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Interim results of the first stage of a multicenter open multi-cohort study of the safety, pharmacokinetics, pharmacodynamics and efficacy of veranafusp alfa in adult patients with mucopolysaccharidosis type II

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This article presents the interim results of the first stage (administration of the drug to patients aged ≥18 years with mucopolysaccharidosis type II) of a multicenter open multi-cohort phase II-III study (IDB-MPS-II-III), **the aim** of which was to assess the safety, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of veranafusp alfa in patients with MPS II.

Material and methods. The interim analysis included data from 3 patients aged 18 years and older who had previously received idursulfase (2/3) and idursulfase beta (1/3). An individual dose increase (1–2–3 mg/kg) was performed after 2 weeks, followed by administration at a dose of 3 mg/kg for up to 52 weeks (a total of 52 weekly infusions). Standard PK parameters were evaluated. The PD criterion was the level of glycosaminoglycans (GAGs) in urine, blood and cerebrospinal fluid (CSF). Efficacy parameters included assessment of the dynamics of GAGs concentration in urine, blood and CSF, range of motion in joints, liver and spleen volume, change in the 6-minute walk test (6MWT, 6-minute test), left ventricular myocardial mass, forced vital capacity of the lungs (FVC). Safety parameters included assessment of the frequency of adverse events (AEs) and adverse reactions (ARs), including allergic and infusion reactions, as well as assessment of the frequency of formation of anti-drug antibodies (ADAs) and their neutralizing activity.

Results. The studied drug demonstrated non-linear PK in the blood and a dose-dependent increase in concentration in the CSF. Patients showed a decrease or stability in the level of GAG in the urine, a decrease in the level of heparan sulfate (HS) in the CSF in 2 (66.6%) of 3 patients, as well as a decrease in the level of dermatan sulfate (DS) in the CSF in the range of 17.19–80.96%. There was an average decrease in liver volume by 42.500 ± 218.496 cm^3, spleen volume by 24.350 ± 9.405 cm^3 and left ventricular myocardial mass by 15.333 ± 43.016 g relative to the baseline level. The average increase in walking distance according to the results of the 6MWT, after 1 year of therapy, was 76.067 ± 83.561 m. The average values of FVC and FEV1 did not change statistically significantly. 9 AEs were registered in 3 patients (100.0%) of mild severity, mainly from the liver and biliary tract, and 3 ARs, which were infusion reactions and were registered mainly in the first 4 months of therapy. During the analyzed period, the frequency of formation of ADAs at screening was in 2 patients, and at week 52 — in 3 patients, which indicates the development of *de novo* ADAs during treatment with veranafusp alfa in 1 patient.

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Conclusion. Weekly intravenous administration of the drug under study to adult patients at a dose of 3 mg/kg for 1 year provided control of the level of GAG in the urine and stabilization and/or improvement of somatic symptoms according to spirometry, echocardiography, 6MWT, range of motion in large joints, liver and spleen size, comparable to the results of the effectiveness of treatment with idursulfase in patients previously receiving enzyme replacement therapy. There was a tendency to decrease the level of HS in the cerebrospinal fluid, which may indicate the ability of veranafusp alfa to penetrate the BBB and deliver idursulfase to brain tissue, preventing the accumulation of pathological substrate in the CNS to prevent neurodegenerative changes.

Keywords: mucopolysaccharidosis type II; Hunter syndrome; glycosaminoglycans; veranafusp alfa; Clotilia; HIR-Fab-IDS; efficacy; safety

Abbreviations: MPS II — type II mucopolysaccharidosis; FK — pharmacokinetics; PD — pharmacodynamics; GAG — glycosaminoglycans; CSF — cerebrospinal fluid; 6MT — 6-minute test; FVC — functional vital capacity of the lungs; AE — adverse events; AR — adverse reactions; SAR — serious adverse reactions; ADA — anti-drug antibodies; HS — heparan sulfate; DS — dermatan sulfate; VFE1 — volume of forced exhalation in the 1st second; BBB — blood-brain barrier; CNS — central nervous system; ERT — enzyme replacement therapy; IEC — independent ethics committee; IDMC — independent data monitoring committee; MRI — magnetic resonance imaging; Echo-CG — echocardiography; SBP — systolic blood pressure; DBP — diastolic blood pressure; HR — heart rate; RR — respiratory rate; CT — clinical trials.

Промежуточные результаты первого этапа многоцентрового открытого мультикогортного исследования безопасности, фармакокинетики, фармакодинамики и эффективности веренафуспа альфа у взрослых пациентов с мукополисахаридозом II типа

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В данной статье представлены промежуточные результаты первого этапа (введение препарата пациентам в возрасте ≥18 лет с мукополисахаридозом II типа) многоцентрового открытого мультикогортного исследования фазы II-III (IDB-MPS-II-III), **целью** которого являлась оценка безопасности, фармакокинетики (ФК), фармакодинамики (ФД) и эффективности веренафуспа альфа у пациентов с МПС II.

Материал и методы. В промежуточный анализ вошли данные 3 пациентов в возрасте от 18 лет, ранее получавших идурсульфазу (2/3) и идурсульфазу бета (1/3). Индивидуальное повышение дозы (1–2–3 мг/кг) выполняли через 2 недели с последующим введением в дозе 3 мг/кг длительностью до 52 недель (всего 52 еженедельные инфузии). Оценивались стандартные параметры ФК. Критерием ФД был уровень гликозаминогликанов (ГАГ) в моче, крови и спинномозговой жидкости (СМЖ). Параметры эффективности включали оценку динамики концентрации ГАГ

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в моче, крови и СМЖ, объема движений в суставах, объема печени и селезенки, изменение теста 6-минутной ходьбы (6МТ), массы миокарда левого желудочка, функциональной жизненной емкости легких (ФЖЕЛ). Параметры безопасности включали оценку частоты нежелательных явлений (НЯ) и нежелательных реакций (НР), включая аллергические и инфузионные реакции, а также оценку частоты образования антилекарственных антител (АЛА) и их нейтрализующей активности.

Результаты. Исследуемый препарат продемонстрировал нелинейную ФК в крови и дозозависимое увеличение концентрации в СМЖ. У пациентов отмечалось снижение или стабильность уровня ГАГ в моче, снижение уровня гепарансульфата (ГС) в СМЖ у 2 (66,6%) из 3 пациентов, а также снижение уровня дерматансульфата (ДС) в СМЖ в диапазоне 17,19–80,96%. Отмечено среднее снижение объема печени на 42,500±218,496 см^3, объема селезенки на 24,350±9,405 см^3 и массы миокарда левого желудочка на 15,333±43,016 г относительно исходного уровня. Средний показатель увеличения дистанции ходьбы по результатам 6МТ после 1 года терапии составил 76,067±83,561 м. Средние показатели ФЖЕЛ и ОФВ1 статистически значимо не изменялись. Были зарегистрированы 9 НЯ у 3 пациентов (100,0%) легкой степени тяжести преимущественно со стороны печени и желчевыводящих путей и 3 НР, которые являлись инфузионными реакциями и регистрировались преимущественно в первые 4 месяца терапии. В анализируемый период образование антилекарственных антител (АЛА) на скрининге отмечалось у 2 пациентов, а на неделе 52 — у 3 пациентов, что свидетельствует о развитии *de novo* АЛА при лечении веренафуспом альфа у 1 пациента.

Заключение. Еженедельное внутривенное введение исследуемого препарата взрослым пациентам в дозе 3 мг/кг в течение 1 года обеспечило контроль уровня ГАГ в моче и стабилизацию и/или улучшение соматических симптомов по показателям спирометрии, эхокардиографии, 6МТ, диапазона движений в крупных суставах, размеров печени и селезенки, сравнимые с результатами эффективности лечения идурсульфазой у пациентов, ранее получавших ферментную заместительную терапию. Наблюдалась тенденция к снижению уровня ГС в спинномозговой жидкости, что может свидетельствовать о способности веренафуспа альфа проникать через ГЭБ и доставлять идурсульфазу в ткани мозга, препятствуя накоплению патологического субстрата в ЦНС для предупреждения нейродегенеративных изменений.

Ключевые слова: мукополисахаридоз II типа; синдром Хантера; гликозаминогликаны; веренафусп альфа; клотилия; HIR-Fab-IDS; эффективность; безопасность

Список сокращений: МПС II — мукополисахаридоз II типа; ФК — фармакокинетика; ФД — фармакодинамика; ГАГ — гликозаминогликаны; СМЖ — спинномозговая жидкость; 6МТ — тест 6-минутной ходьбы; ФЖЕЛ — функциональная жизненная емкость легких; НЯ — нежелательные явления; НР — нежелательные реакции; СНР — серьезные нежелательные реакции; АЛА — антилекарственные антитела; ГС — гепарансульфат; ДС — дерматансульфат; ОФВ1 — объем форсированного выдоха за первую секунду; ГЭБ — гематоэнцефалический барьер; ЦНС — центральная нервная система; ФЗТ — ферментная заместительная терапия; НЭК — независимый этический комитет; НКМД — независимый комитет по мониторингу данных; МРТ — магнитно-резонансная томография; Эхо-КГ — эхокардиография; САД — систолическое артериальное давление; ДАД — диастолическое артериальное давление; ЧСС — частота сердечных сокращений; ЧДД — частота дыхательных движений; КИ — клинические исследования.

INTRODUCTION

Mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome, is a lysosomal storage disease with an X-linked recessive inheritance pattern. In MPS II, mutations in the *IDS* gene reduce the activity of the lysosomal enzyme iduronate-2-sulfatase (I2S, iduronate 2-sulfatase), leading to the accumulation of glycosaminoglycans (GAGs), primarily heparan sulfate (HS) and dermatan sulfate (DS) fractions, in the lysosomes of cells in various tissues. This causes damage to parenchymal organs (hepatosplenomegaly), the musculoskeletal system, and the respiratory and cardiovascular systems. Progressive damage to the central nervous system (CNS) leads to intellectual decline, behavioral abnormalities, seizures, and motor and speech impairments [1]. MPS II is the most common form among all types of mucopolysaccharidoses. The incidence of the disease in the population is estimated at 1:140,000–156,000 newborns [2]. The International Register of Patients with Hunter Syndrome (Hunter Outcome Survey, HOS) includes over 1000 patients [3].

Patients with MPS II require lifelong enzyme replacement therapy (ERT) with recombinant idursulfase (IDS) preparations, which mimic the effect of the endogenous enzyme [4, 5]. In the Russian Federation, the registered drugs Elaprase® and Hunterase® are used [6].

Available ERT IDS drugs do not penetrate the blood-brain barrier (BBB), which limits their ability to influence the course of the neurodegenerative process. Therefore, there is a clinical need for drugs capable to cross the BBB for the treatment of the neuropathic form of MPS II [7–9]. JSC “GENERIUM” is developing the drug veranafusp alfa (Clotilia®, internal code GNR-055), whose active substance is IDS covalently linked to the C-terminal part of the Fab-fragment (Fragment Antigen Binding) of a monoclonal antibody to the human insulin receptor (HIR, Human Insulin Receptor) (Fig. 1). The molecule is created using “Trojan horse” technology, where the Fab fragment acts as a “carrier,” binding with high specificity to its target, the insulin receptor (the half-maximal concentration for interaction with the insulin receptor was EC_{50}=109.7 ± 13.4 pM) [10], on

BBB cells. This initiates the natural process of receptor-mediated transcytosis, which "transports" the entire therapeutic molecule HIR-Fab-IDS across the BBB, allowing the enzyme to reach the brain.

Veranafusp alfa is predicted to have a high degree of distribution and to exert the effect of IDS in the CNS and peripheral organs. Specific binding to mannose-6-phosphate residues on the oligosaccharide chains of membrane mannose-6-phosphate receptors and to the insulin receptor itself, which are present in somatic tissues, is associated with expected improved enzyme internalization and subsequent catabolism of GAGs accumulated in the organs of the main body systems, compared to registered drugs with a similar mechanism of action [8, 9].

The insulin receptor is expressed in virtually all human tissues. For peripheral tissues, it acts as an additional pathway to the mannose-6-phosphate-dependent internalization pathway, increasing the bioavailability of the recombinant enzyme to insulin-sensitive tissues. In the brain, the construct provides the only possible pathway for transcytosis across the capillary endothelium cells of the CNS that form the BBB. The binding site on the receptor is located away from the insulin binding site, thus the antibody does not interfere with insulin transport and binding. Therefore, the hybrid protein fragment of the antibody (Fab portion) with the enzyme should specifically interact with the human insulin receptor while retaining the activity of the unmodified I2S enzyme.

Preclinical studies have shown that IDS, as part of the modified veranafusp alfa molecule, retains the main functional properties of the free recombinant enzyme; its specific enzymatic activity (2.16×10^9 U/mol) was determined to be within the range established for Elaprase® (2.73×10^9 U/mol) and, apparently, slightly exceeded it on an equimolar basis [10], suggesting that the drug can be expected to have at least comparable efficacy in ERT.

Results from Phase I clinical trials (IDB-MPS-I and IDB-MPS-I02) showed good tolerability and a favorable safety profile of veranafusp alfa following single intravenous (IV) administration at doses ranging from 0.3–12 mg/kg in healthy volunteers [11].

THE AIM of the Phase II–III study (IDB-MPS-II-III) is to investigate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of veranafusp alfa in patients of different age groups with MPS II.

MATERIALS AND METHODS

Drug

The active substance of veranafusp alfa (manufactured at a concentration of 5 mg/mL for infusion) is a modified recombinant IDS enzyme within the hybrid protein HIR-FAB-IDS, produced on a Chinese Hamster Ovary (CHO) cell line, which provides IDS with a glycosylation profile similar to the natural profile of the endogenous enzyme (see Fig. 1). The obtained protein is purified using affinity and ion-exchange chromatography, with specific viral and recombinant DNA inactivation and removal processes.

Study Design

A multicenter open multi-cohort study of the safety, PK, PD, and efficacy of veranafusp alfa (JSC "GENERIUM", Russia) in patients with MPS II was conducted at 9 clinical centers in the Russian Federation and 2 centers in the Republic of Kazakhstan (RK). Adult patients were enrolled into cohort 1 at 2 centers: National Medical Research Center of Hematology, and Vernadsky Crimean Federal University.

The Phase II-III study (IDB-MPS-II-III) was initiated after approval by the Ethics Council of the Ministry of Health of Russia (Extract from Minutes No. 273 dated April 20, 2021), the Central Commission for Bioethics of the Ministry of Health of the Republic of Kazakhstan, and obtaining permits from the Ministry of Health of Russia (No. 499 dated September 3, 2021) and the Ministry of Health of the Republic of Kazakhstan. Ethical review was conducted by the Independent Ethics Committees (IECs) of the research centers. An Independent Data Monitoring Committee (IDMC) and a Safety Monitoring Committee were established to assess safety in the study. The study design and protocol complied with the ethical principles of the Declaration of Helsinki of the World Medical Association (1964), as amended (2024), the decision of the Eurasian Economic Commission Council dated November 3, 2016, No. 79 "On Approval of the Good Clinical Practice Rules of the Eurasian Economic Union," the standards of Good Clinical Practice of the International Council for Harmonisation ICH GCP (E6), and the current regulatory requirements of the Russian Federation and the Republic of Kazakhstan.

The study was conducted in three stages with sequential enrollment of patients into age cohorts, considering the assigned dosage. The first stage (cohort 1) included 3 patients aged ≥18 years (Fig. 2).

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After analyzing the data from the first stage and obtaining approval from the IDMC, the second stage (cohorts 2–7) involved the enrollment of 15 patients (at the time of the interim report) aged <18 years (results are being prepared for publication). The presented interim analysis included safety, PK, PD, and efficacy assessment results from the first stage in adult patients with individual dose escalation of 1–2–3 mg/kg, including the screening period (4 weeks) and the treatment period (52 weeks).

Patients

Inclusion Criteria. In the first stage, according to the inclusion criteria, male patients aged ≥18 years who agreed to suspend standard ERT (at a weekly dose of 0.5 mg/kg according to the instructions) 7 days before the first administration of veranafusp alfa were enrolled in the study. Participation in the study was voluntary and included signing an information sheet with an informed consent form.

*Non-inclusion Criteria***.** According to the exclusion criteria, individuals with hypersensitivity to IDS / another component of the drug, with neutralizing antibodies to the standard ERT drug, or with conditions that potentiate the risk of therapeutic intervention were not allowed to participate in the study. Restrictions to participation included contraindications for lumbar puncture and magnetic resonance imaging (MRI), a history of hematopoietic stem cell/bone marrow transplantation, blood/blood component transfusion, or vaccination within 30 days prior to screening. Individuals with positive human immunodeficiency virus test results, active viral hepatitis B and/or C, and a history of poorly controlled seizure disorder were not included in the study.

Exclusion Criteria. In accordance with the exclusion criteria, a patient could discontinue participation in the study if they refused further participation, if there was a condition preventing the execution of protocol procedures or endangering their safety, low adherence to therapy or non-compliance with protocol requirements, development of an adverse reaction (AR) or neutralizing anti-drug antibodies (ADAs) affecting the safety and efficacy of therapy and preventing further participation in the study, loss of contact with the patient, or by the investigator's decision.

Treatment

Dosage and Administration Regimen. Weekly intravenous infusions of the drug were administered at doses of 1–3 mg/kg. Individual dose escalation (1–2–3 mg/kg) was performed every 2 weeks to the next dose level of 2 mg/kg and 3 mg/kg, followed by administration at a dose of 3 mg/kg for up to 52 weeks (a total of 52 weekly infusions). The starting dose of veranafusp alfa in the IDB-MPS-II-III study was selected based on the analysis of dosing regimens in the Phase I study IDB-MPS-I using NOAEL (No Observed Adverse Effect Level) and MABEL (Minimal Anticipated Biological Effect Level) approaches; the dose that produces the minimal expected biological effect, considering information on the efficacy and safety in patients of drugs in this class with similar mechanisms of action [10, 11]. The tenfold maximum administered dose (3 mg/kg) constitutes the NOAEL, while the dose ranges for multiple administration calculated based on preclinical safety data were a maximum of 30 mg/kg for adults (therapeutic index 100)[1,2] [11].

The duration and rate of administration were chosen considering the results of a study of valanafusp alfa, which is similar in formulation and active substance type (IDS with an IgG domain to the insulin receptor) [7]. Veranafusp alfa was administered weekly IV over 3 hours (±10 minutes). The infusion rate was selected based on recommendations for the infusion duration of Elaprase® [6, 12] and the general properties of veranafusp alfa. The course of therapy included 52 infusions.

Study Endpoints

An interim analysis was conducted upon completion of 52 weeks of therapy. The duration of observation and the timing of biological material collection (urine, blood, and CSF) for PK / PD parameter assessment were chosen based on the results of previous studies of veranafusp alfa, published data on Elaprase® [6, 12], and available development data for similar drugs capable of crossing the BBB: valanafusp alfa, a complex molecule of antibody to the insulin receptor and IDS (AGT-181), and pabinaufusp alfa, a complex molecule of antibody to the transferrin receptor and IDS (JR-141, IZCARGO®) [7–9].

[1] European Medicines Agency. Guideline on strategies to identify and mitigate risks for first-in human and early clinical trials with investigational medicinal products», 2018. Available from: https:// www.ema.europa.eu/en/documents/ scientific-guideline/guideline-strategies-identify-and-mitigate-risks-first-human-and-early-clinical-trials-investigational-medicinal-products-revision-1_en.pdf

[2] FDA Guidance for Industry. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 2005. Available from: https:// www.fda.gov/ media/72309/download

PK parameters included C_{max} and C_{min} (maximum and minimum concentrations), AUC_{0-t} and $AUC_{0-\infty}$ (area under the concentration-time curve from time zero to the last measurement time or infinity), $T_{1/2}$ (half-life), and CL (total clearance). Blood samples were collected before infusion, at 3 hours/end of infusion, and at 30 min, 60 min, 90 min, 2 h, 4 h, 6 h, and 24 h after its completion. CSF samples for drug concentration measurement in cerebrospinal fluid were collected before the first drug administration (Day 1) and 2 hours after the end of infusion (Weeks 10 and 52). Concentrations of the investigational drug in serum and CSF were determined by a validated enzyme-linked immunosorbent assay (ELISA) method in accordance with GLP requirements.

PD parameters included analysis of GAG excretion dynamics in urine, as well as their concentration in serum and CSF after multiple administrations of veranafusp alfa compared to baseline. Measurements were performed using ELISA kits "Human HS (Heparan Sulfate) ELISA Kit," cat. No. E-EL-H2364, and "Human DS (Dermatan Sulfate) ELISA Kit," cat. No. E-EL-H1725 (Elabscience®, USA). Samples were collected at screening before the last infusion of IDS as part of standard ERT and during the treatment period on Day 1 (W1), W4, W8, W10, W14, W26, W30, W34, W40, W45, and W52. A general urine analysis was performed at screening and during treatment on Day 1 (W1), W10, W17, W34, W42, and W52. Urinary GAG levels were calculated considering creatinine levels. Determination of GAG (HS and DS) levels in blood was performed at screening before the last infusion of IDS as part of standard ERT and during treatment on Day 1 (W1), W4, W8, W10, W14, W26, W30, W34, W40, W45, and W52. Determination of GAG (HS and DS) levels in CSF was performed during treatment before the first administration of GNR-055 on Day 1 (W1) and 2 hours after the end of infusion at weeks W10 and W52.

Efficacy parameters included the dynamics of changes in the range of motion in large joints, liver and spleen volume by MRI, results of the 6MWT, changes in left ventricular myocardial mass by echocardiography (Echo-CG), forced expiratory volume in the first second (FEV1), and forced vital capacity (FVC) by spirometry. The dynamics of GAG (HS and DS) excretion in urine and their levels in serum (Week 4, Week 8, Week 10, Week 26, and Week 52) and in CSF (Week 10 and Week 52 (W52)) were assessed compared to baseline. The dynamics of changes in the range of motion in large joints, liver and spleen volume by MRI, 6MWT results, left ventricular myocardial mass by Echo-CG, and changes in FVC by spirometry were assessed at 10, 26, and 52 weeks of the study compared to baseline.

A complete physical examination was performed at screening and during treatment on Day 1 (W1), Day 2 (W1), W2, W4, W7, W10, W16, W21, W26, W30, W35, W39, W43, W47, and W52.

Assessment of vital signs included body temperature measurement (axillary temperature), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and respiratory rate (RR), and was performed at screening and during treatment before/after each veranafusp alfa infusion, as well as in case of an infusion reaction at the investigator's discretion and at each new dose level (2 mg/kg and 3 mg/kg) during infusion and 1, 4, 6, and 24 hours after its completion — W4 and W7.

Electrocardiography (ECG) was performed in 12 standard leads at screening and during treatment: W10, W16, W26, W40, and W52. Echo-CG, spirometry, goniometry, 6MWT, and abdominal MRI to monitor liver and spleen sizes were performed at screening and during treatment: W10, W26, and W52.

Complete blood count and biochemical blood tests were performed on Day 1 (W1), W10, W17, W34, W42, and W52.

Safety and immunogenicity parameters included assessment of the frequency and severity of adverse events (AEs), including serious adverse events (SAEs), related to the use of the investigational drug. Qualitative and quantitative analysis of adverse reactions (ARs), serious adverse reactions (SARs), the incidence of allergic and infusion reactions, and the frequency of anti-drug antibody (ADA) formation and their neutralizing activity were assessed. Infusion AEs were recorded and analyzed separately. Determination of ADAs and their neutralizing activity against veranafusp alfa was performed on Day 1 (W1), W4, W10, W26, W40, and W52 using a validated enzyme-linked immunosorbent assay.

Statistical Analysis

The populations for PK and PD parameter assessment consisted of patients for whom sufficient data were obtained to assess at least one parameter. The Safety Analysis Set (SAF) included patients who received at least one dose of the drug. The primary group for describing baseline characteristics and analyzing efficacy parameters was the Full Analysis Set

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(FAS) population. Patients who completed the study without significant protocol deviations were included in the Per-Protocol (PP) Analysis Set.

Given the orphan nature of the disease, it was planned to enroll up to 4 patients in cohort 1 of the first stage of the study. The size of cohort 1 was determined considering the studied dose levels of the investigational drug, the possibility of IDMC review for a decision on proceeding to the second stage of the study, and the availability of patients with MPS II for participation in the study, the total number of whom in the Russian Federation is 140 [13]. Hypothesis testing was not planned. Therefore, the analysis was descriptive. For quantitative indicators, the following were calculated: number of observations (N), minimum and maximum values (Min, Max), arithmetic mean (M), standard deviation (SD), 95% confidence interval for the mean, median (Me), and interquartile range (IQR). For pharmacokinetic parameters, the geometric mean (gMean) and coefficient of variation (CV%) were additionally calculated. For qualitative indicators, absolute values and proportions (%) were determined. To assess the dynamics of quantitative indicators between visits, the t-test (Student's t-test) for dependent samples or the Wilcoxon test was used. The dynamics of qualitative indicators between visits were analyzed using McNemar's test or Cochran's test.

Stata 14 and PkSolver or R version 4.4.2 programs were used for data analysis.

RESULTS

Patients Characteristics

As part of the interim analysis, data from 3 adult male patients of Caucasian ethnicity with a confirmed diagnosis of MPS II (Hunter syndrome), non-neuropathic form, confirmed by molecular genetic analysis and I2S enzyme activity levels, were assessed.

The mean age of the patients was 32.67 ± 13.32 years (range 18.0 to 44 years), mean body weight was 62.93 ± 11.29 kg, and mean height was 158.33 ± 8.96 cm. No deviations from reference values were found in thyroid function parameters. All patients received standard ERT weekly prior to study enrollment in the form of intravenous infusion of IDS — 1 patient, and IDS beta—2 patients.

Analysis of Veranafusp Alfa Pharmacokinetic Parameters

Representative curves of mean veranafusp alfa concentrations in serum after administration of escalating doses of 1 mg/kg, 2 mg/kg, and 3 mg/kg at different weeks of the study are shown in Figure 3.

After multiple IV administrations over 52 weeks, the mean C_{max} was reached at the end of drug administration at the 3-hour mark ± 10 minutes / end of infusion ± 5 minutes, followed by a decrease to the 24-hour mark ± 20 minutes after the end of administration (Table 1, Fig. 3). After multiple administrations of the drug at a dose of 3 mg/kg, the mean veranafusp alfa concentrations at Weeks 26 and 52 increased, reaching 15085.63 ± 4432.99 ng/mL (W52).

During Stage 1, the concentration of veranafusp alfa in CSF increased with increasing dose, and in one of the three patients, after administration at a dose of 3 mg/kg at Week 10, it reached 272.57 pg/mL.

Analysis of Veranafusp Alfa Pharmacodynamic Parameters

Changes in Urinary GAG Levels. Analysis of GAG levels indicates stabilization/reduction of this parameter during veranafusp alfa treatment (without achieving statistically significant differences in mean values). The primary analysis of urinary GAG was based on HS concentration per creatinine in urine (Table 2).

After 1 year of therapy with the investigational drug, the mean urinary HS level showed a tendency to decrease, while the mean DS level remained stable. At Week 52, a decrease in urinary HS level was observed in 2 (66.6 %) out of 3 patients, amounting to 47.59 % in one patient and 61.77 % in the second patient relative to baseline; a decrease in DS level was noted in 2 (66.6%) out of 3 patients, amounting to 15.11 % in one patient and 30.11 % in the second patient relative to baseline.

Changes in Serum GAG Levels. The primary analysis of serum GAG was based on HS and DS concentrations. Changes in HS and DS levels did not reach the threshold of statistical significance. A decrease in serum HS level at Week 52 relative to baseline was observed in 1 (33.3 %) out of 3 patients, amounting to 37.04 % relative to baseline; a decrease in DS level was noted in 2 (66.6 %) out of 3 patients, amounting to 50.5 % in one patient and 69.6 % in the second patient relative to baseline.

Changes in Cerebrospinal Fluid Glycosaminoglycan Levels. The primary analysis of CSF GAG was based on DS and HS concentrations (Figs. 4 and 5).

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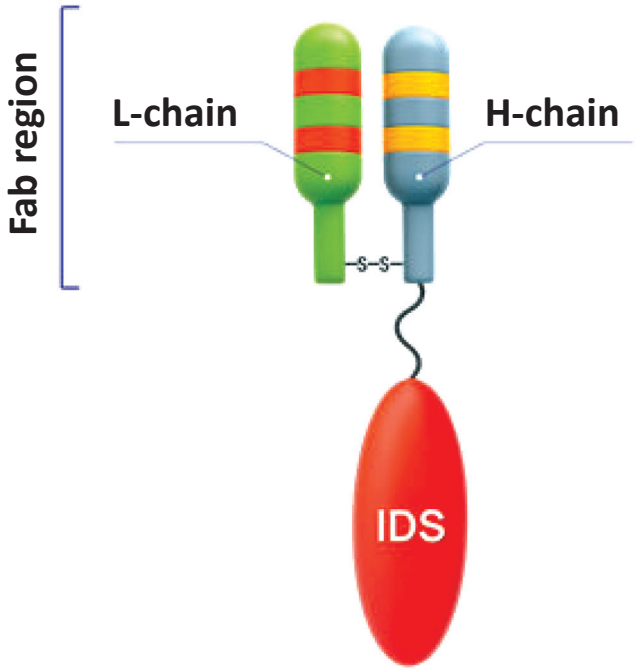

Figure 1 — Structure of the hybrid protein HIR-Fab-IDS (verenafusp alfa).

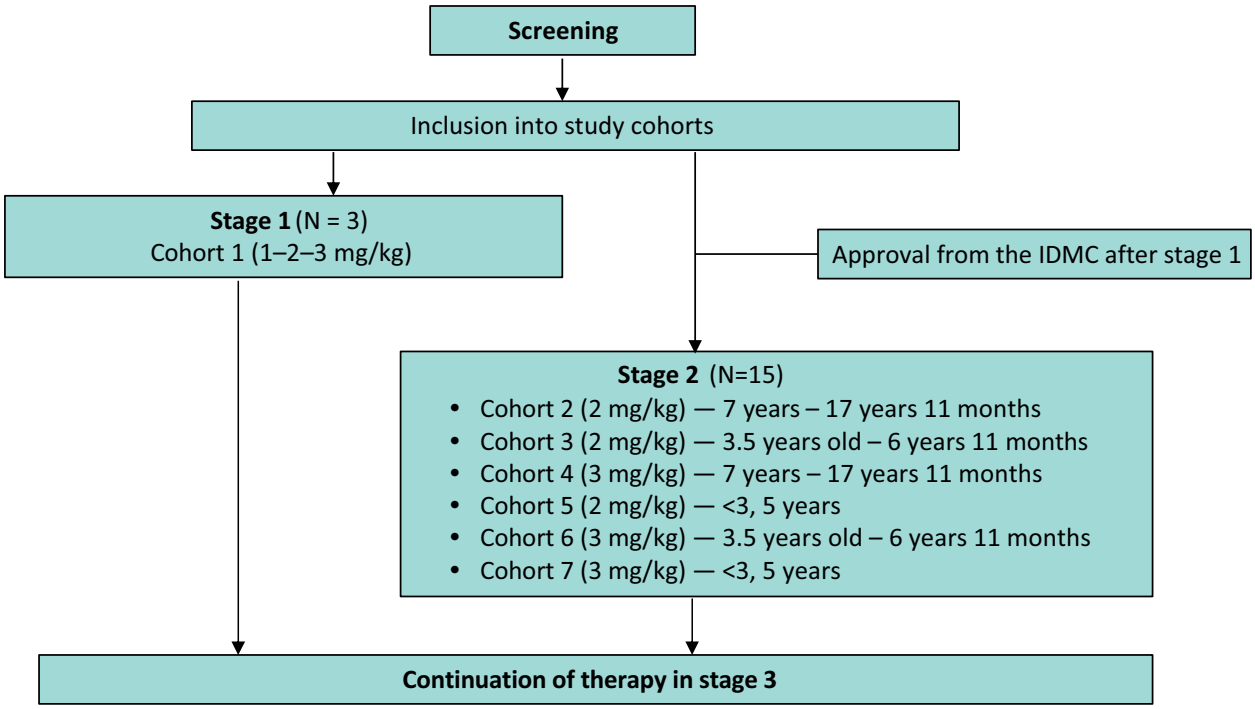

Figure 2 — Study design.
Note: IDMC, An Independent Data Monitoring Committee.

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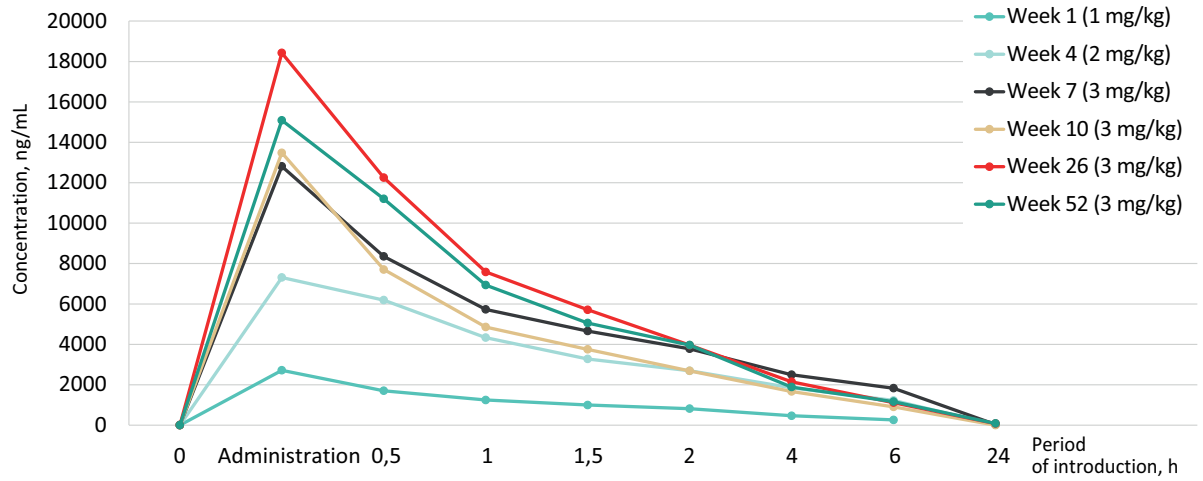

Figure 3 — Veranafusp alfa concentration in serum of adult patients with MPS II 0-24 hours after infusion at escalating doses of 1, 2, or 3 mg/kg.

Note: Week 1 — 1 mg/kg; Week 4 — 2 mg/kg; Weeks 7, 10, 26, and 52 — 3 mg/kg.

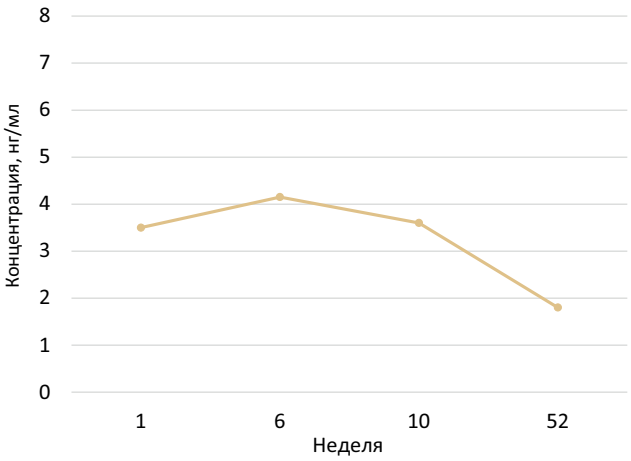

Figure 4 — Dynamics of changes in dermatan sulfate level in cerebrospinal fluid (median) of adult patients with MPS II receiving 3 mg/kg veranafusp alfa.

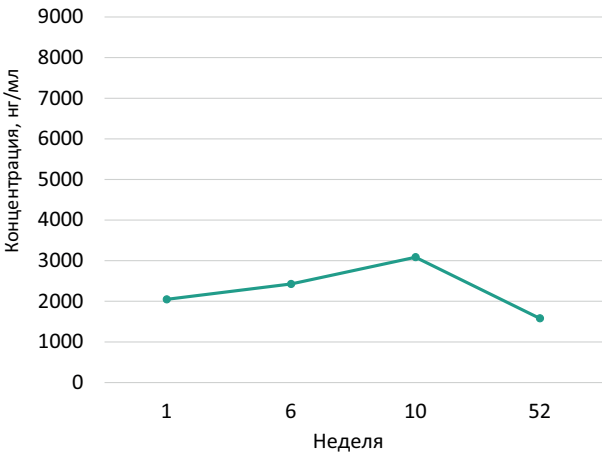

Figure 5 — Dynamics of changes in heparan sulfate level in cerebrospinal fluid (median) of adult patients with MPS II receiving 3 mg/kg veranafusp alfa.

Table 1 — Pharmacokinetic Parameters in Serum of Adult Patients with Mucopolysaccharidosis Type II Receiving 3 mg/kg Veranafusp Alfa

Weeks	Pharmacokinetic Parameters (Me [Q1; Q3])				
	AUC_{0-t}, h×ng/mL	C_{max}, ng/mL	$AUC_{0-\infty}$, h×ng/mL	$T_{1/2}$, h	CL, mL/h
W 10	19 333.97 [15 196.57; 22 558.86]	11 762.17 [10 529.78; 15 568.50]	24 163.24 [18 251.11; 26 818.71]	2.22 [2.20; 2.56]	124.16 [112.97; 183.64]
W 26	24 189.42 [22 632.87; 36 005.87]	19 563.13 [17 489.35; 19 925.37]	24 940.8 [23 343.37; 36 575.70]	1.31 [1.29; 2.44]	120.29 [91.26; 129.12]
W 52	39 131.58 [24 921.26; 41 636.72]	15990.94 [13130.40; 17493.51]	39293.12 [25006.57; 42202.66]	3.25 [1.92; 3.97]	76.35 [71.43; 178.10]

Note: C_{max} — maximum concentration; C_{min} — minimum concentration; AUC_{0-t} — area under the concentration-time curve from time zero to the last measurement time; $AUC_{0-\infty}$ — area under the concentration-time curve from time zero to infinity; $T_{1/2}$ — half-life; CL — total clearance.

Table 2 — Dynamics of Changes in Glycosaminoglycan Levels Relative to Baseline in Adult Patients with Mucopolysaccharidosis Type II Receiving 3 mg/kg Veranafusp Alfa

GAG	Visit	Urinary GAG Level, mg/mmol creatinine		Serum GAG Level, ng/mL		CSF GAG Level, ng/mL	
		Mean±SD	Δ*	Mean±SD	Δ*	Me	Q1; Q3
HS	Screening	0.00815 ± 0.00782	-0.00300 ± 0.00466	695.554 ± 100.089	2.669 ± 256.752	2090.41	1588.5; 2570.8
	Week 52	0.00515 ± 0.00395		698.223 ± 180.357		1579.53	1574.88; 3012.88
DS	Screening	0.00677 ± 0.00659	0.00101 ± 0.00306	4.866 ± 1.800	-0.360 ± 4.504	3.5	3.1; 4.95
	Week 52	0.00778 ± 0.00957		4.506 ± 5.004		1.8	1.15; 4.39

Note: * Δ — change from baseline; GAG — glycosaminoglycans; HS — heparan sulfate; DS — dermatan sulfate; CSF — cerebrospinal fluid.

Table 3 — Change in Range of Motion in Large Joints at Week 52 Compared to Baseline Values in Adult Patients with Mucopolysaccharidosis Type II Receiving 3 mg/kg Veranafusp Alfa

Joint Function	Left Joint (Mean ± SD)	Right Joint (Mean ± SD)
Shoulder Joints		
Flexion	0.000 ± 0.000°	1.000 ± 3.606°
Extension	10.000 ± 17.321°	11.667 ± 12.583°
Abduction	6.667 ± 11.547°	(-)1.667 ± 7.63°
Hip Joints		
Flexion	1.667 ± 2.887°	(-)1.667 ± 7.638°
Extension	1.667 ± 2.887°	0.000 ± 5.000°
Abduction	(-)1.667 ± 2.887°	(-)1.000 ± 3.606°
Elbow Joints		
Flexion	3.333 ± 5.774°	3.333 ± 5.774°
Extension	(-)8.333 ± 7.638°	(-)5.000 ± 5.000°
Knee Joints		
Flexion	3.333 ± 5.774°	3.333 ± 5.774°
Extension	0.000 ± 0.000°	0.000 ± 0.000°

Analysis of GAG levels showed a tendency towards a decrease in HS and DS levels in CSF after dose escalation to 3 mg/kg at week 6, after 1 year of therapy with the investigational drug. At Week 52, a decrease in DS level was noted in 2 (66.6 %) out of 3 patients in the range of 17.19–80.9 6% (Fig. 4).

A decrease in CSF HS level was observed in 2 (66.6 %) out of 3 patients, amounting to 23.30 % in one patient and 48.95% in the second patient relative to baseline (Week 1), starting from week 10 after reaching the 3 mg/kg dose. The HS concentration in these patients by the end of the treatment period (Week 52) was comparable to data from subjects without MPS II, in whom the median HS concentration was 1290.9 ng/mL (Fig. 5).

The dynamics of range of motion in large joints were characterized by stabilization and/or improvement of motor function. Maintenance of a stable state or a tendency towards increased range of motion in large joints after 52 weeks of therapy with the investigational drug was observed in goniometry measurements for the shoulder, hip, elbow, and knee

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joints. A non-significant tendency for a decrease in range of motion after 52 weeks of therapy was recorded for abduction of the right shoulder, flexion of the right hip, and abduction of the left and right hips, and extension of the left elbow (Table 3).

The dynamics of somatic manifestations of MPS II were characterized by a tendency towards an increase in walking distance based on 6MWT results of 76.067 ± 83.561 m (p = 0.25) in the studied cohort of patients at week 52.

After 52 weeks of therapy with the investigational drug, tendencies towards a decrease in liver volume by 42.500 ± 218.496 cm^3, spleen volume by 24.350 ± 9.405 cm^3, and left ventricular myocardial mass by 15.333 ± 43.016 g (~9%; p = 1.0) relative to baseline were noted. Mean FVC and FEV1 values did not change significantly and were 2.63 L and 1.5 L at week 52, respectively.

Analysis of Veranafusp Alfa Safety Parameters

General Characteristics of Safety Parameters. A total of 9 AE episodes were recorded in 100% of patients. AEs were recorded in the system organ classes of infections and infestations (100 %), hepatic and biliary disorders (66.7 %), cardiac disorders (33.3 %), and gastrointestinal disorders (33.3 %); all AEs in all patients were of grade 1 (mild) severity.

No hypoglycemic events were observed during the 52-week treatment period with weekly intravenous administration of the investigational drug GNR-055. 77.8 % of recorded AEs resolved with recovery, and for most of them (66.7 %), no drug therapy was required.

Adverse Reactions. AR episodes occurred in 1 (33.3 %) patient. All three recorded ARs were infusion reactions and were characterized by the occurrence of 1 (33.3 %) episode of paroxysmal tachycardia and 2 (66.7 %) episodes of nausea. All infusion reactions recorded during the analyzed period (100.0 %) resolved completely without the use of drug therapy. These infusion reactions were observed within the first 2 months of therapy with the investigational drug and did not require changes in its administration regimen.

Immunogenicity Analysis. ADAs to IDS were detected in 2 patients at screening before the administration of the investigational drug, and in 3 patients at week 52, indicating the de novo development of ADAs during veranafusp alfa therapy in 1 patient.

The safety profile of veranafusp alfa was consistent with that described for hybrid proteins based on IDS, primarily including manageable AEs of mild to moderate severity, among which only three ARs were observed in the form of transient infusion reactions.

DISCUSSION

The assimilation of scientific knowledge in the field of cellular and molecular mechanisms of MPS II formation and modern biotechnological advancements has led to the development of recombinant analogs of the I2S enzyme. The introduction of IDS into clinical practice has significantly improved the prognosis for patients with MPS II [12]; however, a significant limitation of current ERT is its inability to cross the BBB and influence the course of the neurodegenerative process that develops in most patients. Currently, drugs for the treatment of the neuropathic form of MPS II are being developed that operate on the “Trojan horse” principle, using endogenous receptors on BBB cells to deliver the enzyme to the brain (in Japan, IZCARGO®, based on idursulfase and the transferrin receptor, was registered in 2021) [14]. The investigational veranafusp alfa (Clotilia®, JSC “GENERIUM”) is a medicinal product containing the enzyme IDS covalently linked to the Fab fragment of an antibody to the insulin receptor, for the delivery of ERT to CNS tissues. Similar to the active substance of Elaprase®, membrane mannose-6-phosphate receptors are used for enzyme internalization into tissues, with expected improved distribution of veranafusp alfa due to the favorable distribution profile of the endogenous insulin receptor in the tissues of major organs.

Preclinical studies have demonstrated the efficacy of veranafusp alfa in an animal model of MPS II. The drug successfully crossed the BBB of primates (0.56–1.09 ng equivalent ng substance/g tissue in various brain regions); radiolabeled IDS was not detected in most brain regions [10].

According to the presented interim results of the IDB-MPS-II-III study, the pharmacokinetic profile of veranafusp alfa after multiple administrations in adult patients with MPS II corresponds to the distribution characteristics of hybrid monoclonal antibody-enzyme proteins [7–9].

The results obtained from the analysis of the first stage of the IDB-MPS-II-III study after 1 year of veranafusp alfa therapy were comparable to data obtained from long-term use of IDS regarding GAG

levels in urine and serum in patients with MPS II who had previously received standard enzyme replacement therapy [15, 16].

When analyzing the PD of IDS biosimilars, several authoritative sources rely on the reduction of urinary GAG levels in MPS II patients after one year of therapy [17–19]. However, not all patients show a decrease in urinary GAG levels during the first year of IDS treatment. It has been shown that fluctuations in the average change of this indicator from ~40 % to 60 % are possible during the first year of ERT [20]. Moreover, exceeding the upper limit of normal for this indicator has been described in 31 (32.9 %) out of 94 patients after 3 years of IDS treatment [16, 21], with urinary GAG levels decreasing from 362.0 µg/mg creatinine at baseline to 81.7 µg/mg. A decrease in ERT efficacy in terms of urinary GAG may be associated with the development of antibodies to the drug, while the impact of ADAs on clinical efficacy and safety indicators remains unproven [17, 22–24]. The effect of previously administered ERT in some study participants may also have influenced the magnitude of GAG dynamics. The demonstrated stabilization of urinary GAG excretion during veranafusp alfa use in the IDB-MPS-II-III study is consistent with literature data. Differences in results across cited studies are most likely due to the wide variability of population characteristics in statistically small patient samples.

In our study, one patient showed a decrease in serum HS level at Week 52, amounting to 37.04 % from baseline; a decrease in DS level in two patients was 50.5 % and 69.6 % relative to baseline.

Analysis of CSF GAG levels showed that after 1 year of therapy with the investigational drug, a decrease in HS and DS levels was observed in 2 (66.6 %) patients. At Week 52, the decrease in CSF HS level was 23.30 % in one patient and 48.95% in the second patient relative to baseline (Week 1); a decrease in DS level was noted in 2 (66.6 %) out of 3 patients in the range of 17.19–80.96 %.

It is hypothesized that the accumulation of GAGs, primarily the HS fraction, in the brain parenchyma leads to the development of neurocognitive impairments in MPS II [25]. It has been established that CSF of patients with MPS II contains a higher concentration of HS [16, 25, 26]. In the study by C.J. Hendriksz et al., it was shown that in healthy volunteers, depending on age, the average GAG level in CSF is below ~200 ng/mL and ranges from 50–70 ng/mL. In contrast, in patients with MPS II, the concentration of GAG in CSF is elevated, averaging ≥ 350.0 ng/mL in the absence of cognitive impairment, and ≥850.0 ng/mL in children with the neuropathic form of the disease and cognitive disorders [25]. In another study, the concentration of HS in CSF ranged from 0.8 to 1.7 µmol/L in patients with MPS II without cognitive impairment and from 2.3 to 4.3 µmol/L in patients with MPS II and cognitive impairment [26]. Therefore, monitoring HS levels in CSF provides information about the degree of nervous system involvement in patients with MPS II and can serve as an objective parameter for assessing treatment efficacy [27].

Analysis of CSF GAG levels demonstrated a decrease in HS at Week 52 in most patients from the first stage of the IDB-MPS-II-III study. While the dynamics of mean HS values in CSF were not statistically significant, likely due to the small sample size and the presence of the non-neuropathic form of the disease, the median HS level at Week 52 was comparable to data from patients of similar age without MPS II.

Analysis of the results of the IDB-MPS-II-III study confirms the ability of veranafusp alfa to cross the BBB. The observed tendency towards a decrease in CSF GAGs indicates the drug's ability to deliver IDS to brain tissues and suppress the accumulation of pathological substrate in the CNS. Thus, the decrease in CSF GAGs observed in our study may reflect the catabolic activity of veranafusp alfa.

Another registered ERT drug capable of delivering IDS as part of a hybrid protein to the CNS (IZCARGO®, JCR Pharmaceuticals) uses the transferrin receptor as a target on the surface of BBB cells. The minimal presence of the receptor in muscle tissue cells of peripheral organs may have been the reason for the observed limited therapeutic effect of this drug on the musculoskeletal system and cardiac function in MPS II patients [8]. The presented interim results of the veranafusp alfa study, which uses the insulin receptor, widely distributed in the CNS and peripheral tissues, as a target, may indicate the high efficacy of the drug, including when compared to published results of clinical studies of standard ERT drugs [28–30]. For example, according to the HOS analysis (n = 94), a year-long course of IDS therapy provides stabilization of most somatic manifestations of MPS II [16, 30]. It has been shown that the distance covered in the 6MWT increases by 10.9 % with IDS at a dose of 0.5 mg/kg

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and by 27.9% with IDS at a dose of 1.5 mg/kg over a year [20]. In our study, weekly IV administration of veranafusp alfa to adult patients was associated with a tendency to increase the distance covered in the 6MWT by ~15% (p = 0.250). The increase in patient mobility is consistent with the registered expansion (and/or stabilization) of the range of motion in large joints after a year of veranafusp alfa therapy.

According to spirometry and Echo-CG parameters, the veranafusp alfa therapy course provided control over respiratory and cardiovascular system functions. Literature data indicate that after one year of treatment with recombinant idursulfase-based drugs, respiratory and cardiovascular system functional parameters stabilize or show a tendency towards improvement [18, 20, 21].

The effect of IDS on liver and spleen size described in the literature involves a reduction in these parameters in adult patients by an average of one-third or stabilization of organ volume in the absence of hepatomegaly at the start of therapy [16, 18, 30]. In the IDB-MPS-II-III study, a tendency towards a decrease in organ size was recorded in the adult population, which, however, did not reach statistical significance, most likely due to the small sample size. It should be noted that there was no organomegaly at the initial stage of the IDB-MPS-II-III study, as previously treated patients were included.

Thus, with weekly IV administration of veranafusp alfa for one year in adult patients, control of GAG levels in urine and blood was maintained, and a tendency towards a decrease in HS and DS concentration in CSF was observed, which may indicate veranafusp alfa's ability to penetrate the CNS and exert a therapeutic effect on the symptoms of neurological manifestations of the disease.

The safety profile of veranafusp alfa in the IDB-MPS-II-III study was consistent with that described for recombinant idursulfase-based drugs [16, 31, 32]. The AEs/ARs recorded in the study were of mild or moderate severity, had a predictable spectrum, and were easily managed. In the IDB-MPS-II-III study, the incidence of infusion reactions in adult patients was 33.3 %, comparable to HOS estimates (31.7 %) [32].

Veranafusp alfa treatment for one year was associated with the *de novo* appearance of ADAs to idursulfase in 1 (33.3 %) patient, which is comparable to data from other researchers. Furthermore, ADAs were detected in 2 (66.7 %) other patients at screening, likely against previous ERT drugs. For instance, in the pivotal Phase II/III clinical trial evaluating IDS over 53 weeks of therapy, ADAs to the drug developed in ~50 % of patients [21]. Analysis of data from 15 clinical trials within a systematic review established the incidence of neutralizing ADAs in the range of 15.9–53.6 % [22]. Researchers believe that ADA production is not age- or duration-dependent but is likely a marker of genotype. The presence of antibodies is not considered a factor determining clinical outcomes [22]. The identified ADAs did not affect the efficacy of the ongoing therapy.

Thus, during the analyzed period of the study, veranafusp alfa demonstrated a favorable safety profile.

Study Limitations

The heterogeneity of baseline participant characteristics and the small sample size due to the orphan nature of the disease significantly increase the probability of underestimating the real clinical effect during statistical interpretation of the results. The results of the IDB-MPS-II-III study are limited to a 52-week timeframe. Continuation of this clinical study, as well as conducting additional clinical and observational studies with a larger number of patients and extended observation periods, will enhance the representativeness of the results of veranafusp alfa use in patients with MPS II.

CONCLUSION

The presented interim analysis results of veranafusp alfa (Clotilia®, JSC "GENERIUM", Russia) in adults with MPS II during the first stage of the Phase II–III clinical study demonstrated characteristic PK parameters and the ability to provide pharmacodynamic control of GAG metabolism, including in the CNS. The study confirmed veranafusp alfa's ability to cross the BBB and reduce GAG accumulation in the CNS, which is important for preventing neurodegeneration. During the analyzed period, veranafusp alfa demonstrated stabilization and/or improvement of somatic symptoms based on spirometry, echocardiography, 6MWT, range of motion in large joints, and liver and spleen sizes, with efficacy comparable to the results of treatment in patients previously receiving idursulfase ERT. A favorable safety profile of veranafusp alfa was established.

Continuation of this study and new studies including a larger number of patients will provide additional information on the efficacy and safety of veranafusp alfa in different age groups of patients with MPS II.

FUNDING

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Elena A. Lukina, Rodion V. Ponomarev, Svetlana V. Trishina, Elena S. Gabitova — investigation, data processing and interpretation of results; Nato D. Vashakmadze, George A. Karkashadze, L.S. Namazova-Baranova — investigation, data analysis, selection of literary sources, writing the text of the article. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made significant contributions to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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