**Results of a phase I open randomized comparative crossover clinical trial to assess the safety and pharmacokinetics of glurazyme® (imiglucerase) in comparison with the reference product in healthy volunteers**

**S.B. Fitilev1, 2, A.V. Vozzhaev1, I.I. Shkrebneva1, 2, D.A. Kudlay3, E.V. Gapchenko3, O.A. Markova3,**

**A.Yu. Borоzinets3, А.А. Kazarov4, М.S. Pantyushenko4**

*1Peoples’ Friendship University of Russia; 6 Miklukho-Maklaya St., Moscow 117198, Russia*

*2City Polyclinic No. 2 of the Moscow Department of Health; 12 Fruktovaya St., Moscow 117556 Russia;*

*3JSC GENERIUM; 10 Testovskaya St., Moscow 123112, Russia;*

*4International Biotechnological Center “Generium”; 14 Vladimirskaya St., Volginsky, Vladimir Region 601125, Russia*

***Contacts****: Alexander Vladimirovich Vozzhaev* *alex.vozzhaev@gmail.com*

***Background.*** *Currently, the main treatment for Gaucher disease is enzyme replacement therapy. Recombinant glucocerebrosidase (imiglucerase) is the first biotechnological drug for enzyme replacement therapy with proven clinical efficacy and safety for the treatment of patients of different ages with Gaucher disease type 1 and type 3, used in clinical practice since 1994. In Russia, within the framework of the “Pharma 2020” pharmaceutical industry development strategy, the first biosimilar of Cerezyme® (imiglucerase), the drug Glurazyme®, was developed. The obtained results of preclinical studies became the basis for a phase I randomized comparative crossover clinical trial.*

*The* ***objective of the study*** *was to assess the short-term safety and pharmacokinetic parameters of Glurazyme® in comparison with the Cerezyme® after a single intravenous administration to healthy volunteers.*

***Materials and methods.*** *23 healthy volunteers aged 18–45 years were included in a 3-stage clinical trial. The study during the 1st and 2nd stages was open, randomized, comparative, crossover. At the 1st stage, volunteers from the 1st group received the Glurazyme®, from the 2nd group – the Cerezyme® once in doses of 30 U/kg. At the 2nd stage, Cerezyme® was administered to the 1st group, Glurazyme® ‒ to the 2nd group once at doses of 30 U/kg. After the end of the 1st and 2nd stages, the 3rd stage was carried out for the 3rd group (n = 5) with the administration of the test drug once at a dose of 60 U/kg.*

***Results.*** *For all studied pharmacokinetic parameters, after administration of the test and reference drugs in doses of 30 U/kg, 90% confidence interval was in the range from 80 to 125%, which indicates the pharmacokinetic compared drugs equivalence. A total of 6 adverse events of mild and moderate severity were recorded. Of these, 4 adverse events were noted after administration of the study drug and were not associated with its administration. A comparative analysis of safety assessment parameters in this study (frequency and severity of adverse events, physical examination of healthy volunteers with an assessment of vital signs, laboratory tests, electrocardiography) did not reveal intergroup differences.*

***Conclusion.*** *The pharmacokinetic equivalence of the Glurazyme® and the reference drug in a dose of 30 U/kg has been established. A nonlinear dependence of the main pharmacokinetic parameters on studied drug administered dose was revealed. Safety and the absence of adverse reactions after a single injection of the study drug are shown.*

***Key words:*** *enzyme replacement therapy, imiglucerase, Glurazyme®, safety, pharmacokinetics, healthy volunteers*

***For citation:*** *Fitilev S.B., Vozzhaev A.V., Shkrebneva I.I. et al. Results of a phase I open randomized comparative crossover clinical trial to assess the safety and pharmacokinetics of Glurazyme® (imiglucerase) in comparison with the reference product in healthy volunteers. Onkogematologiya = Oncohematology 2019;14(4):73–83. (In Russ.).*

DOI: 10.17650/1818-8346-2019-14-4-73-83

**Introduction**

Gaucher disease (GD) is the most common form of hereditary enzyme defects combined into the group of lysosomal storage diseases. The disease is based on a hereditary deficiency in the activity of acid β-glucosidase (β-lucocerebrosidase) lysosomal enzyme, which is involved in the degradation of cellular metabolism products, enzymatic intralysosomal cleavage of glycosphingolipids, the most important structural elements of cellular membranes. This enzyme catalyses hydrolysis of glucosylceramide (glucocerebroside), a key component of the lipid structure of cellular membranes, to glucose and ceramide [1–4].

Gaucher disease occurs with a frequency of 1:40,000 to 1:60,000 in representatives of all ethnic groups, while in the Ashkenazi Jewish population the frequency of the disease amounts to 1:450–1:1000 [5, 6]. GD is inherited by an autosomal recessive mechanism; the disease is based on mutations of the glucocerebroside gene located in q21 region on chromosome 1. The presence of 2 mutant gene alleles (autosomal recessive inheritance) is associated with a decrease in the catalytic activity of glucocerebrosidase (or its absence), which leads to accumulation of unutilised complex lipids (glucocerebrosides) in the cytoplasm of macrophages, autocrine stimulation of monocytopoiesis and an increase in the absolute count of macrophages in the locations of their “physiological home”, which leads to splenomegaly, hepatomegaly, bone marrow infiltration with cytopenic syndrome and damage to the osteoarticular system [2, 7, 8].

Currently, the main type of treatment for GD is enzyme replacement therapy (ERT). ERT with recombinant glucocerebrosidase (imiglucerase) in the standard regimen of intravenous infusions once every 2 weeks has been actively used for the treatment of type 1 GD since 1994. ERT leads to regression of cytopenia, a decrease in the spleen and liver size, and prevents the development of irreversible damage to the osteoarticular system [2, 4]. On exposure to imiglucerase, hydrolysis of glucocerebroside to glucose and ceramide follows the usual pathway of membrane lipid metabolism. The efficacy of imiglucerase has been proven in regard to reducing the frequency of bone crises, bone pain, osteonecroses, increasing bone mineral density, and normalising growth in children. The proven clinical efficacy of imiglucerase is combined with good tolerance and the absence of pronounced side effects in the treatment of patients of different ages with type 1 and type 3 GD [7, 9, 10]. In June 2009, Genzyme Ltd. suspended production of Cerezyme® (imiglucerase) due to viral contamination of the bioreactors. The suspension of production led to a serious shortage of the drug for GD patients all over the world, which caused significant difficulties in their treatment. This problem contributed to the development and conduct of clinical studies of Cerezyme® biosimilars as well as new drugs for ERT
[11–13].

In Russia, in order to stimulate the development and production of domestic innovative medicines, “Strategy for the Development of the Pharmaceutical Industry in the Russian Federation for the Period Until 2020” (“Pharma 2020”) was approved in 2009, and, later, a state programme of the Russian Federation “Development of the Pharmaceutical and Medical Industry” was adopted for
2013-2020. The implementation of the programme is aimed at increasing the domestic production and supply of vital and essential medicines including those for treatment of rare diseases such as GD [13, 14].

As part of the “Pharma 2020” strategy, in 2011, the Russian biotechnological company MBC Generium LLC began the development of a biosimilar drug Glurazyme® (imiglucerase) for treatment of type 1 and type 3 GD, which was carried out in accordance with international requirements [15–17]. In the course of product development, comparative non-clinical studies were carried out whose results demonstrated comparability of Glurazyme® and Cerezyme® in terms of quality, physicochemical and biopharmaceutical properties, confirmed the absence of toxicity and good tolerance of Glurazyme® [18, 19]. The obtained results of non-clinical studies served as grounds for a Phase I comparative clinical trial of Glurazyme® versus a reference drug (RD) in healthy volunteers No. KI-33/14, which was approved by the Ministry of Health of Russia (Authorisation No. 130 dated 16/03/2015).

The purpose of the study was to assess the short-term safety and pharmacokinetic parameters of the investigational product (IP) Glurazyme® versus Cerezyme® in healthy volunteers after a single intravenous administration.

**Materials and Methods**

The Clinical Research Centre of the City Polyclinic No. 2 of the DZM [Moscow City Healthcare Department] conducted a Phase I open-label, randomised, comparative, crossover clinical study to assess the safety and pharmacokinetics of Glurazyme® versus Cerezyme® at a dose of 30 U/kg, after a single intravenous administration followed by a safety and pharmacokinetics assessment of Glurazyme® at a dose of 60 U/kg after a single intravenous administration in healthy volunteers (Table 1). A sequential two-stage crossover design is classic for comparative studies to evaluate safety and bioequivalence of compared biological products in healthy volunteers [20].

 Healthy volunteers were randomised for a comparative pharmacokinetics study at the investigational site at a 1:1 ratio by the method of envelopes containing the arm number; the sequence was generated by random normal numbers using the www.randomization.com resource. The healthy volunteers of the 1st arm received first IP, then RP. The healthy volunteers of the 2nd arm received first RP, then IP.

As a result, each of the healthy volunteers who participated at the 1st and 2nd stage of the study was given an intravenous infusion of IP then and RP or, conversely, RP and then IP once at a dose of 30 U/kg.

At the 3rd stage, healthy volunteers who did not participate at the 1st and 2nd stages of the study received IP in the form of a continuous intravenous infusion at a dose of 60 U/kg. A dose of 30 U/kg is a standard initial dose for treating patients with GD type 1, while a dose of 60 U/kg is considered the maximum and is used in type 1 GD patients with severe course of the disease, as well as in patients with GD type 3 [2].

The inclusion criteria were:

* age from 18 to 45 years;
* body mass index ranging from 18.5 to 30 kg/m2, weight from 50 to 100 kg;
* the verified “healthy” diagnosis according to clinical, laboratory, and instrumental examinations;
* the volunteer’s written consent for participation in the study in accordance with applicable law;
* negative pregnancy test for women and consent to adhere to adequate contraception methods (double barrier method).

**Table 1.** *Study stages diagram*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Characteristic** | **Screening** | **Randomization** | **1st stage** | **2nd stage** |  | **3rd stage** |
| **The period of investigational and reference products first administration** | **The monitoring period (2–6 days of the study)** | **The period** **of investigation-al and reference products second administration** | **The monitoring period****(8–12 days of the study)** | **Screening** | **The period of investigational product administration** | **The monitoring period** **2–6 days of the study)** |
| Days of study | –14…–1st | 0th | 1st | 5th | 6th | 7th | 12th | –14…–1st | 1st | 6th |
| Visit |  | 1st | 2nd | 3rd | 4th | 5th | 6th |  | 1st | 2nd |
| Volunteer group | 1st (*n* = 9), 2nd (*n* = 9) | 3rd (*n* = 5) |



The main criteria for non-inclusion in the study were: hypersensitivity to imiglucerase, alglucerase, or to excipients of these drugs; burdened allergic history; chronic diseases of internal organs, mental illnesses; infection with human immunodeficiency virus, hepatitis B or C; acute infectious diseases within 4 weeks prior to the start of the study; medication with a pronounced effect on haemodynamics or internal organ functions within 1 month prior to the start of the study, deviations from the physiological norm of blood pressure and heart rate (HR); alcoholism, drug addiction, substance abuse, positive urine test for potent and narcotic drugs, smoking.

In total, 30 healthy volunteers were screened in the study, 3 of whom did not meet the recruitment criteria. The total volunteer population included in the study (full analysis set, FAS) comprised 27 people including 4 back-ups (Fig. 1). The safety population comprised 23 healthy volunteers (85.2% of the total number of volunteers included in the study). All the study visits and procedures were performed by 23 healthy volunteers included in the per-protocol analysis (PP) population. All 3 groups were comparable to each other (table. 2).

The study studied the following pharmacokinetic parameters:

• АUС0–t (U x min/l) – area under the curve of concentration versus time from zero moment to the last moment of measurement with the measured concentration above the limit of quantification;

*Screening*

*Screened (n = 30)*

*Not enrolled in the study (n = 7)*

*Not eligible for selection criteria (n = 3)*

*Understudies (n = 4)*

*Enrolled in the study (n = 23)*

*Study enrollment*

*Randomised (n = 18)*

1*st group (n = 9)*

*2nd group (n = 9)*

*3rd group (n = 5)*

*Observation*

*1st stage – Glurazyme® 30 U/kg (n = 9)*

*2nd stage – Cerezyme® 30 U/kg (n = 9)*

*1st stage – Cerezyme® 30 U/kg (n = 9)*

*2nd stage – Glurazyme® 30 U/kg (n = 9)*

*3rd stage – Glurazyme® 60 U/kg*

 *(n = 5)*

*Included in the analysis (n = 5)*

*Excluded from analysis (n = 0)*

*Included in the analysis (n = 9)*

*Excluded from analysis (n = 0)*

*Included in the analysis (n = 9)*

*Excluded from analysis (n = 0)*

*Analysis*

**Fig. 1.** *Study flow chart (according to CONSORT standard)*

* Cmax (U/l) – the maximum concentration estimated directly from the recorded concentration values;
* AUC0–∞ (U × min/l) – area under the curve of concentration versus the time from the zero moment with extrapolation to infinity;
* Cmax/AUC0–∞ (min–1) – the ratio of the maximum concentration to the area under the pharmacokinetic curve;
* Tmax (min) – time of the first attained maximum concentration;
* T1/2 (min) – half-life related to the terminal phase;
* Kel (min–1) – elimination rate constant related to the terminal phase;
* Cl (ml/(kg × min)) – total clearance;
* Vd (ml/kg) – volume of distribution;
* Vss (ml/kg) – apparent volume of distribution in steady state;
* MRT (min) – mean retention time of the drug.

All pharmacokinetic parameters were calculated individually for each healthy volunteer based on the one’s time vs blood drug concentration data, using actual blood sampling time, and collected after 0, 10, 20, 30, 60, 70, 80, 90 min after administration of the IP or RP at the studied doses. The concentration of IP and RP in the blood plasma was determined at the central laboratory of the Analytical Department of MBC Generium LLC using an enzymatic technique with substrate-labeled fluorescence. The limit of quantification was 0.2 mU/ml.

Pharmacokinetic equivalence was assessed in accordance with the requirements of the Russian and international regulatory documents to the equivalence study for reproduced biological products [16, 21–23].

Safety of the drugs (number, severity of adverse events (AEs), their relation to the IP) was assessed according to clinical (complaints, physical examination results, state of vital functions: HR, systolic (SBP) and diastolic (DBP) blood pressure, respiratory rate, body temperature; electrocardiography data in 12 standard leads) and laboratory (complete blood cell count, biochemical blood test, urinalysis, urine test for human chorionic gonadotropin) monitoring. The frequency of occurrences when the values of clinical and laboratory parameters fell outside the permissible limits was used as a characterising safety indicator.

Quantitative indicators were calculated in each group as the main statistical indicators: maximum, minimum, and mean values with an indication of the standard error interval or percentiles depending on the nature of data. For categorical (qualitative and ranking) parameters, the frequencies and occurrence percentage were calculated for the corresponding categories (ranks). To determine the influence of study factors on quantitative parameters of the healthy volunteers’ state of health, analysis of variance (ANOVA) was used. Nonparametric techniques (Kruskal-Wallis multiple comparison test) were used as auxiliary methods in dubious cases. To assess the existence of a relationship between qualitative parameters, we used contingency table analysis (χ2 test or Fisher’s exact test in case of small values of the observed frequencies). The proportionality between the main pharmacokinetic parameters (AUC, Cmax) and the administered IP dose was analysed based on the power function, y = a × doseb, where a is the proportionality constant, b is the power exponent. The data were presented taking into account generally accepted recommendations [24].

Results

**Analysis of pharmacokinetics parameters**. Plasma concentrations of the drugs were determined for all healthy volunteers at all planned time points, with no missing values. The maximum IP and RP concentration in blood plasma was attained 60 min after the start of administration, followed by a slow exponential decrease in concentration (Fig. 2).

**Table 2.***Baseline characteristics of healthy volunteers*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristic** | 1st group (*n* = 9) | 2nd group (*n* = 9) | 3rd group (*n* = 5) | Understudy *n* = 4) | ***Р*** |
| Gender, *n* (%)female male | 6 (66.7)3 (33.3) | 4 (44.4)5 (55.6) | 05 (100) | 2 (50.0)2 (50.0) | 0.147 |
| Age (М + SD), years | 30.6 ± 8.5 | 30.6 ± 4.9 | 29.6 ± 9.4 | 30.8 ± 4.5 | 0.994 |
| Weight (М + SD), kg | 67.5 ± 13.6 | 69.2 ± 12.7 | 79.6 ± 9.2 | 62.5 ± 13.0 | 0.221 |
| Height (М + SD), cm | 170.0 ± 11.0 | 170.0 ± 11.0 | 179.6 ± 1.1 | 165.3 ± 9.8 | 0.178 |
| Body mass index (М ± SD), kg/m2 | 23.19 ± 2.91 | 23.79 ± 2.28 | 24.70 ± 2.96 | 22.78 ± 3.88 | 0.735 |

In general, the average blood plasma concentration values of the IP after a single administration at a dose of
30 U/kg were close to those of RP after a single administration at a dose of 30 U/kg at all measured time points.

After administration of Glurazyme® at a dose of
30 U/kg, mean AUC0-t amounted to 4056.0 ± 818.4 mU × min/ml; after administration of the RP at a dose of 30 U/kg – 4610.2 ± 738.0 mU × min/ml; AUC0-∞ – 4111.65 ± 831.93 and 4686.34 ± 752.47 mU × min/ml; Cmах – 84.3 ± 16.9 and 98.0 ± 16.7 mU/ml; Cl – 7.6 ± 1.54 and 6.6 ± 1.15 ml/(kg × min), respectively. The calculated 90% confidence interval (CI) for the ratio of AUC0–t, AUC0–∞, Cmax, Cmax/AUC0–∞, Cl for these pharmacokinetic parameters lies within the allowable range of 80-125% (Table 3). The mean half-life (T1/2) and volume of distribution (Vd) were 7.1 ± 1.0 min for IP and 76.3 ± 13.8 ml/kg for IP and 7.4 ± 1.0 min and 69.7 ± 11.7 ml/kg for RP, respectively. For the 1st and 2nd arms of volunteers, there were no statistically significant differences between the drugs in terms of T1/2 and Kel
(p> 0.05). The results for the indicated pharmacokinetic parameters that were obtained in the study are consistent with the literature data on imiglucerase [9, 10]. In this study, there was no statistically significant *(p* >0.05) effect of the IP administration sequence – there was no effect of drug administration period, and there was no pairwise period × drug interaction (see Table 3).

*Blood drug concentration, mU/mL*

*Time, min*

*Cerezyme***®**

*Glurazyme***®**



Fig. 2. Averaged pharmacokinetic curves after administration of the investigational and reference products (for healthy volunteers of the 1st and 2nd groups). Error bar shows 95% confidence interval

Table 3. Comparison results of investigational and reference products various pharmacokinetic parameter

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Pharmacokinetic parameter** | **Glurazyme®, M ± SD** | **Cerezyme®, M ± SD** | ***p* (interaction****period × drug)** | **90% confidence interval for the ratio of 2 products parameters, %** |
| AUC0–t, mU × min/mL | 4056.0 ± 818.4 | 4610.2 ± 38.0 | 0.902 | 83.7–92.3 |
| AUC0–∞, mU × min/mL | 4111.65 ± 831.93 | 4686.34 ± 752.47 | 0.942 | 83.5–92.0 |
| T1/2, min | 7.1 ± 1.0 | 7.4 ± 1.0 | 0.160 | 92.4–98.2 |
| Kel, min–1 | 0.10 ± 0.02 | 0.09 ± 0.01 | 0.170 | 102.0–108.8 |
| Cmax, mU/mL | 84.3 ± 16.9 | 98.0 ± 16.7 | 0.704 | 80.2–91.8 |
| Cmax /AUC0–∞, min–1 | 0.021 ± 0.001 | 0.021 ± 0.001 | 0.184 | 96.0–100.2 |
| Cl, mL/(kg × min) | 7.58 ± 1.54 | 6.57 ± 1.15 | 0.843 | 109.6–121.1 |
| Vd, mL/kg | 76.31 ± 13.78 | 69.72 ± 11.69 | 0.262 | 104.6–114.3 |
| Vss, mL/kg | 128.50 ± 25.79 | 120.00 ± 23.76 | 0.660 | 100.7–113.5 |
| MRT, min | 17.06 ± 1.60 | 18.20 ± 1.74 | 0.105 | 91.3–96.2 |

For all studied pharmacokinetic parameters, 90% CI for the ratio between the IP and RP falls within the recommended range from 80 to 125%, which makes it possible to draw a conclusion of pharmacokinetic equivalence of these drugs (see Fig. 2).

After administration of the IP at a dose of 60 U/kg, the mean values of AUC0–t amounted to 12,774.3 ± 2646.9 mU × min/ml, AUC0–∞ – 13,455.8 ± 2948.7 mU × min/ml, T1/2 – 10.3 ± 1.7 min, Cl – 4.6 ± 1.0 kg × min, Vd – 67.4 ± 7.1 ml/kg. Mean value of the maximum concentration Cmax after administration of Glurazyme® at a dose of 60 U/kg was attained 60 minutes after the start of administration, which corresponded to the duration of infusion and amounted to 270.3 ± 59.6 mU/ml. An increase in the mean blood plasma IP concentration value with an increase in the dose of the drug administered was obtained by comparing the averaged pharmacokinetic curves for various doses of Glurazyme® – 30 and 60 U/kg (Fig. 3).

 *Blood drug concentration, mU/mL*

*Time, min*

*Glurazyme***®** *(30 U/kg)*

*Glurazyme***®** *(60 U/kg)*



**Fig. 3.** *Averaged pharmacokinetic curves after administration of the investigational product at doses of 30 and 60 U/kg. Error bar shows 95% confidence interval*

The study showed a non-linear dependence of the main pharmacokinetic parameters on the IP dose administered
(30 or 60 U/kg), since the AUC0–t, AUC0–∞, and Cmax exponent was in the range from 1.5 to 2.0 (p <0.001).

**Safety Assessment.** In total, 6 AEs were reported in the study, 4 (66.7%) of them occurred after administration of the IP and 2 – after administration of the RP. Of the 6 AEs registered in this study, 4 (66.7%) had a dubious relation to the IP, 2 (33.3%) – a possible relation to the RP. The 3 AEs registered after administration of the IP were mild (hyperkalemia, decreased haemoglobin, diarrhoea) and 1 was moderate (hyperkalemia). The 2 AEs observed after administration of the RP (hypotension and increased eosinophil count) were mild. No serious or severe AEs were reported in this study. Most AEs (3 out of 4) after administration of the IP were laboratory-reported, which makes up 75% of all AEs after administration of the IP.

The analysis using Fisher’s exact test did not reveal any statistically significant difference between the arms in terms of association between the AEs and intake of the IP or RP
(*p* = 0.067) (Table 4).

A comparative analysis between the drugs found no statistically significant difference in the proportion of healthy volunteers who had deviations from the reference values in the complete blood cell count or biochemical blood test (*p* >0.05). No clinically significant deviations from the urinalysis reference values were observed after administration of the IP or RP.

**Table 4.** *Comparative characteristics of adverse events*

|  |  |  |  |
| --- | --- | --- | --- |
| **Adverse event** | **Glurazyme®** | **Cerezyme®** | ***p* (Fisher test)** |
| ***n*** | **Relation to drug administration** | ***n*** | **Relation to drug administration** |
| Hyperkalemia | 2 | Unlikely | 0 | 0 | 0.067 |
| Hemoglobin level decreased | 1 | Unlikely | 0 | 0 |
| Diarrhea | 1 | Unlikely | 0 | 0 |
| Arterial hypotension | 0 | 0 | 1 | Possible |
| Eosinophils number increased | 0 | 0 | 1 | Possible |
| Total, *n* (%) | 4/4 (100) | 2/2 (100) |

Analysis of the obtained data did not find any statistically significant differences in terms of the SBP, DBP, HR, respiratory rate, or body temperature in the healthy volunteers after administration of IP or RP. A comparative assessment of the vital function parameter dynamics in healthy volunteers between different doses of the IP (30 or 60 U/kg) showed statistically significant differences in terms of SBP (*p* <0.001), DBP (*p* = 0.001), and respiratory rate (*p* = 0.031). In this case, the individual SBP values in most measurement periods did not exceed 120 mm Hg. Individual DBP values after administration of Glurazyme® at a dose of 30 or 60 U/kg ranged from 60 to 80 mm Hg at all visits.

**Discussion**

The results obtained in the course of this comparative clinical study make it possible to draw a conclusion that the IP and RP are characterised by a high degree of comparability of all pharmacokinetic parameters. The individual and averaged profiles of the pharmacokinetic curves of the IP and RP are similar at all measured time points.

A comparison of the averaged pharmacokinetic curves for various doses of Glurazyme® – 30 and 60 U/kg showed an increase in the mean blood plasma IP concentration value with an increase in the dose of the drug administered.

The study showed a non-linear dependence of the main pharmacokinetic parameters on the IP dose administered
(30 or 60 U/kg).

The calculated 90% CI for the ratio of the pharmacokinetic parameters of the two drugs lies within the allowable range from 80 to 125% for all the studied pharmacokinetic parameters.

No AEs (adverse reactions) associated with the use of the drug were reported for the IP. A comparative analysis of safety parameters in this study (frequency and severity of AEs, physical examination of healthy volunteers with an assessment of vital signs, laboratory test results, electrocardiography) did not reveal any differences between the arms.

**Conclusion**

• The results of the Phase I clinical study indicate pharmacokinetic equivalence of the biosimilar drug Glurazyme® and Cerezyme® at a dose of 30 U/kg.

• The study showed a non-linear dependence of the main pharmacokinetic parameters on the dose of Glurazyme® administered (30 or 60 U/kg).

• A single administration of Glurazyme® at the studied doses is safe in healthy volunteers and is not accompanied by the development of adverse reactions. A comparative analysis of the studied safety parameters did not reveal any differences between the arms.

**REFERENCES ЛИТЕРАТУРА/REFERENCES**

1. Lukina E.A. Bolezn Goshe. Prakticheskoye rukovodstvo. M.: Litterra. 2014. 56 s. [Lukina E.A. Gaucher disease. Practical guide. Moscow: Litterra, 2014, 56 p. (In Russ.)].
2. Lukina E.A.. Sysoyeva E.P.. Lukina K.A. i dr. Bolezn Goshe u vzroslykh: diagnostika. lecheniye i monitoring. V kn.: Algoritmy diagnostiki i protokoly lecheniya zabolevaniy sistemy krovi. Pod red. V.G. Savchenko. V 2 tomakh. Tom 1. M.: Praktika. 2018. C. 411-425.

 [Lukina E.A., Sysoeva E.P., Lukina K.A. et al. Gaucher disease in adults: diagnosis, treatment and monitoring. In: Diagnostic algorithms and treatment protocols for blood diseases. Ed.: V.G. Savchenko. In 2 Vol. Vol. 1. Moscow: Praktika, 2018. Pp. 411–425 (In Russ.)].

1. Gaucher disease. A strategic collaborative approach from EMA and FDA. EMA/44410/2014. European Medicines Agency, 2014:9. Available at: [https://ww](http://www/)w. ema.europa.eu/en/documents/regulatory-procedural-guideline/gaucher-disease-strategic-collaborative-approach-european- medicines-agency-food-drug-administration\_en.pdf.
2. Biegstraaten M., Cox T.M., Belmatoug N. et al. Management goals for type 1 Gaucher disease: An expert consensus document from the European working group on Gaucher disease. Blood Cells Mol Dis 2018;68:203–8. DOI: 10.1016/j. bcmd.2016.10.008.
3. Zub N.V. Bolezn Goshe: rasprostranennost. semiotika. kachestvo zhizni i kliniko-ekonomicheskoye obosnovaniye fermentozamestitelnoy terapii. Avtoref. dis. … kand. med. nauk. M.; 2010. [Zub N.V. Gaucher disease: prevalence, semiotics, quality of life, and the clinical and economic rationale for enzyme replacement therapy. Thesis … of candidate of medical sciences. Moscow, 2010. (In Russ)].
4. Gaucher Disease. Eds.: A.H. Futerman, A. Zimran. Boca Raton, FL: Taylor & Francis, 2007.
5. Kaplan P., Baris H., De Meirleir L. et al. Revised recommendations for the management of Gaucher disease in children. Eur J Pediatr 2013;172(4): 447–58. DOI: 10.1007/s00431-012-1771-z.
6. Lukina E.A. Protokol vedeniya patsiyentov s boleznyu Goshe. Onkogematologiya 2009;1:65–71. [Lukina E.A. Gaucher disease management protocol. Onkogematologiya = Oncohematology 2009;1:65–71. (In Russ.)].
7. Serratrice C., Carballo S., Serratrice J., Stirnemann J. Imiglucerase in the management of Gaucher disease type 1: an evidence-based review of its place in therapy. Core Evid 2016;11:37–47. DOI: 10.2147/CE.S93717.
8. Andersson H., Kaplan P., Kacena K., Yee J. Eight-year clinical outcomes of long-term enzyme replacement therapy for 884 children with Gaucher disease type 1. Pediatrics 2008;122(6):1182–90.

 DOI: 10.1542/peds.2007-2144.

1. Hollak C.E., Vom Dahl S., Aerts J.M. et al., Force Majeure: therapeutic measures in response to restricted supply of imiglucerase (Cerezyme) for patients with Gaucher disease, Blood Cells Mol Dis 2009 (Oct 3 Electronic publication ahead of print).
2. Aviezer D., Brill-Almon E., Shaaltiel Y. et al. A plant-derived recombinant human glucocerebrosidase enzyme – a preclinical and phase I investigation. PLoS One 2009;4(3):e4792. DOI: 10.1371/journal. pone.0004792.
3. Prikaz Minpromtorga Rossii ot 23.10.2009 № 965 «Ob utverzhdenii Strategii razvitiya farmatsevtiche- skoy promyshlennosti Rossiyskoy Federatsii na period do 2020 goda». Available at: <http://www.consultant.ru/> cons/cgi/online. [Order of the Ministry of Industry and Trade of Russia dated 10.23.2009 No. 965 “On approval of Pharmaceutical Industry Development Strategy of the Russian Federation for the period until 2020”. Available at:<http://www.consultant.ru/cons/cgi/> online. (In Russ.)].
4. Gosudarstvennaya programma «Razvitiye farmatsevticheskoy i meditsinskoy promyshlennosti» na 2013–2020 gg. Osnovnyye dannyye po gosudarstvennoy programme «Razvitiye farmatsevticheskoy i meditsinskoy promyshlennosti» na 2013–2020 gg. M.: Minpromtorg Rossii. 2014. Available at: <http://minpromtorg.gov.ru/common/> upload/files/docs/MinProm\_02.06.14. pdf. [State program “Development of the pharmaceutical and medical industry” for 2013–2020. Basic data on the state program “Development of the pharmaceutical and medical industry” for 2013–2020. Moscow: Ministry of Industry and Trade of Russia, 2014. Available at: <http://minpromtorg.gov.ru/> common/upload/files/docs/ MinProm\_02.06.14.pdf. (In Russ.)].
5. Pravila provedeniya issledovaniy biologicheskikh lekarstvennykh sredstv Evraziyskogo ekonomicheskogo soyuza. Utverzhdeny resheniyem № 89

 ot 03/11/2016. 714s. Available at: <http://docs.cntd.ru/> document/456026116. [Rules for conducting research on biological drugs of the Eurasian Economic Union. Approved by decision No. 89 of 03/03/2016. 714 p. Available at: http:// docs.cntd.ru/document/ 456026116. (In Russ.)].

1. Committee for Medicinal Products for Human Use (CHMP). Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. EMEA/ CHMP/BMWP/42832/2005 Rev1. European Medicines Agency. 2015:13. Available at: [https://ww](http://www.ema.europa.eu/)w[.ema.europa.eu/](http://www.ema.europa.eu/) en/documents/scientific-guideline/ guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active\_en-2.pdf
2. Ivanov R. Sekareva G. Kravtsova O. i dr. Pravila provedeniya issledovaniy bioanalogovykh lekarstvennykh sredstv (bioanalogov). Farmakokinetika i farmakodinamika 2014;1: 21–36. [Ivanov R., Sekareva G., Kravtsova O. et al. The rules for conducting research on bioanalogous medicines (bioanalogs). Farmakokinetika i farmakodinamika = Pharmacokinetics and pharmacodynamics 2014;1:21–36. (In Russ.)].
3. Degterev M.B.. Smolov M.A.. Vishnevskiy A.Yu.. Shukurov R.R. Fizikokhimicheskaya kharakterizatsiya imiglyutserazy bioanalogichnogo i referentnogo preparata mass-spektrometricheskimi metodami. V kn.: Biotekhnologiya: sostoyaniye i perspektivy razvitiya. Materialy mezhdunarodnogo kongressa. 2019. S. 302–303. [Degterev M.B., Smolov M.A., Vishnevskiy A.Yu., Shukurov R.R. Physico-chemical characterization of imiglucerase bio-analogous and reference preparation by mass spectrometric methods. In: Biotechnology: state and development prospects. Proceedings of the International Congress, 2019. Pp. 302–303. (In Russ.)].
4. Vassarays R.A., Chashchinova D.V., Shamonov N.A. i dr. Covremennyye podkhody k obespecheniyu virusnoy bezopasnosti lekarstvennykh preparatov. proizvedennykh po tekhnologii rekombinantnoy DNK v kletkakh mlekopitayushchikh.

 V kn.: Biotekhnologiya: sostoyaniye i perspektivy razvitiya. Materialy mezhdunarodnogo kongressa. 2019. S. 288–289. [Vassarais R.A., Chashchinova D.V., Shamonov N.A. et al. Modern approaches to virus safety of drugs produced by recombinant DNA technology in mammalian cells. In: Biotechnology: state and development prospects. Proceedings of the International Congress, 2019.

 Pp. 288–289. (In Russ.)].

1. Waller C.F., Bronchud M., Mair S., Challand R. Comparison of the pharmacodynamic profiles of a biosimilar filgrastim and Amgen filgrastim: results from a randomized, phase I trial. Ann Hematol 2010;89(10):971–8. DOI: 10.1007/ s00277-010-0973-6.
2. Committee for Medicinal Products for Human Use (CHMP) Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins, 2007.
3. Expert committee on biological standardization. Guidelines of evolution of similar biotherapeutic product. Geneva, 2009.
4. Rukovodstvo po ekspertize lekarstvennykh sredstv. Tom I. M.: Grif i K. 2014. 328 s. [Guidance on the examination of medicines. Vol. I. Moscow: Grif i K, 2014. 328 p. (In Russ.)].
5. Mamayev A.H., Kudlay D.A. Vizualizatsiya dannykh v prezentatsiyakh. otchetakh i issledovaniyakh. M.: Prakticheskaya meditsina. 2011. 39 s. [Mamaev A.N., Kudlay D.A. Data visualization in presentations, reports and studies. Moscow: Practical Medicine, 2011. 39 p. (In Russ.)].

**Authors’ contributions**

S.B. Fitilev: study design development, analysis of the obtained data, analysis of scientific material;

A.V. Vozzhaev: obtaining data for analysis, analysis of the obtained data, analysis of scientific material, manuscript text supplement;

I.I. Shkrebneva, А.А. Kazarov, М.S. Pantyushenko: obtaining data for analysis, analysis of the obtained data;

D.A. Kudlay: scientific and literary editing of article, reviewing of publications on the article’s topic;

E.V. Gapchenko: study design development, analysis of the obtained data;

O.A. Markova: study design development, analysis of the obtained data, scientific editing of article;

A.Yu. Borоzinets: analysis of scientific material, article writing, reviewing of publications on the article’s topic, preparation of a list of references.

**ORCID of authors**

S.B. Fitilev: https://orcid.org/0000-0001-8395-419X

A.V. Vozzhaev: https://orcid.org/0000-0002-2687-5986

I.I. Shkrebneva: https://orcid.org/0000-0002-0070-3115

D.A. Kudlay: https://orcid.org/0000-0003-1878-4467

O.A. Markova: https://orcid.org/0000-0002-1179-3881

A.Yu. Borоzinets: https://orcid.org/0000-0002-4863-8471

А.А. Kazarov: https://orcid.org/0000-0003-0682-6113

**Conflict of interest.** D.A. Kudlay, E.V. Gapchenko, O.A. Markova, A.Yu. Borozinets are employees of JSC GENERIUM. A.A. Kazarova and M.S. Pantyushenko are employees of IBC “Generium”. Other authors declare no conflict of interest.

**Financing.** The study was conducted with the financial support of IBC "Generium".

**Informed consent.** Participation in the clinical trial was voluntary. A healthy volunteer had the right to refuse to participate in the ongoing research at any stage. The consent of the healthy volunteer to participate in the study was confirmed by signing the Information sheet of the healthy volunteer with an informed consent form at the screening visit before any procedures related to the study were performed.

**Article submitted:** 30.08.2019. **Accepted for publication:** 28.11.2019.