6" ranks	"primary" relative to "control"	-1.717	0	-1.717	3,433	0.621
Ranks "ALT for B3"	"primary" relative to "control"	-4,969	0	-4,969	4,331	0.256
Ranks "ALT for B4"	"primary" relative to "control"	-0.186	0	-0.186	3,746	0.961
Ranks "ALT for B5"	"primary" relative to "control"	2,549	0	2,549	3,428	0.462
Ranks "ALT for B6"	"primary" relative to "control"	0.749	0	0.749	3,446	0.83
Ranks "Bilirubin for B3"	"primary" relative to "control"	6,367	0	6,367	4,127	0.129
Ranks "Bilirubin for B4"	"primary" relative to "control"	5.58	0	5.58	3,835	0.153
Ranks "Bilirubin for B5"	"primary" relative to "control"	1.55	0	1.55	2,316	0.508
Ranks "Bilirubin for B6"	"primary" relative to "control"	0.185	0	0.185	1,908	0.924
"Creatinine for B3" ranks	"primary" relative to "control"	-2,415	0	-2,415	2,609	0.359
Ranks "Creatinine for B4"	"primary" relative to "control"	-4,386	0	-4,386	3,514	0.219
"Creatinine for B5" ranks	"primary" relative to	-0.599	0	-0.599	3,412	0.862

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Parameter	Contrasts	Contrast assessment	Hypothetical value	Difference (estimated - hypothesis)	Std. error	p-value
	"control"					
Ranks "Creatinine for B6"	"primary" relative to "control"	-1.632	0	-1.632	2,875	0.575
Ranks "Glucose for B3"	"primary" relative to "control"	-2,510	0	-2,510	4,125	0.545
Ranks "Glucose for B4"	"primary" relative to "control"	-0.652	0	-0.652	4,094	0.874
Ranks "Glucose for B5"	"primary" relative to "control"	3,364	0	3,364	3,678	0.367
Ranks "Glucose for B6"	"primary" relative to "control"	0.114	0	0.114	0.37	0.761
** This contrast is statistically significant at the 0.05 significance level.*						

Based on the data given in table. 15.4.4.3.3, it can be concluded that there were no statistically significant differences between the groups in terms of the analyzed parameters. The differences that were observed were, as a rule, related to the initial condition of the patients and the CT courses received before the visits.

According to the research protocol, a comparison of groups was performed at the visits according to the conformity of the laboratory parameters of the biochemical blood analysis with normal values. The results are given in the table. 15.4.4.3.4.

Table 15.4.4.3.4 Comparison of groups according to compliance with normal values of laboratory indicators of biochemical blood analysis at each visit

Changeable	Visit	Compliance with the norm / statistical indicator	The main one		Control		p-value [a)]
			n	%	n	%	
AST	B1	Norm	26	92.9	26	89.7	1,000
		Wedge insignificant departure from the norm	2	7.1	3	10.3	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	

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Changeable	Visit	Compliance with the norm / statistical indicator	The main one		Control		p-value [a)]
			n	%	n	%	
AST	B3	Norm	26	92.9	22	75.9	0.195
		Wedge insignificant departure from the norm	2	7.1	6	20.7	
		Wedge significant departure from the norm	0	0.0	1	3,4	
		In total	28	100.0	29	100.0	
AST	B4	Norm	20	76.9	16	76.2	0.247
		Wedge insignificant departure from the norm	6	23.1	3	14.3	
		Wedge significant departure from the norm	0	0.0	2	9.5	
		In total	26	100.0	21	100.0	
AST	B5	Norm	19	79.2	10	83.3	1,000
		Wedge insignificant departure from the norm	4	16.7	1	8.3	
		Wedge significant departure from the norm	1	4.2	1	8.3	
		In total	24	100.0	12	100.0	
AST	B6	Norm	15	78.9	6	66.7	0.120
		Wedge insignificant departure from the norm	4	21.1	1	11.1	
		Wedge significant departure from the norm	0	0.0	2	22.2	
		In total	19	100.0	9	100.0	
ALT	B1	Norm	23	82.1	25	86.2	0.730
		Wedge insignificant departure from the norm	5	17.9	4	13.8	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
ALT	B3	Norm	22	78.6	26	89.7	0.195
		Wedge insignificant departure from the norm	6	21.4	2	6.9	
		Wedge significant departure from the norm	0	0.0	1	3,4	
		In total	28	100.0	29	100.0	
ALT	B4	Norm	22	84.6	15	71.4	0.326
		Wedge insignificant departure from the norm	1	3.8	4	19.0	
		Wedge significant departure from the norm	3	11.5	2	9.5	
		In total	26	100.0	21	100.0	
ALT	B5	Norm	18	75.0	9	75.0	0.715
		Wedge insignificant departure from the norm	4	16.7	1	8.3	
		Wedge significant departure from the norm	2	8.3	2	16.7	
		In total	24	100.0	12	100.0	
ALT	B6	Norm	11	57.9	6	66.7	0.699
		Wedge insignificant departure from the norm	7	36.8	2	22.2	
		Wedge significant departure from the norm	1	5.3	1	11.1	
		In total	19	100.0	9	100.0	
Total bilirubin	B1	Norm	27	96.4	25	86.2	0.352
		Wedge insignificant departure from the norm	1	3.6	4	13.8	
		Wedge significant departure from the norm	0	0	0	0	

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Changeable	Visit	Compliance with the norm / statistical indicator	The main one		Control		p-value [a)]
			n	%	n	%	
		In total	28	100	29	100	
Total bilirubin	B3	Norm	24	85.7	24	82.8	1,000
		Wedge insignificant departure from the norm	4	14.3	4	13.8	
		Wedge significant departure from the norm	0	0.0	1	3,4	
		In total	28	100.0	29	100.0	
Total bilirubin	B4	Norm	24	92.3	20	95.2	0.335
		Wedge insignificant departure from the norm	2	7.7	0	0.0	
		Wedge significant departure from the norm	0	0.0	1	4.8	
		In total	26	100.0	21	100.0	
Total bilirubin	B5	Norm	22	91.7	10	83.3	0.510
		Wedge insignificant departure from the norm	2	8.3	1	8.3	
		Wedge significant departure from the norm	0	0.0	1	8.3	
		In total	24	100.0	12	100.0	
Total bilirubin	B6	Norm	18	94.7	8	88.9	1,000
		Wedge insignificant departure from the norm	1	5.3	1	11.1	
		Wedge significant departure from the norm	0	0	0	0	
		In total	19	100	9	100	
Creatinine	B1	Norm	27	96.4	28	96.6	1,000
		Wedge insignificant departure from the norm	1	3.6	1	3,4	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Creatinine	B3	Norm	28	100.0	28	96.6	1,000
		Wedge insignificant departure from the norm	0	0.0	1	3,4	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Creatinine	B4	Norm	23	88.5	19	90.5	1,000
		Wedge insignificant departure from the norm	2	7.7	2	9.5	
		Wedge significant departure from the norm	1	3.8	0	0.0	
		In total	26	100.0	21	100.0	
Creatinine	B5	Norm	21	87.5	10	83.3	0.729
		Wedge insignificant departure from the norm	2	8.3	2	16.7	
		Wedge significant departure from the norm	1	4.2	0	0.0	
		In total	24	100.0	12	100.0	
Creatinine	B6	Norm	18	94.7	7	77.8	0.095
		Wedge insignificant departure from the norm	0	0.0	2	22.2	
		Wedge significant departure from the norm	1	5.3	0	0.0	
		In total	19	100.0	9	100.0	
Glucose	B1	Norm	22	78.6	25	86.2	0.504
		Wedge insignificant departure from the norm	6	21.4	4	13.8	

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Changeable	Visit	Compliance with the norm / statistical indicator	The main one		Control		p-value [a)]
			n	%	n	%	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100	29	100	
Glucose	B3	Norm	22	78.6	26	89.7	0.355
		Wedge insignificant departure from the norm	5	17.9	3	10.3	
		Wedge significant departure from the norm	1	3.6	0	0.0	
		In total	28	100.0	29	100.0	
Glucose	B4	Norm	20	76.9	18	85.7	0.711
		Wedge insignificant departure from the norm	6	23.1	3	14.3	
		Wedge significant departure from the norm	0	0	0	0	
		In total	26	100	21	100	
Glucose	B5	Norm	17	70.8	11	91.7	0.441
		Wedge insignificant departure from the norm	5	20.8	1	8.3	
		Wedge significant departure from the norm	2	8.3	0	0.0	
		In total	24	100.0	12	100.0	
Glucose	B6	Norm	15	78.9	9	100.0	0.273
		Wedge insignificant departure from the norm	4	21.1	0	0.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	19	100	9	100	

Conclusions.

Based on the results of the analysis of the dynamics of laboratory parameters of biochemical blood analysis (AST, ALT, total bilirubin, creatinine and glucose), the following conclusions can be drawn.

1. Patients in both groups had elevated levels of ALT, AST, and total bilirubin at certain visits, which was the result of the effects of chemotherapy drugs on the hepatobiliary system.
2. Statistically significant differences between the groups in terms of laboratory indicators of biochemical blood analysis were not found at any of the visits. The differences that were observed were, as a rule, related to the initial condition of the patients and the CT courses received before the visits.
3. Statistically significant differences between the groups in accordance with the laboratory parameters of the biochemical analysis of the analyzed blood, the norm and deviation from it, were not found for any indicator at any of the visits.

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4. The above indicates the absence of a negative effect of the investigated drug on the indicators of biochemical blood analysis.

15.4.4.4 Analysis of the dynamics of general urine analysis indicators

General analysis of urine (indicators: specific gravity, pH, protein, glucose, leukocytes, erythrocytes, cylinders and salts) was performed during screening (B1) and at visits: B3, B4, B5 and B6.

The results of the analysis of the dynamics of the laboratory indicators of the general analysis of urine by the methods of descriptive statistics are given in the table. 15.4.4.4.1 for patients of the main group and in table 15.4.4.4.2 for patients of the control group. Since for the indicator "salt" for some patients, its amount was indicated, and for some only the class of salt was indicated (oxalates, urates, phosphates), a categorical variable was created for this indicator (there is salt / no salt). The comparative analysis of groups according to this variable is given in the table. 15.4.4.4.3.

Table 15.4.4.4.1 Dynamics of laboratory indicators of the general analysis of urine during the study in patients of the main group

Indicator	Visit	n	M	Me	St	MIN	MAX
Specific weight	Visit 1 (screening)	28	1014.50	1014	9.36	1002	1050
	Visit 3 (day 90)	28	1014.11	1013	6.53	1003	1030
	Visit 4 (day 180)	26	1015.85	1015.5	9,16	1002	1050
	Visit 5 (day 270)	24	1014.79	1015	8.04	1003	1037
	Visit 6 (day 360)	20	1017.50	1017.5	11.03	1002	1050
pH	Visit 1 (screening)	28	6.04	6	0.19	6	7
	Visit 3 (day 90)	28	6.25	6	0.65	6	8
	Visit 4 (day 180)	26	6.04	6	0.45	5	8
	Visit 5 (day 270)	24	6.13	6	0.45	6	8
	Visit 6 (day 360)	20	6.50	6	0.83	6	8
Protein in the urine	Visit 1 (screening)	28	0.00	0	0.01	0	0.033
	Visit 3 (day 90)	28	0.00	0	0.01	0	0.033
	Visit 4 (day 180)	26	0.00	0	0.01	0	0.033
	Visit 5 (day 270)	24	0.00	0	0.01	0	0.033
	Visit 6 (day 360)	20	0.00	0	0.02	0	0.066
Glucose in the urine	Visit 1 (screening)	28	0.00	0	N/A	0	0
	Visit 3 (day 90)	28	0.02	0	0.09	0	0.5
	Visit 4 (day 180)	26	0.00	0	N/A	0	0

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Indicator	Visit	n	M	Me	St	MIN	MAX
	Visit 5 (day 270)	24	0.02	0	0.10	0	0.5
	Visit 6 (day 360)	20	0.00	0	N/A	0	0
Leukocytes in urine, cl. in p/z	Visit 1 (screening)	28	4.29	4	3.32	0	15
	Visit 3 (day 90)	28	5.36	3	11.09	0	60
	Visit 4 (day 180)	26	5.81	3	9.06	0	45
	Visit 5 (day 270)	24	4.92	3	6.20	0	20
	Visit 6 (day 360)	20	3.60	3	2.76	1	12
Erythrocytes in urine, cl. in Ave.	Visit 1 (screening)	28	0.54	0	1.00	0	3
	Visit 3 (day 90)	28	0.50	0	1.04	0	4
	Visit 4 (day 180)	26	0.35	0	0.98	0	4
	Visit 5 (day 270)	24	0.46	0	0.98	0	3
	Visit 6 (day 360)	20	0.95	0	1.67	0	5
Cylinders in urine, cl. in Ave.	Visit 1 (screening)	28	0.04	0	0.19	0	1
	Visit 3 (day 90)	28	0.00	0	N/A	0	0
	Visit 4 (day 180)	26	0.04	0	0.20	0	1
	Visit 5 (day 270)	24	0.00	0	N/A	0	0
	Visit 6 (day 360)	20	0.05	0	0.22	0	1

Table 15.4.4.4.2 Dynamics of laboratory indicators of the general analysis of urine during the study in patients of the control group

Indicator	Visit	n	M	Me	St	MIN	MAX
Specific weight	Visit 1 (screening)	29	1013.48	1013	5.62	1002	1024
	Visit 3 (day 90)	29	1016.45	1013	18.92	1002	1111
	Visit 4 (day 180)	21	1013.24	1013	5.77	1002	1027
	Visit 5 (day 270)	12	1011.92	1011	7.04	1003	1028
	Visit 6 (day 360)	9	1013.78	1014	6.85	1005	1027
pH	Visit 1 (screening)	29	6.52	6	0.87	6	8
	Visit 3 (day 90)	29	6.28	6	0.70	6	8
	Visit 4 (day 180)	21	6.19	6	0.60	6	8
	Visit 5 (day 270)	12	6.67	6	0.98	6	8
	Visit 6 (day 360)	8	6.50	6	0.93	6	8
Protein in the urine	Visit 1 (screening)	29	0.00	0	0.01	0	0.033
	Visit 3 (day 90)	29	0.01	0	0.02	0	0.099
	Visit 4 (day 180)	21	0.00	0	0.01	0	0.04
	Visit 5 (day 270)	12	0.00	0	N/A	0	0
	Visit 6 (day 360)	8	0.00	0	0.01	0	0.033
Glucose in the urine	Visit 1 (screening)	29	0.00	0	N/A	0	0
	Visit 3 (day 90)	29	0.01	0	0.06	0	0.3
	Visit 4 (day 180)	21	0.00	0	N/A	0	0
	Visit 5 (day 270)	12	0.00	0	N/A	0	0

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Indicator	Visit	n	M	Me	St	MIN	MAX
	Visit 6 (day 360)	9	0.00	0	N/A	0	0
Leukocytes in urine, cl. in sight	Visit 1 (screening)	29	6.72	3	13.01	1	70
	Visit 3 (day 90)	29	5.86	3	11,21	0	60
	Visit 4 (day 180)	21	5.52	3	8.65	1	40
	Visit 5 (day 270)	12	3.33	2.5	2.39	1	8
	Visit 6 (day 360)	9	4.44	5	1.24	2	6
Erythrocytes in urine, cl. in sight	Visit 1 (screening)	29	0.76	0	1.48	0	5
	Visit 3 (day 90)	29	1.28	0	3.29	0	16
	Visit 4 (day 180)	21	0.29	0	0.72	0	2
	Visit 5 (day 270)	12	0.17	0	0.39	0	1
	Visit 6 (day 360)	9	2.22	0	5.07	0	15
Cylinders in urine, cl. in sight	Visit 1 (screening)	29	0.07	0	0.37	0	2
	Visit 3 (day 90)	29	0.07	0	0.37	0	2
	Visit 4 (day 180)	21	0.00	0	N/A	0	0
	Visit 5 (day 270)	12	0.00	0	N/A	0	0
	Visit 6 (day 360)	9	0.11	0	0.33	0	1

Table 15.4.4.4.3 Dynamics of the presence of salts in urine in groups

Changeable	Visit	Category	The main one		Control		p-value
			n	%	n	%	
Salts in the urine	B1	There are no salts	20	71.4	21	72.4	1,000
		There is salt	8	28.6	8	27.6	
		In total	28	100.0	29	100.0	
Salts in the urine	B3	There are no salts	23	82.1	21	72.4	0.530
		There is salt	5	17.9	8	27.6	
		In total	28	100.0	29	100.0	
Salts in the urine	B4	There are no salts	19	70.4	15	71.4	1,000
		There is salt	8	29.6	6	28.6	
		In total	27	100.0	21	100.0	
Salts in the urine	B5	There are no salts	19	79.2	11	91.7	0.640
		There is salt	5	20.8	1	8.3	
		In total	24	100.0	12	100.0	
Salts in the urine	B6	There are no salts	19	79.2	11	91.7	0.675
		There is salt	5	20.8	1	8.3	
		In total	24	100.0	12	100.0	

Since the presence of protein, glucose, and cylinders and urine was detected in only a few patients in small amounts in both groups, or, at some visits, were absent at all, further analysis by quantitative values of these parameters was not conducted, but only by compliance with the norm.

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Thus, group comparisons were made for such quantitative variables as specific gravity, pH, leukocytes, and erythrocytes.

To assess differences between groups at visits B3, B4, B5, and B6, group comparisons were performed using analysis of covariance (ANCOVA). This is due to the fact that the initial homogeneity of the groups could be disturbed due to the elimination of patients during the study and, by entering the covariance analysis model of the initial values as a covariate, an informational correction of the initial heterogeneity took place.

The covariance analysis model was as follows: the dependent variable is the value of the analyzed indicator at the corresponding visit (B3 - B6); factor "group" - fixed {levels: "main" and "control"}; covariate - the value of the corresponding indicator at the time of inclusion in the study, followed by the use of contrast analysis to compare groups (simple contrasts; "control" level = reference). The results of the analysis are given in Appendix D, table. D.4. The results of checking the normality of the distribution of ANCOVA residuals are given in Appendix D, table. G.5. For those dependent variables whose residuals were not normally distributed, ANCOVA on ranks was conducted (Appendix D, Table D.6). The results of the contrast analysis are shown in the table. 15.4.4.3.4.

Table 15.4.4.4.4 Results of comparison of groups according to laboratory indicators of general urinalysis at visits B3, B4, B5 and B6 using simple contrasts

Parameter	Contrasts	Contrast assessment	Hypothetical value	Difference (estimated - hypothesis)	Std. error	p-value
"Specific gravity for B3" ranks	"primary" relative to "control"	-0.211	0	-0.211	4,275	0.961
Ranks "Specific weight for B4"	"primary" relative to "control"	4,023	0	4,023	3,852	0.302
Ranks "Specific gravity for B5"	"primary" relative to "control"	2,198	0	2,198	2,518	0.389
Ranks "Specific weight for B6"	"primary" relative to "control"	2,699	0	2,699	3,262	0.416
Ranks "pH for	"primary"	-0.13	0	-0.13	2,891	0.964

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Parameter	Contrasts	Contrast assessment	Hypothetical value	Difference (estimated - hypothesis)	Std. error	p-value
B3"	relative to "control"					
Ranks "pH for B4"	"primary" relative to "control"	-1.426	0	-1.426	2,057	0.492
"pH for B5" ranks	"primary" relative to "control"	-5.748*	0	-5,748	2,367	0.021
"pH for B6" ranks	"primary" relative to "control"	0.350	0	0.350	2,774	0.901
Ranks "Leukocytes for B3"	"primary" relative to "control"	0.198	0	0.198	4,377	0.964
Ranks "Leukocytes for B4"	"primary" relative to "control"	1.69	0	1.69	3,727	0.652
Ranks "Leukocytes for B5"	"primary" relative to "control"	0.598	0	0.598	3,854	0.878
"Leukocytes for B6" ranks	"primary" relative to "control"	-6.003	0	-6.003	3,552	0.103
"Erythrocytes for B3" ranks	"primary" relative to "control"	-0.826	0	-0.826	3,330	0.805
"Erythrocytes for B4" ranks	"primary" relative to "control"	0.805	0	0.805	2,543	0.753
"Erythrocytes for B5" ranks	"primary" relative to "control"	1,454	0	1,454	2,682	0.591
"Erythrocytes for B6" ranks	"primary" relative to "control"	2,131	0	2,131	2,582	0.417

** This contrast is statistically significant at the 0.05 significance level.*

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Based on the data given in table. 15.4.4.4.4, it can be concluded that there were no statistically significant differences between the groups in terms of the analyzed parameters, except for pH on B5.

According to the study protocol, a comparison of groups was performed at the visits according to the conformity of the laboratory parameters of the general urinalysis with normal values. The results are given in the table. 15.4.4.4.5.

Table 15.4.4.4.5 Comparison of groups according to compliance with normal values of laboratory indicators of general urinalysis at each visit

Changeable	Visit	Compliance with the norm / statistical indicator	The main one		Control		p-value
			n	%	n	%	
Specific weight	B1	Norm	18	64.3	18	62.1	1,000
		Wedge insignificant departure from the norm	10	35.7	11	37.9	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
Specific weight	B3	Norm	17	60.7	18	62.1	1,000
		Wedge insignificant departure from the norm	11	39.3	10	34.5	
		Wedge significant departure from the norm	0	0.0	1	3,4	
		In total	28	100.0	29	100.0	
Specific weight	B4	Norm	17	65.4	13	61.9	1,000
		Wedge insignificant departure from the norm	9	34.6	8	38.1	
		Wedge significant departure from the norm	0	0	0	0	
		In total	26	100.0	21	100.0	
Specific weight	B5	Norm	14	58.3	6	50.0	0.729
		Wedge insignificant departure from the norm	10	41.7	6	50.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	24	100.0	12	100.0	
Specific weight	B6	Norm	11	55.0	6	66.7	0.694
		Wedge insignificant departure from the norm	9	45.0	3	33.3	
		Wedge significant departure from the norm	0	0	0	0	
		In total	20	100.0	9	100.0	
pH	B1	Norm	28	100.0	25	86.2	0.112
		Wedge insignificant departure from the norm	0	0.0	4	13.8	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
pH	B3	Norm	27	96.4	27	93.1	1,000
		Wedge insignificant departure from the norm	1	3.6	2	6.9	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
pH	B4	Norm	25	96.2	19	90.5	0.579

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Changeable	Visit	Compliance with the norm / statistical indicator	The main one		Control		p-value
			n	%	n	%	
		Wedge insignificant departure from the norm	1	3.8	2	9.5	
		Wedge significant departure from the norm	0	0	0	0	
		In total	26	100.0	21	100.0	
pH	B5	Norm	22	91.7	10	83.3	0.588
		Wedge insignificant departure from the norm	2	8.3	2	16.7	
		Wedge significant departure from the norm	0	0	0	0	
		In total	24	100.0	12	100.0	
pH	B6	Norm	16	80.0	9	100.0	0.280
		Wedge insignificant departure from the norm	4	20.0	0	0.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	20	100.0	9	100.0	
Protein in the urine	B1	Norm	27	96.4	25	86.2	0.352
		Wedge insignificant departure from the norm	1	3.6	4	13.8	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
Protein in the urine	B3	Norm	24	85.7	25	86.2	1,000
		Wedge insignificant departure from the norm	4	14.3	3	10.3	
		Wedge significant departure from the norm	0	0.0	1	3,4	
		In total	28	100.0	29	100.0	
Protein in the urine	B4	Norm	24	92.3	19	90.5	1,000
		Wedge insignificant departure from the norm	2	7.7	2	9.5	
		Wedge significant departure from the norm	0	0	0	0	
		In total	26	100.0	21	100.0	
Protein in the urine	B5	Norm	23	95.8	12	100.0	1,000
		Wedge insignificant departure from the norm	1	4.2	0	0.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	24	100.0	12	100.0	
Protein in the urine	B6	Norm	18	90.0	7	77.8	0.568
		Wedge insignificant departure from the norm	2	10.0	2	22.2	
		Wedge significant departure from the norm	0	0	0	0	
		In total	20	100.0	9	100.0	
Glucose in the urine	B1	Norm	28	100.0	29	100.0	N/A
		Wedge insignificant departure from the norm	0.0	0.0	0.0	0.0	
		Wedge significant departure from the norm	0.0	0.0	0.0	0.0	
		In total	28	100.0	29	100.0	
Glucose in the urine	B3	Norm	27	96.4	28	96.6	1,000
		Wedge insignificant departure from the norm	1	3.6	1	3,4	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	

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Changeable	Visit	Compliance with the norm / statistical indicator	The main one		Control		p-value
			n	%	n	%	
Glucose in the urine	B4	Norm	26	100.0	21	100.0	N/A
		Wedge insignificant departure from the norm	0.0	0.0	0.0	0.0	
		Wedge significant departure from the norm	0.0	0.0	0.0	0.0	
		In total	26	100.0	21	100.0	
Glucose in the urine	B5	Norm	23	95.8	12	100.0	1,000
		Wedge insignificant departure from the norm	1	4.2	0	0.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	24	100.0	12	100.0	
Glucose in the urine	B6	Norm	20	100.0	9	100.0	N/A
		Wedge insignificant departure from the norm	0.0	0.0	0.0	0.0	
		Wedge significant departure from the norm	0.0	0.0	0.0	0.0	
		In total	20	100.0	9	100.0	
Leukocytes in the urine	B1	Norm	22	78.6	22	75.9	0.793
		Wedge insignificant departure from the norm	5	17.9	4	13.8	
		Wedge significant departure from the norm	1	3.6	3	10.3	
		In total	28	100.0	29	100.0	
Leukocytes in the urine	B3	Norm	25	89.3	23	79.3	0.384
		Wedge insignificant departure from the norm	3	10.7	3	10.3	
		Wedge significant departure from the norm	0	0.0	3	10.3	
		In total	28	100.0	29	100.0	
Leukocytes in the urine	B4	Norm	20	76.9	18	85.7	0.088
		Wedge insignificant departure from the norm	6	23.1	1	4.8	
		Wedge significant departure from the norm	0	0.0	2	9.5	
		In total	26	100.0	21	100.0	
Leukocytes in the urine	B5	Norm	20	83.3	11	91.7	0.646
		Wedge insignificant departure from the norm	4	16.7	1	8.3	
		Wedge significant departure from the norm	0	0	0	0	
		In total	24	100.0	12	100.0	
Leukocytes in the urine	B6	Norm	16	80.0	8	88.9	1,000
		Wedge insignificant departure from the norm	4	20.0	1	11.1	
		Wedge significant departure from the norm	0	0	0	0	
		In total	20	100.0	9	100.0	
Erythrocytes in the urine	B1	Norm	22	78.6	25	86.2	0.504
		Wedge insignificant departure from the norm	6	21.4	4	13.8	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
Erythrocytes in the urine	B3	Norm	23	82.1	23	79.3	1,000
		Wedge insignificant departure from the norm	5	17.9	6	20.7	
		Wedge significant departure from the norm	0	0	0	0	

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Changeable	Visit	Compliance with the norm / statistical indicator	The main one		Control		p-value
			n	%	n	%	
		In total	28	100.0	29	100.0	
Erythrocytes in the urine	B4	Norm	23	88.5	18	85.7	1,000
		Wedge insignificant departure from the norm	3	11.5	3	14.3	
		Wedge significant departure from the norm	0	0	0	0	
		In total	26	100.0	21	100.0	
Erythrocytes in the urine	B5	Norm	19	79.2	12	100.0	0.146
		Wedge insignificant departure from the norm	5	20.8	0	0.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	24	100.0	12	100.0	
Erythrocytes in the urine	B6	Norm	15	75.0	7	77.8	1,000
		Wedge insignificant departure from the norm	5	25.0	2	22.2	
		Wedge significant departure from the norm	0	0	0	0	
		In total	20	100.0	9	100.0	
Cylinders	B1	Norm	28	100.0	28	96.6	1,000
		Wedge insignificant departure from the norm	0	0.0	1	3,4	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
Cylinders	B3	Norm	28	100.0	28	96.6	1,000
		Wedge insignificant departure from the norm	0	0.0	1	3,4	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
Cylinders	B4	Norm	25	96.2	21	100.0	1,000
		Wedge insignificant departure from the norm	1	3.8	0	0.0	
		Wedge significant departure from the norm	0	0	0	0	
		In total	26	100.0	21	100.0	
Cylinders	B5	Norm	24	100.0	12	100.0	N/A
		Wedge insignificant departure from the norm	0.0	0.0	0.0	0.0	
		Wedge significant departure from the norm	0.0	0.0	0.0	0.0	
		In total	24	100.0	12	100.0	
Cylinders	B6	Norm	19	95.0	8	88.9	0.532
		Wedge insignificant departure from the norm	1	5.0	0	0.0	
		Wedge significant departure from the norm	0	0.0	1	11.1	
		In total	20	100.0	9	100.0	
Salt	B1	Norm	23	82.1	25	86.2	0.730
		Wedge insignificant departure from the norm	5	17.9	4	13.8	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
Salt	B3	Norm	26	92.9	23	79.3	0.253
		Wedge insignificant departure from the norm	2	7.1	6	20.7	

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Changeable	Visit	Compliance with the norm / statistical indicator	The main one		Control		p-value
			n	%	n	%	
		Wedge significant departure from the norm	0	0	0	0	
		In total	28	100.0	29	100.0	
Salt	B4	Norm	21	80.8	18	85.7	0.715
		Wedge insignificant departure from the norm	5	19.2	3	14.3	
		Wedge significant departure from the norm	0	0	0	0	
		In total	26	100.0	21	100.0	
Salt	B5	Norm	23	95.8	11	91.7	1,000
		Wedge insignificant departure from the norm	1	4.2	1	8.3	
		Wedge significant departure from the norm	0	0	0	0	
		In total	24	100.0	12	100.0	
Salt	B6	Norm	18	90.0	7	77.8	0.568
		Wedge insignificant departure from the norm	2	10.0	2	22.2	
		Wedge significant departure from the norm	0	0	0	0	
		In total	20	100.0	9	100.0	

Conclusions.

1. The results of the analysis of laboratory indicators of the general analysis of urine allow us to conclude that statistically significant differences between groups were not found for all indicators and at each of the visits, with the exception of pH on B4. However, these differences were clinically insignificant.
2. There were no statistically significant differences between the groups in accordance with the laboratory parameters of the general analysis of the analyzed urine, the norm and deviations from it for any indicator at each of the visits.
3. The above indicates the absence of a negative effect of the investigated drug on the indicators of the general analysis of urine.

15.4.4.5 Analysis of ECG data dynamics

A 12-lead resting ECG study was performed at screening (B1) and at visits B4, B5, and B6. Some patients did not have an ECG at visits B4, B5 and B6 due to the severity of their condition. The majority of patients, according to the ECG, had the same changes that were registered at the screening stage, such as: diffuse-dystrophic changes in the myocardium, moderate hypertrophy of the left ventricle, incomplete blockade of the leg of the bundle of His, impaired intraventricular conduction,

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reduced voltage of the T wave, shortening the PQ interval, etc. The doctor-researcher evaluated these changes and made a conclusion in the categories of "norm" or "deviation from the norm". The results of the comparative analysis of groups according to the presence or absence of pathology by visits are shown in table. 15.4.4.5.1.

Table 15.4.4.5.1 Comparison of groups according to ECG data at the respective visits

Visit	Compliance with the norm / statistical indicator	The main one		Control		p-value
		n	%	n	%	
B1	Norm	5	17.9	6	20.7	1,000
	Deviation from the norm	23	82.1	23	79.3	
	In total	28	100.0	29	100.0	
B4	Norm	4	15.4	5	23.8	0.486
	Deviation from the norm	22	84.6	16	76.2	
	In total	26	100.0	21	100.0	
B5	Norm	3	13.0	2	18.2	1,000
	Deviation from the norm	20	87.0	9	81.8	
	In total	23	100.0	11	100.0	
B6	Norm	2	10.0	2	22.2	0.568
	Deviation from the norm	18	90.0	7	77.8	
	In total	20	100.0	9	100.0	

As can be seen from the above table, no statistically significant differences in the presence of cardiovascular system pathology according to ECG data were found between the groups during the study.

Conclusion.

Based on the results of the statistical analysis, it can be concluded that the differences between the groups in the presence of cardiovascular system pathology according to ECG data were statistically insignificant at each of the respective visits (B1, B4, B5 and B6).

15.4.4.6 Analysis of Chemotherapy Toxicity by NCIC CTC Scale

In the analysis of CT toxicity according to the CTC NCIC scale, patients who received at least 3 courses of CT were included, including 26 patients of the main group and 24 patients of the control group. Patients who received less than 3 courses of CT did not continue treatment with anticancer drugs due to progressive deterioration of the condition associated with the underlying disease.

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In this study, chemotherapy toxicities were assessed at each visit beginning at Visit 3 using the NCIC CTC toxicity scale (Appendix B).

In patients who received CT, complications developed in most patients, but most often they were of a mild nature. The toxicities observed were predictable, manageable, and mostly grade 1 and 2 toxicities on the CTC NCIC scale. Grade 3 toxicity was observed in 8 patients (16.0%), grade 4 toxicity in one (2.0%). Most often, hematological toxicity was noted in patients, its manifestations of the 1st-2nd degree were noted in 34 (68.0%) patients and the 3rd degree - in 3 (6.0%). Gastrointestinal toxicity of the 1st-2nd degree was the second most frequent and was observed in 33 patients (66.0%), in 3 (6.0%) patients it reached the 3rd degree. An increase in transaminases of the 1st-2nd degree was found in 16 patients (32.0%), bilirubin - in 4 (8.0%) patients. Complications from the cardiovascular system developed in 14 (28, 0%) patients, in 1 (2.0%) patient these complications had the 3rd degree of severity. Neurotoxicity in the form of increased drowsiness was observed in 4 (8.0%) patients. Reduction of treatment courses due to the development of toxic effects - in 2 patients (4.0%).

15.4.4.7 Analysis of hematological toxicity in groups

As mentioned above, 26 patients of the main group and 24 patients of the control group were included in the analysis of hematological toxicity.

Hematological toxicity was detected in 18 (69.2%) patients of the main group and in 16 (66.7%) patients of the control group. The results of the comparative analysis of the groups according to the presence of hematological toxicity are shown in the table. 15.4.4.6.1.

Table 15.4.4.6.1 – Comparative analysis of groups according to the presence of hematological toxicity

Changeable	Category	The main one		Control		p-value
		n	%	n	%	
Hematological toxicity	There is hematological toxicity	18	69.2	16	66.7	1,000
	There is no hematological toxicity	8	30.8	8	33.3	
	In total	26	100	24	100	

The development of leukopenia was the most frequent complication of the CT from the side of the blood system. Leukopenia of the 1st degree was detected in 7 (26.9%) patients of the main group and in 5 (20.8%) patients of the control group, of the 2nd degree - in 10 (38.5%) patients of the main group and in 7 (29.2%) of control

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and 3rd degree patients – in 1 (3.8%) primary patient and in 1 (4.2%) control patient. Thrombocytopenia of the 1st-2nd degree - in 7 (26.9%) patients of the main group and in 2 (8.3%) patients of the control group, and of the 3rd degree - in 1 (4.1%) patient of the control group. Anemia of the 1st-2nd degree was observed in 4 (15.4%) patients of the main group and in 5 (20.8%) patients of the control group.

The frequency of detection and the percentage of the presence of hematological toxicity of chemotherapy in the groups are presented in the table. 15.4.4.6.2.

Table 15.4.4.6.2 – Analysis of the frequency of CT hematological toxicity in groups

Parameter	**Degree toxicity**	**Main group n=26**		**Control group n=24**		**P-value ***
		n	**%**	**n**	**%**	
Leukopenia	1	7	26.9	5	20.8	0.805
	2	10	38.5	7	29.2	
	3	1	3.8	1	4.2	
Anemia	1	1	3.8	4	16.7	0.262
	2	3	11.4	1	4.2	
	3	0	0.0	0	0.0	
Thrombocytopenia	1	4	15.4	2	8.3	0.209
	2	3	11.4	0	0.0	
	3	0	0.0	1	4.2	

** Analysis performed using Fisher's exact test. The conclusion is made at a significance level of 0.05.*

Conclusion

Based on the results of the analysis, no statistically significant differences were found between the groups in terms of the frequency of hematological toxicity of CT according to the CTC NCIC scale.

15.4.4.8 Analysis of non-hematological toxicity

The most frequent complications of chemotherapy from the gastrointestinal tract were constipation and nausea/vomiting. 16 (61.5%) patients of the main group and 11 (45.8%) patients of the control group complained of constipation of the 1st-2nd degree. 12 (46.2%) patients of the main group and 8 (33.3%) patients of the control group complained of nausea/vomiting of varying intensity.

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Diarrhea was observed in 5 (19.2%) patients of the main group and in 4 (16.7%) patients of the control group.

Hepatotoxicity was manifested mainly in the form of an increase in transaminases. An increase in the level of ALT and AST according to the 1st-2nd degree of toxicity was observed in 8 (30.8%) patients of the main group and in 6 (25.0%) patients of the control group, in 1 (3.8%) patient of the main group it was recorded increase in transaminases according to the 3rd degree of toxicity. An increase in bilirubin was observed in 2 (7.7%) patients of the main group and in 2 (8.3%) patients of the control group.

Neurotoxicity of the 1st degree (sleep disturbance) - in 1 (3.8%) patient of the main group and in 3 (12.5%) patients of the control group, of the 3rd degree in 1 (3.8%) patient of the main group.

Cardiotoxicity of the 1st-2nd degree (according to ECG data) was observed in 6 (23.1%) patients of the main group and in 3 (12.5%) patients of the control group, of the 3rd degree - in 1 (4.2%) patient control group. Heart rhythm disturbances of the 1st-2nd degree in 2 (7.7%) patients of the main group and in 4 (16.7%) patients of the control group.

The detection frequency and percentage ratio of non-hematological toxicity of chemotherapy in the groups are shown in the table. 15.4.4.7.1.

Table 15.4.4.7.1 Analysis of non-hematological toxicity of chemotherapy in groups

Parameter	Degree toxicity	Main group n=26		Control group n=24		P-value*
		n	%	n	%	
Constipation	1	5	19.2	6	25.5	0.290
	2	11	42.3	5	20.8	
	3	0	0	0	0	
Nausea/vomiting	1	9	34.6	6	25.5	0.782
	2	2	7.7	1	4.2	
	3	1	3.8	1	4.2	
Diarrhea	1	2	7.7	3	12.5	0.293
	2	3	11.5	0	0	
	3	0	0	1	4.2	
ALT/AST	1	6	23.1	3	12.5	0.652
	2	2	7.7	3	12.5	
	3	1	3.8	0	0	
Bilirubin	1	2	7.7	1	4.2	0.797
	2	0	0	1	4.2	
	3	0	0	0	0	

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Parameter	Degree toxicity	Main group n=26		Control group n=24		P-value*
		n	%	n	%	
Neurotoxicity	1	1	3.8	3	12.5	0.340
	2	0	0	0	0	
	3	1	3.8	0	0	
Cardiotoxicity	1	3	11.5	2	8.3	0.746
	2	3	11.5	1	4.2	
	3	0	0	1	4.2	
Violation of heart rhythm	1	1	3.8	4	16.7	0.182
	2	1	3.8	0	0	
	3	0	0	0	0	
** Analysis performed using Fisher's exact test. The conclusion is made at a significance level of 0.05.*						

Conclusion.

Based on the results of the statistical analysis given in table. 15.4.4.7.1, it can be concluded that no statistically significant differences were found between the groups in the frequency of non-hematological toxicity of CT according to the CTC NCIC scale.

Summarizing the above, it can be stated that the overall toxicity profile for the group of patients who received the study drug Donovit-VS on the background of CT was not statistically significantly different from the group that received only CT.

15.5 Evaluation of the quality of life according to the EORTC QLQ-C30 questionnaire

Determining the quality of life is one of the important criteria for evaluating the effectiveness of treatment in oncology. In this study, the EORTC QLQ-C30 Quality of Life Assessment Questionnaire of the European Organization for Research and Treatment of Cancer (Appendix B) was used for assessment.

The level of quality of life was assessed in all patients before the start of chemotherapy, then at each visit, starting with Visit 3.

We analyzed the QL2 quality of life scale, which is formed on the basis of two scales (the "quality of life" scale and the "general health status" scale) of the EORTC QLQ-C30 questionnaire. The maximum possible amount of points that can be scored on each of the scales is 7 points. According to the data processing rules of the

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EORTC QLQ-C30 Questionnaire, the arithmetic mean ("raw scores" – Raw Score = RS) of the corresponding scale is first calculated according to the formula:

$$\text{Raw Score} = RS = (I_1 + I_2 + ... + I_n)/n, \quad (4)$$

where: n is the number of questions for a certain scale

$I_1 ... I_n$ - answers to each question.

Next, for the scale of symptoms and the scale of general health status (QL2), the number of points (Score) is estimated according to the formula:

$$\text{Score} = \{(RS - 1)/\text{range}\} \times 100, \quad (5)$$

where range is the range of the scale (for the QL2 scale = 6).

The results of the descriptive analysis of the dynamics of assessments of the general health status according to the QL2 scale are given in table. 15.5.1 for the main group and in table. 15.5.2 for the control room. The graphic interpretation of the dynamics is shown in fig. 15.5.1.

Table 15.5.1 Dynamics of assessments of general health status according to the QL2 scale in the main group

Indicator	Visit	n	M	Me	St	MIN	MAX
QL2, points	Visit 1 (screening)	28	59.82	62.50	13.62	33,33	100.00
	Visit 3 (day 90)	28	63.39	66,67	20,33	16.67	100.00
	Visit 4 (day 180)	27	63.27	66,67	19.92	33,33	100.00
	Visit 5 (day 270)	24	63.89	66,67	23.91	16.67	100.00
	Visit 6 (day 360)	20	64.58	66,67	19.09	33,33	100.00

Table 15.5.2 Dynamics of assessments of general health status according to the QL2 scale in the control group

Indicator	Visit	n	M	Me	St	MIN	MAX
QL2, points	Visit 1 (screening)	29	66,67	66,67	16.67	33,33	100.00
	Visit 3 (day 90)	29	61.49	66,67	19.72	16.67	100.00
	Visit 4 (day 180)	21	59.92	66,67	22.15	16.67	100.00
	Visit 5 (day 270)	12	64.58	66,67	25,16	16.67	100.00
	Visit 6 (day 360)	9	79.63	83.33	16,20	50.00	100.00

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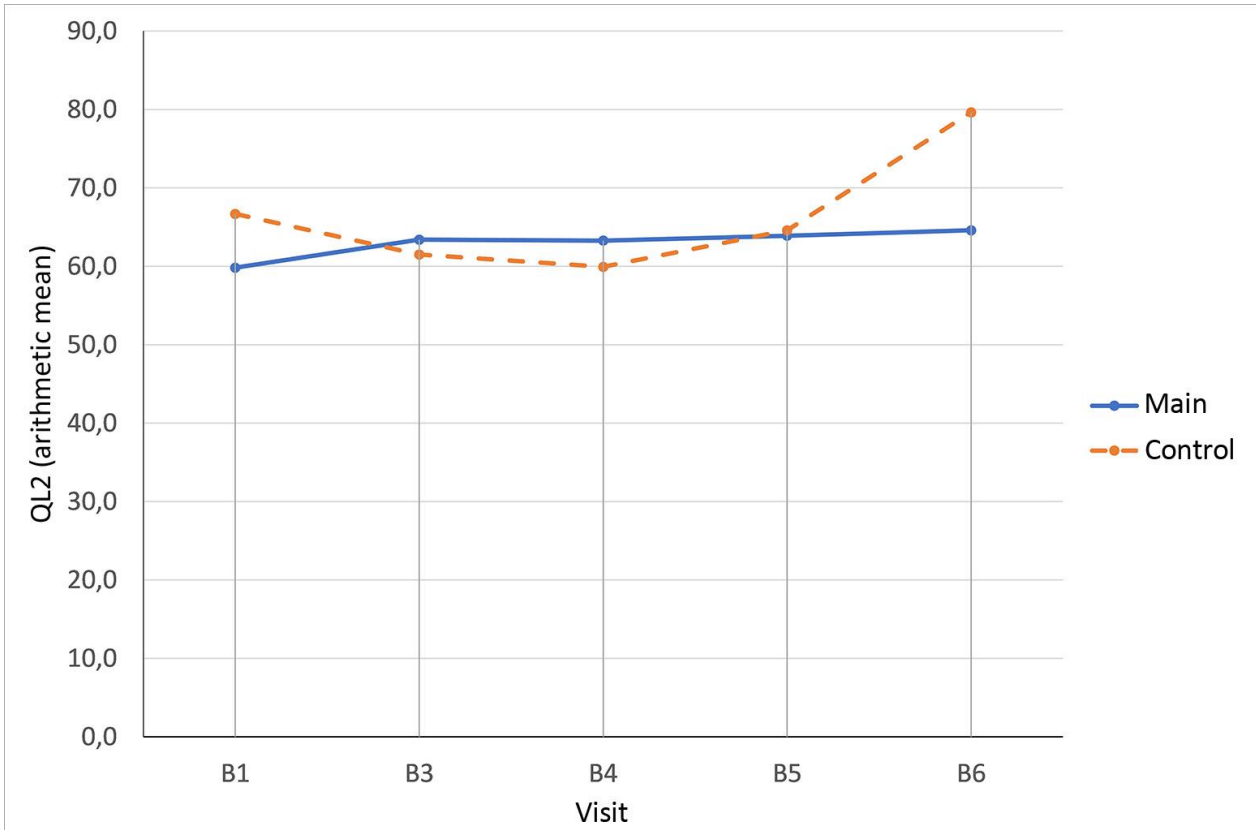

Fig. 5.5.1 – Graphical interpretation of the dynamics of general health status assessments on the QL2 scale in groups (arithmetic mean)

As can be seen from fig. 5.5.1, the dynamics of the QL2 scale of the EORTC QLQ-C30 questionnaire during treatment was insignificant in both groups. However, when assessing the dynamics of QL2 quality of life assessments, it should be taken into account that, firstly, not all data on certain visits were distributed normally (Appendix D, table D.11), and secondly, these indicators were influenced courses of CT, the number of which was different for different patients, and, thirdly, the number of patients at visits also constantly changed, and more patients dropped out in the control group than in the main one. Therefore, estimates of the dynamics of the quality of life are approximate.

To assess differences between groups at visits B3, B4, B5 and B6, they were compared using analysis of covariance (ANCOVA). This is due to the fact that the initial homogeneity of the groups could be disturbed due to the elimination of patients during the study and, by entering the covariance analysis model of the initial values as a covariate, an informational correction of the initial heterogeneity took place.

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The covariance analysis model was as follows: the dependent variable is the value of the analyzed indicator at the corresponding visit (B3 - B6); factor "group" - fixed {levels: "main" and "control"}; covariate - the value of the corresponding indicator at the time of inclusion in the study, followed by the use of contrast analysis to compare groups (simple contrasts; "control" level = reference). The results of the analysis are given in Appendix D, table. D.4. The results of checking the normality of the distribution of ANCOVA residuals are given in Appendix D, table. G.5. For those dependent variables whose residuals were not normally distributed, ANCOVA on ranks was conducted (Appendix D, Table D.6). The results of the contrast analysis are shown in the table. 15.5.3.

Table 15.5.3 Results of comparison of groups according to QL2 quality of life scores at visits B2, B3, B4 and B5 using simple contrasts

Parameter	Contrasts	Contrast assessment	Hypothetical value	Difference (estimated - hypothesis)	Std. error	p-value*
QL2 for B3	"primary" relative to "control"	4,686	0	4,686	5,221	0.373
QL2 for B4	"primary" relative to "control"	6.1	0	6.1	6,187	0.329
QL2 for B5	"primary" relative to "control"	-2,466	0	-2,466	9,217	0.791
QL2 for B6	"primary" relative to "control"	-13,267	0	-13,267	7,736	0.098

** This contrast is statistically significant at the 0.05 significance level.*

Conclusions .

1. The dynamics of quality of life assessments during the study, according to the QL2 scale of the EORTC QLQ-C30 questionnaire, were insignificant in both groups. Some increase in mean values in the control group at the last visit was due to the fact that in this group only 9 patients were included in the assessment (patients with poor quality of life assessments were excluded), while in the main group there were 20 patients (part of patients with poor quality of life assessments was still present at the last visit).

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2. As a result of the analysis, no statistically significant differences in quality of life scores on the QL2 scale of the EORTC QLQ-C30 questionnaire were found between the groups at any of the visits.

15.6 Evaluation of the general condition of patients according to the ECOG scale

The general condition of the patient according to the ECOG scale was assessed at screening (B1) and at visits B3, B4, B5 and B6. The results of a comparative analysis of the dynamics of assessments of the patient's condition according to the specified scale are given in table. 15.6.1 for the main group and in table. 15.6.2 for the control group. The graphic interpretation of the dynamics is shown in fig. 15.6.1.

Table 15.6.1 Results of the analysis of the dynamics of patient condition assessments according to the ECOG scale in the main group

Indicator	Visit	n	M	Me	St	MIN	MAX
ECOG, points	Visit 1 (screening)	28	0.96	1	0.331	0	2
	Visit 3 (day 90)	28	0.86	1	0.705	0	2
	Visit 4 (day 180)	27	0.93	1	0.675	0	2
	Visit 5 (day 270)	24	1.04	1	0.999	0	4
	Visit 6 (day 360)	20	0.75	1	0.639	0	2

Table 15.6.2 Results of the analysis of the dynamics of patient condition assessments according to the ECOG scale in the control group

Indicator	Visit	n	M	Me	St	MIN	MAX
ECOG, points	Visit 1 (screening)	29	0.79	1	0.620	0	2
	Visit 3 (day 90)	29	1.00	1	0.655	0	2
	Visit 4 (day 180)	21	1.00	1	0.632	0	2
	Visit 5 (day 270)	12	0.83	1	0.937	0	3
	Visit 6 (day 360)	9	0.33	0	0.500	0	1

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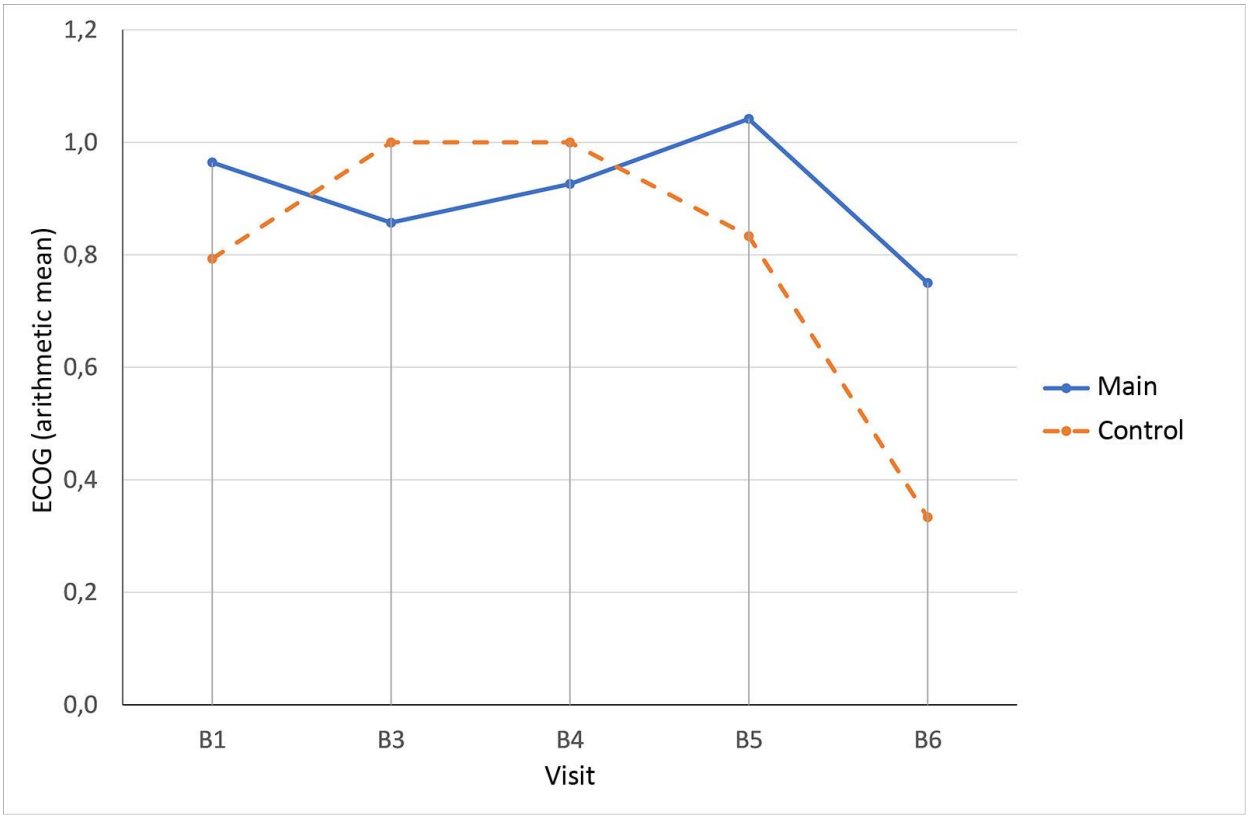

Fig. 15.6.1 – Graphical interpretation of the dynamics of patient condition assessments on the ECOG scale in groups (arithmetic mean)

As can be seen from fig. 15.6.1 evaluations of patients' condition according to the ECOG scale at the last visits (B4 and B5) decreased less pronounced in the main group compared to the control group.

However, when assessing the dynamics of patient condition assessments according to ECOG, it is necessary to take into account that, firstly, not all data at certain visits were distributed normally (Appendix D, table D.11), and secondly, these indicators were influenced by the courses CT, the number of which was different for different patients, and, thirdly, the number of patients at visits also constantly changed, and more patients dropped out in the control group than in the main one. Therefore, assessments of the dynamics of patients' condition according to ECOG are approximate.

To assess differences between groups at visits B3, B4, B5 and B6, they were compared using analysis of covariance (ANCOVA). This is due to the fact that the initial homogeneity of the groups could be disturbed due to the elimination of patients during the study and, by entering the covariance analysis model of the initial values as a covariate, an informational correction of the initial heterogeneity took place.

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The covariance analysis model was as follows: the dependent variable is the value of the analyzed indicator at the corresponding visit (B3 - B6); factor "group" - fixed {levels: "main" and "control"}; covariate - the value of the corresponding indicator at the time of inclusion in the study, followed by the use of contrast analysis to compare groups (simple contrasts; "control" level = reference). The results of the analysis are given in Appendix D, table. D.4. The results of checking the normality of the distribution of ANCOVA residuals are given in Appendix D, table. G.5. For those dependent variables whose residuals were not normally distributed, ANCOVA on ranks was conducted (Appendix D, Table D.6). The results of the contrast analysis are shown in the table. 15.6.3.

Table 15.6.3 Results of comparison of groups according to QL2 quality of life scores at visits B3, B4, B5 and B6 using simple contrasts

Parameter	Contrasts	Contrast assessment	Hypothetical value	Difference (estimated - hypothesis)	Std. error	p-value*
"ECOG for B3" ranks	"primary" relative to "control"	-4,587	0	-4,587	3,933	0.249
"ECOG for B4" ranks	"primary" relative to "control"	-3,462	0	-3,462	3,654	0.349
"ECOG for B5" ranks	"primary" relative to "control"	2,987	0	2,987	3.57	0.409
ECOG for B6	"primary" relative to "control"	0.432	0	0.432	0.249	0.094

** This contrast is statistically significant at the 0.05 significance level.*

Conclusions .

1. The dynamics of assessments of patients' condition according to ECOG were insignificant in both groups. Some reduction in mean values in the control group at visits B5 and B6 was due to the fact that in this group only 9 patients were included in the assessment, while in the main group - 20 patients.
2. As a result of the statistical analysis, no statistically significant differences in the ECOG scores of the patients were found between the groups at any of the visits.

15.7 Conclusion on excess effectiveness

The conclusion regarding the superior effectiveness of the therapy including the study drug Donovit-VS (main group), which is used against the background of Main CT, in comparison with the Main CT without the drug, was made on the basis of the presence of statistically significant differences between the groups for the main efficacy variable.

The main efficacy variable in this study was the overall survival of patients within 12 months from the moment of inclusion in this study (the date of signing the Informed Consent).

Analysis of the main change in groups was done using survival methods (construction of survival curves by the Kaplan-Meier method and their comparison using the log-rank test).

The results of comparing the curves of one-year (365-day) overall survival in groups using the log-rank test allow us to state that one-year overall survival was statistically significantly higher in the main group compared to the control group ($p = 0.030$), which allows us to draw a conclusion about the superior effectiveness of therapy with the use of the drug Donovit-VS in comparison with therapy without the use of this drug.

15.8 Analysis of transferability

During the study, 42 AE/AR were registered in 17 (56.7%) patients of the main group (with the use of Donovit-VS) and 35 AE/AR in 10 (34.5%) patients of the control group (without the use of Donovit-VS).

Of them, in the main group, 10 serous AE/AR were registered in 8 (26.7%) patients and in the control group - 14 serious AE/AR in 3 (10.3%) patients.

In this study, the following AE/AR were most often encountered: leukopenia, thrombocytopenia, increased transaminase levels; from the gastrointestinal tract, such phenomena as constipation and nausea/vomiting. Almost all AE/AR registered during the study were directly related to the course of the underlying disease and corresponded to the toxicity profile of the chemotherapeutic drugs used.

In the course of the study, no allergic and anaphylactic reactions were recorded in the group of patients who took the studied drug.

On the basis of the conducted statistical analysis, it is possible to conclude that there is no negative effect of the studied drug on hemodynamic indicators and body temperature, laboratory indicators of general blood analysis, biochemical blood analysis, general analysis of urine and on ECG indicators.

Only in one case (patient No. 60, male, 51 years old, main group), on the 3rd day after taking Donovit-VS, an increase in body temperature was observed, probably related to its use. The patient was discontinued from the study drug and withdrawn from the study.

On the basis of the above, it can be assumed that the tolerability of the drug Donovit-VS was good in 96.3% of patients.

The list of serious AE/AR is given in the table. 15.8.1. The final results of the analysis of AE/AR in groups are given in table. 15.8.2. The results of the analysis of the frequency with which AE/AR occurred and their share in each of the groups are shown in the table. 15.8.3 for the main group and in table. 15.8.4 for the control group.

Table 15.8.1 List of serious AE/AR

RN	Group	Description of AE/AR	Start date	Completion date	Cause and effect relationship	Measures taken	Result categories
2	Main	Leukopenia	14.07.2017		cannot be estimated	treatment is prescribed	It is unknown
11	Main	Thrombocytopenia	01.02.201		missing	treatment is prescribed	Recovery without consequences
12	Main	Increase in ALT	01.11.2017		missing	treatment is prescribed	Unchanged.
13	Main	Increase in ALT	19.06.2017		missing	treatment is prescribed	Recovery with consequences
18	Main	Increase in ALT	03/07/2018		missing	treatment is prescribed	Unchanged
18	Main	Increase in AST	03/07/2018		missing	treatment is prescribed	Unchanged
20	Control	Leukopenia	10.01.2018		missing	treatment is prescribed	Unchanged
21	Main	Thrombocytopenia	10.10.2017		missing	treatment is prescribed	Unchanged

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RN	Group	Description of AE/AR	Start date	Completion date	Cause and effect relationship	Measures taken	Result categories
27	Main	Thromboembolism of the pulmonary artery	11/16/2017		missing		Fatal case
39	Control	Increase in ALT	28.08.2018		missing	treatment is prescribed	Unchanged
39	Control	Increase in AST	28.08.2018		missing	treatment is prescribed	Unchanged
39	Control	Increase in ALT	21.11.2018		missing	treatment is prescribed	Unchanged
39	Control	Increase in AST	21.11.2018		missing	treatment is prescribed	Unchanged
41	Control	Thrombocytopenia	08/09/2018	12.09.2018	missing	treatment is prescribed	Recovery without consequences
41	Control	Leukopenia	07.11.2018		missing	treatment is prescribed	Recovery without consequences
41	Control	Increase in ALT			missing	treatment is prescribed	Recovery without consequences
41	Control	Increase in AST			missing	treatment is prescribed	Recovery without consequences
60	Main	An increase in body temperature	21.04.2019	23.04.2019	possible	Stopping the study drug	Recovery without consequences
60	Main	An increase in body temperature	27.04.2019	28.04.2019	probable	Cancellation of the study drug	Recovery without consequences

Table 15.8.2 Summary results of the analysis of AE/AR in groups

	Main group n (%)	Control group n (%)
Subjects evaluated for the analysis of AE/AR	30	29
The number of AE/AR	42	36
Patients with AE/AR	17 (56.7)	10 (35.5)
Number of serious AE/AR	10	14
Patients with severe AE/AR	8 (26.7)	3 (10.3)

Patients are included through AE/AR	1 (3.3)	0 (0.0)
Patients who had their dose reduced due to AE/AR	0 (0)	0 (0.0)
N = number of patients in the analyzed population; n = number of patients with events; In one row, patients were included only once.		

Table 15.8.3 Results of the analysis of AE/AR for the main group

Name according to PT	**AE/AR***		**Patients****	
	n	**%**	**n**	**%**
In total	**42**	**100**	**17**	**56.7**
Leukocytopenia	8	19.0	5	16.7
Increase in ALT	9	21.4	4	13.3
Increase in AST	2	4.8	2	6,7
Increased creatinine	2	4.8	1	3.3
An increase in body temperature	2	4.8	1	3.3
Thrombosis of the pulmonary artery	1	2.4	1	3.3
Thrombocytopenia	11	26.2	7	23.3
42 = 100% (N – Number of AE/AR).* * 30 = 100%, It is possible to include patients several times (n is the number of patients in the group (carryover analysis)*				

Table 15.8.4 Results of the analysis of AE/AR for the control group

Name according to PT	**AE/AR***		**Patients****	
	n	**%**	**n**	**%**
In total	**36**	**100**	**10**	**35.5**
Fasten	1	2.8	1	3,4
Leukocytopenia	10	27.8	4	13.8
Increase in ALT	7	19.4	4	13.8
Increase in AST	9	25.0	5	17.2
Increased creatinine	3	8.3	1	3,4
Thrombocytopenia	12	33.3	7	24.1
36 = 100% (N – Number of AE/AR).* * 29 = 100%, It is possible to include patients several times (n is the number of patients in the group (carryover analysis)*				

15.9 Discussion of research results

This open, single-center, randomized, comparative, parallel study was conducted from 07/01/2016 to 02/27/2020 in the Department of Adjuvant Treatment Methods for CNS Tumors of the State Institution "Institute of Neurosurgery named

after Acad. A.P. Romodanova of the National Academy of Sciences of Ukraine". The protocol and materials of the clinical study were approved by the Central Committee of the Ministry of Health of Ukraine and the Ethics Committee of the State University "Institute of Neurosurgery named after Acad. A.P. Romodanov of the National Academy of Sciences of Ukraine", in which the research was conducted. The study was conducted in accordance with the Declaration of Helsinki, the International Principles of Clinical Research (ICH GCP), the current legislation of Ukraine, as well as the approved Research Protocol. All patients gave written informed consent to participate in the study before any screening procedures.

The purpose of this study was to evaluate the effectiveness and tolerability of the drug Donovit-VS, tablets, manufactured by Astrapharm LLC, which was used in patients with glioblastoma on the background of chemotherapy in comparison with a group of patients who received only chemotherapy.

The main efficacy variable was the overall survival of patients within 12 months from the start of treatment.

Secondary variables were: one-year progression-free survival, median survival, degree of toxicity of chemotherapy according to the CTC NCIC scale, quality of life according to the scale of the European Organization for Research and Treatment of Cancer - EORTC - QLQ - C30.

The general research plan included screening for 3-7 days, treatment and observation for 360 days.

The study included patients of both sexes aged 18 to 65 years with a histologically confirmed diagnosis of glioblastoma, stage IV anaplasia. The study included patients after surgical resection or biopsy of the tumor and a course of radiation therapy (total radiation dose 60 Gray). All patients included in the study had a functional status according to the ECOG scale from 0 to 2 points and an expected life expectancy of at least 12 weeks. Additional criteria included: sufficient bone marrow reserve (leukocyte content $\geq$ 2.0 x x10^9/l, platelets $\geq$ 100 x 10^9/l, hemoglobin $\geq$ 100 g/l), as well as sufficient liver and kidney function (creatinine does not exceed the upper limit of normal by more than 1.25 times, AST, ALT do not exceed the upper limit of normal by more than 2.5 times; total bilirubin does not exceed the upper limit of normal by more than 1.5 times). Patients were excluded from the study if they had any unstable therapeutic or psychiatric condition that, in the opinion of the

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investigator, could impair the patient's ability to complete the study or prevent participation in it. Pregnant or lactating women could not participate in the study.

60 patients were randomized into the study, of which: 30 patients - in group c with the appointment of the drug Donovit-VS (main group) and 30 patients - in the group without the appointment of the drug Donovit-VS (control group).

The studied groups were compared in terms of gender and age, clinical symptoms, laboratory data, as well as in all parameters relevant to the assessment of efficacy and safety.

Patients of the main and control groups were prescribed chemotherapy in accordance with international standards for the treatment of glioblastoma according to one of the following schemes:

1. Temozolomide in the form of 6 cycles of adjuvant therapy at a dose of 150-200 mg/m^2 1 time per day for 5 days of a 28-day cycle (5 days - taking temozolomide, 23 days - without taking the drug).
2. Lomustine 130 mg/m^2 per os once every 4-6 weeks. The course is 12 months.
3. PCV scheme: procarbazine + lomustine + vincristine every 4-6 weeks: 1st day - lomustine 130 mg/m^2 per os, 8th, 28th days - vincristine 1.0 mg/m^2 intravenously. From the 8th to the 22nd day inclusive, procarbazine 50 mg 2 times a day per os.

In addition, the patients of the main group received the study drug Donovit-VS, tablets produced by Astrapharm LLC, 1 tablet 3 times a day for 12 months. The drug was prescribed immediately after the end of the course of radiation therapy, simultaneously with the appointment of CT.

57 patients were included in the efficiency analysis, of which: 28 patients of the main group and 29 patients of the control group. Patients No. 27 (development of AE with a fatal outcome 2 months after Visit 1 – pulmonary embolism), No. 42 (incorrect inclusion in the study – the diagnosis of glioblastoma was not confirmed) and No. 60 (development of AR on the 3rd day after taking the study drug, which required its withdrawal).

59 patients were included in the safety and tolerability analysis, including 29 patients of the main group who received the study drug Donovit-VS on the background of antitumor chemotherapy and 30 patients of the control group who received only chemotherapy.

Final results of the performance analysis

The results of the study showed that in patients who received the drug Donovit-VS in combination with CT, a significant increase in overall one-year survival and progression-free survival was achieved.

Analysis of the toxic profile of CT, in general, did not reveal significant differences between groups. Also, no statistically significant difference between the groups was found when analyzing the quality of life according to the QL2 scale of the EORTC QLQ-C30B questionnaire and when analyzing the condition of patients according to the ECOG scale during the study.

Evaluation of efficiency by the main variable.

The arithmetic mean of one-year (365-day) overall survival time (the estimate was limited to the largest censored survival time) was 347.5 days in the main group and 309.45 days in the control group, which indicates in favor of the excess effectiveness of treatment in the main group.

According to the results of the comparison of the curves of the overall one-year (365-day) survival in the groups using the log-rank test, the one-year survival in the main group was statistically significantly higher compared to the control group ($p = 0.030$), which allows us to draw a conclusion about the superior effectiveness of therapy with the use of the drug Donovit-VS in comparison with therapy without the use of this drug.

Evaluation of efficiency by secondary variables:

1. The arithmetic mean of the one-year recurrence-free survival time (the estimate was limited to the largest censored recurrence-free survival time, subject to 12-month follow-up) was 11.5 months in the main group and 9.2 months in the control group, which indicates the benefit of the excess effectiveness of treatment in the main group.

2. Median one-year recurrence-free survival in the main group was not available, since less than 50% of patients in the main group relapsed during the study, and in the control group, the median recurrence-free survival was 9 months.

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3, According to the results of comparing the one-year recurrence-free survival curves in the groups using the logrank test, the one-year recurrence-free survival in the main group was statistically significantly higher compared to the control group ($p < 0.001$), which allows us to draw a conclusion about the superior effectiveness of therapy with the use of Donovit-VS in the preparation compared with therapy without the use of this drug.

4. The overall one-year (365 days) survival of patients in the main group was 78.6%, and in the control group - 51.7%. Formally, the differences between the groups are statistically insignificant ($p = 0.052$). However, the fact that the difference in the percentage of patients who survived [primary - control] is 26.8%, indicates in favor of the superior effectiveness of therapy with the use of the drug Donovit-VS in comparison with therapy without the use of this drug.

5. The relapse-free one-year survival of patients in the main group was 75.0%, and in the control group - 34.5%. The difference in proportions [main - control] was 40.5%. The differences between the groups are statistically significant ($p = 0.003$), which allows us to draw a conclusion about the superior effectiveness of therapy with the use of the drug Donovit-VS in comparison with therapy without the use of this drug.

6. Based on the statistical analysis of the toxicity data of CT and the safety of the treatment in the groups, the following data were obtained:

1) Analysis of hemodynamic indicators showed the absence of significant changes during the study, in most cases, in both groups. Slight fluctuations in blood pressure, heart rate, and body temperature were noted at different stages of observation, but they were not clinically significant. This indicates the absence of a negative effect of the therapy on hemodynamic indicators and body temperature.

2) A decrease in the level of leukocytes and platelets was noted in the patients of both groups during the study. These changes corresponded to the toxicity profile of chemotherapy drugs used and indicated the negative effect of CT on the hematopoietic system.

3) Differences between groups in the presence of leukocytopenia and thrombocytopenia were not statistically significant at all visits, although there was

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some trend at Visit 6 for a lower proportion of patients with leukocytopenia in primary group 7 (35.0%) compared with control group 5 (55.6%). However, when interpreting these results, it should be taken into account that at the end of the study, 20 patients of the main group and only 9 patients of the control group were included in the analysis.

4) Differences between groups in terms of hematological indicators were statistically insignificant at all visits, which indicates the absence of a negative effect of the investigated drug on the hematopoietic system.

5) Patients in both groups had elevated levels of ALT, AST, and total bilirubin at certain visits, which was a result of the effects of CT on the hepatobiliary system.

6) Statistically significant differences between the groups in terms of laboratory indicators of biochemical blood analysis were not found at any of the visits. The differences that were observed were, as a rule, related to the initial condition of the patients and the CT courses received before the visits.

7) Statistically significant differences between the groups were not found for any of the indicators at any of the visits in accordance with the laboratory parameters of the biochemical analysis of the analyzed blood, the norm and the deviation from it.

8) The above indicates the absence of a negative effect of the investigated drug on the indicators of biochemical blood analysis.

9) According to the results of the analysis of the laboratory indicators of the general urinalysis, no statistically significant differences between the groups were found for any of the indicators at any of the visits, which indicates the absence of a negative effect of the studied drug on the indicators of the general urinalysis.

10) Differences between groups in the pathology of the cardiovascular system, according to ECG data, were statistically insignificant at each of the visits, which indicates the absence of a negative effect of the studied drug on ECG parameters.

11) In the course of treatment, according to the ECG, nonspecific pathological changes were detected in 6 patients (21.4%) of the main group and in 4 (13.8%) patients of the control group, and the differences between the groups were statistically insignificant ($p = 0.504$). Heart rhythm disturbances of the 1st-2nd degree of toxicity were observed in 2 (7.7%) patients of the main group and in 4 (16.7%) patients of the control group. Differences between groups were also statistically insignificant ($p = 0.670$).

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12) There were also no statistically significant differences between groups in other parameters of non-hematological toxicity of CT, such as gastrointestinal toxicity (constipation, nausea/vomiting, diarrhea), its manifestations were noted in 20 (71.4%) patients of the main group and in 16 (55 .2%) of control patients.

13) Summarizing the above, it can be stated that the overall toxicity profile for the group of patients who received Donovit-VS on the background of CT was not statistically significantly different from the group that received only CT.

7. The dynamics of quality of life assessments on the QL2 scale of the EORTC QLQ-C30 questionnaire during treatment was insignificant in both groups. Some increase in mean values in the control group at the last visit was due to the fact that in the control group patients with poor quality of life scores dropped out, while in the main group some patients with poor quality of life scores were still present at the last visit (20 patients of the main group and only 9 patients of the control group were included in the analysis).

9) As a result of the statistical analysis of the evaluations of the patients' condition according to the ECOG scale, no statistically significant differences between the groups were found at any of the visits.

The results of the transferability analysis.

During the study, 42 AE/AR were registered in 17 (56.7%) patients of the main group (with the use of Donovit-VS) and 35 AE/AR in 10 (34.5%) patients of the control group (without the use of Donovit-VS).

Of them, in the main group, 10 serous AE/AR were registered in 8 (26.7%) patients and in the control group - 14 serious AE/AR in 3 (10.3%) patients.

In this study, the following AE/AR were most often encountered: leukopenia, thrombocytopenia, increased transaminase levels; from the gastrointestinal tract, such phenomena as constipation and nausea/vomiting. Almost all AE/AR registered during the study were directly related to the course of the underlying disease and corresponded to the toxicity profile of the chemotherapeutic drugs used.

In the course of the study, no allergic and anaphylactic reactions were recorded in the group of patients taking the studied drug.

On the basis of the conducted statistical analysis, it is possible to draw a conclusion regarding the absence of a negative effect of the studied drug on hemodynamic indicators and body temperature, laboratory indicators of the general blood test, biochemical blood test, general urinalysis and ECG indicators.

Only in one case (patient No. 60, male, 51 years old, main group) was observed an increase in body temperature, probably related to the use of the study drug Donovit-VS. The patient was discontinued from Donovit-VS and withdrawn from the study.

On the basis of the above, it can be assumed that the tolerability of the drug Donovit-VS was good in 96.3% of patients.

15.10 Conclusions and recommendations

1. The drug Donovit-VS, tablets produced by "Astrapharm" LLC, which was prescribed 1 tablet 3 times a day for 12 months on the background of CT, is an effective tool in the treatment of patients with glioblastoma.

2. Based on the analysis of the data of the clinical study, it was proved that the treatment of patients with glioblastoma was more effective in the group of patients who received the drug Donovit-VS, tablets produced by Astrapharm LLC, against the background of antitumor CT, compared to the group of patients who received only CT. This was manifested in terms of overall one-year patient survival and one-year recurrence-free survival. Thus, the arithmetic mean of overall one-year survival was 347.5 days in the main group and 309.45 in the control group, the differences between the groups are statistically significant ($p = 0.030$). The arithmetic mean of one-year recurrence-free survival was 11.5 months in the main group and 9.2 months in the control group, the differences between the groups are statistically significant ($p < 0.001$).

The overall one-year survival of patients in the main group was 78.6%, and in the control group - 51.7%. The difference in the percentage of surviving patients is 26.8%. The relapse-free one-year survival of patients in the main group was 75.0%, and in the control group - 34.5%. The difference in proportions is 40.5%, the differences between groups are statistically significant ($p = 0.003$).

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The above allows us to draw a conclusion about the superior effectiveness of therapy with the use of the drug Donovit-VS in comparison with therapy without the use of this drug in patients with glioblastoma.

3. The overall toxicity profile for the group of patients who received the drug Donovit-VS on the background of CT was not statistically significantly different from the group that received only chemotherapy.

4. There were no statistically significant differences in QL2 scores of the EORTC QLQ-C30 and ECOG scores between groups at any of the visits.

5. The data obtained during the research show the safety and good tolerability of the drug Donovit-VS, a tablet produced by Astrapharm LLC, which is prescribed 1 tablet 3 times a day for 12 months against the background of antitumor CT in patients with glioblastoma.

6. On the basis of the above, the drug Donovit-VS, tablets produced by Astrapharm LLC, can be recommended for medical use in patients with glioblastoma as an accompanying drug during the course of CT. Recommended treatment regimen: 1 tablet 3 times a day for 12 months.

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Appendix A

Scheme of randomization

Table A.1 - Randomization scheme for 60 patients allocated in a 1:1 ratio

Randomization number	A random number	Group
01	0.830996	Control
02	0.792088	The main one
03	0.148496	The main one
04	0.797718	Control
05	0.382219	Control
06	0.969718	Control
07	0.371711	The main one
08	0.109764	Control
09	0.751012	The main one
10	0.198545	The main one
11	0.929615	The main one
12	0.952896	The main one
13	0.921078	The main one
14	0.839958	Control
15	0.800542	The main one
16	0.204617	Control
17	0.82241	The main one
18	0.416479	The main one
19	0.479426	Control
20	0.192624	Control
21	0.034415	The main one
22	0.502388	The main one
23	0.305927	The main one
24	0.710435	Control
25	0.739038	The main one
26	0.864348	Control
27	0.042558	The main one
28	0.283013	Control
29	0.92389	Control
30	0.852028	The main one
31	0.702807	The main one
32	0.682393	The main one
33	0.83537	The main one
34	0.038733	Control

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Randomization number	A random number	Group
35	0.629264	Control
36	0.693304	Control
37	0.681789	Control
38	0.112023	The main one
39	0.821748	Control
40	0.128793	Control
41	0.586501	Control
42	0.014343	Control
43	0.515425	The main one
44	0.095858	Control
45	0.791022	Control
46	0.333643	Control
47	0.008941	The main one
48	0.511061	Control
49	0.108156	The main one
50	0.944008	Control
51	0.742543	Control
52	0.866164	The main one
53	0.625123	Control
54	0.89628	Control
55	0.626203	The main one
56	0.243747	The main one
57	0.656681	The main one
58	0.558686	Control
59	0.617747	The main one
60	0.582835	The main one

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Appendix B

CTC NCIC Chemotherapy Toxicity Rating Scale

(CTC NCIC - Common Toxicity Criteria National Cancer Institute)

Note: *the table is filled out by the researcher on the basis of patient survey DBRa, as well as laboratory and objective examination. DBRa registrations are made starting from the 3rd visit.*

Points	Degree of toxicity
0 points	0
1 point	I
2 points	II
3 points	III
4 points	IV

Indicator	Degree toxicity	Before treatment	Visit 3	Visit 4	Visit 5	Visit 6
		date				
Hemoglobin, g/l						
>110 g/l	0					
95-109 g/l	I					
80-94 g/l	II					
65-79 g/l	III					
<65 g/l	IV					
Leukocytes, 10^9 /l						
> 4.0	0					
3-3.9	I					
2-2.9	II					
1.0-2.0	III					
<1.0	IV					
Granulocytes 10^9 /l						
>2	0					
1.5-1.9	I					
1.0-1.4	II					
0.5-0.9	III					
<0.5	IV					
Platelets 10^9 /l						
>100	0					
75-99	I					
50-74	II					
25-49	III					
<25	IV					
Bleeding						
absent	0					

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Weak petechiae	I					
Does not require treatment or blood transfusion	II					
Expressed, requires a blood transfusion up to 4 times of 500 ml	III					
A blood transfusion is required > than 4 times 500 ml each	IV					
Bilirubin						
<1.25 x N [a]	0					
1.25-2.5 x N [a]	I					
1.25-5.0 x N [a]	II					
5.1-10.0 x N [a]	III					
> 10.0 x N [a]	IV					
AST, ALT						
<1.25 x N [a]	0					
1.25-2.5 x N [a]	I					
1.25-5.0 x N [a]	II					
5.1-10.0 x N [a]	III					
> 10.0 x N [a]	IV					
Diarrhea						
Absent	0					
Disappears in less than 2 days	I					
Tolerating more than 2 days	II					
Intolerable, requires treatment	III					
Hemorrhages and dehydration, requiring intravenous fluid infusion	IV					
Nausea, vomiting						
Absent	0					
Nausea	I					
Vomiting that passes	II					
Vomiting that requires treatment	III					
Unbearable vomiting	IV					
State of the oral cavity						
No changes	0					
Itching, heartburn, erythema	I					
Erythema, ulcers, free food intake	II					
Ulcers, it is difficult to take food, only liquid food is necessary	III					
It is impossible to take food	IV					
Proteinuria						
Absent	0					
1+<0.3 g/l	I					
2-3+<3-10 g/l	II					
4+<10 g/l	III					
Nephrotic syndrome	IV					
Obstructive uropathy	0					
Pulmonary changes						
Absent	0					
X-ray changes are minimal	I					
Moderate symptoms that do not require	II					

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special treatment						
Periodic shortness of breath at rest	III					
Shortness of breath is constant, requires constant stay in bed	IV					
Temperature						
Normal	0					
Less than 38°C	I					
38°C-40°C	II					
More than 40°C	III					
An increase in temperature with a decrease in blood pressure/collapse	IV					
Allergic reactions						
Absent	0					
Dermatitis or edema	I					
Bronchospasm not requiring treatment	II					
Bronchospasm requiring treatment	III					
Anaphylactic shock	IV					
Skin manifestations						
Absent	0					
Erythema	I					
Dry peeling, vesicles, itching	II					
Wet peeling, ulcers	III					
Necrosis requiring surgical intervention, dermatitis with peeling	IV					
hair						
No changes	0					
Minimal hair loss	I					
Moderate alopecia areata	II					
Complete but reversible alopecia	III					
Complete, but irreversible alopecia	IV					
Infection						
Absent	0					
local	I					
Medium grade	II					
heavy	III					
Threatening, sepsis	IV					
Heart rhythm disorders						
Absent	0					
Sinus tachycardia > 100 bpm at rest	I					
Unifocal ventricular extrasystole, atrial fibrillation	II					
Multifocal extrasystole	III					
Ventricular tachycardia	IV					
Violations of heart function						
Absent	0					
Asymptomatic disorders of cardiac activity	I					
Transient symptomatic dysfunction that does not require treatment	II					
Symptomatic dysfunction corrected by treatment	III					

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Symptomatic dysfunction not corrected by treatment	IV					
Pericarditis						
Absent	0					
Asymptomatic fluid accumulation	I					
Symptomatic disorders that do not require treatment	II					
Tamponade, requiring treatment, myocardial function	III					
Tamponade requiring surgical intervention	IV					
Neurotoxicity: state						
Vigilance	0					
Passing drowsiness	I					
Drowsiness/sleepless time <50%	II					
Drowsiness/sleepless time >50%	III					
Coma	IV					
Peripheral neuropathies						
Absent	0					
Paresthesias/or decreased tendon reflexes	I					
Severe paresthesias, moderate weakness	II					
Intolerable paresthesias, loss of motor reactions	III					
Paralysis	IV					
Constipation						
Absent	0					
rare	I					
Moderate	II					
Abdominal itching	III					
Abdominal distension, vomiting	IV					
Pain						
Absent	0					
weak	I					
moderate	II					
Strong	III					
Intolerable, requiring the use of drugs	IV					
Total points						

N^a is the upper limit of normal indicators.

b - constipation that is not associated with the use of drugs.

c - pain associated with treatment, not with the disease.

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Appendix B
Questionnaire for quality of life assessment of the European Organization for Cancer Research and Treatment EORTC QLQ-C30 (version 3.0)

We want to ask you a few questions about you and your health. Please answer all the questions yourself, circling the number of the answer that most accurately reflects your situation. There are no "right" or "wrong" answers here. All information provided by you will be kept confidential.

Please specify:

Your initials (the first letters of your first name)_____ _____

date of birth (day, month, hour):_____

Today's date (day, month, hour): _____

		No	Rather no than yes	Rather yes than no	Yes
1	Do you experience any difficulties when performing work that requires significant physical effort, for example, when you carry a heavy utility bag or suitcase?				
2	Do you experience any difficulties while taking a long walk?				
3	Do you experience any difficulties while taking a short walk on the street?				
4	Do you have to spend most of the day in bed or in a chair?				
5	Do you need help eating, dressing, washing or using the toilet?				

During the last week:

		No	Rather no than yes	Rather yes than no	Yes
6	Did anything limit you in one way or another when you performed your work or other daily tasks?				
7	Has anything limited you in one way or another while doing your favorite business or other leisure activities?				
8	Have you had shortness of breath?				
9	Did you have pain?				
10	Did you need a vacation?				
11	Did you have a disturbed sleep?	1	2	3	4
12	Did you feel weak?	1	2	3	4

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thirteen	Have you had a loss of appetite?	1	2	3	4
14	Did you feel nauseous?	1	2	3	4
15	Did you vomit?	1	2	3	4
16	Have you been constipated?	1	2	3	4
17	Have you had diarrhea?	1	2	3	4
18	Did you feel tired?	1	2	3	4
19	Has the pain prevented you from doing your daily activities?	1	2	3	4
20	Was it difficult for you to concentrate on something, for example, reading a newspaper or watching TV?	1	2	3	4
21	Have you experienced a feeling of tension?	1	2	3	4
22	Have you experienced a feeling of anxiety?	1	2	3	4
23	Have you experienced a feeling of irritation?	1	2	3	4
24	Have you experienced a feeling of depression?	1	2	3	4
25	Was it difficult for you to remember something?	1	2	3	4
26	Has your physical condition or treatment interfered with your family life?	1	2	3	4
27	Did your physical condition or the treatment you were undergoing prevent you from appearing in public (visiting, going to the movies, etc.)?	1	2	3	4
28	Has your physical condition or treatment caused you financial difficulties?	1	2	3	4

When answering the following questions, please circle the answer number from 1 to 7 that most accurately reflects your situation.

How would you rate your overall health over the past week?

1 2 3 4 5 6 7

Very bad Excellent

30.How would you rate your overall quality of life over the past week?

1 2 3 4 5 6 7

Very bad Excellent

Total points_____

APPENDIX D
Additional results of statistical analysis

Table D.1 Results of testing the normality of the distribution of data describing patients included in the PP-analysis of effectiveness

Parameter	Shapiro-Wilk statistics	df	p-value	Conclusion on the normality of the distribution*
Age, years	0.898	59	<0.001	Not normal
Body weight, kg	0.982	59	0.545	Normal
BMI, kg/m ^{2}	0.974	59	0.250	Normal
ECOG, points	0.702	59	<0.001	Not normal
Leukocytes, x 10 ^{9} cells/l	0.953	59	0.024	Normal
Neutrophils	0.974	59	0.241	Normal
Platelets, x 10 ^{9} cells/l	0.936	59	0.004	Not normal
Hemoglobin, g/l	0.988	59	0.837	Normal
ALT, units/l	0.964	59	0.076	Normal
AST, Od, l	0.849	59	<0.001	Not normal
Total bilirubin, mlmol/l	0.929	59	0.002	Not normal
Creatinine, μmol/l	0.972	59	0.185	Normal
** Done at a significance level of 0.01.*				

Table D.2 Results of checking the normality of data distribution when checking the initial homogeneity of groups and analyzing efficiency and transferability

Parameter	Group	Shapiro-Wilk statistics	df	p-value	Conclusion on the normality of the distribution*
Age	The main one	0.859	28	0.001	Not normal
	Control	0.918	29	0.027	Normal
Height	The main one	0.976	28	0.737	Normal
	Control	0.928	29	0.048	Normal
Body weight	The main one	0.979	28	0.832	Normal
	Control	0.967	29	0.475	Normal
BMI	The main one	0.972	28	0.638	Normal
	Control	0.935	29	0.074	Normal
ECOG for visit 1, points	The main one	0.451	28	<0.001	Not normal

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Parameter	Group	Shapiro-Wilk statistics	df	p-value	Conclusion on the normality of the distribution*
	Control	0.770	29	<0.001	Not normal
Number of CT courses	The main one	0.950	28	0.196	Normal
	Control	0.904	29	0.012	Normal
SBR for B1	The main one	0.879	28	0.004	Not normal
	Control	0.934	29	0.069	Normal
DBR for B1	The main one	0.879	28	0.004	Not normal
	Control	0.945	29	0.138	Normal
Heart rate for B1	The main one	0.933	28	0.072	Normal
	Control	0.837	29	<0.001	Not normal
Body temperature for B1	The main one	0.697	28	<0.001	Not normal
	Control	0.530	29	<0.001	Not normal
Leukocytes for B1	The main one	0.929	28	0.057	Normal
	Control	0.926	29	0.042	Normal
Erythrocytes for B1	The main one	0.974	28	0.702	Normal
	Control	0.970	29	0.556	Normal
Hematocrit for B1	The main one	0.554	28	0.000	Not normal
	Control	0.969	29	0.521	Normal
Hemoglobin for B1	The main one	0.971	28	0.609	Normal
	Control	0.944	29	0.129	Normal
Platelets for B1	The main one	0.913	28	0.024	Normal
	Control	0.898	29	0.009	Not normal
Neutrophils for B1	The main one	0.959	28	0.327	Normal
	Control	0.967	29	0.482	Normal
Lymphocytes for B1	The main one	0.950	28	0.197	Normal
	Control	0.949	29	0.169	Normal
Monocytes for B1	The main one	0.872	28	0.003	Not normal
	Control	0.888	29	0.005	Not normal
Eosinophils for B1	The main one	0.823	28	0.000	Not normal
	Control	0.406	29	0.000	Not normal
Basophils for B1	The main one	0.433	28	0.000	Not normal
	Control	0.412	29	0.000	Not normal
ESR for B1	The main one	0.780	28	0.000	Not normal
	Control	0.816	29	0.000	Not normal
AST for B1	The main one	0.905	28	0.015	Normal

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Parameter	Group	Shapiro-Wilk statistics	df	p-value	Conclusion on the normality of the distribution*
	Control	0.838	29	0.000	Not normal
ALT for B1	The main one	0.975	28	0.710	Normal
	Control	0.942	29	0.115	Normal
Bilirubin is common to B1	The main one	0.907	28	0.017	Normal
	Control	0.946	29	0.141	Normal
The protein is common to B1	The main one	0.992	28	0.998	Normal
	Control	0.912	29	0.019	Normal
Creatinine for B1	The main one	0.811	28	0.000	Not normal
	Control	0.982	29	0.879	Normal
Glucose for B1	The main one	0.905	28	0.015	Normal
	Control	0.838	29	0.000	Not normal
Specific gravity for B1	The main one	0.841	28	0.001	Not normal
	Control	0.970	29	0.571	Normal
pH for B1	The main one	0.188	28	0.000	Not normal
	Control	0.572	29	0.000	Not normal
Protein in urine for B1	The main one	0.188	28	0.000	Not normal
	Control	0.412	29	0.000	Not normal
Leukocytes in urine for B1	The main one	0.854	28	0.001	Not normal
	Control	0.419	29	0.000	Not normal
Erythrocytes in urine for B1	The main one	0.589	28	0.000	Not normal
	Control	0.584	29	0.000	Not normal
Cylinders for B1	The main one	0.188	28	0.000	Not normal
	Control	0.184	29	0.000	Not normal

Table D.3 Additional rank statistics obtained when comparing groups

Changeable	Group	n	Average rank	Sum of ranks
Age	The main one	28	31.52	882.50
	Control	29	26,57	770.50
	In total	57		
ECOG for B1	The main one	28	31,43	880
	Control	29	26.66	773
	In total	57		
SBR for B1	The main one	28	28.93	810.00
	Control	29	29.07	843.00

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Changeable	Group	n	Average rank	Sum of ranks
	In total	57		
DBR for B1	The main one	28	27.93	782.00
	Control	29	30.03	871.00
	In total	57		
Heart rate for B1	The main one	28	28.57	800.00
	Control	29	29,41	853.00
	In total	57		
Body temperature for B1	The main one	28	28.64	802.00
	Control	29	29,34	851.00
	In total	57		
Hematocrit for B1	The main one	28	25.93	726.00
	Control	29	31.97	927.00
	In total	57		
Platelets for B1	The main one	28	33.20	929.50
	Control	29	24.95	723.50
	In total	57		
Monocytes for B1	The main one	28	27.63	773.50
	Control	29	30,33	879.50
	In total	57		
Eosinophils for B1	The main one	28	32.05	897.50
	Control	29	26.05	755.50
	In total	57		
Basophils for B1	The main one	28	29,14	816.00
	Control	29	28.86	837.00
	In total	57		
ESR for B1	The main one	28	29.95	838.50
	Control	29	28.09	814.50
	In total	57		
AST for B1	The main one	28	29.63	829.5
	Control	29	28.4	823.5
	In total	57		
Glucose for B1	The main one	28	29,34	821.5
	Control	29	28.67	831.5
	In total	57		
Specific gravity for B1	The main one	28	29.00	812.00
	Control	29	29.00	841.00
	In total	57		

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Changeable	Group	n	Average rank	Sum of ranks
RF for B1	The main one	28	25,39	711.00
	Control	29	32,48	942.00
	In total	57		
Protein in urine for B1	The main one	28	27.52	770.50
	Control	29	30,43	882.50
	In total	57		
Leukocytes in urine for B1	The main one	28	29.43	824.00
	Control	29	28,59	829.00
	In total	57		
Erythrocytes in urine for B1	The main one	28	28.79	806.00
	Control	29	29,21	847.00
	In total	57		
Cylinders for B1	The main one	28	29.00	812.00
	Control	29	29.00	841.00
	In total	57		

Table D.4 Results of comparison of groups on visits using ANCOVA

Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
Leukocytes [B3]	Corrected Model	41,956 [a]	2	20.98	4.35	0.018
	Intercept	47.62	1	47.62	9.88	0.003
	Leukocytes [B1]	41.94	1	41.94	8.70	0.005
	Group	0.15	1	0.15	0.03	0.860
	Error	260.28	54	4.82		
	In total	1694.13	57			
	Corrected Total	302.24	56			
Leukocytes [B4]	Corrected Model	17,837 [a]	2	8.92	0.93	0.403
	Intercept	77.45	1	77.45	8.06	0.007
	Leukocytes [B1]	17.83	1	17.83	1.85	0.180
	Group	0.11	1	0.11	0.01	0.917
	Error	422.99	44	9.61		
	In total	1694.19	47			
	Corrected Total	440.83	46			
Leukocytes [B5]	Corrected Model	,182 [a]	2	0.09	0.01	0.985
	Intercept	138.00	1	138.00	22.34	0.000
	Leukocytes [B1]	0.01	1	0.01	0.00	0.965
	Group	0.18	1	0.18	0.03	0.866

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	Error	203.85	33	6.18		
	In total	1184.77	36			
	Corrected Total	204.04	35			
Leukocytes [B6]	Corrected Model	9,433 [a]	2	4.72	1.05	0.363
	Intercept	71.86	1	71.86	16.07	0.000
	Leukocytes [B1]	1.85	1	1.85	0.41	0.525
	Group	8.47	1	8.47	1.89	0.180
	Error	116.25	26	4.47		
	In total	783.33	29			
	Corrected Total	125.69	28			
Hemoglobin [B3]	Corrected Model	1991,329 [a]	2	995.66	5.38	0.007
	Intercept	4419.49	1	4419.49	23.87	0.000
	Hemoglobin [B1]	1878.72	1	1878.72	10,15	0.002
	Group	60.52	1	60.52	0.33	0.570
	Error	10000.04	54	185.19		
	In total	1049197.00	57			
	Corrected Total	11991.37	56			
Hemoglobin [B4]	Corrected Model	4682.326 [a]	2	2341.16	10.02	0.000
	Intercept	1208.04	1	1208.04	5.17	0.028
	Hemoglobin [B1]	4033.65	1	4033.65	17,26	0.000
	Group	221.58	1	221.58	0.95	0.335
	Error	10281.08	44	233.66		
	In total	830463.00	47			
	Corrected Total	14963.40	46			
Hemoglobin [B5]	Corrected Model	6087,469a	2	3043.73	10.93	0.000
	Intercept	174.80	1	174.80	0.63	0.434
	Hemoglobin [B1]	5807.41	1	5807.41	20.86	0.000
	Group	26,23	1	26,23	0.09	0.761
	Error	9186.17	33	278.37		
	In total	635955.00	36			
	Corrected Total	15273.64	35			
Hemoglobin [B6]	Corrected Model	1424,736a	2	712.37	2.02	0.153
	Intercept	1295.22	1	1295.22	3.67	0.067
	Hemoglobin [B1]	1400.59	1	1400.59	3.97	0.057
	Group	5.79	1	5.79	0.02	0.899
	Error	9182.71	26	353.18		
	In total	484720.00	29			

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	Corrected Total	10607.45	28			
Platelets [B3]	Corrected Model	9556,169a	2	4778.08	1.29	0.283
	Intercept	61599.80	1	61599.80	16.67	0.000
	Platelets [B1]	9297.07	1	9297.07	2.52	0.119
	Group	1276.37	1	1276.37	0.35	0.559
	Error	199578.08	54	3695.89		
	In total	1905068.00	57			
	Corrected Total	209134.25	56			
Platelets [B4]	Corrected Model	10858.020 [a]	2	5429.01	1.97	0.151
	Intercept	30478.10	1	30478.10	11.08	0.002
	Platelets [B1]	10305.64	1	10305.64	3.75	0.059
	Group	1945.01	1	1945.01	0.71	0.405
	Error	121047.90	44	2751.09		
	In total	1335746.00	47			
	Corrected Total	131905.91	46			
Platelets [B5]	Corrected Model	54074,998a	2	27037.50	11.96	0.000
	Intercept	6250.35	1	6250.35	2.77	0.106
	Platelets [B1]	35578.94	1	35578.94	15.74	0.000
	Group	7966.10	1	7966.10	3.52	0.069
	Error	74587.97	33	2260.24		
	In total	1150447.00	36			
	Corrected Total	128662.97	35			
Platelets [B6]	Corrected Model	22538,385a	2	11269.19	2.67	0.088
	Intercept	23623.27	1	23623.27	5.60	0.026
	Platelets [B1]	14627.76	1	14627.76	3.47	0.074
	Group	1935,44	1	1935,44	0.46	0.504
	Error	109688.44	26	4218.79		
	In total	1142218.00	29			
	Corrected Total	132226.83	28			
Erythrocytes [B3]	Corrected Model	4,673 [a]	2	2.34	10.02	0.000
	Intercept	1.75	1	1.75	7.51	0.008
	Erythrocytes [B1]	4.17	1	4.17	17.87	0.000
	Group	0.44	1	0.44	1.88	0.176
	Error	12.59	54	0.23		
	In total	1106.66	57			
	Corrected Total	17,26	56			

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
Erythrocytes [B4]	Corrected Model	4,891 [a]	2	2.45	6.59	0.003
	Intercept	1.07	1	1.07	2.88	0.097
	Erythrocytes [B1]	4.19	1	4.19	11.30	0.002
	Group	0.39	1	0.39	1.06	0.309
	Error	16.33	44	0.37		
	In total	870.84	47			
	Corrected Total	21,22	46			
Erythrocytes [B5]	Corrected Model	4,581 [a]	2	2.29	5.44	0.009
	Intercept	0.30	1	0.30	0.72	0.403
	Erythrocytes [B1]	4.31	1	4.31	10.23	0.003
	Group	0.20	1	0.20	0.47	0.499
	Error	13.89	33	0.42		
	In total	665.41	36			
	Corrected Total	18.47	35			
Erythrocytes [B6]	Corrected Model	3,866 [a]	2	1.93	4.26	0.025
	Intercept	0.12	1	0.12	0.27	0.605
	Erythrocytes [B1]	3.84	1	3.84	8.45	0.007
	Group	0.00	1	0.00	0.00	0.999
	Error	11.81	26	0.45		
	In total	535.08	29			
	Corrected Total	15.67	28			
Neutrophils [B3]	Corrected Model	1440,643 [a]	2	720.32	9,11	0.000
	Intercept	1688.44	1	1688.44	21.35	0.000
	Neutrophils [B1]	1105.06	1	1105.06	13.98	0.000
	Group	401.88	1	401.88	5.08	0.028
	Error	4269.59	54	79.07		
	In total	258417.29	57			
	Corrected Total	5710.24	56			
Neutrophils [B4]	Corrected Model	546,321 [a]	2	273.16	3.24	0.049
	Intercept	1958,81	1	1958,81	23,24	0.000
	Neutrophils [B1]	536.48	1	536.48	6.37	0.015
	Group	10.58	1	10.58	0.13	0.725
	Error	3707.82	44	84.27		
	In total	211953.62	47			
	Corrected Total	4254.14	46			

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
Neutrophils [B5]	Corrected Model	728,718 [a]	2	364.36	1.96	0.158
	Intercept	1631.07	1	1631.07	8.75	0.006
	Neutrophils [B1]	594.24	1	594.24	3.19	0.083
	Group	176.64	1	176.64	0.95	0.337
	Error	6149.66	33	186.35		
	In total	176292.94	36			
	Corrected Total	6878.38	35			
Neutrophils [B6]	Corrected Model	367,824 [a]	2	183.91	1.10	0.348
	Intercept	1881.12	1	1881.12	11.23	0.002
	Neutrophils [B1]	105.04	1	105.04	0.63	0.436
	Group	335.54	1	335.54	2.00	0.169
	Error	4353.64	26	167.45		
	In total	133819.33	29			
	Corrected Total	4721.47	28			
Lymphocytes [B3]	Corrected Model	1763.785 [a]	2	881.89	15.03	0.000
	Intercept	1374.32	1	1374.32	23.43	0.000
	Lymphocytes [B1]	1511.27	1	1511.27	25.76	0.000
	Group	235.25	1	235.25	4.01	0.050
	Error	3167.90	54	58,66		
	In total	41548.49	57			
	Corrected Total	4931.68	56			
Lymphocytes [B4]	Corrected Model	433,224 [a]	2	216.61	2.59	0.087
	Intercept	2296.21	1	2296.21	27.43	0.000
	Lymphocytes [B1]	385.16	1	385.16	4.60	0.037
	Group	71.48	1	71.48	0.85	0.360
	Error	3682.76	44	83.70		
	In total	33887.31	47			
	Corrected Total	4115.98	46			
Lymphocytes [B5]	Corrected Model	466,722 [a]	2	233.36	2.11	0.137
	Intercept	1680.54	1	1680.54	15,21	0.000
	Lymphocytes [B1]	255.57	1	255.57	2.31	0.138
	Group	214.28	1	214.28	1.94	0.173
	Error	3645.73	33	110.48		
	In total	22758.35	36			
	Corrected Total	4112.45	35			
Lymphocytes	Corrected Model	376,404 [a]	2	188.20	1.76	0.191
	Intercept	1904,43	1	1904,43	17.84	0.000

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
[B6]	Lymphocytes [B1]	159.40	1	159.40	1.49	0.233
	Group	292.58	1	292.58	2.74	0.110
	Error	2775.98	26	106.77		
	In total	21277.38	29			
	Corrected Total	3152.38	28			
ESR [B3]	Corrected Model	1132,403a	2	566.20	9.41	0.000
	Intercept	1006.02	1	1006.02	16.71	0.000
	ESR [B1]	941.31	1	941.31	15.64	0.000
	Group	211.40	1	211.40	3.51	0.066
	Error	3250.58	54	60.20		
	In total	11727.00	57			
	Corrected Total	4382.98	56			
ESR [B4]	Corrected Model	919,697 [a]	2	459.85	4.08	0.024
	Intercept	1135.99	1	1135.99	10.09	0.003
	ESR [B1]	913.02	1	913.02	8,11	0.007
	Group	3.40	1	3.40	0.03	0.863
	Error	4955.71	44	112.63		
	In total	12959.00	47			
	Corrected Total	5875.40	46			
ESR [B5]	Corrected Model	507,818a	2	253.91	0.94	0.402
	Intercept	2299.48	1	2299.48	8.48	0.006
	ESR [B1]	16.93	1	16.93	0.06	0.804
	Group	497.36	1	497.36	1.84	0.185
	Error	8943.82	33	271.03		
	In total	16819.00	36			
	Corrected Total	9451.64	35			
ESR [B6]	Corrected Model	96,859a	2	48,43	0.23	0.799
	Intercept	1694.29	1	1694.29	7.90	0.009
	ESR [B1]	86.55	1	86.55	0.40	0.531
	Group	4.11	1	4.11	0.02	0.891
	Error	5577.14	26	214.51		
	In total	11358.00	29			
	Corrected Total	5674.00	28			
AST [B3]	Corrected Model	740,907 [a]	2	370.45	2.00	0.145
	Intercept	4617.08	1	4617.08	24.92	0.000
	AST [B1]	158.24	1	158.24	0.85	0.360
	Group	575.03	1	575.03	3.10	0.084

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	Error	10005.30	54	185.28		
	In total	51034.58	57			
	Corrected Total	10746.21	56			
AST [B4]	Corrected Model	37,507 [a]	2	18.75	0.07	0.931
	Intercept	4796.16	1	4796.16	18.31	0.000
	AST [B1]	1.99	1	1.99	0.01	0.931
	Group	35,37	1	35,37	0.14	0.715
	Error	11522.33	44	261.87		
	In total	45607.18	47			
	Corrected Total	11559.84	46			
AST [B5]	Corrected Model	149,529 [a]	2	74,76	0.23	0.793
	Intercept	3349.57	1	3349.57	10.47	0.003
	AST [B1]	38.52	1	38.52	0.12	0.731
	Group	117.41	1	117.41	0.37	0.549
	Error	10558.99	33	319.97		
	In total	37670.16	36			
	Corrected Total	10708.52	35			
AST [B6]	Corrected Model	1476,473a	2	738.24	1.37	0.273
	Intercept	5370.82	1	5370.82	9.95	0.004
	AST [B1]	57.43	1	57.43	0.11	0.747
	Group	1470.68	1	1470.68	2.72	0.111
	Error	13496.74	25	539.87		
	In total	39470.18	28			
	Corrected Total	14973.21	27			
ALT [B3]	Corrected Model	1134,953a	2	567.48	1.65	0.201
	Intercept	4489.37	1	4489.37	13.07	0.001
	ALT [B1]	836.48	1	836.48	2.44	0.124
	Group	184.01	1	184.01	0.54	0.467
	Error	18549.88	54	343.52		
	In total	78733.20	57			
	Corrected Total	19684.83	56			
ALT [B4]	Corrected Model	6731.380 [a]	2	3365.69	3.79	0.030
	Intercept	207.46	1	207.46	0.23	0.631
	ALT [B1]	6670.46	1	6670.46	7.51	0.009
	Group	175.74	1	175.74	0.20	0.659
	Error	39083.79	44	888.27		
	In total	100528.64	47			

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	Corrected Total	45815.17	46			
ALT [B5]	Corrected Model	36677,235a	2	18338.62	2.90	0.069
	Intercept	3815.62	1	3815.62	0.60	0.443
	ALT [B1]	34539.75	1	34539.75	5.45	0.026
	Group	2341.76	1	2341.76	0.37	0.547
	Error	208992.74	33	6333.11		
	In total	332419.86	36			
	Corrected Total	245669.98	35			
ALT [B6]	Corrected Model	641,757a	2	320.88	0.47	0.630
	Intercept	2709.58	1	2709.58	3.97	0.057
	ALT [B1]	514.04	1	514.04	0.75	0.394
	Group	68,41	1	68,41	0.10	0.754
	Error	17059.10	25	682.36		
	In total	55384.42	28			
	Corrected Total	17700.85	27			
Bilirubin [B3]	Corrected Model	1348,161 [a]	2	674.08	8.90	0.000
	Intercept	139.05	1	139.05	1.84	0.181
	Bilirubin [B1]	1317.06	1	1317.06	17.40	0.000
	Group	24,20	1	24,20	0.32	0.574
	Error	4088.47	54	75,71		
	In total	19041.44	57			
	Corrected Total	5436.63	56			
Bilirubin [B4]	Corrected Model	542,264a	2	271.13	7.60	0.001
	Intercept	166.07	1	166.07	4.66	0.036
	Bilirubin [B1]	542.26	1	542.26	15,20	0.000
	Group	46,21	1	46,21	1.30	0.261
	Error	1569.87	44	35.68		
	In total	10369.40	47			
	Corrected Total	2112,13	46			
Bilirubin [B5]	Corrected Model	1065,136a	2	532.57	14.58	0.000
	Intercept	5.99	1	5.99	0.16	0.688
	Bilirubin [B1]	988.50	1	988.50	27.06	0.000
	Group	16.36	1	16.36	0.45	0.508
	Error	1205.55	33	36.53		
	In total	9069.51	36			
	Corrected Total	2270.69	35			
Bilirubin [B6]	Corrected Model	216,491a	2	108.25	5.51	0.010

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	Intercept	167.98	1	167.98	8.54	0.007
	Bilirubin [B1]	195.32	1	195.32	9.93	0.004
	Group	0.19	1	0.19	0.01	0.924
	Error	491.56	25	19.66		
	In total	5062.07	28			
	Corrected Total	708.05	27			
Creatinine [B3]	Corrected Model	3481,307a	2	1740.65	18,19	0.000
	Intercept	2733.20	1	2733.20	28.56	0.000
	Creatinine [B1]	3475.36	1	3475.36	36,31	0.000
	Group	82.02	1	82.02	0.86	0.359
	Error	5168.24	54	95.71		
	In total	314448.52	57			
	Corrected Total	8649.55	56			
Creatinine [B4]	Corrected Model	2686.937 [a]	2	1343.47	5.61	0.007
	Intercept	2498.02	1	2498.02	10.43	0.002
	Creatinine [B1]	2570.19	1	2570.19	10.73	0.002
	Group	127.10	1	127.10	0.53	0.470
	Error	10540.65	44	239.56		
	In total	273031.02	47			
	Corrected Total	13227.59	46			
Creatinine [B5]	Corrected Model	2773.824 [a]	2	1386.91	3.17	0.055
	Intercept	988.70	1	988.70	2.26	0.143
	Creatinine [B1]	2479.27	1	2479.27	5.66	0.023
	Group	100.14	1	100.14	0.23	0.636
	Error	14456.70	33	438.08		
	In total	207834.08	36			
	Corrected Total	17230.53	35			
Creatinine [B5]	Corrected Model	2931,500 [a]	2	1465.75	3.26	0.055
	Intercept	318.14	1	318.14	0.71	0.408
	Creatinine [B1]	2920.89	1	2920.89	6.50	0.017
	Group	12.07	1	12.07	0.03	0.871
	Error	11242.65	25	449.71		
	In total	181655.47	28			
	Corrected Total	14174.15	27			
Glucose [B3]	Corrected Model	10,303 [a]	2	5.15	2.66	0.079
	Intercept	42.06	1	42.06	21.75	0.000
	Glucose [B1]	9,14	1	9,14	4.73	0.034

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	Group	0.57	1	0.57	0.29	0.590
	Error	104.40	54	1.93		
	In total	1995,24	57			
	Corrected Total	114.70	56			
Glucose [B4]	Corrected Model	1,246a	2	0.62	0.40	0.676
	Intercept	56.00	1	56.00	35,49	0.000
	Glucose [B1]	0.89	1	0.89	0.56	0.458
	Group	0.29	1	0.29	0.19	0.670
	Error	69.43	44	1.58		
	In total	1469.09	47			
	Corrected Total	70.67	46			
Glucose [B5]	Corrected Model	32,788 [a]	2	16.39	2.90	0.069
	Intercept	7.87	1	7.87	1.39	0.246
	Glucose [B1]	21.82	1	21.82	3.86	0.058
	Group	7.79	1	7.79	1.38	0.249
	Error	186.42	33	5.65		
	In total	1681.00	36			
	Corrected Total	219.21	35			
Glucose [B6]	Corrected Model	13,929a	2	6.97	8.36	0.002
	Intercept	5.33	1	5.33	6.40	0.018
	Glucose [B1]	13.70	1	13.70	16.45	0.000
	Group	0.08	1	0.08	0.09	0.761
	Error	20.82	25	0.83		
	In total	898.33	28			
	Corrected Total	34.75	27			
Specific gravity [B3]	Corrected Model	134,832 [a]	2	67.42	0.33	0.722
	Intercept	2451.56	1	2451.56	11.91	0.001
	Specific gravity [B1]	56.75	1	56.75	0.28	0.602
	Group	86,91	1	86,91	0.42	0.519
	Error	11113.10	54	205.80		
	In total	58768588.00	57			
	Corrected Total	11247.93	56			
Specific gravity [B4]	Corrected Model	364,424a	2	182.21	3.24	0.049
	Intercept	1351.89	1	1351.89	24.03	0.000
	Specific gravity [B1]	285.41	1	285.41	5.07	0.029
	Group	75.14	1	75.14	1.34	0.254
	Error	2475.79	44	56,27		

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	In total	48392970.00	47			
	Corrected Total	2840.21	46			
Specific gravity [B5]	Corrected Model	438,894 [a]	2	219.45	4.37	0.021
	Intercept	937.13	1	937.13	18.65	0.000
	Specific gravity [B1]	372.77	1	372.77	7.42	0.010
	Group	38,29	1	38,29	0.76	0.389
	Error	1658.11	33	50.25		
	In total	37004986.00	36			
	Corrected Total	2097.00	35			
Specific gravity [B6]	Corrected Model	336,506a	2	168.25	1.79	0.186
	Intercept	967.26	1	967.26	10.32	0.003
	Specific gravity [B1]	250.51	1	250.51	2.67	0.114
	Group	62.85	1	62.85	0.67	0.420
	Error	2438.05	26	93.77		
	In total	29958522.00	29			
	Corrected Total	2774.55	28			
pH [B3]	Corrected Model	,016a	2	0.01	0.02	0.983
	Intercept	22.67	1	22.67	48,89	0.000
	pH [B1]	0.01	1	0.01	0.02	0.904
	Group	0.02	1	0.02	0.03	0.860
	Error	25.04	54	0.46		
	In total	2261.00	57			
	Corrected Total	25.05	56			
pH [B4]	Corrected Model	,627a	2	0.31	1.16	0.322
	Intercept	9.45	1	9.45	35.10	0.000
	pH [B1]	0.36	1	0.36	1.33	0.255
	Group	0.08	1	0.08	0.31	0.581
	Error	11.84	44	0.27		
	In total	1765.00	47			
	Corrected Total	12.47	46			
pH [B5]	Corrected Model	3,369a	2	1.69	3.90	0.030
	Intercept	14.85	1	14.85	34,34	0.000
	pH [B1]	1.02	1	1.02	2.36	0.134
	Group	3.09	1	3.09	7,14	0.012
	Error	14,27	33	0.43		
	In total	1449.00	36			
	Corrected Total	17.64	35			

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
pH [B6]	Corrected Model	,000a	1	0.00	0.00	1,000
	Intercept	0.00	0	.	.	.
	pH [B1]	0.00	0	.	.	.
	Group	0.00	1	0.00	0.00	1,000
	Error	19.00	26	0.73		
	In total	1202.00	28			
	Corrected Total	19.00	27			
Leukocytes in urine [B3]	Corrected Model	374,756a	2	187.38	1.57	0.218
	Intercept	718.55	1	718.55	6.00	0.018
	Leukocytes in urine [B1]	371.12	1	371.12	3.10	0.084
	Group	0.35	1	0.35	0.00	0.957
	Error	6464.75	54	119.72		
	In total	8636.00	57			
	Corrected Total	6839.51	56			
Leukocytes in urine [B4]	Corrected Model	1290,909a	2	645.46	12.58	0.000
	Intercept	0.39	1	0.39	0.01	0.931
	Leukocytes in urine [B1]	1289.97	1	1289.97	25.15	0.000
	Group	16.65	1	16.65	0.33	0.572
	Error	2257.30	44	51.30		
	In total	5065.00	47			
	Corrected Total	3548.21	46			
Leukocytes in urine [B5]	Corrected Model	22,486a	2	11,24	0.39	0.678
	Intercept	194.96	1	194.96	6.82	0.013
	Leukocytes in urine [B1]	2.43	1	2.43	0.09	0.773
	Group	22.41	1	22.41	0.78	0.383
	Error	944.07	33	28.61		
	In total	1660.00	36			
	Corrected Total	966.56	35			
Leukocytes in urine [B6]	Corrected Model	4,449a	2	2.22	0.37	0.695
	Intercept	174.49	1	174.49	28.90	0.000
	Leukocytes in urine [B1]	0.02	1	0.02	0.00	0.952
	Group	4.05	1	4.05	0.67	0.420
	Error	157.00	26	6.04		
	In total	594.00	29			

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	Corrected Total	161.45	28			
Erythrocytes in urine [B3]	Corrected Model	13,304a	2	6.65	1.10	0.342
	Intercept	24.44	1	24.44	4.02	0.050
	Erythrocytes in urine [B1]	4.73	1	4.73	0.78	0.382
	Group	7.41	1	7.41	1.22	0.274
	Error	328.06	54	6.08		
	In total	387.00	57			
	Corrected Total	341.37	56			
Erythrocytes in urine [B4]	Corrected Model	2,291a	2	1.15	1.58	0.218
	Intercept	1.10	1	1.10	1.52	0.224
	Erythrocytes in urine [B1]	2.25	1	2.25	3.10	0.085
	Group	0.22	1	0.22	0.30	0.587
	Error	31.92	44	0.73		
	In total	39.00	47			
	Corrected Total	34,21	46			
Erythrocytes in urine [B5]	Corrected Model	1,062a	2	0.53	0.75	0.479
	Intercept	1.48	1	1.48	2.10	0.156
	Erythrocytes in urine [B1]	0.38	1	0.38	0.54	0.467
	Group	0.86	1	0.86	1.22	0.277
	Error	23,24	33	0.70		
	In total	29.00	36			
	Corrected Total	24,31	35			
Erythrocytes in urine [B6]	Corrected Model	17,783a	2	8.89	0.92	0.410
	Intercept	25.00	1	25.00	2.59	0.119
	Erythrocytes in urine [B1]	7.74	1	7.74	0.80	0.379
	Group	5.17	1	5.17	0.54	0.471
	Error	250.77	26	9.65		
	In total	321.00	29			
	Corrected Total	268.55	28			
QL2 [B3]	Corrected Model	2171.057 [a]	2	1085.53	2.94	0.061
	Intercept	4074.82	1	4074.82	11.04	0.002
	QL2 [B1]	2119.71	1	2119.71	5.74	0.020
	Group	297.27	1	297.27	0.81	0.373
	Error	19929.33	54	369.06		

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	In total	244236.11	57			
	Corrected Total	22100.39	56			
QL2 [B4]	Corrected Model	1323,827a	2	661.91	1.57	0.219
	Intercept	4198.08	1	4198.08	9.98	0.003
	QL2 [B1]	1191.18	1	1191.18	2.83	0.099
	Group	408.88	1	408.88	0.97	0.329
	Error	18930.80	45	420.69		
	In total	203611,11	48			
	Corrected Total	20254.63	47			
QL2 [B5]	Corrected Model	202,540a	2	101.27	0.17	0.846
	Intercept	10196.59	1	10196.59	16.90	0.000
	QL2 [B1]	198.68	1	198.68	0.33	0.570
	Group	43,21	1	43,21	0.07	0.791
	Error	19911.27	33	603.37		
	In total	168125.00	36			
	Corrected Total	20113.81	35			
QL2 [B6]	Corrected Model	1612,002a	2	806.00	2.38	0.113
	Intercept	3362.51	1	3362.51	9.91	0.004
	QL2 [B1]	206.82	1	206.82	0.61	0.442
	Group	997.68	1	997.68	2.94	0.098
	Error	8819.03	26	339.19		
	In total	149513.89	29			
	Corrected Total	10431.03	28			
ECOG [B3]	Corrected Model	2,010 [a]	2	1.00	2.29	0.111
	Intercept	5.17	1	5.17	11.77	0.001
	ECOG [B1]	1.72	1	1.72	3.92	0.053
	Group	0.57	1	0.57	1.30	0.259
	Error	23.71	54	0.44		
	In total	75.00	57			
	Corrected Total	25.72	56			
ECOG [B4]	Corrected Model	1,731a	2	0.87	2.14	0.129
	Intercept	3.79	1	3.79	9.38	0.004
	ECOG [B1]	1.67	1	1.67	4.12	0.048
	Group	0.35	1	0.35	0.87	0.355
	Error	18,19	45	0.40		
	In total	64.00	48			
	Corrected Total	19.92	47			

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
ECOG [B5]	Corrected Model	1,186a	2	0.59	0.62	0.546
	Intercept	11.40	1	11.40	11.83	0.002
	ECOG [B1]	0.84	1	0.84	0.87	0.358
	Group	0.60	1	0.60	0.62	0.437
	Error	31.79	33	0.96		
	In total	67.00	36			
	Corrected Total	32.97	35			
ECOG [B6]	Corrected Model	1,130a	2	0.57	1.52	0.239
	Intercept	2.47	1	2.47	6.63	0.016
	ECOG [B1]	0.05	1	0.05	0.14	0.711
	Group	1.13	1	1.13	3.02	0.094
	Error	9.70	26	0.37		
	In total	22.00	29			
	Corrected Total	10.83	28			

Table D.5 Results of ANCOVA normality test of residuals

Dependent variable	Shapiro-Wilk statistics	df	p-value	Conclusion on the normality of the distribution*
Leukocytes for B3	0.865	57	<0.001	Not normal
Leukocytes for B4	0.835	47	<0.001	Not normal
Leukocytes for B5	0.908	36	0.006	Not normal
Leukocytes for B6	0.950	29	0.178	Normal
Hemoglobin for B3	0.983	57	0.590	Normal
Hemoglobin for B4	0.965	47	0.173	Normal
Hemoglobin for B5	0.981	36	0.769	Normal
Hemoglobin for B6	0.975	29	0.703	Normal
Platelets for B3	0.985	57	0.707	Normal
Platelets for B4	0.969	47	0.243	Normal
Platelets for B5	0.987	36	0.939	Normal
Platelets for B6	0.951	29	0.192	Normal
Erythrocytes for B3	0.989	57	0.879	Normal
Erythrocytes for B4	0.922	47	0.004	Not normal
Erythrocytes for B5	0.979	36	0.721	Normal
Erythrocytes for B6	0.973	29	0.644	Normal
Neutrophils for B3	0.988	57	0.842	Normal
Neutrophils for B4	0.923	47	0.004	Not normal

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Dependent variable	Shapiro-Wilk statistics	df	p-value	Conclusion on the normality of the distribution*
Neutrophils for B5	0.950	36	0.106	Normal
Neutrophils for B6	0.981	29	0.866	Normal
Lymphocytes for B3	0.974	57	0.252	Normal
Lymphocytes for B4	0.966	47	0.192	Normal
Lymphocytes for B5	0.947	36	0.086	Normal
Lymphocytes for B6	0.927	29	0.045	Normal
ESR for B3	0.951	57	0.021	Normal
ESR for B4	0.841	47	<0.001	Not normal
ESR for B5	0.732	36	<0.001	Not normal
ESR for B6	0.751	29	<0.001	Not normal
AST for B2	0.742	57	<0.001	Not normal
AST for B3	0.836	47	<0.001	Not normal
AST for B4	0.732	36	<0.001	Not normal
AST for B5	0.758	28	<0.001	Not normal
ALT for B2	0.856	57	<0.001	Not normal
ALT for B3	0.791	47	<0.001	Not normal
ALT for B4	0.609	36	<0.001	Not normal
ALT for B5	0.846	28	0.001	Not normal
Bilirubin for B2	0.778	57	<0.001	Not normal
Bilirubin for B3	0.915	47	0.002	Not normal
Bilirubin for B4	0.967	36	0.339	Normal
Bilirubin for B5	0.962	28	0.387	Normal
Creatinine for B2	0.985	57	0.709	Normal
Creatinine for B3	0.923	47	0.004	Not normal
Creatinine for B4	0.878	36	0.001	Not normal
Creatinine for B5	0.769	28	<0.001	Not normal
Glucose for B2	0.618	57	<0.001	Not normal
Glucose for B3	0.885	47	<0.001	Not normal
Glucose for B4	0.710	36	<0.001	Not normal
Glucose for B5	0.971	28	0.610	Normal
Specific gravity for B2	0.468	57	<0.001	Not normal
Specific gravity for B3	0.816	47	<0.001	Not normal
Specific gravity for B4	0.924	36	0.017	Normal
Specific gravity for B5	0.887	29	0.005	Not normal
pH for B2	0.435	57	<0.001	Not normal
pH for B3	0.505	47	<0.001	Not normal
pH for B4	0.752	36	<0.001	Not normal

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Dependent variable	Shapiro-Wilk statistics	df	p-value	Conclusion on the normality of the distribution*
pH for B5	0.590	28	<0.001	Not normal
Leukocytes in urine for B2	0.471	57	<0.001	Not normal
Leukocytes in urine for B3	0.836	47	<0.001	Not normal
Leukocytes in urine for B4	0.727	36	<0.001	Not normal
Leukocytes in urine for B5	0.847	29	0.001	Not normal
Erythrocytes in the urine for B2	0.504	57	<0.001	Not normal
Erythrocytes in the urine for B3	0.639	47	<0.001	Not normal
Erythrocytes in the urine for B4	0.664	36	<0.001	Not normal
Erythrocytes in urine for B5	0.636	29	<0.001	Not normal
QL2 for B2	0.982	57	0.533	Normal
QL2 for B3	0.969	48	0.235	Normal
QL2 for B4	0.958	36	0.185	Normal
QL2 for B5	0.947	29	0.149	Normal
ECOG for B2	0.927	57	0.002	Not normal
ECOG for B3	0.925	48	0.005	Not normal
ECOG for B4	0.873	36	0.001	Not normal
ECOG for B5	0.904	29	0.012	Normal
* Done at a significance level of 0.01.				

Table D.6 Results of ANCOVA comparison of groups at visits using ranks

Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
Ranks "Leukocytes [B3]"	Corrected Model	2423,913 [a]	2	1211.96	5.04	0.010
	Intercept	900.09	1	900.09	3.74	0.058
	Leukocytes [B1]	2419.96	1	2419.96	10.06	0.002
	Group	3.14	1	3.14	0.01	0.910
	Error	12986.59	54	240.49		
	In total	63347.50	57			
	Corrected Total	15410.50	56			
Ranks "Leukocytes [B4]	Corrected Model	391,495a	2	195.75	1.04	0.361

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	Intercept	1830.16	1	1830.16	9.76	0.003
	Leukocytes [B1]	321.58	1	321.58	1.72	0.197
	Group	42,16	1	42,16	0.23	0.638
	Error	8250.51	44	187.51		
	In total	35714.00	47			
	Corrected Total	8642.00	46			
Ranks "Leukocytes [B5]	Corrected Model	34,539a	2	17,27	0.15	0.863
	Intercept	1409.37	1	1409.37	12.09	0.001
	Leukocytes [B1]	19.41	1	19.41	0.17	0.686
	Group	11.60	1	11.60	0.10	0.754
	Error	3846.96	33	116.58		
	In total	16202.50	36			
	Corrected Total	3881.50	35			
Ranks "Erythrocytes [B4]	Corrected Model	2472,910 [a]	2	1236.45	8.82	0.001
	Intercept	559.81	1	559.81	3.99	0.052
	Erythrocytes [B1]	1720.37	1	1720.37	12,27	0.001
	Group	537.44	1	537.44	3.83	0.057
	Error	6171.59	44	140.26		
	In total	35716.50	47			
	Corrected Total	8644.50	46			
Ranks "Neutrophils [B4]	Corrected Model	1305,361a	2	652.68	3.91	0.027
	Intercept	113.91	1	113.91	0.68	0.413
	Neutrophils [B1]	1253.69	1	1253.69	7.52	0.009
	Group	54,25	1	54,25	0.33	0.571
	Error	7340.64	44	166.83		
	In total	35718.00	47			
	Corrected Total	8646.00	46			
"ESR [B4]" ranks	Corrected Model	1463,757a	2	731.88	4.52	0.016
	Intercept	7323.55	1	7323.55	45.23	0.000
	ESR [B1]	946.74	1	946.74	5.85	0.020
	Group	483.09	1	483.09	2.98	0.091
	Error	7124.24	44	161.92		
	In total	35660.00	47			
	Corrected Total	8588.00	46			
"ESR [B5]" ranks	Corrected Model	279,734a	2	139.87	1.29	0.289
	Intercept	3690.82	1	3690.82	34.01	0.000

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	ESR [B1]	163.45	1	163.45	1.51	0.228
	Group	127.26	1	127.26	1.17	0.287
	Error	3580.77	33	108.51		
	In total	16181.50	36			
	Corrected Total	3860.50	35			
Ranks "ESR [B6]	Corrected Model	142,400 [a]	2	71.20	0.99	0.386
	Intercept	2144.27	1	2144.27	29.77	0.000
	ESR [B1]	74.69	1	74.69	1.04	0.318
	Group	50.23	1	50.23	0.70	0.411
	Error	1872.60	26	72.02		
	In total	8540.00	29			
	Corrected Total	2015.00	28			
"AST [B3]" ranks	Corrected Model	1294,429 [a]	2	647.21	2.47	0.094
	Intercept	3912.46	1	3912.46	14.96	0.000
	AST [B1]	693.81	1	693.81	2.65	0.109
	Group	584.54	1	584.54	2.23	0.141
	Error	14127.07	54	261.61		
	In total	63358.50	57			
	Corrected Total	15421.50	56			
"AST [B4]" ranks	Corrected Model	698,704a	2	349.35	1.93	0.157
	Intercept	2596.27	1	2596.27	14.37	0.000
	AST [B1]	147.79	1	147.79	0.82	0.371
	Group	545.92	1	545.92	3.02	0.089
	Error	7948.30	44	180.64		
	In total	35719.00	47			
	Corrected Total	8647.00	46			
Ranks "AST [B5]"	Corrected Model	319,002a	2	159.50	1.48	0.243
	Intercept	922.97	1	922.97	8.54	0.006
	AST [B1]	170.22	1	170.22	1.58	0.218
	Group	164.87	1	164.87	1.53	0.225
	Error	3565.00	33	108.03		
	In total	16205.00	36			
	Corrected Total	3884.00	35			
Ranks "AST [B6]"	Corrected Model	61,120a	2	30.56	0.43	0.654
	Intercept	631.76	1	631.76	8.94	0.006
	AST [B1]	35.54	1	35.54	0.50	0.485

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	Group	17.68	1	17.68	0.25	0.621
	Error	1765.88	25	70.64		
	In total	7714.00	28			
	Corrected Total	1827.00	27			
"ALT [B3]" ranks	Corrected Model	1219,528a	2	609.76	2.32	0.108
	Intercept	3533.03	1	3533.03	13.43	0.001
	ALT [B1]	730.10	1	730.10	2.78	0.102
	Group	346.32	1	346.32	1.32	0.256
	Error	14206.47	54	263.08		
	In total	63363.00	57			
	Corrected Total	15426.00	56			
"ALT [B4]" ranks	Corrected Model	1503, 183a	2	751.59	4.63	0.015
	Intercept	774.94	1	774.94	4.78	0.034
	ALT [B1]	1492.77	1	1492.77	9.20	0.004
	Group	0.40	1	0.40	0.00	0.961
	Error	7139.32	44	162.26		
	In total	35714.50	47			
	Corrected Total	8642.50	46			
Ranks "ALT [B5]"	Corrected Model	782,142a	2	391.07	4.16	0.024
	Intercept	299.71	1	299.71	3.19	0.083
	ALT [B1]	734.61	1	734.61	7.81	0.009
	Group	51.97	1	51.97	0.55	0.462
	Error	3102.36	33	94.01		
	In total	16205.50	36			
	Corrected Total	3884.50	35			
Ranks "ALT [B6]"	Corrected Model	42,438a	2	21,22	0.30	0.745
	Intercept	489.60	1	489.60	6.87	0.015
	ALT [B1]	41,41	1	41,41	0.58	0.453
	Group	3.37	1	3.37	0.05	0.830
	Error	1782.56	25	71.30		
	In total	7712.00	28			
	Corrected Total	1825.00	27			
Ranks "Bilirubin [B3]	Corrected Model	3374,540 [a]	2	1687.27	7.56	0.001
	Intercept	1017.08	1	1017.08	4.56	0.037
	Bilirubin [B1]	3325.24	1	3325.24	14.90	0.000
	Group	531.32	1	531.32	2.38	0.129

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	Error	12051.96	54	223.18		
	In total	63363.50	57			
	Corrected Total	15426.50	56			
Ranks "Bilirubin [B4]	Corrected Model	1760,623a	2	880.31	5.62	0.007
	Intercept	562.97	1	562.97	3.60	0.064
	Bilirubin [B1]	1718.96	1	1718.96	10.98	0.002
	Group	331.27	1	331.27	2.12	0.153
	Error	6886.88	44	156.52		
	In total	35719.50	47			
	Corrected Total	8647.50	46			
Ranks "Creatinine [B4]	Corrected Model	2334,506 [a]	2	1167.25	8,14	0.001
	Intercept	163.20	1	163.20	1.14	0.292
	Creatinine [B1]	2123.59	1	2123.59	14.81	0.000
	Group	223.48	1	223.48	1.56	0.219
	Error	6310.49	44	143.42		
	In total	35717.00	47			
	Corrected Total	8645.00	46			
Ranks "Creatinine [B5]	Corrected Model	871,473a	2	435.74	4.77	0.015
	Intercept	69.01	1	69.01	0.76	0.391
	Creatinine [B1]	865.35	1	865.35	9.48	0.004
	Group	2.81	1	2.81	0.03	0.862
	Error	3013.53	33	91.32		
	In total	16206.00	36			
	Corrected Total	3885.00	35			
Ranks "Creatinine [B6]	Corrected Model	584,466 [a]	2	292.23	5.88	0.008
	Intercept	106.61	1	106.61	2.14	0.156
	Creatinine [B1]	583.44	1	583.44	11.74	0.002
	Group	16.01	1	16.01	0.32	0.575
	Error	1242.53	25	49.70		
	In total	7714.00	28			
	Corrected Total	1827.00	27			
Ranks "Glucose [B3]	Corrected Model	2438,353a	2	1219.18	5.09	0.009
	Intercept	0.17	1	0.17	0.00	0.979
	Glucose [B1]	2420.38	1	2420.38	10,10	0.002
	Group	88.72	1	88.72	0.37	0.545
	Error	12942.65	54	239.68		

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	In total	63318.00	57			
	Corrected Total	15381.00	56			
Ranks "Glucose [B4]	Corrected Model	93,360a	2	46,68	0.24	0.787
	Intercept	771.73	1	771.73	3.98	0.052
	Glucose [B1]	90.76	1	90.76	0.47	0.497
	Group	4.92	1	4.92	0.03	0.874
	Error	8531.64	44	193.90		
	In total	35697.00	47			
	Corrected Total	8625.00	46			
Ranks "Glucose [B5]	Corrected Model	349,320a	2	174.66	1.63	0.211
	Intercept	43.85	1	43.85	0.41	0.526
	Glucose [B1]	225.29	1	225.29	2.11	0.156
	Group	89.51	1	89.51	0.84	0.367
	Error	3530.18	33	106.98		
	In total	16200.50	36			
	Corrected Total	3879.50	35			
Ranks "Specific weight [B3]	Corrected Model	1255,629 [a]	2	627.81	2.42	0.098
	Intercept	1140.31	1	1140.31	4.40	0.041
	Specific gravity [B1]	1253.10	1	1253.10	4.84	0.032
	Group	0.63	1	0.63	0.00	0.961
	Error	13994.37	54	259.16		
	In total	63187.00	57			
	Corrected Total	15250.00	56			
Ranks "Specific weight [B4]	Corrected Model	1002,542a	2	501.27	2.91	0.065
	Intercept	734.41	1	734.41	4.26	0.045
	Specific gravity [B1]	804.21	1	804.21	4.67	0.036
	Group	188.03	1	188.03	1.09	0.302
	Error	7581.46	44	172.31		
	In total	35656.00	47			
	Corrected Total	8584.00	46			
Ranks "Specific weight [B6]	Corrected Model	309,245a	2	154.62	2.36	0.115
	Intercept	224.42	1	224.42	3.42	0.076
	Specific gravity [B1]	244.80	1	244.80	3.73	0.064
	Group	44.91	1	44.91	0.68	0.416

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	Error	1705.76	26	65,61		
	In total	8540.00	29			
	Corrected Total	2015.00	28			
Ranks "pH [B3]	Corrected Model	1,621a	2	0.81	0.01	0.992
	Intercept	525.92	1	525.92	5.07	0.028
	pH [B1]	1.62	1	1.62	0.02	0.901
	Group	0.21	1	0.21	0.00	0.964
	Error	5598.38	54	103.67		
	In total	53537.00	57			
	Corrected Total	5600.00	56			
Ranks "pH [B4]	Corrected Model	102,645a	2	51,32	1.18	0.318
	Intercept	56,41	1	56,41	1.29	0.262
	pH [B1]	48.84	1	48.84	1.12	0.296
	Group	20.99	1	20.99	0.48	0.492
	Error	1921,36	44	43.67		
	In total	29096.00	47			
	Corrected Total	2024.00	46			
Ranks "pH [B5]	Corrected Model	269,725a	2	134.86	3.28	0.050
	Intercept	323.98	1	323.98	7.87	0.008
	pH [B1]	89.23	1	89.23	2.17	0.150
	Group	242.64	1	242.64	5.90	0.021
	Error	1357.78	33	41.15		
	In total	13948.50	36			
	Corrected Total	1627.50	35			
Ranks "pH [B6]	Corrected Model	,700 a	1	0.70	0.02	0.901
	Intercept	0.00	0	.	.	.
	pH [B1]	0.00	0	.	.	.
	Group	0.70	1	0.70	0.02	0.901
	Error	1143.30	26	43.97		
	In total	7031.00	28			
	Corrected Total	1144.00	27			
Ranks "Leukocytes in urine [B3]"	Corrected Model	405,531a	2	202.77	0.76	0.475
	Intercept	31949.25	1	31949.25	119.02	0.000
	Leukocytes in urine [B1]	402.09	1	402.09	1.50	0.226
	Group	0.55	1	0.55	0.00	0.964

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	Error	14495.97	54	268.44		
	In total	62838.50	57			
	Corrected Total	14901.50	56			
Ranks "Leukocytes in urine [B4]	Corrected Model	1412,244a	2	706.12	4.41	0.018
	Intercept	6732.03	1	6732.03	42.04	0.000
	Leukocytes in urine [B1]	1406.02	1	1406.02	8.78	0.005
	Group	32.92	1	32.92	0.21	0.652
	Error	7045.76	44	160.13		
	In total	35530.00	47			
	Corrected Total	8458.00	46			
Ranks "Leukocytes in urine [B5]	Corrected Model	109,359a	2	54,68	0.50	0.613
	Intercept	3637.08	1	3637.08	33.05	0.000
	Leukocytes in urine [B1]	107.83	1	107.83	0.98	0.329
	Group	2.65	1	2.65	0.02	0.878
	Error	3632.14	33	110.07		
	In total	16062.50	36			
	Corrected Total	3741.50	35			
Ranks "Leukocytes in urine [B6]	Corrected Model	199,595a	2	99.80	1.47	0.248
	Intercept	2958.01	1	2958.01	43.68	0.000
	Leukocytes in urine [B1]	7.83	1	7.83	0.12	0.737
	Group	193.39	1	193.39	2.86	0.103
	Error	1760.91	26	67.73		
	In total	8485.50	29			
	Corrected Total	1960.50	28			
Ranks "Erythrocytes in urine [B3]	Corrected Model	778,125a	2	389.06	2.48	0.093
	Intercept	32952.63	1	32952.63	210.28	0.000
	Erythrocytes in urine [B1]	747.17	1	747.17	4.77	0.033
	Group	9.63	1	9.63	0.06	0.805
	Error	8462.38	54	156.71		
	In total	57177.50	57			
	Corrected Total	9240.50	56			
Ranks "Erythrocytes in urine [B4]	Corrected Model	110,416a	2	55,21	0.76	0.475
	Intercept	17916.84	1	17916.84	245.97	0.000

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	Erythrocytes in urine [B1]	109.64	1	109.64	1.51	0.226
	Group	7.30	1	7.30	0.10	0.753
	Error	3205.08	44	72.84		
	In total	30387.50	47			
	Corrected Total	3315.50	46			
Ranks "Erythrocytes in urine [B5]	Corrected Model	21,339a	2	10.67	0.19	0.826
	Intercept	7731.31	1	7731.31	139.37	0.000
	Erythrocytes in urine [B1]	8.84	1	8.84	0.16	0.692
	Group	4:30 p.m	1	4:30 p.m	0.29	0.591
	Error	1830.66	33	55,48		
	In total	14173.00	36			
	Corrected Total	1852.00	35			
Ranks "Erythrocytes in urine [B6]	Corrected Model	266,160a	2	133.08	3.49	0.046
	Intercept	2775.80	1	2775.80	72.69	0.000
	Erythrocytes in urine [B1]	265.80	1	265.80	6.96	0.014
	Group	26.02	1	26.02	0.68	0.417
	Error	992.84	26	38,19		
	In total	7784.00	29			
	Corrected Total	1259.00	28			
Ranks "ECOG [B3]	Corrected Model	1012,321a	2	506.16	2.37	0.103
	Intercept	6557.28	1	6557.28	30.67	0.000
	ECOG [B1]	863.78	1	863.78	4.04	0.049
	Group	290.91	1	290.91	1.36	0.249
	Error	11545.68	54	213.81		
	In total	60495.00	57			
	Corrected Total	12558.00	56			
Ranks "ECOG [B4]	Corrected Model	636,356a	2	318.18	2.18	0.125
	Intercept	3248.00	1	3248.00	22,22	0.000
	ECOG [B1]	611.89	1	611.89	4.19	0.047
	Group	131.20	1	131.20	0.90	0.349
	Error	6578.64	45	146.19		
	In total	36027.00	48			
	Corrected Total	7215.00	47			
Ranks "ECOG [B5]	Corrected Model	118,446a	2	59.22	0.61	0.550

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Dependent variable	Source	Type III Sum of Squares	df	Middle square	F	p-value
	Intercept	3291.84	1	3291.84	33.84	0.000
	ECOG [B1]	75.67	1	75.67	0.78	0.384
	Group	68,12	1	68,12	0.70	0.409
	Error	3210.05	33	97.27		
	In total	15649.50	36			
	Corrected Total	3328.50	35			