Federal State-Financed Institution "Research Institute for Influenza"
RF Ministry of Health

APPROVED
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Director of FSFI "RII", RF Ministry of Health
"____"_____ 2015

STUDY REPORT
General toxicity, safety pharmacology, and local tolerance studies of Fullerene polyaminocaproic acid (FPACA) substance at repeated peroral administration in rabbits ("Chronic toxicity")

Sponsor:

ZAO "Intelpharm", Russia

Legal Address: ZAO "Intelpharm", Russia, Pushkin str. 36, Nizhegorodskaya region, Chkalovsk, 606540, Russia

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Test facility:

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Study Director:

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SUMMARY

Report: 57 pages, 6 tables, 8 references, 1 Annex.

SUBSTANCE, SUBCHRONIC, CHRONIC TOXICITY, PERORAL ADMINISTRATION, RABBITS, BIOCHEMISTRY, HEMATOLOGY, PHYSIOLOGY, PATHOMORPHOLOGY, LOCAL TOLERANCE STUDY.

The study objective was chronic toxicity (character and intensity of damaging action), safety pharmacology and local tolerance studies of Fullerene polyaminocaproic acid (FPACA) substance produced by ZAO “Intelpharm” at peroral administration in rabbits.

It was demonstrated that repeated daily peroral administration of the substance in doses 3.7 mg/kg and 37 mg/kg (the doses 3.2 and 32 times higher than an intended maximal daily dose of the preparation contained in a tablet dosage form) during 90 days in male and female rabbits did not cause lethality or any pathological signs in animal status and behavior. No changes in integral indexes of vital activity or disorders in thermoregulation system have been found. There were no differences between indices in male and female rabbits. No changes in mass coefficients of experimental animals’ organs compared to control were noted.

Daily administration of the substance during 90 days in rabbits of both sexes did not cause development of dystrophic or destructive changes in internal organs and brains of experimental animals.

Safety pharmacology study of FPACA substance demonstrated the absence of toxic effects on the organs and systems with functions that could be temporarily disordered because of adverse pharmacodynamic effects of the substance without irreversible damages (hepato-biliary system, blood circulation system, and metabolic system) and vital organs and systems having fuctions essential for survival (respiratory, cardio-vascular, and central vervous systems).

Local irritant effect has not been detected.

CONTENTS

GUIDANCE DOCUMENTS

–Federal Law of April 12 2010 #61 “On circulation of therapeutics”;

- Rules for Laboratory Practice in the Russian Federation” (Order of the Russian Ministry of Health #708n of August 23, 2010);
- The Russian Federation Standard (GOST 53434-2009 of 02.12.2009) “GLP Principles of Laboratory Practice”, Moscow, Standartinform, 2010;
- Laboratory Animals (Guidance and Provisions, Russian Academy of Medical Sciences, M., 2003);

–Guidance on conducting non-clinical trials of pharmaceuticals, Part I: - Moscow, Grif &Co, 2012, 536 p.;

- Guidance on conducting non-clinical trials of pharmaceuticals (Immunobiological therapeutics), Part II: - Moscow, Grif &Co, 2012, 536 p.;
- Sanitary rules on arrangement, equipping and maintenance of experimental biological clinics (vivariums). RF, approved 06.04.1973;
- Guidance on care and use of laboratory animals. FELASA, 2010.

ABBREVIATIONS

AlAT — alanine aminotransferase

AsAT — aspartate aminotransferase

GIT — gastrointestinal tract

BR — breathing rate

HR — heart rate

ECG — electrocardiogram

AP — alkaline phosphatase

GLP — Good Laboratory Practice

Ht — hematocrit

F — female

M — male

MCV — mean cell volume

MCH — mean cell hemoglobin

MCHC — mean corpuscular hemoglobin concentration

RDWc — red cell distribution width

INTRODUCTION

Study title:

Studies of general toxic effects, safety pharmacology, and local tolerance of Fullerene poly-aminocaproic acid (FPACA) substance produced by ZAO “Intelpharm” at peroral administration in rabbits.

Study objective: studies of chronic toxicity (character and intensity of damaging action), safety pharmacology and local tolerance of Fullerene polyaminocaproic acid substance produced by ZAO “Intelpharm” at peroral administration in rabbits.

Study tasks:

- study chronic toxicity of the preparation at daily peroral administration in rabbits of both sexes in doses 3.2 and 32 times higher than maximal daily dose for humans during 3 months;

- evaluate local irritant effect of the substance;

- study safety pharmacology of the substance on rabbits of both sexes during 3-month exposure.

Study object:

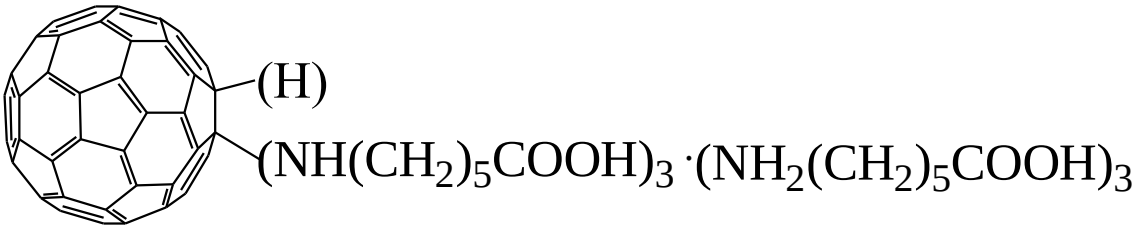
Fullerene polyaminocaproic acid (FPACA) substance, batch 16SB (for non-clinical studies).

Chemical name:

N-fullerene-poly-ε-aminocaproic acid

N-fullerene-poly-6-aminocaproic acid

Formula



N-fullerene-poly-aminocaproic acid is a mixture of positional isomers of covalently bound amino acid groups, in which polar groups of amino acid fragments are coordinated on fullerene-amino-acid derivatives with formation of either ionic links between carboxyl group of fullerene amino acid and ammonium group, (NH_3^+-), amino acids, or hydrogen binding like L-COO ---H----NH2-L’. The ratio of fullerene to coordinated amino acid in the product is 1:6.

Empirical formula

$C_{96}H_{72}O_{12}N_6$

Molecular mass 1500 + (nH_2O)

Description: The test substance is an amorphous powder of brown to dark brown color

Physical properties: temperature of decomposition without melting - 200^{o} C

Solubility:

- Freely soluble in DMSO (dimethyl sulphoxide)
- Soluble in dimethyl formamide (10 mg of substance in 10 ml DMF)
- Almost non-soluble in water, 95% ethyl alcohol, 1, 2 – dichlorbenzene.

The most suitable mixtures for dilution are DMSO – H2O (1:10), DMFA-H2O (1:10), ethanolamine, polyethylene glycol. Dissolution in polar solvents occurs due to the decrease in carboxylic group association. That is why alkali salts, ammonium salts and salts of organic amines (for example, Tris-amine) of fullerene-amino acids (FAA) have much higher water solubility (solubility Na-FAA is at the level of 50 mg/ml). Solutions have an intense red-brown color. For analysis buffer solutions with pH = 8. 9 ("boronic" buffer) can be used.

pH: 5.2

Substance characteristics and stability

The data characterizing Fullerene polyaminocaproic acid substance (production, purification, composition and stability analysis) are kept by the Sponsor.

Intended dosing schedule of the substance as a component of a tablet dosage form for clinical practice: Killevir preparation, sublingual tablets 20 mg (by the substance amount).

In HIV-infection therapy - 1 tablet twice daily.

In hepatitis C therapy– 1 tablet twice daily during 3-6 months depending on results of biochemical, immunological and morphological studies reflecting the process severity.

For prevention of Ebola virus disease – 1 tablet twice daily, in Ebola virus disease therapy – 1 tablet 4 times daily up to complete cure.

Therapeutic class:

Antiviral drug of systemic action.

Pharmacological effect

The data obtained in the study of mechanism of FPACA antiviral effects on HIV1 and HIV2 viruses demonstrated inhibition of joining, fusion, and entry simultaneously.

In vitro FPACA studies demonstrated its activity against all HIV wild strains. Mean EC_{50} was 6 μg/ml, mean EC_{95} – 1.33 μg/ml; cytotoxicity was not detected at concentrations of the preparation up to 100 μg/ml.

Fullerene polyaminocaproic acid demonstrated activity against Ebola virus (Zaire strain) (mean EC_{50} - 6.76 μg/ml).

Fullerene polyaminocaproic acid demonstrated activity against hepatitis C virus (mean EC_{50} - 0.99 μg/ml).

The substance developer:

ZAO "Intelpharm"

Legal address: Pushkin str. 36, Nizhegorodskaya region, Chkalovsk, 606540, Russia

Study organizer:

ZAO "Intelpharm"

Legal address: Pushkin str. 36, Nizhegorodskaya region, Chkalovsk, 606540, Russia

Test facility:

FSFI "RII", RF Ministry of Health

Legal address: prof. Popov str. 15/17, St. Petersburg, 197376, Russia

Study design, justification of doses and route of administration

are stated in Non-clinical Study Plan # LBL/OT-025/15 (Annex)

Study procedures

All procedures within the study were performed in accordance with the approved written Study protocol and Standard operating procedures (SOPs) of the Drug Safety Laboratory.

The test substance was administered orally – the route intended for use in clinical practice. Upon receipt of the test substance Pharmaceutical Unit kept records on its consumption. All manipulations with the substance were performed in compliance with standard safety rules.

Data storage

All raw data and a properly attested copy of the non-clinical study protocol, study report, conclusions of Bioethics Committee and Quality Assurance Unit are stored in a specially allotted room. Storage period is determined by the internal act of the organization.

Key dates:

Study initiation date – December 23, 2014

First dose date – February 26, 2015

Autopsy date - May 27, 2015

MAIN PART

1 MATERIALS AND METHODS

1.1. Animals (test-system) and their handling

Experiments were conducted on Chinchilla rabbits of both sexes.

1.1.2 Source and date of purchase and complement documents on animals

Veterinary Certificate 247 #0138904 of February 18, 2015 of Animal Nursery “Rappolovo”, RAS. Animals before shipment were kept in quarantine at Animal Nursery “Rappolovo” during 30 days. During the quarantine period the material taken from animals was examined by FSFI “LMVL”.

1.1.3 Compliance with legal and ethical norms in animal handling

Laboratory animals were handled in compliance with “Sanitary rules on arrangement, equipping and maintenance of experimental biological clinics (vivariums)”, Russian Federation, approved 06.04.1973, “Guidance on care and use of laboratory animals. FELASA, 2010, Laboratory Animals (Guidance and Provisions, Russian Academy of Medical Sciences, M., 2003).

All animal procedures were considered and approved by Bioethics Committee of FSFI “RII”, RF Ministry of Health (Protocol #29 of January 6, 2015).

1.1.4 Acclimatization (quarantine) of animals at FSFI “RII”, RF Ministry of Health

All animals were acclimated to laboratory conditions for 7 days prior to the start of dosing. During that period, the health status of the animals (general status and behavior) was daily examined; twice daily animals were observed in cages for sickness and death.

1.1.5 Assigning to groups

Prior to the study the animals were assigned to groups at random based on body weight. No animal was considered for assignment if out of the ±20% range from mean body weight.

1.1.6 Identification

Each animal selected for the study was individually enumerated with biological paint on the internal surface of an ear. The individual numbers of animals were indicated on the cage label.

1.1.7 Diet

Animals were fed *ad libitum* with full-ration diet for laboratoty animals, formulation PK-120-2_173 “Laboratorkorm” Ltd. (Moscow), and with hay. The diet was free of phatogenic microflora that could interfere with the results of the study.

1.1.8 Water

Animals were given *ad libitum* pure drinking water. The water was filtered and contained no phatogenic microflora that could interfere with the results of the study.

1.1.9 Bedding

Hay was used for bedding.

1.1.10 Care and maintenance

Laboratory animals were kept in animal facility of FSFI “RII”, RF Ministry of Health under controlled environmental conditions (temperature, humidity, 12-hour light/dark cycle maintained by artificial daylights, ventilation (air exchange 15 volumes/hour), CO_2 concentration no more than 0.15 volume %, ammonia – no more than 0.001 mg/l) throughout the whole period of the study. During the study animals were daily inspected for changes in general health status and behavior. On the days of exposure the animals were examined 2 hours after administration of the preparation. Results of inspection were recorded in tables.

Animals were handled and cared in accordance with SOPs approved by FSFI “RII”, RF Ministry of Health.

1.1.11 Cages

Animals were kept in the individual cages (stainless steel, floor square 2000 cm^2, height 40 cm), with removable floor, removable trays for collection of excrements, bins for hay and diet and drinking bowls.

1.1.12 Animal observation

Daily observation. During the study animals were daily inspected for changes in general health status and behavior.

Animal observation in cages. All groups of animals were daily examined in cages: immediately after exposure and at the end of the day.

1.2 Parameters to be registered

1.2.1 Body weight

The laboratory balance accuracy was verified before the start of the experiment. Each animal was weighed prior to the study and once weekly thereafter hroughout the experiment.

1.2.2 Rectal temperature

Body temperature was measured using electronic thermometer DT-623, "A&D Company Ltd", Japan. Before inserting into the rectum the thermometer tip was lubricated with Vaseline.

1.2.3 Electrocardiography

ECG was recorded using standard leads on veterinary cardiograph "PolySpectr - 8B" (Neurosoft, Russia) with reusable electrodes of "crocodile" type. ECG indices were calculated by II standard lead. HR computation was performed by ECG parameters.

1.2.4 Breathing rate

Frequency of breathing excursions – a breathing rate (BR) – was assessed by palpation and expressed in breathing excursions per minute.

1.2.5 Clinical laboratory studies

1.2.5.1 Hematology studies

Blood sampling for hematological tests was performed as follows: blood in volume 1.5 ml was taken to collection tubes with EDTA, and blood parameters were evaluated on automatic hematological analyzer Abacus Jun Vet (Diatron, Austria-Hungary): ESR, number of erythrocytes, hemoglobin concentration, hematocrit, mean value of hemoglobin count in a cell, mean concentration of hemoglobin in a cell, quantity of leukocytes, leukogram, and quantity of throbocytes.

1.2.5.2 Analysis of blood serum biochemistry

Blood sampling procedure:

animals were deprived of food 12 hours before taking blood. Blood was taken from marginal vein of rabbit's ear. Blood in volume 4.5 ml was collected in tubes without anticoagulant. To form a clot, blood was kept in thermostat at 37^0C during 30 min. Coagulated blood was centrifuged at 3000 rpm during 5 minutes, and in the obtained serum indices of albumin, total protein, globulins, activity of alanine aminotransferase (AlT), activity of aspartate aminotransferase (AsT), activity of alkaline phoshatase (AP), total bilirubin, glu-

cose¸ total cholesterol, triglycerides (TAG), urea, creatinine, sodium, and potassium were evaluated on automatic biochemical analyzer KeyLab Automatic Analyzer (BPC+BioSed, Italy) using special kits for clinical biochemistry.

1.2.5.3 Analysis of blood plasma biochemistry

Blood in volume 2 ml was collected in Vacuette tubes (Greiner Bio-one, Austria) with 3.8% sodium citrate and centrifuged at 1200 rpm during 15 minutes. The obtained plasma was transferred to new test tubes. Prothrombin time (PTT) and Activated Partial Thromboplastin Times (APTT) were determined using Recombiplastin 2Zh, Sintasil (Hemosil, Italy) kits on a blood coagulometer Coag 4D (Diagon, Hungary). Calibration was performed using RNP-plasma kit (Technologia-Standart).

1.3 Pathomorphology and histology

1.3.1 Euthanasia

In the study animals were subjected to the scheduled euthanasia by air embolism.

1.3.2 Pathomorphological examinations

All experimental animals underwent a pathomorphological examination, control animals - at the study termination. Necropsy was performed under supervision of a pathologist. After euthanasia animals were thoroughly examined to detect external pathological signs. Examination of thoracic and abdominal cavities and macro- and microscopic studies of internal organs were carried out.

1.3.2.1 Organs to be weighed

Heart, lungs with trachea or without it, thymus, spleen, liver, kidneys, adrenal glands, brain, testicles or ovaries were weighed. The laboratory balance accuracy was verified before the start of the experiment.

1.3.2.2 Animal organs subjected to microscopic study:

skin, lymph nodes, mammary glands, aorta, heart, larynx, trachea, lungs with bronchi, thymus, esophagus, stomach, duodenum, small intestine, large intestine, liver, pancreas, spleen, kidneys, adrenal glands, urinary bladder, uterus, ovaries, testicles, submaxillary salivary gland, thyroid gland, brain.

1.3.3 Histological study

All experimental animals exposed to maximal substance dose and control animals were taken to this study.

1.3.3.1 Organs subjected to histological examination:

Heart, lungs with bronchi, thymus, stomach, liver, spleen, kidneys, adrenal glands, thyroid gland, pancreas, testicles, ovaries, brain.

Histological study steps: preparation of fixing liquids, sampling material during necropsy, material fixation, excision of pieces of the fixed material, dehydrate compacting of the pieces and paraffin embedding, cutting pieces on freezing microtome, cutting blocks on a sledge microtome, dying frozen sections, dying paraffin sections, revision of histological preparations, description of the preparations, photomicrography, making prints.

1.4 Raw data and statistical processing

For statistical prcessing the data from the initial documentation were downloaded to MSExcel 2010 program for accumulation and analysis. The data processing was performed using a statistical software package Statistica 6.0 (StatSoft, USA).

In order to obtain registered quantitative variables, parameters of descriptive statistics characterizing the data on each group were calculated. Parameters of descriptive statistics included: mean value of the parameter in a group (Mean), standard deviation of the mean (Std.Dev), variation coefficient in groups (CV), standard error (Std.Err), Median, 25 and 75 percentiles. Differences between the samples were evaluated by Kruskal-Wallis and Mann-Whitney nonparametic criteria and considered significant at $p<0.05$. The data in tables are presented as a mean (M) and Mean Error (±m).

1.5 Archive

All the study related documentation (non-clinical study protocol, amendments and deviations, study report, conclusions of Bioethics Committee and Quality Assurance Unit, veterinary certificate, diet certificate, all raw data, a copy of Agreement for conducting non-clinical studies) are filed. All documentation, a test specimen, biological specimens (smear slides, paraffin blocks, histological slices on glasses, etc.) have been stored at the archive of the FSFI “Research Institute for Influenza” for 5 years and will be destroyed upon completion of this term.

1.6 Quality Assurance

In the study the internal quality control was provided. Control of the SOPs observance during the study was a responsibility of the Study Director. Quality Assurance Unit of FSFI “RII” inspected Study protocol, key phases of the study, raw data and the study report. Conclusion of Quality Assurance Unit is kept in archive of of FSFI “RII”, RF Ministry of Health.

2 TOXICITY

Maximal daily clinical dose of substance as a component of the preparation in the tablet dosage form is 80 mg pro dosi or 1.14 mg/kg.

In the study 30 rabbits (male and female) were taken.

Before the dosing (a dose per group was calculated based on total body mass of rabbits in group) the substance was ground with a pestle in onyx mortar to fine-dispersed powder and added with 1.0% starch in volume 0.5 ml/kg of body mass.

The obtained solution was administered per oral with insulin syringe daily during 90 days in doses 3.2 and 32 times higher than the intended maximal daily dose - 3.7 mg/kg and 37 mg/kg (in volume 0.5 ml/kg of body mass). Control animals in the same conditions of the experiment were dosed with 1.0% starch in volume 0.5 ml/kg of body mass. Number of animals in experimental group - 5 rabbits of each sex.

During 90 days at daily inspection of animals of experimental group and control no changes in general status and behavior were noted.

There were no differences in feed and water consumption of experimental and control animals.

2.1 Effects of FPACA substance on dynamics of body mass gain, temperature, and MC values of internal organs' and brain

Table 1 Dynamics of body mass change during the experiment (delta, M±m, g)

Term	**Experimental groups (n=5), substance, dose, mg/kg**					
	Control		**3.7**		**37**	
	M	**F**	**M**	**F**	**M**	**F**
14 days	380±66	430±64	370±51	420±92	410±58	220±58*
30 days	740±133	1010±111	950±75	890±112	930±60	560±114*
60 days	910±125	1040±121	1030±66	1030±116	1030±82	830±93
90 days	1080±119	1140±164	1130±73	1180±108	1110±102	1080±98
*- $p \leq 0.05$ to control						

Table 2 Dynamics of rectal temperature changes during the experiment (^{0}C, M±m)

Term n=10	**Experimental groups (n=5), substance, dose, mg/kg**					
	Control		**3.7**		**37**	
	M	**F**	**M**	**F**	**M**	**F**
Background	39.0±0.2	38.9±0.2	39.0±0.1	39.0±0.2	39.0±0.1	39.0±0.1
30 days	39.0±0.2	39.1±0.1	39.0±0.1	39.0±0.2	38.9±0.2	39.0±0.1
90 days	39.0±0.1	39.2±0.1	39.1±0.2	39.0±0.1	39.1±0.1	39.2±0.1
No reliable differences between mean values in the experiment and control have been detected ($p \geq 0.05$)						

Table 3 Mass coefficients of organs (g/kg, M±m, on completion of dosing)

Organs	**Experimental groups (n=5), substance, dose, mg/kg**					
	Control		**3.7**		**37**	
	M	**F**	**M**	**F**	**M**	**F**
Heart	2.39±0.09	2.48±0.17	2.45±0.13	2.59±0.11	2.62±0.11	2.47±0.15
Lungs	3.86±0.15	3.60±0.14	3.54±0.22	3.67±0.17	3.59±0.23	3.56±0.18
Thymus	0.77±0.08	0.81±0.09	0.70±007	0.97±0.03	0.64±0.09	0.70±0.06
Liver	33.16±2.41	32.95±1.06	32.98±1.76	33.61±1.45	34.13±1.85	31.99±1.77
Spleen	0.56±0.09	0.70±0.08	0.59±0.10	0.58±0.08	0.55±0.10	0.57±0.04
Kidneys	6.34±0.18	5.88±0.43	6.25±0.18	6.02±0.23	6.51±0.31	5.64±0.24
Adrenal glands	0.09±0.01	0.11±0.01	0.09±0.01	0.10±0.01	0.09±0.01	0.09±0.01
Testicles/ovaries	2.61±0.12	0.16±0.02	2.65±0.12	0.15±0.02	2.72±0.09	0.15±0.01
Brain	2.87±0.21	2.68±0.24	2.83±0.11	2.74±0.05	2.71±0.13	2.53±0.10
No reliable differences between mean experimental values and control have been detected ($p \geq 0.05$) ($p \geq 0.05$)						

Above data analysis has demonstrated that daily intragastric administration of substance during 90 days did not cause toxic effects or changes in integral parameters of vital activity of rabbits, thermoregulation system, and mass coefficients of internal organs and brain.

It was noted that in female group, exposed to the test substance in dose 37 mg/kg, at the beginning of the experiment some delay in dinamics of body mass gain compared to control was observed; however, this difference was later leveled.

2.2 Necropsy data

2.2.1 Pathomorphological examination

30 rabbits were subjected to necropsy and macroscopic analysis.

Macroscopic examination did not reveal any pathological alterations in test organs of animals; no visible macroscopic morphological differences between animals in experimental groups and control were noted.

Hair of both experimental and control rabbits was shining without baldness sites. Discharges from natural orifices were absent. Front and rear extremities were not changed. Deformations were absent. Teeth were preserved. In thoracic and abdominal cavities no changes in position of organs were found. Pulmonary, pericardium, and peritoneum pleurae were thin, shining and smooth. Lymph nodes were yellowish, oval or rounded, had smooth surface and dense whitish capsule. Nodes were not adhered to each other and to adjacent tissues. Salvary glands were oval, yellowish, moderately dense, and granular on the section. Thyroid gland was rosy-red, of normal size and form, moderately dense. Thymus was trian-

gular, whitish, slightly dense and elastic. Diameter of aorta was uniform in all its length. Aorta intima was smooth, shining, and whitish. Form and size of heart was not changed. Myocardium was slightly dense and elastic, shining, uniformly brown. Heart valves were thin, shining, and smooth. In heart cavities there was a small quantity of liquid blood. Lungs got fallen at opening of the chest cavity. Their form and size were not changed. Pleura was smooth, shining, transparent and uniformly pale-pink. Lung tissues were airy. Lumen of trachea and large bronchi was free and wide. Mucous membranes were shining, smooth, pale-pink. Mucous membrane of esophagus was shining, smooth, pale-pink. Stomach was of usual size and form. In the lumen there was a small amount of feed. Mucous membrane of stomach was folded, shining, and pale. Duodenum lumen was not changed. Mucous membrane was pale- pink, smooth, shining. Mucous membranes of other sections of small intestine were pale- pink, shining, and smooth. Mucous membrane of large intestine was shining, smooth, pale- pink. Form and size of liver were not changed; it was slightly dense and elastic. Surface of liver была smooth, shining, uniformly brown, and covered with a transparent, thin, shining capsule. Liver tissues on the section were brown and uniform. Gallbladder was neither tense nor enlarged and had a usual form. Serous coat was smooth and shining, the wall was thin and elastic, mucous membrane - velvety. In the lumen there was liquid dark-yellow bile. Pancreas was of usual form and size, elastic and uniform. Tissues on the section were lobed and pale pink. Spleen was of usual form, of dark cherry color, elastic with smooth, had shining surface and was covered with thin transparent capsule. Form and size of kidneys were not changed. Kidney capsules were easily removed. Kidneys were slightly dense and elastic, surface was smooth, shining, and uniformly light-brown. On the section cortical and brain substances-were distinctly visible.

Adrenal glands were rounded, whitish yellow and moderately dense. On the section dark-brown brain substance was visible. Urinary bladder was filled with transparent, light urine. Mucous membrane of the bladder was smooth, shining, of milky-white color. Uterus bodies of female rabbits were moderately dense, form and sizes were not changed, mucous membrane of tubes was pale, shining, and smooth. Ovaries were of normal size and density, grayish, with uneven surface. Testicles of male rabbits were whitish, had usual sizes and density, surface of section was grainy and uniformly pale. The capsule was dense, nontransparent. Membranes of brain were thin, transparent.

Sulci and gyri were clear-cut. Substance of brain was softly elastic. Surface of brains was smooth. No expansion of ventricles was observed.

2.2.2 Histological study

For histological study organs of control animals and experimental animals exposed to the maximal dose of the test compound were taken.

Examination of histological preparations taken from animals of both groups did not reveal any significant changes or differences.

Cytoarchitectonics of brain large hemispheres cortex was not broken; there were no symptoms of acute or chronic neurons disease. Glial cells (astrocytes and oligodendroglia) were not changed. Nuclei of glial cells contained sufficient quantity of chromatin. Regressive and progressive changes in glia were absent. Cross-striation of myofibrillas of left and right heart ventricles and interventricular partition was clearly visible; nuclei of cardiomyocytes were light, cytoplasm was oxyphilous. Focal disorders in tinctorial properties of cytoplasm were absent. No changes in tissue-connecting stroma of myocardium were found. Alveoli of all lung lobules contained air. Nuclei of alveolar epithelium were visible. Epithelium of alveoli and intrapulmonary bronchial tubes was not changed. Bronchial lumen was wide. Acute inflammatory changes were absent. Liver had a distinct lobed structure. Trabecular structure of lobules was not disturbed. Hepatocytes boundaries were observable; cytoplasm was grainy and weakly oxyphilous. Focal disorders in tinctorial properties of cytoplasm were absent. Nuclei contained distinct nucleoli and sufficient amount of chromatin. Sinusoids of liver were full-blooded. Epithelium of convoluted tubules of kidneys was not changed. Cytoplasm was oxyphilous, nuclei were distinct and had thin membrane and sufficient quantity of chromatin; cells boudaries were observable. Capillars of tufts and vessels located between the tubules were full-blooded. All sites of adrenal cortex were clearly visible. Cells boudaries were observable, nuclei were light. In cell cytoplasm of zona fasiculata the vacuoles – fat drops on the Sudan-dyed preparations were observed. Vessels of brain substance were full-blooded. Lymphoid elements of spleen had clear nuclei; no destruction or atrophy of follicles was found. Reticular cells had large light nuclei. Endothelium of sinuses was not changed. Thymus had a clear lobed structure. Lynphoid cells (thimocytes) had distinct nuclei with sufficient quantity of chromatin and thin nuclear membrane. Brain substance of thymus contained small quantity of lymphoid elements and light epithelial cells with large pale nuclei. Stroma of thymus was moderately blooded. Architectonics of stom-

ach was preserved and clearly divided into different sections by structure of glands at the same time maintaining a complete set of cells corresponding to different types of glands. In the proper plate a moderate quantity of eosinophilic leukocytes was observed. Architectonics of small intestine was preserved. The thickness of mucous membrane, quantity and height of villi matched the intestine divisions. Epitheliocytes were high and had a cylindrical form. In the proper plate a weak plethora of vessels of microcircular cycle and small quantity of lymphocytes was noted. Large intestine architectonics was preserved, with the presence of crypts rich in goblet cells, covered with high epitheliocytes. In the proper plate a weak plethora of vessels of microcircular cycle and small quantity of lymphocytes was noted. In cortical substance of ovaries of female rabbits follicles of different sizes and maturity were observed. Follicular epithelium was not changed; nuclei were distinct, brain substance of ovaries was full-blooded. Epithelium of seminiferous tubules of male rabbits' testicles and interstitial cells were not changed. Nuclei were clear-cut, cytoplasm was oxyphilous.

Conclusion on results of necropsy and histological examination:

In organs of both control and experimental animals neither acute (inflammatory, dystrophic ordestructive), nor chronic (atrophic or sclerotic) changes in parenchymal organs and stromal component have been revealed.

CONCLUSION ON THE SECTION

Repeated daily administration of the test substance orally during 90 days in doses 3.7 and 37 mg/kg in male and female rabbits did not cause lethality or any pathological signs in animal status and behavior; no changes of integral indexes of vital activity or disorders in thermoregulation system were found. There were no significant differences between indices of male and female rabbits. Values of mass coefficients of animals' organs were within the range of reference values in control.

In organs of both control and experimental animals neither acute (inflammatory, dystrophic ordestructive), nor chronic (atrophic or sclerotic) changes in parenchymal organs and stromal component have been revealed.

3 SAFETY PHARMACOLOGY STUDY

The test substance effects on the organs and systems having functions that could be temporarily disordered because of adverse pharmacodynamic effects of the substance without irreversible damages, and on the vital organs and systems having fuctions essential for survival (respiratory, cardio-vascular, and central vervous systems) were studied.

Experiments were conducted on Chinchilla rabbits of both sexes.

The file number of the Veterinary certificate, quarantine conditions and animal handling, substance doses, regimen and duration of dosing, a set of parameters to be evaluated are presented in Sections 1 and 2.

Results of the study of test compound effects on functions of cardio-vasculary and respiratory systems are presented below.

Table 4 FPACA substance effects on breathing rate and ECG

Parameters (M±m)	**Experimental groups (n=5), substance, dose, mg/kg**					
	Control		**3.7**		**37**	
	M	**F**	**M**	**F**	**M**	**F**
30 days						
BR, ex/min	93.6±9.0	91.2±8.4	88.8±8.1	98.4±7.7	96.0±10.4	96.0±10.2
HR, hb/min	254.4±26.2	240.4±13.0	253.8±7.6	225.0±15.7	246.6±23.0	283.4±9.5
P, mV	0.05±0.01	0.05±0.00	0.05±0.01	0.05±0.00	0.07±0.01	0.05±0.00
R, mV	0.21±0.03	0.18±0.01	0.17±0.02	0.18±0.03	0.20±0.03	0.15±0.02
PQ, msec	68.6±1.5	67.0±1.8	69.0±2.0	74.4±3.5	65.8±2.8	64.6±3.1
QT, msec	147.2±12.1	143.6±2.9	145.8±6.6	143.2±4.3^	138.2±9.7	130.8±4.0*^
90 days						
BR, ex/min	90.4±5.5	100.0±2.3	94.4±7.7	96.0±4.2	94.8±5.5	91.6±8.0
HR, hb/min	202.6±13.7	228.4±16.8	233.8±20.0	222.0±19.6	245.8±24.1	255.0±12.3
P, mV	0.06±0.00	0.05±0.00	0.06±0.01	0.05±0.01	0.05±0.00	0.06±0.01
R, mV	0.23±0.02	0.19±0.01	0.17±0.02	0.21±0.03	0.17±0.01	0.18±0.02
PQ, msec	73.8±2.2	66.2±4.8	68.2±2.4	74.0±2.9	69.2±2.5	70.8±3.0
QT, msec	161.6±6.1	150.0±4.3	155.6±7.5	157.0±4.8^	141.8±8.5	139.0±5.1^
*- $p \leq 0.05$ to control ($p=0.047$); ^ - $p \leq 0.05$ at doses comparison						

The data demonstrate that all animals had heart rate wthin the specific and age-related physiological norm. All animals had a correct sine rhythm of heartbeat (in 2nd standard lead a positive P spike was constantly present before typical ventricular complex). No signs of ectopic arythmia were detected. In ECG there were no signs of intracardic conduction.

As a tendency a slight increase of HR and shortening of QT interval (reliable only when registered in 30 days after start of dosing, $p=0.047$) in rabbits exposed to the test sub-

stance in dose 37 mg/kg, in absolute terms not coming out of limits of physiological norm for rabbits can be noted.

Differences in BR indicies of experimental rabbits in comparison to control were not found.

In can be concluded that daily administration of FPACA substance during 90 days did not change automatism, excitability and cardial conduction and did not affect the of breathing frequency.

Table 5 FPACA substance effects on blood biochemistry indices

Parameters (M± m)	**Experimental groups (n=5), substance, dose, mg/kg**					
	Control		**3.7**		**37**	
	M	**F**	**M**	**F**	**M**	**F**
30 days						
Albumin, g/l	35.8±1.0	32.0±0.2	34.5±0.9	33.5±0.6	35.7±0.6	32.7±1.0
Total protein, g/l	79.0±0.8	71.0±0.8	73.2±1.6*	74.9±0.8*	77.8±0.6	72.6±1.9
Globulins, g/l	43.1±0.5	39.0±1.0	38.8±0.7*^	41.3±0.9	42.2±0.8^	39.8±2.0
AlAT, IU/l	70.0±3.0	70.6±7.4	81.7±6.4	56.4±7.9	77.5±5.2	107.0±30.8
AsAT, IU/l	91.1±14.8	95.9±11.7	79.1±9.0	57.1±5.9*	70.7±4.1	165.9±102.2
AP, U/l	212.1±31.3	173.1±27.7	182.6±23.8	190.6±19.8	161.4±24.8	188.4±38.8
Total bilirubin, μmol/l	11.5±4.0	9.5±1.4	10.4±1.2	9.5±1.2	8.9±0.5	5.8±0.8*
Glucose, mmol/l	9.4±1.0	9.6±0.4	10.0±0.5	8.0±0.2*	8.7±0.2	8.8±0.5
Cholesterol, mmol/l	1.14±0.12	1.56±0.34	0.81±0.08	1.79±0.08	1.00±0.12	1.99±0.15
TAG, mmol/l	0.73±0.09	0.91±0.18	0.58±0.09	1.07±0.12	0.61±0.10	1.29±0.15
Urea, mmol/l	7.4±0.3	6.8±0.6	7.1±0.4	7.0±0.5	8.0±0.6	6.9±0.6
Creatinine, μmol/l	65.4±5.7	61.6±5.8	59.3±3.3	70.4±5.5	76.0±10.3	68.4±5.7
Potassium, mmol/l	3.68±0.20	3.74±0.21	4.04±0.35	3.88±0.24	4.10±0.36	3.92±0.25
Sodium, mmol/l	139.7±2.5	138.1±2.6	138.2±2.6	140.7±2.1	137.5±4.4	139.6±3.0
PTT, sec	21.1±2.7	17.8±2.6	16.1±2.2	17.2±2.5	17.3±2.4	16.8±1.8
APTT, sec	31.8±3.0	28.9±3.3	29.7±2.3	28.0±2.6	30.3±3.3	28.3±2.1
90 days						
Albumin, g/l	31.2±1.1	32.5±0.8	29.5±0.9^	30.5±0.4^	33.1±0.5^	33.9±0.5^
Total protein, g/l	69.2±2.7	71.1±0.8	65.6±2.1^	74.5±0.8*	80.4±3.3*^	76.3±3.1
Globulins, g/l	38.0±1.7	38.5±1.5	36.2±1.2^	44.0±1.1	47.3±3.2*^	42.3±3.3
AlAT, IU/l	63.2±3.8	66.1±9.1	73.5±12.8	54.6±1.4^	59.6±1.3	76.2±5.3^
AsAT, IU/l	72.9±12.2	64.0±4.1	57.7±8.2	62.3±3.0	54.3±4.5	74.0±8.4

AP, U/l	149.5±26.5	193.9±24.1	94.4±9.2	85.3±5.1^	87.5±3.9*	111.2±3.6^
Total bilirubin, μmol/l	5.8±1.1	7.4±1.2	6.2±0.5^	7.7±1.0^	8.9±0.2*^	10.4±1.2^
Glucose, mmol/l	9.7±0.7	9.3±1.1	8.2±0.5^	9.2±0.2	11.3±0.1^	9.6±0.2
Cholesterol, mmol/l	1.26±0.29	1.43±0.23	0.77±0.07	1.71±0.06^	0.90±0.04	2.01±0.06^
TAG, mmol/l	0.67±0.03	1.14±0.06	1.03±0.08*	1.12±0.14	1.24±0.09*	1.38±0.10
Urea, mmol/l	7.6±0.6	7.8±0.4	6.6±0.5	9.3±0.9	7.2±0.4	9.9±0.8
Creatinine, μmol/l	104.0±9.8	105.1±8.0	88.8±6.2	123.8±3.3	107.8±7.6	119.5±6.9
Potassium, mmol/l	3.96±0.25	3.88±0.19	4.32±0.31	4.02±0.26	4.30±0.19	4.46±0.02
Sodium, mmol/l	139.4±2.7	145.0±1.1	143.0±2.4	143.5±1.4	142.5±3.0	140.5±1.8
PTT, sec	11.8±0.7	11.5±0.9	11.3±0.4	11.8±0.7	12.0±0.4	11.2±0.7
APTT, sec	31.4±1.1	34.6±1.5	31.4±0.9	31.8±1.0	31.7±1.6	31.7±2.7
*- $p \leq 0.05$ compared to control; ^ - $p \leq 0.05$ at doses comparison						

Analysis of the obtained data demonstrated that biochemical indices of peripheral blood of all experimental rabbits were within the physiological norm.

Single noted differences in indices of experimental animals compared to control, although being reliable, almost did not differ from indices in control in absolute terms, and the revealed reliability depended not on a real change in activity or on the level of test indices but on a low value of mean deviation in groups (see “Statistical characteristics” section). In addition, the changes detected had an evident stochastic character as they did not depend on the dose or duration of exposure. For example, in male rabbits exposed to the test substance in dose 3.7 mg/kg, but not 37 mg/kg, in 30 days after initiation of dosing (but not after 90 days) some lowered indices of total protein and globulins compared to control were noted. In female rabbits exposed to the test substance in dose 3.7 mg/kg, but not 37 mg/kg, on the contrary, an increased value of total protein was noted. Also, in females exposed to the test substance in dose 3.7 (but not 37 mg/kg) and in 30 days (but not 90 days) after the start of dosing some lowered indices of AsAT activity and glucose, and in females exposed to the test substance in dose 37 mg/kg – lowered indices of bilirubin ($p=0.047$) were noted.

In 90 days after the start of dosing in male rabbits exposed to the test substance in both doses some increase of TAG level was observed. In male rabbits that received the test substance in dose 37 mg/kg the indices of total protein, globulin and bilirubin were slightly increased, and the index of alkaline phosphatase activity was dicreased compared to control.

In female rabbits exposed to the test substance in the same dose after 90 days all the revealed deviations from control were on the border of reliability (p=0.047).

We can conclude that the conducted experiment did not reveal toxic effects of the test compound on liver protein synthesis and protein metabolism, carbohydrate metabolism and pancreas activity, the processes of filtration and excretion of protein exchange final metabolites by kidneys. Electrolyte metabolism was characterized by normal relation of concentrations of intercellular (potassium) and extracellular (sodium) ions. No deviations from the side of coagulation blood system were noted.

Table 6 FPACA substance effects on peripheral blood indices

Parameter (M±m)	**Experimental groups (n=5), substance, dose, mg/kg**					
	Control		**3.7**		**37**	
	M (n=5)	**F (n=5)**	**M (n=5)**	**F (n=5)**	**M (n=5)**	**F (n=5)**
30 days						
Erythrocytes, 10^{12}/l	6.8±0.5	6.7±0.1	6.9±0.3	6.3±0.13	6.5±0.2	6.9±0.2
Hemoglobin, g/l	144.2±7.5	145.0±2.1	143.6±6.2	142.6±2.5	138.0±5.7	144.4±4.5
Ht, %	45.8±3.7	44.7±0.9	44.1±2.0	44.1±0.9	43.0±1.2	45.4±0.8
MCV, fl	66.6±0.2	66.8±0.2	64.2±0.5*^	69.8±1.0	66.2±0.4^	66.0±0.8
MCH, pg	21.2±0.6	21.7±0.3	20.9±0.1	22.6±0.4^	21.2±0.5	21.0±0.4^
MCHC, g/l	314.0±12.4	324.8±5.2	326.0±1.6	323.2±1.7	321.0±7.9	318.6±5.4
RDWc, %	16.4±0.3	15.5±0.5	16.6±0.1	17.1±0.4	16.5±0.8	15.4±0.7
Reticulocytes, 10^{9}/l	88.6±1.7	88.4±1.1	89.4±2.1	90.2±1.0	91.8±1.7	88.4±1.7
Thrombocytes, 10^{9}/l	409.0±32.7	402.6±51.4	410.6±23.4	382.4±12.0	409.6±19.6	488.8±16.7
ESR, mm/h	4.0±0.5	3.8±0.4	3.6±0.5	4.4±0.2	3.2±0.4	4.0±0.3
Leukocytes, 10^{9}/l	11.5±0.7	11.8±1.3	8.3±0.4*	10.1±0.6^	6.7±0.7	12.6±0.5^
Myelocytes, %	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Metamyelocytes, %	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Stab neutrophils, %	3.0±0.0	3.0±0.0	2.4±0.4	3.4±0.5	2.2±0.4	2.4±0.2
Segmented neutrophils, %	50.6±5.1	58.6±6.1	47.8±4.9	65.2±14.7^	54.2±3.0	46.4±3.0^
Eosinophiles, %	0.6±0.4	1.2±0.5	0.0±0.0	0.4±0.2	1.0±0.5	0.2±0.2
Basophiles, %	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Monocytes,	4.2±0.7	4.8±1.5	6.4±0.8	3.0±1.2	6.6±1.2	3.8±1.1

%						
Lymphocytes, %	41.6±5.8	32.4±4.7	43.4±5.0	28.0±7.6^	36.0±3.0	47.2±2.5^
Plasma cells, %	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Neutrophils, 10^9/l	6.02±0.26	7.00±0.22	4.19±0.51*	7.08±1.07	3.88±0.63*	6.10±0.31
Eosinophiles 10^9/l	0.06±0.04	0.16±0.07	0.00±0.00	0.04±0.02	0.07±0.03	0.03±0.03
Basophiles 10^9/l	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
Monocytes 10^9/l	0.47±0.07	0.62±0.22	0.52±0.05	0.32±0.14	0.44±0.10	0.48±0.14
Lymphocytes 10^9/l	4.91±0.89	4.06±0.95	3.57±0.36^	2.69±0.65^	2.33±0.08^	5.95±0.48^
90 days						
Erythrocytes, $10^{12/l}$	6.8±0.2	6.6±0.2	6.9±0.2	6.6±0.1	6.9±0.2	6.2±0.2
Hemoglobin, g/l	134.8±3.4	132.2±3.3	139.6±3.8	129.2±1.4	135.8±5.5	128.2±1.7
Ht, %	44.5±1.3	44.8±1.3	46.0±1.4	43.6±0.4	46.5±1.5	43.0±0.9
MCV, fl	65.8±0.5	67.4±0.2	67.2±0.6	66.4±1.0^	67.8±0.4*	69.0±0.5*^
MCH, pg	20.0±0.3	19.9±0.3	20.3±0.3	19.6±0.2	19.8±0.3	20.5±0.4
MCHC, g/l	303.2±5.4	295.6±4.0	304.2±4.9	296.2±3.4	292.0±2.8	296.6±4.7
RDWc, %	14.8±0.3	14.7±0.1	15.0±0.1	15.7±0.1*	14.8±0.3	14.7±0.4
Reticulocytes, $10^{9/l}$	93.2±1.3	92.2±2.0	89.4±1.0	93.6±1.4	92.2±2.2	93.2±1.7
Thrombocytes, $10^{9/l}$	401.4±33.1	277.8±40.5	383.8±15.1	327.8±62.3	506.0±46.9	385.0±44.5
ESR, mm/h	4.0±0.6	4.0±0.5	3.8±0.4	4.8±0.2	4.6±0.5	5.0±0.6
Leukocytes, 10^9/l	12.7±0.5	8.5±0.4	9.8±0.8*	11.0±0.4*	10.9±0.8	11.1±0.8*
Myelocytes, %	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Metamyelocytes, %	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Stab neutrophils, %	2.4±0.2	2.8±0.2	2.6±0.2	2.6±0.4	2.6±0.2	1.8±0.4
Segmented neutrophils, %	27.8±7.0	54.2±7.5	39.8±3.3	34.6±1.4*	47.6±4.3	29.4±10.3
Eosinophiles, %	0.6±0.2	1.0±0.5	1.0±0.3	0.6±0.4	1.8±0.4	0.8±0.4
Basophiles, %	0.2±0.2	0.2±0.2	0.2±0.2	0.4±0.2	0.4±0.2	0.2±0.2
Monocytes, %	3.0±0.7	4.0±0.9	4.8±1.4	5.8±0.8	5.2±0.4*	3.6±0.4
Lymphocyt	66.0±6.5	37.8±7.4	51.6±4.2	56.0±1.7	42.4±4.7*	64.2±10.7

es, %						
Plasma cells, %	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Neutrophil, 10^9/l	3.77±0.79	4.90±0.79	4.08±0.26^	4.16±0.24	5.39±0.47^	3.22±0.82
Eosinophiles 10^9/l	0.08±0.03	0.09±0.04	0.09±0.03	0.06±0.04	0.20±0.05	0.08±0.03
Basophiles 10^9/l	0.02±0.02	0.02±0.02	0.02±0.02	0.04±0.03	0.05±0.03	0.02±0.02
Monocytes 10^9/l	0.38±0.09	0.33±0.07	0.43±0.11	0.63±0.07*	0.56±0.05	0.40±0.06
Lymphocytes 10^9/l	8.43±1.01	3.14±0.49	5.16±0.81*	6.15±0.32*	4.69±0.79*	7.35±1.39
*- $p \leq 0.05$ compared to control; ^ - $p \leq 0.05$ at doses comparison						

Analysis of the obtained data demonstrated that quantitative and qualitative morphological composition of peripheral blood of rabbits from all experimental groups was within the limits of species-specific physiological norm.

Some noted differences in indices in experimental animals compared to control, although being reliable, almost did not differ from control in absolute terms.

For example, in male rabbits exposed to the test substance in dose 3.7 mg/kg but not 37 mg/kg, in 30 days after the start of dosing (but not after 90 days) minor decrease of the estimated MCV index (in female rabbits– increased index) and index of absolute neutrophil count were noted. In addition, in male rabbits, exposed to the test substance in the same dose, during the experiment an ulterior decrease of the level of circulating leukocytes was observed mainly due to lymphocytic cell pool ($p=0.047$). In male rabbits exposed to the test substance in dose 37 mg/kg, after 30 days only decrease of neutrophils level was noted. At that, in female rabbits the differences with control were absent.

In females exposed to the test substance in both doses, after 90 days a slight and not dose-dependent increase of the level of circulating leukocytes (at decreasing the count of segmented neutrophils) was noted. In females exposed to the test substance in dose 3.7 mg/kg, but not 37 mg/kg, a slightly increased count of monocytes compared to control was noted. In male rabbits exposed to the test substance in dose 37 mg/kg, an ulterior increase of the level of monocytes and decreased level of lymphocytes was observed.

Therefore, the experiment conducted has not revealed hematotoxic effect of the test substance.

Conclusion on the section

Safety pharmacology study demonstrated that repeated daily oral administration of FPACA substance during 90 days in rabbits of both sexes in doses 3.7 mg/kg and 37 mg/kg did not have toxic effects on the organs and systems having functions that could be temporarily disordered because of adverse pharmacodynamic effects of the substance without irreversible damages (hepato-biliary system, blood circulation system, and metabolic system) and vital organs and systems having fuctions essential for survival (respiratory, cardiovascular, and central vervous systems).

4 LOCAL TOLERANCE STUDY

Local tolerance study was carried out by morphological and histological methods.

Architectonics of stomach was preserved and clearly divided into different sections by structure of glands at the same time maintaining a complete set of cells corresponding to different types of glands. In the proper plate a moderate quantity of eosinophilic leukocytes was observed. Architectonics of small intestine was preserved. The thickness of mucous membrane, quantity and height of villi matched the intestine divisions. Epitheliocytes were high and cylindrical. In the proper plate a weak plethora of vessels of microcircular cycle and small quantity of lymphocytes was found. Large intestine architectonics was preserved with the presence of crypts rich in goblet cells covered with high epitheliocytes. In the proper plate a weak plethora of vessels of microcircular cycle and a small quantity of lymphocytes was observed.

Based on above said we can conclude that Fullerene polyaminocaproic acid (FPACA) substance does not have local irritant effect at intragastrical administration in conditions of repeat-dose experiment.

CONCLUSION ON THE SECTION

Results of necropsy and histological study demonstrated that FPACA substance at daily oral administration in tested doses during 90 days in rabbits of both sexes did not cause any changes in the structure of gastrointestinal tract – the site of exposure.

CONCLUSION ON THE STUDY

The objective was non-clinical studies of general toxic effects, safety pharmacology and local tolerance of Fullerene polyaminocaproic acid (FPACA) substance produced by ZAO “Intelpharm” at peroral administration in rabbits.

It was demonstrated that repeated daily peroral administration of the substance in doses 3.7 and 37 mg/kg during 90 days in male and female rabbits did not cause lethality or any pathological signs in animal status and behavior; no changes of integral indexes of vital activity or disorders in thermoregulation system were found. There were no differences between indices of male and female rabbits. No changes in mass coefficients of experimental animals’ organs compared to control were noted.

In parenchymal organs and stromal component neither acute (inflammatory, dystrophic ordestructive), nor chronic (atrophic or sclerotic) changes have been revealed.

Safety pharmacology study of FPACA substance demonstrated the absence of toxic effects on the organs and systems with functions that could be temporarily disordered because of adverse pharmacodynamic effects of the substance without irreversible damages (hepato-biliary system, blood circulation system, and metabolic system) and vital organs and systems having fuctions essential for survival (respiratory, cardio-vascular, and central vervous systems).

Local tolerance study performed based on results of necropsy and histological examination demonstrated that daily oral administration of FPACA substance in rabbits of both sexes during 90 days did not cause any changes in the structure of gastrointestinal tract – the site of exposure.

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STATISTICAL CHARACTERISTICS

Delta of body mass change

Control (male)

Parameter	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
delta 14 days, g	5	0	380.00	66.33	148.32	250.00	450.00	450.00
delta 30 days, g	5	0	740.00	132.66	296.65	550.00	600.00	950.00
delta 60 days, g	5	0	910.00	124.90	279.28	700.00	800.00	1100.00
delta 90 days, g	5	0	1080.00	118.95	265.99	900.00	1000.00	1250.00

Control (female)

Parameter	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
delta 14 days, g	5	0	430.00	64.42	144.05	400.00	450.00	550.00
delta 30 days, g	5	0	1010.00	111.13	248.50	1000.00	1050.00	1150.00
delta 60 days, g	5	0	1040.00	120.83	270.19	1000.00	1100.00	1200.00
delta 90 days, g	5	0	1140.00	163.86	366.40	1000.00	1150.00	1450.00

Dose 1 (male)

Parameter	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
delta 14 days, g	5	0	370.00	51.48	115.11	300.00	350.00	400.00
delta 30 days, g	5	0	950.00	57.01	127.48	850.00	900.00	1000.00
delta 60 days, g	5	0	1030.00	66.33	148.32	900.00	1000.00	1100.00
delta 90 days, g	5	0	1130.00	73.48	164.32	1000.00	1100.00	1300.00

Dose 1 (female)

Parameter	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
delta 14 days, g	5	0	420.00	91.65	204.94	350.00	350.00	450.00
delta 30 days, g	5	0	890.00	112.25	251.00	700.00	1000.00	1100.00
delta 60 days, g	5	0	1030.00	115.76	258.84	900.00	1050.00	1100.00
delta 90 days, g	5	0	1180.00	107.94	241.35	1100.00	1150.00	1300.00

Dose 2 (male)

Parameter	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
delta 14 days, g	5	0	410.00	57.88	129.42	350.00	400.00	450.00
delta 30 days, g	5	0	930.00	60.42	135.09	850.00	950.00	1000.00
delta 60 days, g	5	0	1030.00	81.55	182.35	950.00	1100.00	1150.00
delta 90 days, g	5	0	1110.00	101.73	227.49	1050.00	1150.00	1300.00

Dose 2 (female)

Parameter	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
delta 14 days, g	5	0	220.00	58.31	130.38	100.00	200.00	300.00
delta 30 days, g	5	0	560.00	114.46	255.93	550.00	600.00	650.00
delta 60 days, g	5	0	830.00	93.01	207.97	750.00	950.00	950.00
delta 90 days, g	5	0	1080.00	98.23	219.66	900.00	1100.00	1150.00

Mass coefficients of organs

Control (male)

Parameter	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
Body mass, g	5	0	3920.00	118.95	265.99	3750.00	3750.00	4100.00
Liver, mg/g	5	0	33.16	2.41	5.39	29.61	32.46	37.09
Kidneys, mg/g	5	0	6.34	0.18	0.39	6.18	6.36	6.43
Adrenal glands, mg/g	5	0	0.09	0.01	0.01	0.08	0.09	0.11
Heart, mg/g	5	0	2.39	0.09	0.20	2.28	2.32	2.42
Thymus, mg/g	5	0	0.77	0.08	0.19	0.71	0.77	0.77
Lungs, mg/g	5	0	3.86	0.15	0.35	3.68	3.71	3.97
Brain, mg/g	5	0	2.87	0.21	0.46	2.50	2.74	3.12
Testicles/Ovaries, mg/g	5	0	2.61	0.12	0.28	2.49	2.71	2.73
Spleen, mg/g	5	0	0.56	0.09	0.21	0.48	0.50	0.52

Control (female)

Parameter	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
Body mass, g	5	0	3710.00	203.35	454.70	3250.00	3950.00	3950.00
Liver, mg/g	5	0	32.95	1.06	2.38	30.91	32.43	35.02
Kidneys, mg/g	5	0	5.88	0.34	0.77	5.22	5.91	6.05
Adrenal glands, mg/g	5	0	0.11	0.01	0.02	0.10	0.10	0.11
Heart, mg/g	5	0	2.48	0.17	0.37	2.44	2.46	2.48
Thymus, mg/g	5	0	0.81	0.09	0.20	0.70	0.72	1.00
Lungs, mg/g	5	0	3.60	0.14	0.32	3.43	3.62	3.67
Brain, mg/g	5	0	2.68	0.24	0.54	2.39	2.46	3.08
Testicles/Ovaries, mg/g	5	0	0.16	0.02	0.04	0.12	0.15	0.19
Spleen, mg/g	5	0	0.70	0.08	0.18	0.63	0.69	0.80

Dose 1 (male)

Parameter	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
Body mass, g	5	0	3820.00	81.55	182.35	3750.00	3800.00	3850.00
Liver, mg/g	5	0	32.98	1.67	3.73	30.58	31.79	33.71
Kidneys, mg/g	5	0	6.25	0.18	0.40	6.07	6.32	6.50
Adrenal glands, mg/g	5	0	0.09	0.01	0.01	0.09	0.10	0.10
Heart, mg/g	5	0	2.45	0.13	0.29	2.25	2.52	2.69
Thymus, mg/g	5	0	0.70	0.07	0.17	0.62	0.64	0.81
Lungs, mg/g	5	0	3.54	0.22	0.50	3.06	3.53	3.99
Brain, mg/g	5	0	2.83	0.11	0.24	2.69	2.90	3.01
Testicles/Ovaries, mg/g	5	0	2.65	0.12	0.26	2.45	2.66	2.76
Spleen, mg/g	5	0	0.59	0.10	0.23	0.49	0.59	0.77

Dose 1 (female)

Parameter	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
Body mass, g	5	0	3900.00	72.46	162.02	3750.00	4000.00	4000.00
Liver, mg/g	5	0	33.61	1.45	3.25	31.83	32.58	36.81

Kidneys, mg/g	5	0	6.02	0.23	0.52	5.79	6.00	6.43
Adrenal glands, mg/g	5	0	0.10	0.01	0.02	0.09	0.10	0.11
Heart, mg/g	5	0	2.59	0.11	0.25	2.43	2.49	2.59
Thymus, mg/g	5	0	0.79	0.03	0.07	0.74	0.74	0.82
Lungs, mg/g	5	0	3.67	0.17	0.38	3.44	3.66	3.86
Brain, mg/g	5	0	2.74	0.05	0.11	2.70	2.76	2.79
Testicles/Ovaries, mg/g	5	0	0.15	0.02	0.03	0.14	0.15	0.17
Spleen, mg/g	5	0	0.58	0.08	0.17	0.51	0.60	0.73

Dose 2 (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Body mass, g	5	0	3690.00	141.77	317.02	3400.00	3600.00	4000.00
Liver, mg/g	5	0	34.13	1.85	4.13	31.31	33.81	34.01
Kidneys, mg/g	5	0	6.51	0.31	0.69	5.83	6.73	7.12
Adrenal glands, mg/g	5	0	0.09	0.01	0.01	0.09	0.10	0.11
Heart, mg/g	5	0	2.62	0.11	0.26	2.55	2.56	2.84
Thymus, mg/g	5	0	0.64	0.09	0.20	0.47	0.65	0.69
Lungs, mg/g	5	0	3.59	0.23	0.52	3.13	3.63	3.70
Brain, mg/g	5	0	2.71	0.13	0.28	2.60	2.74	2.81
Testicles/Ovaries, mg/g	5	0	2.72	0.09	0.19	2.62	2.66	2.72
Spleen, mg/g	5	0	0.55	0.10	0.22	0.41	0.43	0.69

Dose 2 (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Body mass, g	5	0	3750.00	93.54	209.17	3650.00	3700.00	3850.00
Liver, mg/g	5	0	31.99	1.77	3.95	30.03	31.12	33.06
Kidneys, mg/g	5	0	5.64	0.24	0.54	5.16	5.71	5.81
Adrenal glands, mg/g	5	0	0.09	0.01	0.02	0.08	0.09	0.10
Heart, mg/g	5	0	2.47	0.15	0.33	2.25	2.27	2.76
Thymus, mg/g	5	0	0.70	0.06	0.14	0.66	0.73	0.75
Lungs, mg/g	5	0	3.56	0.18	0.40	3.32	3.40	3.62
Brain, mg/g	5	0	2.53	0.10	0.21	2.40	2.42	2.62
Testicles/Ovaries, mg/g	5	0	0.15	0.01	0.03	0.15	0.16	0.17
Spleen, mg/g	5	0	0.57	0.04	0.10	0.51	0.56	0.56

Body temperature

Control (male)

Term	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Background	5	0	39.04	0.14	0.30	38.80	39.00	39.30
30 days	5	0	38.98	0.15	0.33	38.70	39.00	39.20
90 days	5	0	39.04	0.12	0.27	38.90	39.00	39.00

Control (female)

Term	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Background	5	0	38.94	0.16	0.35	38.70	38.90	39.00

30 days	5	0	39.08	0.14	0.30	39.00	39.20	39.20
90 days	5	0	39.16	0.12	0.26	39.00	39.20	39.40

Dose 1 (male)

Term	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Background	5	0	39.04	0.13	0.29	38.80	39.10	39.20
30 days	5	0	38.98	0.07	0.15	38.90	39.00	39.00
90 days	5	0	39.14	0.16	0.36	38.90	39.10	39.40

Dose 1 (female)

Term	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Background	5	0	39.04	0.16	0.36	38.90	38.90	39.30
30 days	5	0	38.96	0.19	0.43	38.70	39.00	39.20
90 days	5	0	39.00	0.08	0.19	38.90	38.90	39.20

Dose 2 (male)

Term	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Background	5	0	38.96	0.14	0.30	38.70	39.00	39.20
30 days	5	0	38.94	0.16	0.35	38.80	38.80	39.30
90 days	5	0	39.10	0.05	0.12	39.10	39.10	39.20

Dose 2 (female)

Term	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Background	5	0	38.98	0.14	0.31	38.80	38.90	39.00
30 days	5	0	39.00	0.08	0.19	38.90	39.00	39.00
90 days	5	0	39.18	0.12	0.26	39.10	39.20	39.30

Breathing rate

Control (male)

Term	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
30 days	5	0	93.60	9.02	20.17	78.00	90.00	108.00
90 days	5	0	90.40	5.53	12.36	84.00	86.00	94.00

Control (female)

Term	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
30 days	5	0	91.20	8.36	18.69	78.00	84.00	108.00
90 days	5	0	100.00	2.28	5.10	96.00	100.00	104.00

Dose 1 (male)

Term	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
30 days	5	0	88.80	8.14	18.20	78.00	90.00	96.00
90 days	5	0	94.40	9.64	21.56	78.00	104.00	106.00

Dose 1 (female)

Term	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
30 days	5	0	98.40	7.73	17.29	84.00	102.00	108.00
90 days	5	0	96.00	4.15	9.27	90.00	98.00	100.00

Dose 2 (male)

Term	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
30 days	5	0	96.00	10.39	23.24	78.00	90.00	114.00
90 days	5	0	94.80	5.54	12.38	86.00	100.00	102.00

Dose 2 (female)

Term	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
30 days	5	0	96.00	10.22	22.85	84.00	96.00	108.00
90 days	5	0	91.60	7.98	17.85	78.00	98.00	104.00

Cardio-vasculary system

30 days

Control (male)

Parameter	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
HR	5	0	254.40	26.24	58.67	220.00	266.00	299.00
P, mV	5	0	0.05	0.01	0.02	0.03	0.05	0.05
R, mV	5	0	0.21	0.03	0.07	0.18	0.24	0.24
PQ	5	0	68.60	1.54	3.44	66.00	70.00	71.00
QT	5	0	147.20	12.06	26.98	129.00	140.00	155.00

Control (female)

Parameter	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
HR	5	0	240.40	13.00	29.07	219.00	258.00	261.00
P, mV	5	0	0.05	0.00	0.01	0.04	0.05	0.05
R, mV	5	0	0.18	0.01	0.02	0.17	0.17	0.20
PQ	5	0	67.00	1.79	4.00	66.00	68.00	68.00
QT	5	0	143.60	2.87	6.43	139.00	140.00	149.00

Dose 1 (male)

Parameter	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
HR	5	0	253.80	7.57	16.92	240.00	258.00	261.00
P, mV	5	0	0.05	0.01	0.01	0.05	0.05	0.06
R, mV	5	0	0.17	0.02	0.04	0.14	0.15	0.21
PQ	5	0	69.00	1.95	4.36	68.00	68.00	69.00
QT	5	0	145.80	6.61	14.77	138.00	140.00	142.00

Dose 1 (female)

Parameter	N		Mean	Standard error of mean	Standard deviation	Percentile		
	Valid	Missed				25	50	75
HR	5	0	225.00	15.74	35.19	199.00	232.00	257.00
P, mV	5	0	0.05	0.00	0.01	0.05	0.05	0.05

R, mV	5	0	0.18	0.03	0.06	0.15	0.17	0.22
PQ	5	0	74.40	3.54	7.92	70.00	74.00	80.00
QT	5	0	143.20	4.32	9.65	136.00	138.00	148.00

Dose 2 (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
HR	5	0	246.60	23.01	51.45	241.00	245.00	275.00
P, mV	5	0	0.07	0.01	0.02	0.06	0.07	0.08
R, mV	5	0	0.20	0.03	0.07	0.19	0.24	0.25
PQ	5	0	65.80	2.75	6.14	67.00	68.00	69.00
QT	5	0	138.20	9.65	21.57	129.00	130.00	134.00

Dose 2 (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
HR	5	0	283.40	9.47	21.17	276.00	281.00	303.00
P, mV	5	0	0.05	0.00	0.01	0.04	0.05	0.06
R, mV	5	0	0.15	0.02	0.05	0.13	0.17	0.19
PQ	5	0	64.60	3.09	6.91	60.00	62.00	68.00
QT	5	0	130.80	4.03	9.01	128.00	128.00	130.00

90 days

Control (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
HR	5	0	202.60	13.70	30.63	182.00	197.00	203.00
P, mV	5	0	0.06	0.00	0.00	0.06	0.06	0.06
R, mV	5	0	0.23	0.02	0.06	0.20	0.20	0.25
PQ	5	0	73.80	2.20	4.92	70.00	72.00	78.00
QT	5	0	161.60	6.05	13.52	160.00	162.00	164.00

Control (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
HR	5	0	228.40	16.82	37.61	196.00	218.00	254.00
P, mV	5	0	0.05	0.00	0.01	0.05	0.05	0.05
R, mV	5	0	0.19	0.01	0.01	0.18	0.19	0.19
PQ	5	0	66.20	4.76	10.64	61.00	66.00	72.00
QT	5	0	150.00	4.34	9.70	144.00	154.00	158.00

Dose 1 (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
HR	5	0	233.80	20.03	44.78	224.00	254.00	260.00
P, mV	5	0	0.06	0.01	0.02	0.04	0.07	0.07
R, mV	5	0	0.17	0.02	0.04	0.15	0.16	0.19
PQ	5	0	68.20	2.40	5.36	65.00	70.00	70.00
QT	5	0	155.60	7.47	16.70	150.00	154.00	156.00

Dose 1 (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
HR	5	0	222.00	19.58	43.79	190.00	192.00	261.00

P, mV	5	0	0.05	0.01	0.02	0.03	0.06	0.06
R, mV	5	0	0.21	0.03	0.08	0.15	0.19	0.24
PQ	5	0	74.00	2.88	6.44	70.00	73.00	80.00
QT	5	0	157.00	4.75	10.63	150.00	161.00	166.00

Dose 2 (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
HR	5	0	245.80	24.11	53.91	199.00	280.00	287.00
P, mV	5	0	0.05	0.00	0.00	0.05	0.05	0.05
R, mV	5	0	0.17	0.01	0.03	0.14	0.16	0.17
PQ	5	0	69.20	2.48	5.54	68.00	69.00	72.00
QT	5	0	141.80	8.49	18.98	128.00	137.00	154.00

Dose 2 (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
HR	5	0	255.00	12.31	27.53	246.00	248.00	262.00
P, mV	5	0	0.06	0.01	0.02	0.06	0.06	0.07
R, mV	5	0	0.18	0.02	0.03	0.16	0.17	0.21
PQ	5	0	70.80	3.01	6.72	68.00	70.00	74.00
QT	5	0	139.00	5.13	11.47	137.00	143.00	147.00

Hematology
30 days

Control (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Erythrocytes, 10*12/l	5	0	6.84	0.51	1.14	6.07	6.57	6.70
Hb, g/l	5	0	144.20	7.48	16.72	137.00	138.00	148.00
Ht, %	5	0	45.80	3.65	8.17	40.70	44.00	44.30
MCV, fl	5	0	66.60	0.24	0.55	66.00	67.00	67.00
MCH, pg	5	0	21.24	0.55	1.23	21.00	21.10	22.10
MCHC, g/l	5	0	314.00	12.37	27.67	313.00	318.00	334.00
RDWc, %	5	0	16.36	0.30	0.67	15.80	16.20	16.60
Rt, 10*9/l	5	0	88.60	1.66	3.71	87.00	88.00	90.00
Thrombocytes, 10*9/l	5	0	409.00	32.67	73.05	356.00	407.00	459.00
ESR, mm/h	5	0	4.00	0.45	1.00	3.00	4.00	5.00
Leukocytes, 10*9/l	5	0	11.46	0.68	1.52	10.00	12.50	12.60
Myelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Metamyelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
stab,%	5	0	3.00	0.00	0.00	3.00	3.00	3.00
segmented,%	5	0	50.60	5.08	11.35	42.00	48.00	55.00
Eosinophiles %	5	0	0.60	0.40	0.89	0.00	0.00	1.00
Basophiles,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Monocytes, %	5	0	4.20	0.73	1.64	3.00	5.00	5.00
Lymphocytes, %	5	0	41.60	5.77	12.90	36.00	45.00	52.00
Plasma cells,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Neutrophils, 10*9/l	5	0	6.02	0.26	0.59	5.62	5.80	6.43
Eosinophiles, 10*9/l	5	0	0.06	0.04	0.09	0.00	0.00	0.12

Basophiles,10*9/l	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Monocytes, 10*9/l	5	0	0.47	0.07	0.16	0.38	0.48	0.60
Lymphocytes, 10*9/l	5	0	4.91	0.89	1.99	3.60	5.67	6.55

Control (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Erythrocytes, 10*12/l	5	0	6.69	0.13	0.29	6.48	6.59	6.96
Hb, g/l	5	0	145.00	2.12	4.74	144.00	145.00	147.00
Ht, %	5	0	44.66	0.90	2.01	43.40	43.70	46.50
MCV, fl	5	0	66.80	0.20	0.45	67.00	67.00	67.00
MCH, pg	5	0	21.68	0.33	0.75	21.30	21.40	22.30
MCHC, g/l	5	0	324.80	5.16	11.54	318.00	320.00	336.00
RDWc, %	5	0	15.50	0.51	1.14	14.60	15.60	15.80
Rt, 10*9/l	5	0	88.40	1.08	2.41	87.00	89.00	90.00
Thrombocytes, 10*9/l	5	0	402.60	51.41	114.96	319.00	333.00	492.00
ESR, mm/h	5	0	3.80	0.37	0.84	3.00	4.00	4.00
Leukocytes, 10*9/l	5	0	11.84	1.32	2.94	10.10	10.60	14.60
Myelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Metamyelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
stab,%	5	0	3.00	0.00	0.00	3.00	3.00	3.00
segmented,%	5	0	58.60	6.14	13.74	47.00	60.00	60.00
Eosinophiles %	5	0	1.20	0.49	1.10	0.00	2.00	2.00
Basophiles,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Monocytes, %	5	0	4.80	1.50	3.35	2.00	5.00	7.00
Lymphocytes, %	5	0	32.40	4.72	10.55	30.00	33.00	40.00
Plasma cells,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Neutrophils, 10*9/l	5	0	7.00	0.22	0.49	6.68	7.14	7.15
Eosinophiles, 10*9/l	5	0	0.16	0.07	0.15	0.00	0.20	0.29
Basophiles,10*9/l	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Monocytes, 10*9/l	5	0	0.62	0.22	0.49	0.20	0.74	0.76
Lymphocytes, 10*9/l	5	0	4.06	0.95	2.12	3.18	3.34	5.84

Dose 1 (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Erythrocytes, 10*12/l	5	0	6.86	0.26	0.58	6.65	7.09	7.26
Hb, g/l	5	0	143.60	6.17	13.79	136.00	150.00	154.00
Ht, %	5	0	44.10	1.99	4.46	41.90	46.20	47.30
MCV, fl	5	0	64.20	0.49	1.10	63.00	65.00	65.00
MCH, pg	5	0	20.90	0.14	0.32	20.70	20.90	21.10
MCHC, g/l	5	0	326.00	1.58	3.54	324.00	325.00	328.00
RDWc, %	5	0	16.64	0.10	0.22	16.40	16.80	16.80
Rt, 10*9/l	5	0	89.40	2.06	4.62	87.00	88.00	90.00
Thrombocytes, 10*9/l	5	0	410.60	23.37	52.27	364.00	434.00	445.00
ESR, mm/h	5	0	3.60	0.51	1.14	3.00	4.00	4.00
Leukocytes, 10*9/l	5	0	8.28	0.39	0.88	7.70	8.00	9.20
Myelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00

Metamyelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
stab,%	5	0	2.40	0.40	0.89	2.00	3.00	3.00
segmented,%	5	0	47.80	4.94	11.05	47.00	50.00	52.00
Eosinophiles %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Basophiles,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Monocytes, %	5	0	6.40	0.81	1.82	5.00	7.00	8.00
Lymphocytes, %	5	0	43.40	4.96	11.08	39.00	41.00	45.00
Plasma cells,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Neutrophils, 10*9/l	5	0	4.19	0.51	1.15	4.08	4.60	4.96
Eosinophiles, 10*9/l	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Basophiles,10*9/l	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Monocytes, 10*9/l	5	0	0.52	0.05	0.10	0.46	0.56	0.58
Lymphocytes, 10*9/l	5	0	3.57	0.36	0.81	3.00	3.77	4.14

Dose 1 (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Erythrocytes, 10*12/l	5	0	6.32	0.09	0.21	6.14	6.35	6.48
Hb, g/l	5	0	142.60	2.50	5.59	140.00	143.00	145.00
Ht, %	5	0	44.12	0.92	2.05	43.30	43.50	45.60
MCV, fl	5	0	69.80	0.97	2.17	68.00	71.00	71.00
MCH, pg	5	0	22.58	0.36	0.80	21.90	22.90	23.00
MCHC, g/l	5	0	323.20	1.74	3.90	321.00	322.00	325.00
RDWc, %	5	0	17.06	0.35	0.78	16.50	16.70	17.90
Rt, 10*9/l	5	0	90.20	0.97	2.17	89.00	91.00	92.00
Thrombocytes, 10*9/l	5	0	382.40	12.00	26.83	360.00	393.00	397.00
ESR, mm/h	5	0	4.40	0.24	0.55	4.00	4.00	5.00
Leukocytes, 10*9/l	5	0	10.12	0.63	1.41	9.20	10.90	11.00
Myelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Metamyelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
stab,%	5	0	3.40	0.51	1.14	3.00	3.00	4.00
segmented,%	5	0	65.20	6.55	14.65	57.00	60.00	80.00
Eosinophiles %	5	0	0.40	0.24	0.55	0.00	0.00	1.00
Basophiles,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Monocytes, %	5	0	3.00	1.22	2.74	1.00	1.00	6.00
Lymphocytes, %	5	0	28.00	7.55	16.88	15.00	31.00	39.00
Plasma cells,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Neutrophils, 10*9/l	5	0	7.08	1.07	2.40	4.86	6.88	9.46
Eosinophiles, 10*9/l	5	0	0.04	0.02	0.06	0.00	0.00	0.09
Basophiles,10*9/l	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Monocytes, 10*9/l	5	0	0.32	0.14	0.31	0.09	0.11	0.65
Lymphocytes, 10*9/l	5	0	2.69	0.65	1.44	1.71	3.16	3.37

Dose 2 (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Erythrocytes, 10*12/l	5	0	6.50	0.18	0.40	6.14	6.53	6.73

Hb, g/l	5	0	138.00	5.73	12.81	129.00	129.00	151.00
Ht, %	5	0	42.98	1.20	2.68	40.90	43.30	43.90
MCV, fl	5	0	66.20	0.37	0.84	66.00	66.00	67.00
MCH, pg	5	0	21.20	0.46	1.04	21.00	21.10	21.40
MCHC, g/l	5	0	321.00	7.91	17.68	315.00	321.00	322.00
RDWc, %	5	0	16.46	0.78	1.74	14.70	16.80	18.10
Rt, 10*9/l	5	0	91.80	1.66	3.70	90.00	91.00	95.00
Thrombocytes, 10*9/l	5	0	409.60	19.55	43.71	385.00	399.00	434.00
ESR, mm/h	5	0	3.20	0.37	0.84	3.00	3.00	4.00
Leukocytes, 10*9/l	5	0	6.72	0.74	1.66	5.10	6.80	8.10
Myelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Metamyelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
stab,%	5	0	2.20	0.37	0.84	2.00	2.00	3.00
segmented,%	5	0	54.20	2.99	6.69	49.00	55.00	56.00
Eosinophiles %	5	0	1.00	0.45	1.00	0.00	1.00	2.00
Basophiles,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Monocytes, %	5	0	6.60	1.21	2.70	5.00	7.00	8.00
Lymphocytes, %	5	0	36.00	2.97	6.63	30.00	34.00	42.00
Plasma cells,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Neutrophils, 10*9/l	5	0	3.88	0.63	1.42	2.55	3.94	4.70
Eosinophiles, 10*9/l	5	0	0.07	0.03	0.07	0.00	0.07	0.10
Basophiles,10*9/l	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Monocytes, 10*9/l	5	0	0.44	0.10	0.23	0.26	0.41	0.48
Lymphocytes, 10*9/l	5	0	2.33	0.08	0.18	2.20	2.31	2.43

Dose 2 (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Erythrocytes, 10*12/l	5	0	6.89	0.20	0.45	6.53	6.70	7.20
Hb, g/l	5	0	144.40	4.50	10.06	134.00	150.00	151.00
Ht, %	5	0	45.38	0.81	1.80	43.90	45.50	46.00
MCV, fl	5	0	66.00	0.84	1.87	64.00	67.00	67.00
MCH, pg	5	0	21.02	0.36	0.81	20.50	20.60	21.10
MCHC, g/l	5	0	318.60	5.40	12.07	306.00	321.00	330.00
RDWc, %	5	0	15.38	0.72	1.62	13.80	16.00	16.80
Rt, 10*9/l	5	0	88.40	1.66	3.71	87.00	89.00	90.00
Thrombocytes, 10*9/l	5	0	488.80	16.71	37.37	468.00	477.00	525.00
ESR, mm/h	5	0	4.00	0.32	0.71	4.00	4.00	4.00
Leukocytes, 10*9/l	5	0	12.56	0.53	1.18	11.50	13.00	13.10
Myelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Metamyelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
stab,%	5	0	2.40	0.24	0.55	2.00	2.00	3.00
segmented,%	5	0	46.40	2.98	6.66	42.00	47.00	50.00
Lymphocytes, %	5	0	0.20	0.20	0.45	0.00	0.00	0.00
Basophiles,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Monocytes, %	5	0	3.80	1.07	2.39	2.00	4.00	5.00
Lymphocytes, %	5	0	47.20	2.48	5.54	44.00	45.00	52.00
Plasma cells,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00

Neutrophils, 10*9/l	5	0	6.10	0.31	0.70	5.84	5.90	6.56
Lymphocytes, 10*9/l	5	0	0.03	0.03	0.06	0.00	0.00	0.00
Basophiles,10*9/l	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Monocytes, 10*9/l	5	0	0.48	0.14	0.32	0.23	0.44	0.70
Lymphocytes, 10*9/l	5	0	5.95	0.48	1.08	4.92	6.30	6.76

90 days

Control (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Erythrocytes, 10*12/l	5	0	6.76	0.16	0.36	6.50	6.70	7.02
Hb, g/l	5	0	134.80	3.41	7.63	133.00	133.00	137.00
Ht, %	5	0	44.54	1.31	2.94	43.00	45.00	46.40
MCV, fl	5	0	65.80	0.49	1.10	66.00	66.00	66.00
MCH, pg	5	0	19.98	0.33	0.74	19.70	19.80	20.50
MCHC, g/l	5	0	303.20	5.38	12.03	296.00	309.00	309.00
RDWc, %	5	0	14.76	0.25	0.57	14.70	15.00	15.10
Rt, 10*9/l	5	0	93.20	1.28	2.86	91.00	93.00	95.00
Thrombocytes, 10*9/l	5	0	401.40	33.10	74.02	350.00	429.00	459.00
ESR, mm/h	5	0	4.00	0.55	1.22	4.00	4.00	5.00
Leukocytes, 10*9/l	5	0	12.68	0.48	1.07	11.90	12.60	12.80
Myelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Metamyelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
stab,%	5	0	2.40	0.24	0.55	2.00	2.00	3.00
segmented,%	5	0	27.80	6.95	15.53	18.00	20.00	30.00
Lymphocytes, %	5	0	0.60	0.24	0.55	0.00	1.00	1.00
Basophiles,%	5	0	0.20	0.20	0.45	0.00	0.00	0.00
Monocytes, %	5	0	3.00	0.71	1.58	2.00	3.00	4.00
Lymphocytes, %	5	0	66.00	6.54	14.63	62.00	74.00	76.00
Plasma cells,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Neutrophils, 10*9/l	5	0	3.77	0.79	1.76	2.52	3.17	4.10
Lymphocytes, 10*9/l	5	0	0.08	0.03	0.07	0.00	0.12	0.13
Basophiles,10*9/l	5	0	0.02	0.02	0.05	0.00	0.00	0.00
Monocytes, 10*9/l	5	0	0.38	0.09	0.20	0.29	0.38	0.48
Lymphocytes, 10*9/l	5	0	8.43	1.01	2.26	7.94	8.80	9.57

Control (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Erythrocytes, 10*12/l	5	0	6.64	0.21	0.46	6.24	6.85	7.03
Hb, g/l	5	0	132.20	3.28	7.33	125.00	132.00	138.00
Ht, %	5	0	44.76	1.34	2.99	42.30	46.50	46.90
MCV, fl	5	0	67.40	0.24	0.55	67.00	67.00	68.00
MCH, pg	5	0	19.92	0.25	0.56	19.60	20.00	20.10
MCHC, g/l	5	0	295.60	4.01	8.96	292.00	296.00	300.00
RDWc, %	5	0	14.74	0.13	0.30	14.60	14.80	15.00
Rt, 10*9/l	5	0	92.20	1.98	4.44	88.00	94.00	95.00
Thrombocytes, 10*9/l	5	0	277.80	40.46	90.48	222.00	236.00	373.00

ESR, mm/h	5	0	4.00	0.45	1.00	3.00	4.00	5.00
Leukocytes, 10*9/l	5	0	8.46	0.35	0.79	7.80	8.60	9.10
Myelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Metamyelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
stab,%	5	0	2.80	0.20	0.45	3.00	3.00	3.00
segmented,%	5	0	54.20	7.51	16.80	38.00	56.00	70.00
Lymphocytes, %	5	0	1.00	0.45	1.00	0.00	1.00	2.00
Basophiles,%	5	0	0.20	0.20	0.45	0.00	0.00	0.00
Monocytes, %	5	0	4.00	0.89	2.00	3.00	3.00	5.00
Lymphocytes, %	5	0	37.80	7.37	16.48	24.00	34.00	53.00
Plasma cells,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Neutrophils, 10*9/l	5	0	4.90	0.79	1.77	3.12	5.49	6.35
Lymphocytes, 10*9/l	5	0	0.09	0.04	0.09	0.00	0.08	0.18
Basophiles,10*9/l	5	0	0.02	0.02	0.04	0.00	0.00	0.00
Monocytes, 10*9/l	5	0	0.33	0.07	0.15	0.23	0.27	0.46
Lymphocytes, 10*9/l	5	0	3.14	0.49	1.10	2.18	3.16	3.97

Dose 1 (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Erythrocytes, 10*12/l	5	0	6.87	0.15	0.34	6.70	6.90	7.08
Hb, g/l	5	0	139.60	3.82	8.53	136.00	136.00	144.00
Ht, %	5	0	45.98	1.38	3.08	44.40	45.80	48.00
MCV, fl	5	0	67.20	0.58	1.30	66.00	67.00	68.00
MCH, pg	5	0	20.34	0.31	0.70	19.80	20.20	20.40
MCHC, g/l	5	0	304.20	4.91	10.99	298.00	306.00	311.00
RDWc, %	5	0	15.02	0.12	0.26	15.00	15.10	15.10
Rt, 10*9/l	5	0	89.40	1.03	2.30	87.00	90.00	91.00
Thrombocytes, 10*9/l	5	0	383.80	15.10	33.76	362.00	376.00	389.00
ESR, mm/h	5	0	3.80	0.37	0.84	3.00	4.00	4.00
Leukocytes, 10*9/l	5	0	9.78	0.76	1.70	8.10	9.90	10.80
Myelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Metamyelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
stab,%	5	0	2.60	0.24	0.55	2.00	3.00	3.00
segmented,%	5	0	39.80	3.25	7.26	34.00	45.00	45.00
Lymphocytes, %	5	0	1.00	0.32	0.71	1.00	1.00	1.00
Basophiles,%	5	0	0.20	0.20	0.45	0.00	0.00	0.00
Monocytes, %	5	0	4.80	1.39	3.11	2.00	6.00	7.00
Lymphocytes, %	5	0	51.60	4.20	9.40	44.00	50.00	55.00
Plasma cells,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Neutrophils, 10*9/l	5	0	4.08	0.26	0.58	3.89	3.89	3.96
Lymphocytes, 10*9/l	5	0	0.09	0.03	0.07	0.08	0.08	0.11
Basophiles,10*9/l	5	0	0.02	0.02	0.04	0.00	0.00	0.00
Monocytes, 10*9/l	5	0	0.43	0.11	0.24	0.21	0.57	0.59
Lymphocytes, 10*9/l	5	0	5.16	0.81	1.81	3.56	5.40	5.45

Dose 1 (female)

Parameter	N		**Mean**	**Standard**	**Standard**	Percentile		

	Valid	Missed		error of mean	deviation	25	50	75
Erythrocytes, 10*12/l	5	0	6.57	0.11	0.25	6.35	6.60	6.70
Hb, g/l	5	0	129.20	1.36	3.03	126.00	130.00	132.00
Ht, %	5	0	43.62	0.40	0.90	43.00	43.30	44.00
MCV, fl	5	0	66.40	0.98	2.19	64.00	68.00	68.00
MCH, pg	5	0	19.64	0.17	0.38	19.70	19.70	19.80
MCHC, g/l	5	0	296.20	3.40	7.60	291.00	294.00	299.00
RDWc, %	5	0	15.72	0.10	0.22	15.60	15.80	15.90
Rt, 10*9/l	5	0	93.60	1.36	3.05	92.00	93.00	95.00
Thrombocytes, 10*9/l	5	0	327.80	62.26	139.22	299.00	341.00	361.00
ESR, mm/h	5	0	4.80	0.20	0.45	5.00	5.00	5.00
Leukocytes, 10*9/l	5	0	10.98	0.42	0.93	10.60	10.70	10.80
Myelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Metamyelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
stab,%	5	0	2.60	0.40	0.89	2.00	2.00	3.00
segmented,%	5	0	34.60	1.44	3.21	32.00	35.00	36.00
Lymphocytes, %	5	0	0.60	0.40	0.89	0.00	0.00	1.00
Basophiles,%	5	0	0.40	0.24	0.55	0.00	0.00	1.00
Monocytes, %	5	0	5.80	0.80	1.79	5.00	7.00	7.00
Lymphocytes, %	5	0	56.00	1.70	3.81	53.00	58.00	58.00
Plasma cells,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Neutrophils, 10*9/l	5	0	4.16	0.24	0.54	3.67	4.13	4.43
Lymphocytes, 10*9/l	5	0	0.06	0.04	0.09	0.00	0.00	0.11
Basophiles,10*9/l	5	0	0.04	0.03	0.06	0.00	0.00	0.11
Monocytes, 10*9/l	5	0	0.63	0.07	0.16	0.54	0.71	0.74
Lymphocytes, 10*9/l	5	0	6.15	0.32	0.72	5.62	6.12	6.20

Dose 2 (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Erythrocytes, 10*12/l	5	0	6.86	0.24	0.54	6.50	6.70	6.80
Hb, g/l	5	0	135.80	5.51	12.32	125.00	136.00	138.00
Ht, %	5	0	46.50	1.51	3.37	44.00	46.30	46.40
MCV, fl	5	0	67.80	0.37	0.84	67.00	68.00	68.00
MCH, pg	5	0	19.80	0.25	0.55	19.30	19.80	20.30
MCHC, g/l	5	0	292.00	2.77	6.20	287.00	294.00	297.00
RDWc, %	5	0	14.84	0.31	0.68	14.60	15.00	15.20
Rt, 10*9/l	5	0	92.20	2.22	4.97	89.00	90.00	97.00
Thrombocytes, 10*9/l	5	0	506.00	46.88	104.82	491.00	551.00	555.00
ESR, mm/h	5	0	4.60	0.51	1.14	4.00	5.00	5.00
Leukocytes, 10*9/l	5	0	10.90	0.79	1.77	9.10	11.30	12.40
Myelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Metamyelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
stab,%	5	0	2.60	0.24	0.55	2.00	3.00	3.00
segmented,%	5	0	47.60	4.25	9.50	50.00	50.00	52.00
Lymphocytes, %	5	0	1.80	0.37	0.84	1.00	2.00	2.00
Basophiles,%	5	0	0.40	0.24	0.55	0.00	0.00	1.00

Monocytes, %	5	0	5.20	0.37	0.84	5.00	5.00	6.00
Lymphocytes, %	5	0	42.40	4.72	10.55	38.00	38.00	40.00
Plasma cells,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Neutrophils, 10*9/l	5	0	5.39	0.47	1.05	4.82	4.95	6.45
Lymphocytes, 10*9/l	5	0	0.20	0.05	0.11	0.13	0.18	0.23
Basophiles,10*9/l	5	0	0.05	0.03	0.07	0.00	0.00	0.12
Monocytes, 10*9/l	5	0	0.56	0.05	0.11	0.50	0.55	0.57
Lymphocytes, 10*9/l	5	0	4.69	0.79	1.78	3.64	3.95	4.71

Dose 2 (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Erythrocytes, 10*12/l	5	0	6.23	0.15	0.33	6.00	6.20	6.30
Hb, g/l	5	0	128.20	1.66	3.70	125.00	129.00	130.00
Ht, %	5	0	43.04	0.89	1.98	41.80	42.10	44.10
MCV, fl	5	0	69.00	0.45	1.00	68.00	69.00	70.00
MCH, pg	5	0	20.52	0.39	0.88	20.00	20.40	20.70
MCHC, g/l	5	0	296.60	4.74	10.60	292.00	293.00	295.00
RDWc, %	5	0	14.74	0.40	0.89	14.30	14.40	14.60
Rt, 10*9/l	5	0	93.20	1.74	3.90	89.00	95.00	96.00
Thrombocytes, 10*9/l	5	0	385.00	44.52	99.54	329.00	333.00	469.00
ESR, mm/h	5	0	5.00	0.55	1.22	5.00	5.00	6.00
Leukocytes, 10*9/l	5	0	11.08	0.76	1.71	10.40	11.60	11.60
Myelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Metamyelocytes, %	5	0	0.00	0.00	0.00	0.00	0.00	0.00
stab,%	5	0	1.80	0.37	0.84	1.00	2.00	2.00
segmented,%	5	0	29.40	10.30	23.03	19.00	19.00	25.00
Lymphocytes, %	5	0	0.80	0.37	0.84	0.00	1.00	1.00
Basophiles,%	5	0	0.20	0.20	0.45	0.00	0.00	0.00
Monocytes, %	5	0	3.60	0.40	0.89	3.00	3.00	4.00
Lymphocytes, %	5	0	64.20	10.70	23.92	70.00	72.00	77.00
Plasma cells,%	5	0	0.00	0.00	0.00	0.00	0.00	0.00
Neutrophils, 10*9/l	5	0	3.22	0.82	1.84	2.08	2.44	3.56
Lymphocytes, 10*9/l	5	0	0.08	0.03	0.08	0.00	0.12	0.12
Basophiles,10*9/l	5	0	0.02	0.02	0.05	0.00	0.00	0.00
Monocytes, 10*9/l	5	0	0.40	0.06	0.13	0.31	0.40	0.46
Lymphocytes, 10*9/l	5	0	7.35	1.39	3.10	8.01	8.35	9.24

Biochemistry
30 days
Control (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Albumin, g/l	5	0	35.82	0.98	2.18	33.90	35.50	37.60
Total protein, g/l	5	0	78.96	0.75	1.67	78.40	78.50	80.30
Globulins, g/l	5	0	43.14	0.45	1.00	42.70	42.80	42.90
AlAT, U/l	5	0	69.98	2.96	6.63	65.80	69.80	75.80
AsAT, U/l	5	0	91.10	14.82	33.14	73.80	87.40	93.90

Alkaline phosphatase, U/l	5	0	212.14	31.32	70.03	173.20	187.90	213.70
Bilirubin, µmol/l	5	0	11.47	4.00	8.94	5.26	6.64	16.03
Glucose, mM	5	0	9.35	1.02	2.29	8.37	9.06	9.39
TC, mM	5	0	1.14	0.12	0.27	0.90	1.12	1.35
TAG, mM	5	0	0.73	0.09	0.21	0.67	0.67	0.87
Urea, mM	5	0	7.36	0.26	0.59	6.85	7.34	7.58
Creatinine, µmol/l	5	0	65.40	5.65	12.63	55.30	67.90	76.50
Sodium, mmol/l	5	0	139.70	2.45	5.47	136.70	138.90	144.90
Potassium, mmol/l	5	0	3.68	0.20	0.45	3.30	3.60	4.10
PTT, sec	5	0	21.14	2.74	6.13	16.40	21.30	23.30
APTT, sec	5	0	31.82	3.02	6.75	25.60	33.00	36.70

Control (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Albumin, g/l	5	0	31.96	0.24	0.54	31.40	32.10	32.30
Total protein, g/l	5	0	70.98	0.83	1.86	70.40	70.70	72.70
Globulins, g/l	5	0	39.02	1.03	2.31	38.10	38.30	41.30
AlAT, U/l	5	0	70.56	7.42	16.59	59.60	71.50	72.10
AsAT, U/l	5	0	95.90	11.67	26.10	77.40	83.30	121.30
Alkaline phosphatase, U/l	5	0	173.06	27.73	62.00	132.70	167.40	212.70
Bilirubin, µmol/l	5	0	9.47	1.36	3.05	9.10	10.41	11.58
Glucose, mM	5	0	9.56	0.38	0.85	9.01	9.44	9.96
TC, mM	5	0	1.56	0.34	0.76	0.83	1.46	2.31
TAG, mM	5	0	0.91	0.18	0.41	0.56	0.98	1.13
Urea, mM	5	0	6.78	0.55	1.22	6.13	6.41	8.03
Creatinine, µmol/l	5	0	61.64	5.80	12.97	56.80	59.40	67.20
Sodium, mmol/l	5	0	138.12	2.60	5.82	133.60	137.80	141.80
Potassium, mmol/l	5	0	3.74	0.21	0.46	3.30	3.90	4.10
PTT, sec	5	0	17.80	2.63	5.88	14.20	15.00	19.80
APTT, sec	5	0	28.92	3.25	7.28	24.90	26.70	30.20

Dose 1 (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Albumin, g/l	5	0	34.46	0.90	2.01	32.90	33.30	36.60
Total protein, g/l	5	0	73.24	1.57	3.51	71.00	71.10	76.70
Globulins, g/l	5	0	38.78	0.69	1.55	37.70	38.30	40.10
AlAT, U/l	5	0	81.74	6.42	14.35	67.00	89.60	91.40
AsAT, U/l	5	0	79.14	8.99	20.09	66.20	82.00	97.10
Alkaline phosphatase, U/l	5	0	182.62	23.77	53.15	145.20	187.80	221.70
Bilirubin, µmol/l	5	0	10.38	1.18	2.63	8.86	10.21	12.19
Glucose, mM	5	0	10.00	0.51	1.14	9.27	9.36	11.22
TC, mM	5	0	0.81	0.08	0.17	0.64	0.92	0.93
TAG, mM	5	0	0.58	0.09	0.19	0.42	0.54	0.65
Urea, mM	5	0	7.08	0.43	0.97	6.29	7.09	7.84
Creatinine, µmol/l	5	0	59.34	3.32	7.42	56.80	59.10	66.10
Sodium, mmol/l	5	0	138.22	2.59	5.79	137.10	139.30	139.40
Potassium, mmol/l	5	0	4.04	0.35	0.77	3.70	3.80	4.50
PTT, sec	5	0	16.14	2.24	5.01	14.40	14.40	15.30
APTT, sec	5	0	29.70	2.26	5.06	28.00	30.40	30.70

Dose 1 (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Albumin, g/l	5	0	33.54	0.60	1.34	32.80	33.10	34.50
Total protein, g/l	5	0	74.86	0.75	1.69	74.40	74.60	76.40
Globulins, g/l	5	0	41.32	0.85	1.90	39.90	41.20	41.50
AlAT, U/l	5	0	56.36	7.93	17.73	37.80	69.20	69.30
AsAT, U/l	5	0	57.06	5.86	13.11	47.30	57.10	60.20
Alkaline phosphatase, U/l	5	0	190.60	19.83	44.34	165.10	168.00	221.80
Bilirubin, μmol/l	5	0	9.46	1.18	2.63	6.94	10.89	11.29
Glucose, mM	5	0	7.96	0.21	0.46	7.78	8.00	8.01
TC, mM	5	0	1.79	0.08	0.17	1.79	1.79	1.89
TAG, mM	5	0	1.07	0.12	0.28	0.96	0.98	0.99
Urea, mM	5	0	7.00	0.48	1.08	6.31	7.17	7.24
Creatinine, μmol/l	5	0	70.42	5.46	12.21	66.90	67.30	75.40
Sodium, mmol/l	5	0	140.72	2.07	4.64	139.50	141.50	144.30
Potassium, mmol/l	5	0	3.88	0.24	0.53	3.60	3.80	4.30
PTT, sec	5	0	17.20	2.50	5.58	14.40	15.80	16.50
APTT, sec	5	0	28.00	2.58	5.78	24.20	26.70	30.40

Dose 2 (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Albumin, g/l	5	0	35.66	0.55	1.24	34.50	35.40	36.80
Total protein, g/l	5	0	77.82	0.59	1.31	77.30	77.80	78.00
Globulins, g/l	5	0	42.16	0.75	1.68	41.20	41.70	43.30
AlAT, U/l	5	0	77.48	5.19	11.60	75.30	78.60	86.90
AsAT, U/l	5	0	70.74	4.08	9.13	63.80	66.90	79.20
Alkaline phosphatase, U/l	5	0	161.36	24.76	55.35	121.80	166.90	177.60
Bilirubin, μmol/l	5	0	8.87	0.52	1.17	8.22	8.56	9.53
Glucose, mM	5	0	8.72	0.21	0.47	8.53	8.63	9.01
TC, mM	5	0	1.00	0.12	0.26	0.78	1.06	1.06
TAG, mM	5	0	0.61	0.10	0.22	0.54	0.56	0.78
Urea, mM	5	0	7.95	0.63	1.40	6.51	8.45	8.92
Creatinine, μmol/l	5	0	76.04	10.29	23.00	58.30	76.90	89.30
Sodium, mmol/l	5	0	137.54	4.44	9.94	131.70	134.30	138.70
Potassium, mmol/l	5	0	4.10	0.36	0.80	3.60	4.20	4.40
PTT, sec	5	0	17.28	2.43	5.44	14.70	15.20	16.80
APTT, sec	5	0	30.32	3.29	7.36	24.00	30.60	33.10

Dose 2 (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Albumin, g/l	5	0	32.74	1.00	2.23	31.50	32.10	34.40
Total protein, g/l	5	0	72.58	1.94	4.34	69.10	74.40	75.60
Globulins, g/l	5	0	39.84	1.99	4.46	36.80	38.80	44.10
AlAT, U/l	5	0	106.96	30.79	68.86	67.90	71.10	101.70
AsAT, U/l	5	0	165.86	102.18	228.48	61.00	69.40	77.30
Alkaline phosphatase, U/l	5	0	188.40	38.75	86.66	133.80	145.70	228.60
Bilirubin, μmol/l	5	0	5.79	0.83	1.87	4.22	5.05	7.50
Glucose, mM	5	0	8.77	0.52	1.17	7.99	9.22	9.33
TC, mM	5	0	1.99	0.15	0.33	1.84	1.89	2.15

TAG, mM	5	0	1.29	0.15	0.33	1.12	1.23	1.45
Urea, mM	5	0	6.85	0.63	1.40	5.87	7.51	7.54
Creatinine, μmol/l	5	0	68.38	5.67	12.69	61.90	66.30	68.40
Sodium, mmol/l	5	0	139.56	2.98	6.66	137.70	141.70	143.80
Potassium, mmol/l	5	0	3.92	0.25	0.56	3.70	3.80	4.20
PTT, sec	5	0	16.78	1.76	3.94	14.70	16.90	18.70
APTT, sec	5	0	28.24	2.13	4.75	24.70	30.00	30.90

90 days

Control (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Albumin, g/l	5	0	31.16	1.06	2.36	30.10	31.40	33.20
Total protein, g/l	5	0	69.20	2.65	5.93	68.80	70.20	73.10
Globulins, g/l	5	0	38.04	1.65	3.69	38.70	38.80	39.70
AlAT, U/l	5	0	63.22	3.80	8.50	61.40	65.10	69.40
AsAT, U/l	5	0	72.88	12.21	27.29	54.30	72.10	97.80
Alkaline phosphatase, U/l	5	0	149.50	26.45	59.15	106.00	109.80	210.90
Bilirubin, μmol/l	5	0	5.76	1.08	2.42	4.10	4.80	7.70
Glucose, mM	5	0	9.67	0.65	1.45	8.75	9.58	10.62
TC, mM	5	0	1.26	0.29	0.65	0.55	1.72	1.72
TAG, mM	5	0	0.67	0.03	0.08	0.62	0.64	0.71
Urea, mM	5	0	7.62	0.62	1.39	6.30	8.33	8.59
Creatinine, μmol/l	5	0	103.98	9.81	21.94	86.20	97.10	122.30
Sodium, mmol/l	5	0	139.40	2.70	6.04	134.60	141.20	142.60
Potassium, mmol/l	5	0	3.96	0.25	0.55	3.70	3.90	4.10
PTT, sec	5	0	11.80	0.73	1.62	10.20	11.80	13.00
APTT, sec	5	0	31.38	1.06	2.37	29.40	30.90	33.10

Control (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Albumin, g/l	5	0	32.54	0.75	1.68	31.20	33.00	33.80
Total protein, g/l	5	0	71.06	0.80	1.80	69.50	71.40	72.70
Globulins, g/l	5	0	38.52	1.53	3.43	35.70	38.40	41.60
AlAT, U/l	5	0	66.14	9.07	20.27	66.00	66.70	82.50
AsAT, U/l	5	0	63.98	4.10	9.17	63.70	64.20	67.00
Alkaline phosphatase, U/l	5	0	139.86	24.09	53.88	104.20	127.60	193.70
Bilirubin, μmol/l	5	0	7.36	1.15	2.58	6.20	6.90	7.40
Glucose, mM	5	0	9.29	1.14	2.54	7.77	8.18	11.30
TC, mM	5	0	1.43	0.23	0.51	1.19	1.19	1.81
TAG, mM	5	0	1.14	0.06	0.13	1.03	1.12	1.23
Urea, mM	5	0	7.80	0.35	0.79	7.54	8.30	8.32
Creatinine, μmol/l	5	0	105.14	7.96	17.79	89.80	105.60	117.90
Sodium, mmol/l	5	0	145.04	1.12	2.50	145.10	145.20	146.80
Potassium, mmol/l	5	0	3.88	0.19	0.43	3.60	3.80	3.90
PTT, sec	5	0	11.50	0.93	2.07	9.80	11.50	12.80
APTT, sec	5	0	34.62	1.52	3.39	31.80	34.50	37.50

Dose 1 (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Albumin, g/l	5	0	29.48	0.89	1.99	28.10	28.20	31.40

Total protein, g/l	5	0	65.64	2.07	4.62	62.30	62.80	69.90
Globulins, g/l	5	0	36.16	1.18	2.63	34.10	34.70	38.50
AlAT, U/l	5	0	73.50	12.81	28.64	43.60	93.80	93.90
AsAT, U/l	5	0	57.72	8.24	18.42	40.70	66.60	71.70
Alkaline phosphatase, U/l	5	0	94.36	9.21	20.59	79.80	81.40	116.80
Bilirubin, μmol/l	5	0	6.18	0.47	1.04	5.70	5.90	6.80
Glucose, mM	5	0	8.20	0.48	1.07	7.31	7.75	9.09
TC, mM	5	0	0.77	0.07	0.16	0.59	0.88	0.89
TAG, mM	5	0	1.03	0.08	0.18	0.86	1.13	1.15
Urea, mM	5	0	6.56	0.53	1.20	5.35	7.40	7.43
Creatinine, μmol/l	5	0	88.76	6.16	13.77	74.00	96.80	97.20
Sodium, mmol/l	5	0	143.02	2.43	5.43	138.20	146.10	146.30
Potassium, mmol/l	5	0	4.32	0.31	0.68	4.20	4.50	4.80
PTT, sec	5	0	11.30	0.40	0.90	10.70	11.60	11.70
APTT, sec	5	0	31.44	0.93	2.08	30.30	31.50	32.60

Dose 1 (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Albumin, g/l	5	0	30.52	0.38	0.84	30.20	30.50	31.20
Total protein, g/l	5	0	74.52	0.82	1.83	73.10	74.70	75.80
Globulins, g/l	5	0	44.00	1.09	2.43	41.70	45.30	45.40
AlAT, U/l	5	0	54.64	1.37	3.05	53.10	53.80	57.50
AsAT, U/l	5	0	62.32	3.01	6.73	57.80	57.90	66.00
Alkaline phosphatase, U/l	5	0	85.28	5.10	11.41	76.60	81.80	96.00
Bilirubin, μmol/l	5	0	7.70	0.96	2.15	5.80	8.80	9.10
Glucose, mM	5	0	9.16	0.23	0.52	8.63	9.46	9.54
TC, mM	5	0	1.71	0.06	0.13	1.61	1.65	1.81
TAG, mM	5	0	1.12	0.14	0.32	0.90	0.91	1.42
Urea, mM	5	0	9.32	0.91	2.03	7.86	8.00	11.35
Creatinine, μmol/l	5	0	123.80	3.25	7.26	122.30	126.40	127.00
Sodium, mmol/l	5	0	143.50	1.44	3.22	140.80	144.80	145.20
Potassium, mmol/l	5	0	4.02	0.26	0.57	3.60	4.10	4.40
PTT, sec	5	0	11.78	0.72	1.60	10.70	12.20	12.50
APTT, sec	5	0	31.76	1.00	2.23	30.90	31.00	31.50

Dose 2 (male)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Albumin, g/l	5	0	33.06	0.51	1.13	33.00	33.10	33.20
Total protein, g/l	5	0	80.36	3.33	7.46	76.40	79.30	87.00
Globulins, g/l	5	0	47.30	3.15	7.03	43.30	44.70	53.80
AlAT, U/l	5	0	59.62	1.34	2.99	57.60	59.80	61.30
AsAT, U/l	5	0	54.34	4.48	10.03	50.90	53.40	54.60
Alkaline phosphatase, U/l	5	0	87.54	3.93	8.79	81.10	82.50	96.30
Bilirubin, μmol/l	5	0	8.92	0.22	0.48	8.50	8.90	9.30
Glucose, mM	5	0	11.32	0.13	0.30	11.29	11.30	11.35
TC, mM	5	0	0.90	0.04	0.09	0.82	0.90	0.99
TAG, mM	5	0	1.24	0.09	0.21	1.13	1.21	1.39
Urea, mM	5	0	7.18	0.39	0.88	6.59	7.53	7.76
Creatinine, μmol/l	5	0	107.84	7.57	16.92	92.80	110.10	110.90
Sodium, mmol/l	5	0	142.52	3.04	6.79	138.40	142.80	146.30

Potassium, mmol/l	5	0	4.30	0.19	0.44	3.90	4.40	4.60
PTT, sec	5	0	11.96	0.40	0.88	11.50	12.20	12.40
APTT, sec	5	0	31.66	1.58	3.53	30.30	30.90	31.60

Dose 2 (female)

Parameter	N		**Mean**	**Standard error of mean**	**Standard deviation**	Percentile		
	Valid	**Missed**				**25**	**50**	**75**
Albumin, g/l	5	0	33.94	0.46	1.03	33.60	33.90	34.40
Total protein, g/l	5	0	76.28	3.11	6.95	70.80	75.90	78.50
Globulins, g/l	5	0	42.34	3.30	7.38	37.20	41.50	43.20
AlAT, U/l	5	0	76.24	5.25	11.73	72.60	76.00	86.60
AsAT, U/l	5	0	74.00	8.38	18.74	66.10	76.80	89.40
Alkaline phosphatase, U/l	5	0	111.20	3.57	7.98	107.60	109.10	110.50
Bilirubin, μmol/l	5	0	10.36	1.22	2.72	10.30	10.30	11.60
Glucose, mM	5	0	9.63	0.19	0.42	9.39	9.72	9.94
TC, mM	5	0	2.01	0.06	0.13	1.91	1.99	2.13
TAG, mM	5	0	1.38	0.10	0.23	1.26	1.27	1.61
Urea, mM	5	0	9.92	0.83	1.85	9.12	9.31	11.58
Creatinine, μmol/l	5	0	119.50	6.93	15.50	104.20	124.40	129.20
Sodium, mmol/l	5	0	140.52	1.79	4.01	140.80	141.50	141.60
Potassium, mmol/l	5	0	4.46	0.20	0.44	4.10	4.60	4.80
PTT, sec	5	0	11.24	0.69	1.54	10.40	11.80	12.10
APTT, sec	5	0	31.74	2.70	6.04	30.30	33.90	34.00

Comparison

Body mass delta

Control and dose 1

Parameter	**p (male)**	**p (female)**
delta 14 days, g	0.917	0.602
delta 30 days, g	0.296	0.403
delta 60 days, g	0.403	0.835
delta 90 days, g	0.531	0.917

Control and dose 2

Parameter	**p (male)**	**p (female)**
delta 14 days, g	0.835	0.047
delta 30 days, g	0.296	0.037
delta 60 days, g	0.403	0.095
delta 90 days, g	0.754	0.531

dose 1 and dose 2

Parameter	**p (male)**	**p (female)**
delta 14 days, g	0.531	0.095
delta 30 days, g	0.835	0.095
delta 60 days, g	0.835	0.251
delta 90 days, g	0.917	0.531

Mass coefficients of organs

Control and dose 1

Parameter	**p (male)**	**p (female)**
Liver	0.917	0.602
Kidneys	0.754	0.602

Adrenal glands	0.917	0.465
Heart	0.754	0.754
Thymus	0.602	0.602
Lungs	0.465	0.602
Brain	0.917	0.602
Testicles/Ovaries	0.917	0.602
Spleen	0.754	0.347

Control and dose 2

Parameter	p (male)	p (female)
Liver	0.602	0.602
Kidneys	0.602	0.465
Adrenal glands	0.602	0.175
Heart	0.175	0.754
Thymus	0.175	0.602
Lungs	0.251	0.602
Brain	0.754	0.754
Testicles/Ovaries	0.754	0.754
Spleen	0.754	0.251

dose 1 and dose 2

Parameter	p (male)	p (female)
Liver	0.465	0.602
Kidneys	0.347	0.175
Adrenal glands	0.754	0.465
Heart	0.251	0.347
Thymus	0.754	0.347
Lungs	0.602	0.602
Brain	0.465	0.117
Testicles/Ovaries	0.754	0.754
Spleen	0.754	0.754

Body temperature

Control and dose 1

Term	p (male)	p (female)
background	1.000	0.754
30 days	1.000	0.676
90 days	0.676	0.296

Control and dose 2

Term	p (male)	p (female)
background	0.531	0.754
30 days	0.917	0.465
90 days	0.296	0.917

dose 1 and dose 2

Term	p (male)	p (female)
background	0.602	0.835
30 days	0.754	0.917
90 days	1.000	0.296

Breathing rate

Control and dose 1

Term	p (male)	p (female)
30 days	0.754	0.531
90 days	0.835	0.531

Control and dose 2

Term	p (male)	p (female)
30 days	0.835	0.754
90 days	0.602	0.676

dose 1 and dose 2

Term	p (male)	p (female)
30 days	0.676	0.917
90 days	0.835	0.835

Cardio-vasculary system

30 days

Control and dose 1

Parameter	p (male)	p (female)
HR	0.754	0.210
P, mV	0.403	0.531
R, mV	0.251	0.917
PQ	0.835	0.117
QT	0.835	0.403

Control and dose 2

Parameter	p (male)	p (female)
HR	0.754	0.047
P, mV	0.060	0.531
R, mV	0.917	0.403
PQ	0.403	0.465
QT	0.602	0.047

dose 1 and dose 2

Parameter	p (male)	p (female)
HR	0.917	0.028
P, mV	0.117	0.835
R, mV	0.251	0.531
PQ	0.676	0.076
QT	0.117	0.047

90 days

Control and dose 1

Parameter	p (male)	p (female)
HR	0.210	0.347
P, mV	0.602	0.835
R, mV	0.076	0.917
PQ	0.175	0.175
QT	0.347	0.251

Control and dose 2

Parameter	p (male)	p (female)
HR	0.251	0.251

P, mV	0.117	0.175
R, mV	0.060	0.602
PQ	0.175	0.403
QT	0.117	0.175

dose 1 and dose 2

Parameter	p (male)	p (female)
HR	0.347	0.251
P, mV	0.602	0.210
R, mV	0.917	0.602
PQ	0.835	0.465
QT	0.296	0.047

Biochemistry
30 days

Control and dose 1

Parameter	p (male)	p (female)
Albumin, g/l	0.175	0.047
Total protein, g/l	0.022	0.028
Globulins, g/l	0.009	0.175
AlAT, U/l	0.251	0.175
AsAT, U/l	0.754	0.016
Alkaline phosphatase, U/l	0.602	0.602
Bilirubin, μmol/l	0.602	1.000
Glucose, mM	0.465	0.016
TC, mM	0.175	0.602
TAG, mM	0.144	0.676
Urea, mM	0.676	0.754
Creatinine, μmol/l	0.347	0.347
Sodium, mmol/l	0.917	0.602
Potassium, mmol/l	0.465	0.676
PTT, sec	0.117	0.917
APTT, sec	0.531	0.917

Control and dose 2

Parameter	p (male)	p (female)
Albumin, g/l	0.917	0.676
Total protein, g/l	0.175	0.465
Globulins, g/l	0.347	0.754
AlAT, U/l	0.251	0.465
AsAT, U/l	0.251	0.175
Alkaline phosphatase, U/l	0.251	0.754
Bilirubin, μmol/l	0.602	0.047
Glucose, mM	0.602	0.347
TC, mM	0.347	0.347
TAG, mM	0.403	0.175
Urea, mM	0.602	0.917
Creatinine, μmol/l	0.465	0.465

Sodium, mmol/l	0.347	0.917
Potassium, mmol/l	0.347	0.754
PTT, sec	0.347	0.917
APTT, sec	0.602	1.000

dose 1 and dose 2

Parameter	p (male)	p (female)
Albumin, g/l	0.175	0.465
Total protein, g/l	0.047	0.531
Globulins, g/l	0.016	0.465
AlAT, U/l	0.347	0.175
AsAT, U/l	0.347	0.117
Alkaline phosphatase, U/l	0.465	0.465
Bilirubin, μmol/l	0.347	0.076
Glucose, mM	0.047	0.347
TC, mM	0.175	0.296
TAG, mM	0.754	0.251
Urea, mM	0.175	0.917
Creatinine, μmol/l	0.251	0.754
Sodium, mmol/l	0.465	0.917
Potassium, mmol/l	1.000	0.917
PTT, sec	0.465	0.754
APTT, sec	0.754	0.835

90 days

Control and dose 1

Parameter	p (male)	p (female)
Albumin, g/l	0.403	0.095
Total protein, g/l	0.347	0.028
Globulins, g/l	0.251	0.047
AlAT, U/l	0.602	0.117
AsAT, U/l	0.347	0.602
Alkaline phosphatase, U/l	0.175	0.060
Bilirubin, μmol/l	0.602	0.754
Glucose, mM	0.117	0.602
TC, mM	0.602	0.403
TAG, mM	0.009	0.602
Urea, mM	0.175	0.465
Creatinine, μmol/l	0.347	0.095
Sodium, mmol/l	0.347	0.347
Potassium, mmol/l	0.296	0.676
PTT, sec	0.465	0.917
APTT, sec	0.917	0.175

Control and dose 2

Parameter	p (male)	p (female)
Albumin, g/l	0.347	0.175
Total protein, g/l	0.028	0.251
Globulins, g/l	0.028	0.465
AlAT, U/l	0.175	0.347

AsAT, U/l	0.251	0.251
Alkaline phosphatase, U/l	0.009	0.465
Bilirubin, μmol/l	0.037	0.210
Glucose, mM	0.076	0.602
TC, mM	0.602	0.047
TAG, mM	0.009	0.117
Urea, mM	0.465	0.047
Creatinine, μmol/l	0.602	0.251
Sodium, mmol/l	0.465	0.047
Potassium, mmol/l	0.347	0.047
PTT, sec	0.835	0.917
APTT, sec	1.000	0.347

dose 1 and dose 2

Parameter	p (male)	p (female)
Albumin, g/l	0.022	0.009
Total protein, g/l	0.016	0.754
Globulins, g/l	0.016	0.347
AlAT, U/l	0.602	0.009
AsAT, U/l	0.754	0.175
Alkaline phosphatase, U/l	0.917	0.009
Bilirubin, μmol/l	0.009	0.047
Glucose, mM	0.009	0.175
TC, mM	0.175	0.016
TAG, mM	0.144	0.175
Urea, mM	0.175	0.602
Creatinine, μmol/l	0.175	0.754
Sodium, mmol/l	1.000	0.347
Potassium, mmol/l	0.676	0.210
PTT, sec	0.347	0.465
APTT, sec	0.835	0.754

Hematology

30 days

Control and 1 dose

Parameter	p (male)	p (female)
Erythrocytes, 10*12/l	0.602	0.060
Hb, g/l	0.917	0.403
Ht, %	0.754	0.602
MCV, fl	0.009	0.028
MCH, pg	0.403	0.076
MCHC, g/l	0.602	0.754
RDWc, %	0.251	0.047
Rt, 10*9/l	0.835	0.210
Thrombocytes, 10*9/l	0.917	0.602
ESR, mm/h	0.602	0.251
Leukocytes, 10*9/l	0.009	0.602
Myelocytes, %	1.000	1.000
Metamyelocytes, %	1.000	1.000

stab,%	0.296	0.602
segmented,%	0.917	0.403
Lymphocytes, %	0.296	0.251
Basophiles,%	1.000	1.000
Monocytes, %	0.117	0.296
Lymphocytes, %	1.000	0.602
Plasma cells,%	1.000	1.000
Neutrophils, 10*9/l	0.009	0.917
Lymphocytes, 10*9/l	0.296	0.251
Basophiles,10*9/l	1.000	1.000
Monocytes, 10*9/l	0.917	0.144
Lymphocytes, 10*9/l	0.347	0.347

Control and dose 2

Parameter	**p (male)**	**p (female)**
Erythrocytes, 10*12/l	0.754	0.347
Hb, g/l	0.754	0.835
Ht, %	0.676	0.465
MCV, fl	0.465	0.754
MCH, pg	0.917	0.117
MCHC, g/l	0.754	0.465
RDWc, %	0.754	0.917
Rt, 10*9/l	0.175	1.000
Thrombocytes, 10*9/l	0.917	0.347
ESR, mm/h	0.251	0.676
Leukocytes, 10*9/l	0.009	0.602
Myelocytes, %	1.000	1.000
Metamyelocytes, %	1.000	1.000
stab,%	0.117	0.117
segmented,%	0.403	0.144
Lymphocytes, %	0.531	0.175
Basophiles,%	1.000	1.000
Monocytes, %	0.144	0.602
Lymphocytes, %	0.251	0.016
Plasma cells,%	1.000	1.000
Neutrophils, 10*9/l	0.028	0.047
Lymphocytes, 10*9/l	0.917	0.175
Basophiles,10*9/l	1.000	1.000
Monocytes, 10*9/l	0.754	0.754
Lymphocytes, 10*9/l	0.117	0.117

dose 1 and dose 2

Parameter	**p (male)**	**p (female)**
Erythrocytes, 10*12/l	0.251	0.028
Hb, g/l	0.465	0.676
Ht, %	0.465	0.296
MCV, fl	0.022	0.037
MCH, pg	0.403	0.028
MCHC, g/l	0.144	0.835

RDWc, %	0.835	0.175
Rt, 10*9/l	0.347	0.465
Thrombocytes, 10*9/l	1.000	0.009
ESR, mm/h	0.531	0.403
Leukocytes, 10*9/l	0.175	0.016
Myelocytes, %	1.000	1.000
Metamyelocytes, %	1.000	1.000
stab,%	0.676	0.144
segmented,%	0.403	0.028
Lymphocytes, %	0.117	0.602
Basophiles,%	1.000	1.000
Monocytes, %	0.917	0.531
Lymphocytes, %	0.251	0.047
Plasma cells,%	1.000	1.000
Neutrophils, 10*9/l	0.754	0.754
Lymphocytes, 10*9/l	0.117	0.754
Basophiles,10*9/l	1.000	1.000
Monocytes, 10*9/l	0.347	0.175
Lymphocytes, 10*9/l	0.016	0.009

90 days

Control and dose 1

Parameter	**p (male)**	**p (female)**
Erythrocytes, 10*12/l	0.531	0.754
Hb, g/l	0.465	0.754
Ht, %	0.465	0.602
MCV, fl	0.144	0.917
MCH, pg	0.465	0.403
MCHC, g/l	0.754	0.917
RDWc, %	0.531	0.009
Rt, 10*9/l	0.076	0.676
Thrombocytes, 10*9/l	0.754	0.754
ESR, mm/h	0.602	0.210
Leukocytes, 10*9/l	0.028	0.009
Myelocytes, %	1.000	1.000
Metamyelocytes, %	1.000	1.000
stab,%	0.602	0.531
segmented,%	0.144	0.037
Lymphocytes, %	0.403	0.531
Basophiles, %	1.000	0.602
Monocytes, %	0.347	0.175
Lymphocytes, %	0.175	0.060
Plasma cells, %	1.000	1.000
Neutrophils, 10*9/l	0.465	0.602
Lymphocytes, 10*9/l	0.917	0.754
Basophiles,10*9/l	0.917	0.465
Monocytes, 10*9/l	0.676	0.028
Lymphocytes, 10*9/l	0.047	0.009

Control and dose 2

Parameter	p (male)	p (female)
Erythrocytes, 10*12/l	0.835	0.117
Hb, g/l	0.917	0.347
Ht, %	0.531	0.251
MCV, fl	0.016	0.028
MCH, pg	0.676	0.296
MCHC, g/l	0.175	0.835
RDWc, %	0.835	0.347
Rt, 10*9/l	0.602	0.465
Thrombocytes, 10*9/l	0.076	0.175
ESR, mm/h	0.465	0.175
Leukocytes, 10*9/l	0.117	0.037
Myelocytes, %	1.000	1.000
Metamyelocytes, %	1.000	1.000
stab,%	0.602	0.076
segmented,%	0.076	0.060
Lymphocytes, %	0.047	0.754
Basophiles,%	0.602	1.000
Monocytes, %	0.037	1.000
Lymphocytes, %	0.016	0.076
Plasma cells,%	1.000	1.000
Neutrophils, 10*9/l	0.117	0.117
Lymphocytes, 10*9/l	0.076	0.754
Basophiles,10*9/l	0.531	0.917
Monocytes, 10*9/l	0.117	0.403
Lymphocytes, 10*9/l	0.016	0.117

dose 1 and dose 2

Parameter	p (male)	p (female)
Erythrocytes, 10*12/l	0.676	0.095
Hb, g/l	0.602	0.531
Ht, %	0.917	0.465
MCV, fl	0.403	0.047
MCH, pg	0.296	0.095
MCHC, g/l	0.060	0.917
RDWc, %	0.754	0.117
Rt, 10*9/l	0.531	0.835
Thrombocytes, 10*9/l	0.117	0.917
ESR, mm/h	0.251	0.465
Leukocytes, 10*9/l	0.251	0.754
Myelocytes, %	1.000	1.000
Metamyelocytes, %	1.000	1.000
stab,%	1.000	0.210
segmented,%	0.076	0.117
Lymphocytes, %	0.175	0.676
Basophiles,%	0.602	0.602
Monocytes, %	0.754	0.076

Lymphocytes, %	0.076	0.117
Plasma cells,%	1.000	1.000
Neutrophils, 10*9/l	0.047	0.117
Lymphocytes, 10*9/l	0.076	0.602
Basophiles,10*9/l	0.465	0.602
Monocytes, 10*9/l	0.835	0.076
Lymphocytes, 10*9/l	0.602	0.117