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Phase I pharmacokinetics study of drug «COVID-globulin» (specific human immunoglobulin against COVID-19)

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Abstract

Introduction. Coronavirus infection is an acute viral disease involving a predominant lesion of the upper respiratory tract caused by an RNA-containing virus of the Coronaviridae family. However, it is known that neutralizing antibodies play an important role in antiviral therapy due to their effective inhibition of the reproduction of viruses, which reduces the severity of the disease. Polyclonal antibodies contained in convalescent plasma are usually used as emergency therapy for emerging infectious diseases. In this aspect, the use of a human immunoglobulin G preparation containing specific antibodies to SARS-CoV-2 ("COVID-globulin") appears to be safer and more effective.

Aim. The aim is to carry out a pharmacokinetic study of drug "COVID-globulin" (specific human immunoglobulin against COVID-19, solution for infusions, not less than 160 anti-COVID units/mL (ACU/mL), JSC "NPO Microgen", owner of the registration certificate of JSC "Natsibio", Russia), in addition to standard therapy for the treatment of patients with middle-grade COVID-19.

Materials and methods. The clinical and analytical stages of the study of the pharmacokinetics of the drug "COVID-globulin", as well as an analysis of the safety and pharmacokinetic parameters, were carried as part of a clinical study of the safety, tolerability and pharmacokinetics of the drug immunoglobulin ("COVID-globulin"), involving not less than 160 anti-COVID units/mL (ACU/mL), JSC "NPO Microgen", owner of the registration certificate of JSC "Natsibio", Russia. A quantitative determination of antibody concentrations against SARS-CoV-2 was carried out by enzyme-linked immunosorbent assay using spectrophotometric detection in the visible range of the spectrum on an automatic plate enzyme-linked immunosorbent assay analyzer Lazurite (Dynex Technologies Inc., USA). A calculation of pharmacokinetic parameters was carried out using the Microsoft Excel package with the Boomer extension for pharmacokinetic analysis (Department of Pharmacokinetics and Drug Metabolism, Allergan, Irvine, CA 92606, USA).

Results and discussion. No serious adverse events were reported in the study; the only adverse event, which resulted in a volunteer withdrawing from the study, was not related to the use of the drug. The pharmacokinetic parameters of the drug "COVID-globulin" were calculated for two batches of drugs. The pharmacokinetics of "COVID-globulin" (the content of antibodies to SARS-CoV-2 – 330 ACU/ml) was assessed on a sample of 8 volunteers. The maximum concentration of specific IgG antibodies to the SARS-CoV-2 virus was 25.46 ± 8.71 ACU/ml (Mean ± SD, where Mean is the arithmetic mean; SD is the standard deviation). The median value of the time to maximum concentration of specific IgG antibodies to the SARS-CoV-2 virus was 0.25 hours. Specific IgG antibodies to the SARS-CoV-2 virus were eliminated from blood plasma with a half-life value of 266.89 ± 59.92 hours. The pharmacokinetics of the "COVID-globulin" (the content of antibodies to SARS-CoV-2 – 250 ACU/ml) was assessed on a sample of 15 volunteers. The maximum concentration of specific IgG antibodies to the SARS-CoV-2 virus was 20.93 ± 3.82 ACU/ml. The median value of the time to maximum concentration of specific IgG antibodies to the SARS-CoV-2 virus was 0.25 hours. Specific IgG antibodies to the SARS-CoV-2 virus were eliminated from blood plasma with a half-life value of 295.56 ± 50.68 hours.

Conclusion. According to the results of the study, the safety profile of the drug "COVID-globulin" is assessed as favorable. Based on the concentrations of specific IgG antibodies to the SARS-CoV-2 virus obtained during the analytical stage of the study, the main pharmacokinetic parameters were calculated, and the average pharmacokinetic profiles of the test drug "COVID-globulin" were plotted after a single injection. The results obtained were the basis for the subsequent phases of clinical trials of the drug "COVID-globulin".

Keywords: COVID-19, immunoglobulin, antibodies, plasma, pharmacokinetics

Conflict of interest. The authors declare that they have no obvious and potential conflicts of interest related to the publication of this article.

Contribution of the authors. Tatyana I. Smolyanova, Alevtina M. Nikolaeva, Tatyana V. Vyaznikova, Anastasiya A. Pankratova, Ekaterina A. Bykova participated in the clinical phase of the study. Maria A. Kolganova participated in the analytical phase of the study. Natalia S. Bagaeva carried out statistical processing of the obtained results and calculated of pharmacokinetic parameters. Igor E. Shohin carried out the organization of work in this direction. All the above authors participated in the discussion of the results in the format of scientific discussion.

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Изучение фармакокинетики препарата «КОВИД-глобулин» (специфический иммуноглобулин человека против COVID-19) (АО «Нацимбио», Россия) в рамках фазы I клинического исследования

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Резюме

Введение. *Коронавирусная инфекция* – острое вирусное заболевание с преимущественным поражением верхних дыхательных путей, вызванное РНК-содержащим вирусом семейства *Coronaviridae*. Вместе с тем известно, что нейтрализующие антитела играют важную роль в противовирусной терапии, поскольку они эффективно ингибируют размножение вирусов и снижают тяжесть заболевания. Поликлональные антитела, содержащиеся в реконвалесцентной плазме, обычно используют в качестве неотложной терапии возникающих инфекционных заболеваний. В этом аспекте применение препарата иммуноглобулина G человека, содержащего специфические антитела к SARS-CoV-2 («КОВИД-глобулин»), представляется более безопасным и эффективным.

Цель. Целью исследования является изучение фармакокинетики препарата «КОВИД-глобулин» (специфический иммуноглобулин человека против COVID-19, раствор для инфузий, не менее 160 антиковидных единиц/мл (АКЕ/мл), АО «НПО Микроген», владелец регистрационного удостоверения АО «Нацимбио») в дополнение к стандартной терапии для лечения пациентов со среднетяжелым течением COVID-19.

Материалы и методы. Клинический и аналитический этапы исследования фармакокинетики препарата «КОВИД-глобулин», а также анализ безопасности и параметров фармакокинетики проводились в рамках клинического исследования изучения безопасности, переносимости и фармакокинетики препарата иммуноглобулина («КОВИД-глобулин»), раствор для инфузий, не менее 160 АКЕ/мл (АО «НПО Микроген», владелец регистрационного удостоверения АО «Нацимбио»). Количественное определение концентраций антител против SARS-CoV-2 проводилось методом иммуноферментного анализа с использованием спектрофотометрического детектирования в видимом диапазоне спектра на автоматическом планшетном иммуноферментном анализаторе Lazurite (Dynex Technologies Inc., США). Расчет фармакокинетических параметров проводился с помощью пакета Microsoft Excel с расширением для проведения фармакокинетического анализа Boomer (Department of Pharmacokinetics and Drug Metabolism, Allergan, Irvine, CA 92606, США).

Результаты и обсуждение. В исследовании не зарегистрировано ни одного серьезного нежелательного явления, а единственное нежелательное явление, которое привело к выбыванию добровольца из исследования, не связано с применением препарата. Рассчитаны фармакокинетические параметры исследуемого препарата «КОВИД-глобулин» для двух серий препаратов. Фармакокинетика препарата «КОВИД-глобулин» (содержание антител к SARS-CoV-2 – 330 АКЕ/мл) оценена на выборке из 8 добровольцев. Максимальное значение концентраций специфических антител IgG к вирусу SARS-CoV-2 составило 25,46 ± 8,71 АКЕ/мл. Значение медианы времени достижения максимальной концентрации специфических антител IgG к вирусу SARS-CoV-2 составило 0,25 часа. Специфические антитела IgG к вирусу SARS-CoV-2 элиминировались из плазмы крови со значением периода полувыведения 266,89 ± 59,92 часов. Фармакокинетика препарата «КОВИД-глобулин» (содержание антител к SARS-CoV-2 – 250 АКЕ/мл) оценена на выборке из 15 добровольцев. Максимальное значение концентрации специфических антител IgG к вирусу SARS-CoV-2 составило 20,93 ± 3,82 АКЕ/мл (Mean ± SD, где Mean – среднее арифметическое, SD – стандартное отклонение). Значение медианы времени достижения максимального значения концентрации специфических антител IgG к вирусу SARS-CoV-2 составило 0,25 часа. Специфические антитела IgG к вирусу SARS-CoV-2 элиминировались из плазмы крови со значением периода полувыведения 295,56 ± 50,68 часов.

Заключение. По результатам исследования профиль безопасности исследуемого препарата оценивается как благоприятный. По полученным в ходе аналитического этапа исследования значениям концентраций специфических антител IgG к вирусу SARS-CoV-2 рассчитаны основные фармакокинетические параметры, а также построены усредненные фармакокинетические профили исследуемого вещества после однократного введения препарата «КОВИД-глобулин». Полученные результаты явились основанием для проведения последующих фаз клинических испытаний препарата «КОВИД-глобулин».

Ключевые слова: COVID-19, иммуноглобулин, антитела, плазма, фармакокинетика

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. Т. И. Смолянова, А. М. Николаева, Т. В. Вязникова, А. А. Панкратова, Е. А. Быкова участвовали в проведении клинического этапа исследования. М. А. Колганова участвовала в проведении аналитического этапа исследования. Н. С. Багаева проводила статистическую обработку данных и расчет фармакокинетических параметров. И. Е. Шохин отвечал за организационную часть исследования. Все вышеуказанные авторы участвовали в обсуждении полученных результатов в форме научной дискуссии.

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INTRODUCTION

Coronavirus infection is an acute viral disease predominantly affecting the upper respiratory tract and caused by an RNA-containing virus of the Coronaviridae family [1]. COVID-19 (COronaVIrus Disease 2019) is an infectious disease caused by the most recently discovered virus of the Coronaviridae family, SARS-CoV-2 [2].

An outbreak of COVID-19 has developed into the world-sweeping pandemic. As of January 23, 2022[1], over 346 million cases have been registered worldwide, with over 5.5 million lethal outcomes. The epidemic situation creates an urgent requirement for effective, specific and accessible medicines [3].

Neutralizing antibodies are known to comprise important antiviral agents that function as effective inhibitors of viral replication to alleviate symptoms of the disease [4–6]. Polyclonal antibodies contained in convalescent plasma are commonly used for the emergency treatment of new infectious diseases [7–10].

According to the WHO recommendations, convalescent plasma from confirmed COVID-19 donors in recovery provides for passive immunization and is therefore suitable for treating epidemic diseases lacking a specific therapy. Published evidence reveals that convalescent (anticovid) plasma from COVID-19 donors has been applied in China and other countries. Currently, the use of anticovid plasma in severe COVID-19 is included in the "Prevention, diagnosis and treatment of new coronavirus infection COVID-19" interim guidelines by the Ministry of Health of the Russian Federation[2]. The method is grounded in neutralizing the virus and boosting the patient's immune system upon acquiring the antiviral antibodies with donor plasma. Such therapies have been successfully applied to improve survival in patients with other serious coronavirus-induced acute respiratory syndromes, including SARS and MERS. However, the usage of blood plasma always associates with the risk of various post-transfusion complications, including blood-transmissible infections. In this respect, a medicine based on SARS-CoV-2-specific antibody-containing human immunoglobulin G (COVID-globulin) appears to be safer and more efficient.

After testing the efficacy and safety of COVID-globulin on animal subjects, it was decided to conduct a phase I clinical trial to evaluate the drug's safety, tolerability and pharmacokinetics in infusion to healthy volunteers.

MATERIALS AND METHODS

The clinical and analytical phases of the pharmacokinetic study of SARS-CoV-2-specific antibody-containing human immunoglobulin G (COVID-globulin, NPO Microgen JSC, Natsimbio JSC as registration certificate holder; infusion solution, min. 160 ACU/mL), as well as safety and pharmacokinetic analyses, have been performed as part of a clinical trial on the safety, tolerability and pharmacokinetics of immunoglobulin G (COVID-globulin, NPO Microgen JSC, Natsimbio JSC as registration certificate holder; infusion solution, min. 160 ACU/mL).

Clinical phase

The study enrolled 24 healthy volunteers aged 18–60 years. An ulnar vein cubital catheter was installed one day prior to the procedure to facilitate infusion and blood sampling for pharmacokinetic studies, as well as reduce volunteer discomfort. The catheter was removed no later than 24 h after administration of the drug. COVID-globulin was administered once by drop infusion of 4 mL/kg intravenously. The initial infusion rate was 0.01–0.02 mL/kg body weight per min for 30 min. If the drug was well tolerated, the rate was gradually increased to max. 0.12 mL/kg body weight per min. An infusion pump was used to control the infusion rate. Each volunteer was taken 11 blood samples for pharmacokinetics analyses prior to infusion (–0.25 h), after 0.25, 6, 12, 24 and 48 h on days 4, 8, 12, 16 and 21 following drug administration.

Blood samples were further collected into ethylenediaminetetraacetic acid (EDTA)-treated Vacutainer® tubes and centrifuged for 10 min at 3,000 rpm. The outcome plasma was aliquoted to equal study and control samples. The study aliquots were frozen, stored and transported to an analytic laboratory at –20°C or below.

Safety analysis

Safety data were interpreted in 24 volunteers for the following evidence: incidence of drug-associated adverse and serious adverse events; physical findings

[1] Weekly epidemiological update on COVID-19 – 23 January 2022. Available at: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---23-january-2022. Accessed: 01/23/2022.

[2] Interim guidelines "Prevention, diagnosis and treatment of new coronavirus infection COVID-19. Version 14 (27.12.2021)", approved by the Ministry of Health of the Russian Federation. Available at: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/059/041/original/%D0%92%D0%9C%D0%A0_COVID-19_V14_27-12-2021.pdf. Accessed: 01/25/2022.

(body temperature, blood pressure, heart and respiratory movement rates); laboratory and instrumental findings; self-monitoring diaries.

Analytical phase

Anti-SARS-CoV-2 antibody concentrations were quantitatively determined in enzyme-linked immunosorbent assays (ELISA) with visible-spectrum spectrophotometry on a Lazurite automated ELISA plate analyzer (Dynex Technologies Inc., USA). The method is grounded on the interaction of antibodies with polystyrene plate-immobilized recombinant SARS-CoV-2 structural protein domain S1. The bound antibodies are detected by secondary antibody conjugation with chromogenic horseradish peroxidase (HRP) enzyme and substrate (tetramethylbenzidine). Following arrest of the peroxidase reaction with a stop reagent, the solution optical density is measured in wells at detection wavelength of 450 nm and reference wavelength of 630 nm. The intensity of yellowing is directly proportional to anti-SARS-CoV-2 antibody concentration in the sample. The calibration curve (an optical density vs. anti-SARS-CoV-2 antibody concentration plot) was constructed for a manufacturer's standard sample diluted with pooled intact human plasma and used for determining the antibody concentration. The assays utilized Anti-SARS-CoV-2 ELISA (IgG) chemistry (Euroimmun AG, Germany). The analytical range was 0.01215–0.48600 ACU/mL.

Statistical and pharmacokinetic analyses

The pharmacokinetic parameters of COVID-globulin were estimated for two drug batches, P3 (anti-SARS-CoV-2 antibodies concentration 330 ACU/mL; 8 volunteers) and P4 (250 ACU/mL; 16 volunteers).

The individual dynamic profiles of plasma SARS-CoV-2-specific IgG antibody concentrations following administration of COVID-globulin is described by maximum antibody concentration C_{max} and time to maximum T_{max}, area under the IgG concentration vs. time curve estimated by the trapezoidal method for period from the first infusion to last detection point at time t ($AUC_{0\text{-}t}$), as well as the area under the IgG concentration vs. time curve for period from the first infusion to infinity ($AUC_{0\text{-}\infty}$). The following additional pharmacokinetic parameters were determined: SARS-CoV-2-specific IgG antibody half-life $T_{1/2}$; elimination rate constant K_{el} estimated from the slope of linear regression, least squares and log-transformed concentrations vs. last-detectable time; drug distribution volume V_d.

The pharmacokinetic parameters were calculated with the Boomer pharmacokinetic analysis add-in for Microsoft Excel (Department of Pharmacokinetics and Drug Metabolism, Allergan, Irvine, CA 92606, USA). The parameter distributions were described in the terms of central tendency (mean, geometric mean, median) and data scattering (standard deviation, coefficient of variation, minimum and maximum values). Descriptive pharmacokinetic statistics were calculated with Microsoft Excel (Microsoft Corporation, USA).

RESULTS AND DISCUSSION

Safety

No serious adverse events have been reported in the study; the only adverse event that entailed a volunteer withdrawal was unrelated to the drug usage.

Pharmacokinetic parameters of COVID-globulin, batch P3. Pharmacokinetics was evaluated on a sample of 8 volunteers. The maximum SARS-CoV-2-specific IgG antibodies concentration was 25.46 ± 8.71 ACU/mL (Mean ± SD; SD for standard deviation). The median time to maximum concentration was 0.25 h. The area under the IgG concentration vs. time curve for period from the first infusion to last detection at time t ($AUC_{0\text{-}t}$) was 4970.92 ± 1642.34 ACU · h/mL. The area under the IgG concentration vs. time curve for period from the first infusion to infinity ($AUC_{0\text{-}\infty}$) was 6821.64 ± 2480.07 ACU · h/mL. IgG antibody half-life $T_{1/2}$ in elimination was 266.89 ± 59.92 h. Drug distribution volume V_d comprised 6.40 ± 3.61 L (Table 1).

Pharmacokinetic parameters of COVID-globulin, batch P4. Pharmacokinetics was evaluated on a sample of 15 volunteers (one individual withdrew from the trial due to a non-drug-related SARS-CoV-2 RNA-positive PCR test).

The maximum SARS-CoV-2-specific IgG antibodies concentration was 20.93 ± 3.82 ACU/mL. The median time to maximum concentration was 0.25 h. The area under the IgG concentration vs. time curve for period from the first infusion to last detection at time t ($AUC_{0\text{-}t}$) was 4115.43 ± 686.38 ACU · h/mL. The area under the IgG concentration vs. time curve for period from the first infusion to infinity ($AUC_{0\text{-}\infty}$) was 6078.10 ± 1410.08 ACU · h/mL. IgG antibody half-life $T_{1/2}$ in elimination was 295.56 ± 50.68 h. Drug distribution volume V_d comprised 4.47 ± 0.67 L (Table 1).

Table 1. Summary data of pharmacokinetic parameters after a single dose administration of "COVID-globulin"

Pharmacokinetic parameter of "COVID-globulin"	Batch P3	Batch P4
C_{max}, ACU/ml		
Number of volunteers	8	15
Mean	25.46	20.93
Geometric Mean	23.87	20.60
Median	26.32	20.20
SD	8.71	3.82
CV, %	34.20	18.24
Min	12.21	14.96
Max	36.59	27.44
AUC_{0-t}, ACU · h/ml		
Number of volunteers	8	15
Mean	4970.92	4115.43
Geometric Mean	4693.24	4060.82
Median	5138.37	4055.66
SD	1642.34	686.38
CV, %	33.04	16.68
Min	2558.40	2978.23
Max	7226.83	5348.85
$AUC_{0-\infty}$, ACU · h/ml		
Number of volunteers	8	15
Mean	6821.64	6078.10
Geometric Mean	6420.00	5927.80
Median	6902.60	6162.05
SD	2480.07	1410.08
CV, %	36.36	23.20
Min	3556.20	3964.35
Max	11230.43	8723.66
T_{max}, h		
Number of volunteers	8	15
Mean	1.69	0.63
Geometric Mean	0.55	0.31
Median	0.25	0.25
SD	2.66	1.48
CV, %	157.73	234.42
Min	0.25	0.25
Max	6	6
K_{el}, h^{-1}		
Number of volunteers	8	15
Mean	0.003	0.002
Geometric Mean	0.003	0.002
Median	0.002	0.002
SD	0.001	0.001
CV, %	34.90	20.94
Min	0.002	0.002
Max	0.004	0.003
$T_{1/2}$, h		
Number of volunteers	8	15
Mean	266.89	295.40
Geometric Mean	260.63	291.51
Median	288.67	281.53
SD	59.92	50.53
CV, %	22.45	17.10
Min	188.60	221.19
Max	341.68	391.31

Pharmacokinetic parameter of "COVID-globulin"	Batch P3	Batch P4
V_d, L		
Number of volunteers	8	15
Mean	6.40	4.47
Geometric Mean	5.64	4.42
Median	4.65	4.53
SD	3.61	0.67
CV, %	56.43	14.96
Min	2.78	3.48
Max	12.85	5.54

The averaged pharmacokinetic profiles (linear and semi-logarithmic scales) of SARS-CoV-2-specific IgG antibody concentrations following drug administration are shown in Figure 1.

CONCLUSION

A safety and pharmacokinetic study of COVID-globulin has been carried out with administration of a single intravenous 4 mL/kg drug in healthy volunteers. The drug safety profile was established as favorable. In the analytical phase, the main pharmacokinetic drug parameters and average pharmacokinetic profiles were estimated based on the IgG antibody concentrations after a single COVID-globulin infusion. The results justified the subsequent phases of COVID-globulin clinical trials.

REFERENCE

1. Nikiforov V. V., Suranova T. G., Chernobrovkina T. Yu., Yankovskaya Y. D., Burova S. V. New Coronavirus Infection (Covid-19): Clinical and Epidemiological Aspects. *The Russian Archives of Internal Medicine*. 2020;10(2):87–93. (In Russ.) DOI: 10.20514/2226-6704-2020-10-2-87-93.
2. Baklaushev V. P., Kulemzin S. V., Gorchakov A. A., Ysubalieva G. M., Lesnyak V. N., Sotnikova A. G. COVID-19. Etiology, Pathogenesis, Diagnosis and Treatment. *Journal of Clinical Practice*. 2020;11(1):7–20. (In Russ.) DOI: 10.17816/clinpract26339.
3. Jiang S., Du L., Shi Z. An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies. *Emerging Microbes & Infections*. 2020;9(1):275–277. DOI: 10.1080/22221751.2020.1723441.
4. Corti D., Misasi J., Mulangu S., Stanley D. A., Kanekiyo M., Wollen S., Ploquin A., Doria-Rose N. A., Staupe R. P., Bailey M., Shi W., Choe M., Marcus H., Thompson E. A., Cagigi A., Silacci C., Fernandez-Rodriguez B., Perez L., Sallusto F., Vanzetta F., Agatic G., Cameroni E., Kisalu N., Gordon I., Ledgerwood J. E., Mascola J. R., Graham B. S., Muyembe-Tamfun J. J., Trefry J. C., Lanzavecchia A., Sullivan N. J. Protective monotherapy against lethal Ebola virus infection by a potently neutralizing antibody. *Science*. 2016;351(6279):1339–1342. DOI: 10.1126/science.aad5224.

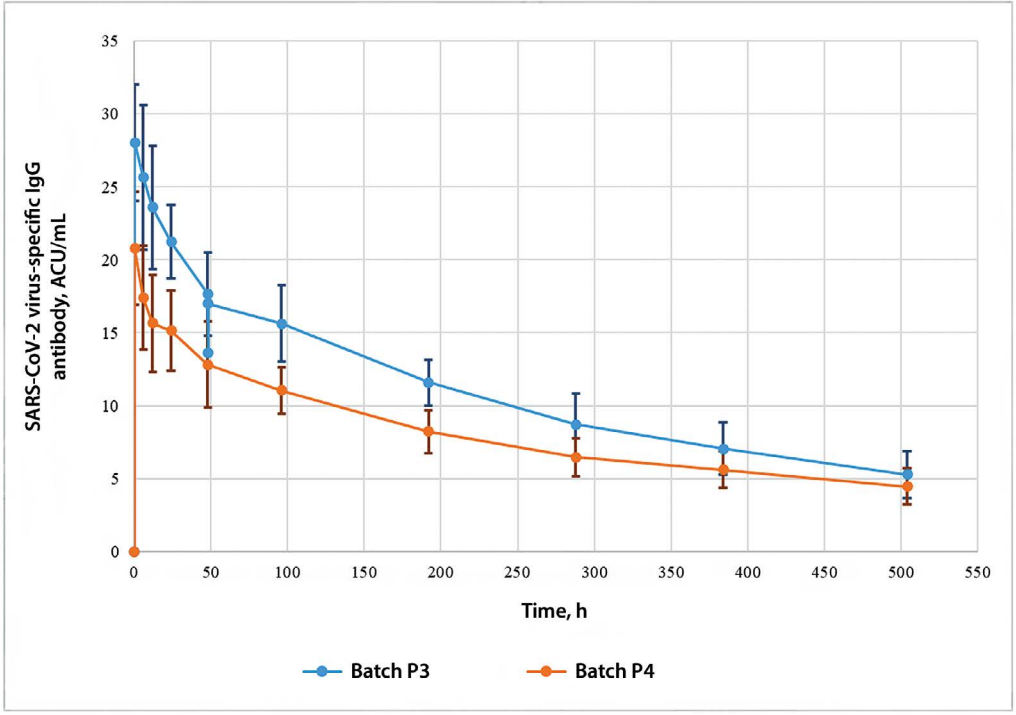

Figure 1. Average pharmacokinetic profiles (in linear scale with standard deviations) of SARS-CoV-2 virus-specific IgG antibody after single dose administration of "COVID-globulin"

5. Sapparapu G., Fernandez E., Kose N., Cao B., Fox J. M., Bombardi R. G., Zhao H., Nelson C. A., Bryan A. I., Barnes T., Davidson E., Mysorekar I. U., Fremont D. H., Doranz B. J., Diamond M. S., Crowe J. E. Neutralizing human antibodies prevent Zika virus replication and fetal disease in mice. *Nature*. 2016;540(7633):443–447. DOI: 10.1038/nature20564.
6. Hastie K. M., Zandonatti M. A., Kleinfelter L. M., Heinrich M. L., Rowland M. M., Chandran K., Branco L. M., Robinson J. E., Garry R. F., Saphire E. O. Structural basis for antibody-mediated neutralization of Lassa virus. *Science*. 2017;356(6341):923–928. DOI: 10.1126/science.aam7260.
7. Shen C., Wang Z., Zhao F., Yang Y., Li J., Yuan J., Wang F., Li D., Yang M., Xing L., Xiao H., Yang Y., Qu J., Qing L., Chen L., Xu Z., Peng L., Li Y., Zheng H., Chen F., Huang K., Jiang Y., Liu D., Zhang Z., Liu Y., Liu L. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *Journal of American Medical Association*. 2020;323(16):1582–1589. DOI: 10.1001/jama.2020.4783.
8. Brown J. F., Dye J. M., Tozay S., Jeh-Mulbah G., Wohl D. A., Fischer W. A., Cunningham C. K., Rowe K., Zacharias P., Hasselt J., Norwood D. A., Thielman N. M., Zak S. E., Hoover D. L. Anti-Ebola Virus Antibody Levels in Convalescent Plasma and Viral Load After Plasma Infusion in Patients With Ebola Virus Disease. *The Journal of Infectious Diseases*. 2018;218(4):555–562. DOI: 10.1093/infdis/jiy199.
9. Ankcorn M., Gallacher J., Ijaz S., Taha Y., Harvala H., Maclennan S., Thomson E. C., Davis C., Singer J. B., Filipe A. S., Smollett K., Niebel M., Semple M. G., Tedder R. S., McPherson S. Convalescent Plasma Therapy for Persistent Hepatitis E Virus Infection. *Journal of Hepatology*. 2019;71(2):434–438. DOI: 10.1016/j.jhep.2019.04.008.
10. Ruggiero H. A., Pérez I. F., Milani H. A., Barri A., Val A., Maglio F., Astarloa L., Gonzalez Cambaceres C., Milani H. L., Tallone J. C. Traitement de la fièvre hémorragique argentine par le plasma de convalescent. 4,433 cas [Treatment of Argentine hemorrhagic fever with convalescent's plasma. 4433 cases]. *Presse Medicale*. 1986;15(45):2239–2242.