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Physiology, pharmacology and prospects for dipeptidilpeptidase-4 inhibitors use

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Modern requirements for the treatment of type 2 diabetes mellitus (DM2) include not only achieving a glycemic control, but also reducing the risk of developing cardiovascular complications. Dipeptidyl peptidase 4 (DPP-4) inhibitors are inferior in the effectiveness to some other actively developing groups of hypoglycemic drugs (SGLT2 inhibitors and GLP-1 receptor agonists); however, they seem relevant at the present time.

The aim of the study is to analyze the literature data on the therapeutic potential and results of the of DPP-4 inhibitors research.

Materials and methods. When searching for the review article materials, the abstracting databases of PubMed, Google Scholar and e-Library were used. The search was carried out on the publications for the period from 2006 to 2022, using the following keywords: DPP-4 inhibitors; glucagonlike peptide-1 (GLP-1); glucose-dependent insulinotropic peptide (GIP); sitagliptin, and other drugs.

Results. DPP-4 belongs to the serine proteases family and is involved in the degradation of various chemokines and peptide hormones, including incretins secreted by intestinal L- and K-cells – GLP-1 and GIP. They regulate a postprandial insulin secretion and a β-cell function, modulate a fasting and postprandial glucagon secretion, regulate the eating behavior and have many pleiotropic (immunomodulatory, anti-inflammatory, antifibrotic, etc.) effects. DPP-4 inhibitors reduce an enzyme activity by 70–90%, increasing plasma incretin levels by 2–4 times and have been used to treat DM2 since 2006. Now there are 13 DPP-4 inhibitors on the market in different countries, differing primarily in pharmacokinetic parameters. They are actively used in the combination therapy for type 2 diabetes, increasing the glycemic control effectiveness without increasing the risk of hypoglycemia. The evidence is emerging about the therapeutic potential of DPP-4 inhibitors in COVID-19.

Conclusion. A peroral form, an ability to create effective combinations with other hypoglycemic drugs without increasing the risk of hypoglycemia, the pleiotropic effects of DPP-4 inhibitors, make this group relevant at the present time.

Keywords: diabetes mellitus; dipeptidyl peptidase 4; glucagonlike peptide-1; glucose-dependent insulinotropic peptide; sitagliptin; COVID-19

Abbreviations: FAP-α – fibroblast activator protein-α; FDA – Federal Food and Drug Administration of the USA; bFGF2 – basic fibroblast growth factor; GRP – gastrin-releasing peptide; MCP-1 – monocytic chemotactic protein-1; MDC – macrophage-derived chemokine; MIP-1α – macrophage inflammatory protein 1α; NHE3 – subtype 3 sodium-hydrogen exchanger; NHE3 NPY – neuropeptide Y; PAI-1 – type 1 plasminogen activation inhibitor; PYY – peptide YY; SDF-1a – Stromal Derived Factor-1α; TGFβ – transforming growth factor beta; ATE2 – angiotensine transforming enzyme 2; AD – Alzheimer's disease; GIP – glucose-dependent insulinotropic peptide; GM-CSF – granulocyte-macrophage colony-stimulating factor; GLP-1 – glu1cagonlike peptide-1; BBB – blood-brain barrier; DPP-4 – dipeptidyl peptidase 4; iDPP-4 – dipeptidyl peptidase-4 inhibitor; CTs – clinical trials; NAFLD – non-alcoholic fatty liver disease; ACS – acute coronary syndrome; DM – Diabetes mellitus; GFR – glomerular filtration rate; COPD – chronic obstructive pulmonary disease; CRF – chronic renal failure.

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Физиология, фармакология и перспективы применения ингибиторов дипептидилпептидазы-4

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Современные требования к терапии сахарного диабета 2 типа (СД 2) включают не только достижение гликемического контроля, но и снижение риска развития сердечно-сосудистых осложнений. Ингибиторы дипептидилпептидазы 4 (ДПП-4) уступают по эффективности некоторым другим активно развивающимся группам гипогликемических препаратов (ингибиторы SGLT2 и агонисты рецепторов ГПП-1), однако представляются актуальными и в настоящее время.

Цель. Проанализировать данные литературы о терапевтическом потенциале и результатах исследований ингибиторов ДПП-4.

Материалы и методы. При поиске материала для написания обзорной статьи использовали реферативные базы PubMed, Google Scholar и e-Library. Поиск осуществлялся по публикациям за период с 2006 по 2022 год, с использованием следующих ключевых слов: ингибиторы ДПП-4; глюкагоноподобный пептид-1 (ГПП-1); глюкозозависимый инсулинотропный пептид (ГИП); ситаглиптин и другие препараты.

Результаты. ДПП-4 принадлежит к семейству сериновых протеаз и участвует в деградации некоторого количества хемокинов и пептидных гормонов, в том числе и инкретинов, секретируемых L- и K-клетками кишечника: ГПП-1 и ГИП, которые регулируют постпрандиальную секрецию инсулина и функцию β-клеток, модулируют тощаковую и постпрандиальную секрецию глюкагона, регулируют пищевое поведение и оказывают множество плейотропных эффектов (иммуномодулирующее, противовоспалительное, антифибротическое действие и др.). Ингибиторы ДПП-4 снижают активность фермента на 70–90%, повышая уровень инкретинов в плазме в 2–4 раза и применяются для лечения СД 2 с 2006 года. Сейчас на рынке разных стран присутствуют 13 ингибиторов ДПП-4, различающихся прежде всего фармакокинетическими параметрами. Они активно используются в комбинированной терапии СД2, повышая эффективность гликемического контроля без увеличения риска развития гипогликемии. Появляются данные о терапевтическом потенциале ингибиторов ДПП-4 при COVID-19.

Заключение. Пероральная форма, возможность создавать эффективные комбинации с другими гипогликемическими препаратами без увеличения риска гипогликемии, плейотропные эффекты ингибиторов ДПП-4 делают данную группу актуальной и в настоящее время.

Ключевые слова: сахарный диабет; дипептидилпептидаза 4; глюкагоноподобный пептид-1; глюкозозависимый инсулинотропный пептид; ситаглиптин; COVID-19

Список сокращений: FAP-α – фибробласт-активирующий белок альфа; FDA – Управление по санитарному надзору за качеством пищевых продуктов и медикаментов США; FGF2 – основной фактор роста фибробластов; GRP – гастрин-рилизинг пептид; MCP-1 – моноцитарный хемотаксический протеин-1; MDC – макрофагальный хемокин; MIP-1α – макрофагальный воспалительный протеин 1α; NHE3 – натрий-водородный обменник 3 подтипа; NPY – нейропептид Y; PAI-1 – ингибитор активации плазминогена 1 типа; PYY – пептид YY; SDF-1a – фактор стромальных клеток 1 альфа; TGFβ – трансформирующий фактор роста бета; АПФ2 – ангиотензинпревращающий фермент 2; БА – болезнь Альцгеймера; ГИП – глюкозозависимый инсулинотропный пептид; ГМ-КСФ – гранулоцитарно-макрофагальный колониестимулирующий фактор; ГПП-1 – глюкагоноподобный пептид-1; ГЭБ – гематоэнцефалический барьер; ДПП-4 – дипептидилпептидаза 4; иДПП-4 – ингибитор дипептидилпептидазы-4; КИ – клинические исследования; НАЖБП – неалкогольная жировая болезнь печени; ОКС – острый коронарный синдром; СД – сахарный диабет; СКФ – скорость клубочковой фильтрации; ХОБЛ – хроническая обструктивная болезнь легких; ХПН – хроническая почечная недостаточность.

INTRODUCTION

Diabetes mellitus (DM) and related diseases will obviously remain a serious threat to the life and health of the population in almost all countries for many decades to come. In 2021, according to the estimates of the International Diabetes Federation, the number of diabetes patients in the world exceeded 536 million, and in 2045, it will amount to 783.2 million people. Modern guidelines for the treatment of DM indicate the feasibility of the early treatment using rational

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combinations of drugs with a high safety profile, and notify the importance of preventing vascular DM complications [1, 2].

Enzyme dipeptidyl peptidase-4 inhibitors (iDPP-4s) have been developed all over the world for more than 30 years and remain in demand nowadays. In 2019, the global market for DPP-4 inhibitors and their combinations exceeded $12 billion [3]. In Russia, this group is actively used in the treatment of diabetes. The characteristics of the domestic market for iDPP-4 are summarized in Fig. 1.

The DPP-4 enzyme was identified in 1966 by Hopsu-Havu and Glenner as glycylproline naptylamidase. DPP-4 was first obtained from the rat liver in 1967, and from the pig kidney – in 1968. DPP-4 is an intramembrane glycoprotein and serine exopeptidase of the S9B subfamily, consisting of 766 amino acids. The active enzyme in rats, mice and humans was found out in epithelial cells of the intestine, kidneys, liver, lungs, thymus, and spleen. In addition to DPP-4, the representatives of the S9B protease subfamily are a fibroblast activator protein-α (FAP-α), DPP-6, DPP-8, DPP-9. However, DPP-4 is the main enzyme responsible for the physiological degradation of incretin hormones [4].

The functions of all isoenzymes have not been *ad finem* understood; it is assumed that FAP is responsible for the cell growth, and their inhibition has a toxic effect, causing thrombocytopenia, splenomegaly, reticulocytopenia, pathology of various organs, which makes the selectivity of the inhibitory action important for the representatives of the drugs with a similar mechanism of action [5]. DPP-4 is a tetramer in which each subunit consists of two domains – an N-terminal β-helical (β-propeller) domain and a C-terminal catalytic domain, which enclose an internal cavity with the active site. This cavity is connected to the main part of the active site by means of an “open screw/propeller” and a “side hole”. Substrates and inhibitors of DPP-4 enter and leave the active site through this side opening [6]. The main parts for binding to DPP-4 ligands are the S1 hydrophobic pocket, which determines the substrate specificity of DPP-4, the S2 hydrophobic pocket with ionic interaction sites, and the S3 pocket. The S1 region in DPP-4, DPP-8, and DPP-9 is almost identical, while S2 in DPP-4 is smaller. The S1 and S1’ regions slightly differ in their composition and conformation: in contrast to DPP-8 and DPP-9, relatively negatively charged groups are attached to S1’ in DPP-4. The S3 region is the most variable for each isoenzyme; in DPP-4, the groups of ligands of a smaller size compared to DPP-8 and DPP-9, are attached to it [7].

The DPP-4 enzyme cleaves many physiologically active substances, including hormones secreted by L- and K-cells of the intestine – glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), which regulate a postprandial insulin secretion and are involved in maintaining carbohydrate homeostasis. Besides, these incretins regulate insulin biosynthesis in a glucose-dependent manner, suppress a glucagon secretion, suppress glucogenesis in the liver, promote the regeneration and differentiation of islet β-cells, and play an important role in the regulation of the eating behavior: the formation of a satiety feeling and slowing gastric emptying [5].

Like GLP-1 receptor agonists, DPP-4 inhibitors are well tolerated and do not cause hypoglycemia. However, a few cases of acute pancreatitis were reported after incretin-based drugs had been introduced to the market, and in 2013, the Federal Food and Drug Administration of the USA (FDA) reported an increased risk of pancreatitis and precancerous cellular changes (metaplasia) of pancreatic ducts against the background of their application. In addition, the FDA warns that patients with a history of pancreatitis are at an increased risk of pancreatitis recurrence when treated with these drugs, so, they should be used with caution. Numerous subsequent studies over the past time have not been able to unambiguously prove a relationship between the use of incretin mimetics and the development of the notified pathologies. At the same time, all authors point out to the need for longer follow-up and additional studies to form conclusions [8–10].

It should be notified that the DPP-4 inhibition also affects the elimination of a large number of substrates: incretins (GLP-1, GLP-2, GIP, gastrin-releasing peptide (GRP), peptide YY (PYY)); cytokines (interleukin-3, a granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin, a basic fibroblast growth factor (bFGF2), etc.); chemokines (monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein 1α. (MIP-1α), Stromal Derived Factor-1α, (SDF-1 α), macrophage-derived chemokine (MDC)), and others); neuropeptides (neuropeptide Y (NPY), substance P) [11].

DPP-4 (also referred to as CD26) is also expressed on the surface cells of the immune system (T- and B-lymphocytes, NK cells, dendritic cells and macrophages [11]. However, in relation to these cells, the regulatory function of DPP-4 (CD26) has not been *ad finem* disclosed. 8, 11 Thus, the pleiotropic potential of DPP-4 inhibitors requires a further evaluation.

THE AIM of the study is to analyze the literature data on the therapeutic potential and results of the of DPP-4 inhibitors research.

MATERIALS AND METHODS

When searching for the review article materials, the abstracting databases of PubMed, Google Scholar and

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e-Library were used. The search was carried out on the publications for the period from 2006 to 2022, using the following keywords: DPP-4 inhibitors (DPP-4 inhibitors); GLP-1 (GLP-1); glucose-dependent insulinotropic peptide (GIP); sitagliptin (sitagliptin); vildagliptin (vildagliptin); dutogliptin (dutogliptin); saxagliptin (saxagliptin); linagliptin (linagliptin); alogliptin (alogliptin); gemigliptin (gemigliptin); teneligliptin (teneligliptin); anagliptin (anagliptin); omarigliptin (omarigliptin); gosogliptin (gosogliptin); denagliptin (denagliptin); melogliptin (melogliptin); trelagliptin (trelagliptin); retagliptin (retagliptin); evogliptin (evogliptin); carmegliptin (carmegliptin). 522 sources were analyzed; after the systematization, the literary sources with similar theoretical information, were removed.

RESULTS AND DISCUSSION

1. Physiology of DPP-4

Native GLP-1 has a short half-life (about 1-2 min) due to its destruction by the DPP-4 enzyme or excretion from the bloodstream by the kidneys. DPP-4 cleaves GLP-1 (7-36 amide) and GLP-1 (7-37) at the N-terminal dipeptide with the formation of the corresponding inactive metabolites: GLP-1 (9-36 amide) or GLP-1 (9-37), which are also excreted by the kidneys. The clearance of GLP-1 and its metabolites is slowed down in the patients with renal insufficiency [12, 13].

DPP-4 exists in two forms – a transmembrane protein and a soluble form that circulates in the blood. In the intestine, DPP-4 is highly expressed in the brush border of enterocytes and in endothelial cells, so most of the secreted GLP-1 is already degraded in the capillaries of the distal intestine. At the same time, approximately, only 25% of active GLP-1 reaches the liver and about 10–15% is distributed in plasma [13].

The DPP-4 activity can change under the influence of various stimuli. Thus, dexamethasone-induced hyperglycemia is accompanied by hyperacetylation of histones in the promoter region of the DPP-4 gene with an increase in its expression, which may be an addition to the knowledge about the already known mechanisms for the development of steroid diabetes, as well as a new goal of pharmacotherapy [14].

2. iDPP-4 pharmacology

iDPP-4 inhibitors improve a glucose control in patients with type 2 diabetes. Thus, iDPP-4s have a large number of biological effects and, unlike other antidiabetic agents, do not cause such undesirable effects as a weight gain and the development of a hypoglycemia state. Therefore, these drugs are in the center of research and development of many pharmaceutical companies and scientific centers, which led to the appearance of such a large number of drugs of the DPP-4 group on the pharmaceutical market. 13 of these, are currently approved and used for the treatment of type 2 diabetes, while 6 others (carmegliptin, retagliptin, melogliptin, denagliptin and dutagliptin) are in the pre-registration/phase 2,3 and/or awaiting the approval.

Based on international non-proprietary names, the common fragment of which is “gliptin”, the entire group of DPP-4 inhibitors is commonly called gliptins. The drugs of this group reduce the activity of the enzyme by 70–90%, do not have a direct effect on the satiety feeling or on the rate of gastric emptying. In the absence of the data on the passage of DPP-4 inhibitors through the blood-brain barrier (BBB), they are able to enhance the central effect of GLP-1 increasing its plasma level by 2–4 times [15, 16]. Despite the same action, various gliptins differ in their pharmacodynamic and pharmacokinetic properties, which may be clinically significant for certain categories of patients (with renal or hepatic insufficiency, pancreatitis, cardiovascular diseases, etc.).

The main advantages of the drugs over other hypoglycemic drugs with the DPP-4 inhibitory activity are a moderate efficacy, a higher safety: a low risk of hypoglycemia, cardiovascular complications; it does not cause edema and a weight gain. The drugs from the DPP-4 group have a number of class-specific properties, which consist in a dual action mechanism (on the function of α- and β-cells). That leads to an improvement in the postprandial profile of glucagon and insulin secretion patterns. The inhibition of the GLP-1 degradation has a positive effect on glucose homeostasis by increasing insulin levels and suppressing a glucagon secretion, slowing gastric emptying and reducing the appetite. DPP-4 inhibitors are characterized by a neutral effect on the body weight and do not provoke hypoglycemia [17, 18]. In patients with type 2 diabetes, their use leads to a steady decrease in the concentration of HbA1c, blood glucose levels on an empty stomach and after a meal. In the work by Korbut A.I. and Klimontov V.V. [19], the data on the effect of GLP-1 and DPP-4 iD analogues on structural and functional changes in the kidneys in DM, have been summarized. In experimental and clinical nephropathy of a diabetic and non-diabetic origin, GLP-1 and DPP-4 iP analogues slow down the development of fibrosis and a decrease in the kidney function. Their nephroprotective effect is due to a decrease in hyperglycemia, an increase in sodium excretion, a suppression of inflammatory and fibrogenic signaling pathways, an oxidative stress and apoptosis in the kidneys.

It is important to note that the effect of incretins (GLP-1 and GIP) on the insulin and glucagon secretion depends on the level of glycemia. Under the conditions

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of normoglycemia, an increase in GLP-1 and GIP does not affect the insulin secretion, while GIP stimulates a glucagon secretion during fasting glycemia and hypoglycemia [20]. An increase in the glucose levels above the physiological values leads to the stimulation of insulin secretion (GLP-1 and GIP) and suppression of the glucagon production (GLP-1). At the same time, under the conditions of hypoglycemia, GIP significantly increases a glucagon secretion, helps maintain glucose homeostasis and prevents a further development of hypoglycemia. By increasing the level of GLP-1 and GIP, which have a glucose-dependent mechanism of action, DPP-4 inhibitors can help normalize the insulin/glucagon balance and improve glucose homeostasis in the patients with type 2 diabetes without increasing the risk of hypoglycemia [18, 21]. Based on the foregoing, and taking into account the recommendations accepted in the world regarding the use of the combination therapy for type 2 diabetes, it can be assumed that the addition of iDPP-4 to the drugs that tend to cause hypoglycemia (sulfonylurea derivatives and thiazolidinediones) will reduce the likelihood of its development, which is often notified in clinical trials. (CTs).

2.1. Classification of iDPP-4s

Kushwaha R.N. et al. [22] divide gliptins into several groups based on their chemical skeleton:

– sitagliptin and related gliptins include retagliptin, gemigliptin, omarigliptin and evogliptin, which had been developed from triazolopiperazine derivatives. Sitagliptin is the first DPP-4 gliptin approved for the treatment of type 2 diabetes;

– cyanopyrrolidine gliptins include vildagliptin, saxagliptin, anagliptin, denagliptin and melogliptin. Vildagliptin is the first inhibitor of this class on the market;

– teneligliptin and gosogliptin are gliptins based on diprolyl;

– linagliptin belongs to the xanthine-based class of gliptins, while alogliptin and trelagliptin belong to the pyrimidinedione class;

– dutagliptin and carmegliptin are boric and tricyclic gliptins, respectively.

Nabeno M. et al. [6] classify iiDPP-4s nto three classes depending on their binding modes in the DPP-4 active site:

Class 1 contains wilda- and saxagliptin, which bind to the S1 and S2 subsites and form a covalent bond with the nitrile group of their cyanopyrrolidine moiety to the Ser630 site of DPP-4. Saxagliptin is 5 times more potent than vildagliptin at inhibiting DPP-4.

Class 2 contains alo- and linagliptin, which interact with “daughter” S1’ subsites, and in the case of linagliptin with S1’ and S2’, in addition to S1 and S2. The uracil rings of both gliptins induce a conformational change in Tyr-547 in the daughter subsites at S1’. Due to the additional interaction of linagliptin with the daughter subsites S2’, it is 8 times more active than alogliptin.

Class 3 has the highest inhibitory activity against DPP-4, since sita- and teneligliptin interact not only with the S1 and S2 regions of DPP-4 (like Class 1), but also with the extensive S2 subsite. Teneligliptin has a unique J-shaped structure with an anchor lock domain, which explains its strong inhibitory activity and low IC value (0.37 nM). Binding to the extensive S2 subsite of some inhibitors also determines their high specificity for DPP-4, since other related peptidases (DPP-8, DPP-9, and FAP) lack this site.

DPP-4i can be also divided according to the effect duration, highlighting the drugs with a prolonged action for the oral administration once a week: omarigliptin (MK-3102, Marizev®, Merck) and trelagliptin (SYR-472, Zafatec®, Takeda/Furiex), which had been approved for use in Japan [23, 24].

In 2006, the FDA approved the first DPP-4 inhibitor, sitagliptin. After that, the development of drugs in this group was continued, and today they are 17 in this group [22].

2.2. Pleiotropic properties of DPP-4 inhibitors

DPP-4 (CD26) is expressed by vascular endothelial cells, lungs, kidneys, liver, small intestine, and heart, as well as the cells of the immune system [11]. In the review article by Zou H. et al. [25], biological functions, key molecular pathways, interactions, and associations of DPP-4 in the context of developing new treatments for lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cancer, are reviewed. The authors note out that DPP-4 may regulate the immune response through the T-cell activation and modulation of chemotaxis, and can be also involved in the development of asthma and COPD. The DPP-4 inhibition can slow down a smooth muscle cell proliferation and facilitate a pulmonary artery remodeling, as well as improve the overall survival of the lung cancer patients.

DPP-4 is constitutively expressed on lung fibroblasts and is involved in the regulation of their functional activity (collagen synthesis and a secretion of inflammatory cytokines). Under conditions of pulmonary hypertension, the inhibition of DPP-4 slows down the transition of vascular remodeling from the reversible to the irreversible stage due to the complex antioxidant, anti-inflammatory and antifibrotic effects, as well as slowing down the proliferation and migration of fibroblasts [26].

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In the study by Zhang S. et al. [27], anagliptin was shown to reduce a lung injury in the mice exposed to the chronic alternating stress for 2 weeks. The chronic stress induced the inflammation and an oxidative stress leading to the lung damage. This was accompanied by an increase in the plasma DPP-4 activity, an increase in the gene expression of several pro-inflammatory cytokines, the adhesion molecules, and a plasminogen activator inhibitor-1 (MCP-1, Vcam-1, Icam-1 and PAI-1), as well as a decrease in the expression of eNOS proteins, Sirt1 and Bcl-2. The inhibition of DPP-4 both by the administration of anagliptin and by generating genetic knockouts (DPP-4$^{-/-}$) prevented a stress-induced lung injury associated with the inflammation, oxidative stress and apoptosis.

In the work by Patel P.M. et al. [28], a DPP-4 role in the development of various skin diseases is discussed. Herewith, the following factors are taken into consideration: its expression, influence on the function of melanocytes, keratinocytes, and fibroblasts, as well as the participation in the formation of a balance between regulatory T-lymphocytes (Treg) and effector T-lymphocytes. In skin diseases, a DPP-4-mediated disruption of Treg immunosuppression is possible, contributing to the development of inflammation. The therapeutic potential of DPP-4 inhibitors in various inflammatory skin diseases (psoriasis, atopic dermatitis, fibrosing diseases, etc.) is being investigated.

The study published in 2011, noted an increase in the DPP-4/CD26 expression in the patients with atopic dermatitis. In the experimental part of the work, a skin inflammation was induced in the knockout animals (DPP-4$^{-/-}$) with a predominance of T-helper 1 (Th1) or type 2 (Th2), respectively, with a predominance of a cellular or humoral immune response. In the animals without DPP-4, a reduced cutaneous inflammatory response was found out in the Th2 inflammation model, which underlies the diseases such as atopic dermatitis, bronchial asthma, etc. On the other hand, in the animals without DPP-4 in the Th1-dominated model, a cutaneous inflammatory response was increased [29]. It can be assumed that the DPP-4 inhibition in inflammatory skin diseases can have both potential benefits and harms, which requires taking into account the individual characteristics of the patient. At the time of writing this review, few publications have been published on the association of the use of DPP-4 inhibitors with inflammatory skin diseases. However, one study showed that the use of DPP-4 inhibitors (vildagliptin and linagliptin) was associated with a 3-fold increase in the risk of bullous pemphigoid, and a therapy discontinuation was associated with improved clinical outcomes [30].

A significant number of cytokines among the substrates of degraded DPP-4 indicates the study prospects of iDPP-4 for the correction of the chronic inflammation in autoimmune rheumatic diseases [31]. However, currently, the information is insufficient and there are conflicting data on both positive [32] and negative [33] effects of DPP-4 inhibitors on the course of rheumatoid arthritis in the experiment.

To reduce potential negative DPP-4i effects associated with a slowdown in the elimination of certain cytokines, the possibility of using antagonists of the corresponding receptors, is being considered [34].

The possibility of using DPP-4i in the immune regulation and therapy of autoimmune rheumatic diseases is discussed.

In the progression of a renal failure, DPP-4 inhibitors can have a protective effect, including antifibrotic effects in diabetic nephropathy [35]. DPP-4 affects a sodium transport in the kidneys, since a 3-subtype sodium-hydrogen exchanger (NHE3) in the brush border membranes of the epithelium of the proximal tubule exists in combination with DPP-4, and the decrease/suppression of the expression/signaling and/or activity of DPP-4 can lead to an increased excretion of sodium and water [36]. Investigating gemigliptin effects in the mice in the ureteral obstruction model, Min H.S. et al. [37] found out that in the animals receiving gemigliptin at the dose of 150 mg/kg p.s. with food, a decrease in proteinuria and kidneys structural changes was observed within 14 days. Against the background of the administration of the drug, a urinary excretion of 8-isoprostane (a marker of the oxidative stress level) in the mice decreased. The authors note that the nephroprotective effect of gemigliptin is realized through several mechanisms associated with fibrosis, inflammation, and an oxidative damage, regardless of its hypoglycemic effects.

As mentioned above, colony-stimulating factors and various cytokines are also DPP-4 targets, which can have a significant potential in the organ and tissue transplantation (islet cells of the pancreas, lungs, skin, hematopoietic stem cells, etc.) [11, 38].

An increased DPP-4 expression in the liver contributes to the development of a non-alcoholic fatty liver disease (NAFLD) and insulin resistance. This is associated with a reduced level of GLP-1, as well as auto- and paracrine DPP-4effects. In the experimental studies, gemigliptin reduced the inflammation severity, an oxidative stress and alleviated the course of liver fibrosis. DPP-4 is considered as a promising target for the NAFLD treatment [39].

Jung E et al. [40] studied the effect of gemigliptin on retinal pericytes and the process of neovascularization in a model of ischemic proliferative retinopathy in the

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mice prone to DM type 2 (db/db). The administration of gemigliptin for 12 weeks led to a significant decrease in the intensity of retinal pericyte apoptosis and improved the retinal neovascularization. The authors note a pronounced retinoprotective effect of gemigliptin due to the DPP-4 suppression and the suppression of the plasminogen activator-1 (PAI-1) expression.

The review paper [41] summarizes the research results studies that indicate the ability of DPP-4i to prevent the onset and progression of diabetic microangiopathy.

Some well-known drugs have an inhibitory activity against DPP-4, mitoxantrone has a significant inhibitory activity against DPP-4 both *in vitro* and *in vivo* [42]; being inhibitors of metalloaminopeptidases and bacterial proteases, bestatin and bacitracin also inhibit a DPP-4 activity and, therefore, are considered as a structural element for creating new compounds [43]. Oxytocin is considered as a peptide endogenous inhibitor of the DPP-4 activity [44]. The inhibitory activity against DPP-4 was found out in bovine α-lactalbumin hydrolysates [45].

Curcumin, syringic acid, resveratrol [46], berberine [47], garlic extract [48] have a high affinity for the DPP-4 enzyme, which increases interest in these natural products.

Currently, despite the discovery of a large number of substances that exhibit an inhibitory activity against DPP-4, medical chemistry continues to develop new compounds.

2.3. Potential for use of DPP-4 inhibitors in COVID-19

A potential use of DPP-4 inhibitors in the complex treatment of COVID-19 is of particular interest. It is hypothesized that DPP-4 inhibitors can play a role in reducing the COVID-19 severity by preventing the virus from entering the cells. This led to the hypothesis that the use of DPP-4 inhibitors can be the optimal strategy for the COVID-19 treatment in the diabetic patients, who are at a double risk of a severe infection [49, 50].

In silico modeling of the SARS-CoV-2 spike protein predicted its potential interaction with DPP-4 in addition to the angiotensine transforming enzyme 2 (ATE2, ACE2) [51]. These models suggest that DPP-4 can be a co-receptor for the SARS-CoV-2 virus entry. DPP-4 (a membrane and soluble form) is a target not only for SARS-CoV-2, but also for MERS-CoV [52]. In the literature, the possibility of using a monoclonal antibody to CD26 (Begelomab) to block the interaction of SARS-CoV-2 with DPP-4 has been considered, but there are no data on any clinical studies of this approach [53].

The fact that DPP-4 exists in soluble and membrane forms complicates understanding of the iDPP-4 potential in COVID-19. The previous studies have shown that a soluble DPP-4 form acts as a decoy molecule for MERS-CoV, as it does for SARS-CoV-2, blocking a viral S-protein binding to the cell surface [54, 55]. The research by Schlicht K. et al. [56] in the severe COVID-19 patients showed a reduced level of soluble DPP-4, which correlated with the severity of the disease. However, it is not clear whether a decrease in the soluble DPP-4 was a consequence of the disease or an individual initial condition that causes an increased susceptibility to MERS-CoV or SARS-CoV-2. The level of soluble DPP-4 in serum can also be reduced in various clinical diseases, such as diabetes, obesity and metabolic syndrome, which can lead to a severe course of an infectious disease [4]. Herewith, the administration of DPP-4 inhibitors can increase the level of soluble DPP-4 [57]. Thus, there is a hypothesis that DPP-4 inhibitors can help retain viral particles in the bloodstream by increasing the level of soluble DPP-4, which, in turn, can limit the reproduction of the virus in the human body.

DPP-4 is expressed by the immune system cells and is involved in the regulation of inflammatory processes. The anti-inflammatory effects of DPP-4 inhibitors can be useful in COVID-19 patients to prevent a “cytokine storm” in order to reduce the disease severity [49, 58]. DPP-4 also enhances a fibroblast activation by increasing transforming growth factor β (TGFβ), which indicates the antifibrotic potential of DPP-4 inhibitors, confirmed by experimental models of pulmonary and skin fibrosis [59].

3. Representatives of DPP-4 inhibitors group

Summarized information about the representatives of DPP-4 inhibitors is given in Table 1.

3.1. Sitagliptin (MK-0431, Januvia®, Merck)

Sitagliptin was developed by the pharmaceutical company Merck (Germany) based on triazolopiperazine. Since 2006, it has been approved by the FDA for use in type 2 diabetes. It is highly active against DPP-4 (IC_{50}=18 nM) and selective (for DPP-8 – 48000 nM, for DPP-9 – >100000 nM); it improves the function of pancreatic β-cells, as well as a glycemic control on an empty stomach and after a food intake in patients with type 2 diabetes. The presence of a trifluoromethyl group in the triazole ring improves its bioavailability [22]. Sitagliptin dose-dependently inhibits a DPP-4 plasma activity up to 80 and 47% when measuring the enzyme activity at the 2nd and 24th h, respectively, after a single dose of 25 mg (in the type 2 diabetes patients) [60]. Only a small part of the drug is metabolized with the participation of CYP3A4 and CYP2C8 enzymes.

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The metabolites are conjugates of N-sulfate and N-carbamoylglucuronic acid of the parent drug, a mixture of hydroxylated derivatives, a glucuronide ester of the hydroxylated metabolite, and two metabolites formed by an oxidative desaturation of the piperazine ring followed by the cyclization. All 6 metabolites lack a DPP-4 inhibitory activity. Sitagliptin is the most studied DPP-4 inhibitor and the effectiveness of its combinations with hypoglycemic drugs of other groups is being actively studied.

Hou L. et al. [61] conducted a meta-analysis of the studies published up to 2012, which evaluated the efficacy and safety of the combined therapy with metformin + sitagliptin and a combination of metformin (≥1500 mg) and sulfonylurea derivatives (glipizide, glibepiride, glibenclamide) in patients with type 2 diabetes and an inadequate glycemic control. The authors showed that sitagliptin and sulfonylurea drugs are comparable in effectiveness (in reducing HbA1c) when the baseline metformin therapy is added. However, in the combination therapy with metformin and sulfonylurea drugs, the risk of developing hypoglycemia remained high, while the addition of sitagliptin to metformin did not increase the risk of developing a hypoglycemic state.

Hayes J. et al. [62] evaluated the efficacy and safety of the sitagliptin+metformin combination in the treatment of type 2 diabetes patients. The authors compared the results of 11 studies lasting from 24 to 104 weeks. This research included the studies where the following drugs had been used: sitagliptin and metformin in fixed doses separately or in the dual therapy; sitagliptin and metformin compared with other hypoglycemic drugs and metformin; sitagliptin and metformin as a part of a triple combination therapy (sitagliptin + metformin + sulfonylurea or insulin). The authors have found out that the combination of sitagliptin and metformin reduced HbA1c and other glycemic parameters better than either drug separately. This combination had a high safety profile and was well tolerated by patients. The risk of hypoglycemia was lower with the combination of metformin and sitagliptin than with the combination of metformin, glipizide, or gliperimide.

Fonseca V. et al. [63] evaluated the efficacy and safety of sitagliptin in the triple combination therapy with metformin (≥1500 mg per day) and pioglitazone (≥30 mg per day) in type 2 diabetes patients (HbA1c=7.5–11%) during a placebo controlled, double-blind study for 26 weeks. The addition of sitagliptin resulted in significant (p <0.001) changes from the baseline compared to placebo in HbA1c (-0.7%), fasting plasma glucose (-1.0 mmol/L) and 2 h *postprandial* (-2.2 mmol/l). In patients with baseline HbA1c ≥9.0%, the mean changes from the baseline in HbA1c were -1.6 and -0.8% for the sitagliptin and placebo groups, respectively (between the groups the difference was -0.8%; p <0.001). The frequency of adverse events was generally comparable between the treatment groups, the episodes of hypoglycemia were observed in 4.5 and 3.8% in the sitagliptin and placebo groups, respectively (p=0.786). The authors conclude that the addition of sitagliptin to the combination therapy with metformin and pioglitazone resulted in the improved glycemic control and was generally well tolerated.

In the domestic multicenter observational program "Dia-Da", in type 2 diabetes patients and the HbA1c concentration of 7–8%, who had received the sitagliptin therapy at the dosage of 100 mg per day in combination with metformin for 6 months, there was a decrease in HbA1c levels by 1.1%. In patients with a more pronounced violation of carbohydrate metabolism (HbA1c >10%), the decrease in this indicator was 4.1%. On average, over 6 months of treatment, the level of HbA1c decreased by 1.7%. In the combination of sitagliptin + metformin, the level of fasting plasma glucose also decreased from the initial level of 8.8 to 6.1 mmol/l after 6 months [64].

Sitagliptin helps to reduce the visceral fat depot in type 2 diabetes patients when added to metformin, which was noted in the study by Ametov A.S. et al. [65]. After 6 months of treatment, in addition to improving the glycemic parameters (glucose levels measured on an empty stomach and *postprandial*, as well as HbA1c), there was a decrease in the body mass index (BMI) by an average of 5.29% in the sitagliptin+metformin group, and in the group metformin monotherapy – by 1.96%. The area of the visceral fat decreased by an average of 7.52% in the combination therapy group (p <0.001), while in the metformin monotherapy group it decreased by an average of 1.76%

The presented above results show that the inclusion of sitagliptin in the hypoglycemic therapy composition leads to a significant increase in the effectiveness of the glucose metabolism control and the safety of treatment in general. It should be notified that sitagliptin is the most studied representative of this pharmacotherapeutic group, and at the same time, the interest of researchers and doctors in it does not decrease.

3.2. Vildagliptin (LAF-237, Galvus®, Novartis)

Vildagliptin is a representative of the first generation of inhibitors and the first gliptin of the cyanopyrrolidine class, developed by Novartis (Switzerland), approved for the treatment of type 2 diabetes. This is active (IC_{50}=3.5 nM) and moderately selective for DPP-4 against DPP-8 (>250-fold) and DPP-9 (>23-fold), but much more selective for DPP-2 and FAP. The vildagliptin half-life is

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1.5 h, its bioavailability is 85%; it improves a glycemic control (reduces HbA1c levels by 0.7%), causes the DPP-4 inhibition by 80% within 7 h and is maintained by 40% for 24 h after a single dose of 100 mg. 69% of the received drug dose undergoes a biotransformation, the main metabolite – LAY151 (57% of the dose) – is pharmacologically inactive; it is a hydrolysis product of the cyanocomponent. It improves a β-cell function and an insulin sensitivity. It is used in monotherapy and in combination with other antidiabetic drugs. The drug was approved by the European Medicines Agency in 2008 for use in the European Union [22].

Numerous trials have shown the efficacy of adding vildagliptin to metformin, insulin, sulfonylurea derivatives, and thiazolidinediones. The level of glycated hemoglobin decreased by an average of 0.6–1.1%. In most patients, the body weight remained stable, and in some cases, there was a tendency to decrease it, especially when the drugs had been combined with metformin [66].

Azuma K. et al. [67] investigated the effect of vildagliptin (100 mg per day) on the β-cell function in type 2 diabetes patients. Against the background of the vildagliptin use, the concentration of *postprandial* GLP-1 and GIP increased by 3 times and bid, respectively. The insulin secretion increased by 50% (p <0.01), the concentration of glucose in the blood plasma measured on an empty stomach and after a meal, decreased by 1.3±0.3 and 1.6±0.3 mmol/l (p <0.01), respectively, and glucagon *postprandially* – by 16% (p <0.01). The authors found out that against the background of the vildagliptin use, the *postprandial* concentration of glucagon was 41% lower than in the placebo group. It was also found out that under the conditions of hypoglycemia, the difference between the level of glucagon and insulin was 38%, indicating an increase in the α-cells function. The authors conclude that vildagliptin enhanced the response of α-cells to both the inhibitory effect of glucagon under the conditions of hyperglycemia and its stimulatory effect under the conditions of hypoglycemia, indicating the efficacy and safety in DM 2.

Odawara M. et al. [68] reviewed two open-label studies in patients with a poorly controlled type 2 DM who were taking one of the oral hypoglycemic agents – sulfonylurea, metformin, thiazolidinedione, an α-glucosidase inhibitor, and glinide. After 52 weeks of treatment, the addition of vildagliptin (50 mg per day) to these drugs reduced HbA1c compared to monotherapy by -0.64, -0.75, -0.92, -0.94 and -0.64%, respectively. The episodes of hypoglycemia were rare, with a slight advantage in the sulfonylurea group. The decrease in the HbA1c concentration in the combined use of vildagliptin with insulin secretogens (sulfonylureas or glinides) was less compared with its combination with other drugs. In all combination therapy groups, mean fasting glucose concentrations decreased, as did triglyceride and cholesterol levels. The HOMA-β index increased only in the patients treated with vildagliptin/sulfonylurea, in the rest ones, this indicator decreased. The authors conclude that vildagliptin has a good tolerability profile in DM 2 patients.

Ametov A.S. [69] reported the results of several vildagliptin studies, one of which examined the efficacy and safety of adding vildagliptin to the basic therapy. The study identified three groups of patients who had received various types of therapy: group 1 – metformin at the dose of ≥1500 mg per day; group 2 – gliclazide MB at the dose of 90–120 mg per day; group 3 – a combined therapy with metformin + gliclazide MB at the maximum therapeutic doses. After 24 weeks of therapy in groups 1, 2 and 3, the reduction in HbA1c was -1.2, -1.32 and -1.26%, respectively, and the target values of HbA1c ≤7.0% were achieved in 54, 60 and 32%. Even in the patients treated with gliclazide, the risk of hypoglycemia did not increase with vildagliptin. There was also a significant decrease in the glycemic variability in all three groups, which improves the long-term prognosis of the disease.

Kosaraju J. et al. [70] studied the effect of vildagliptin on the rats with streptozotocin-modeled Alzheimer's disease (AD): 3 months after the AD induction, vildagliptin was administered *p.o.* at the doses of 2.5, 5, and 10 mg/kg/day for 30 days. The treatment of the animals with vildagliptin resulted in an increase in the concentration of GLP-1, a decrease in the severity of cognitive deficits, and a dose-dependent decrease in the tau-phosphorylation, Aß, and inflammatory markers. Based on the foregoing, the authors conclude that vildagliptin has pronounced neuroprotective properties.

Arruda-Junior D.F. et al. [71] investigated the effects of vildagliptin in the rats with a simulated heart failure. Six weeks after the surgery, vildagliptin (120 mg/kg/day) was administered *p.o.* to the rats for 28 days. As evidenced by a fluid retention, the untreated rats had an impaired renal function, a low glomerular filtration rate (GFR), and a high urinary protein excretion. The treatment with vildagliptin restored the GFR, protein excretion, and Na^+. A restoration of the kidney function in the rats was associated with increased levels of active GLP-1, suppression of the DPP-4 activity, and an increase in protein kinase A in the renal cortex. Based on this, the authors concluded that vildagliptin has a reno- and cardioprotective effect.

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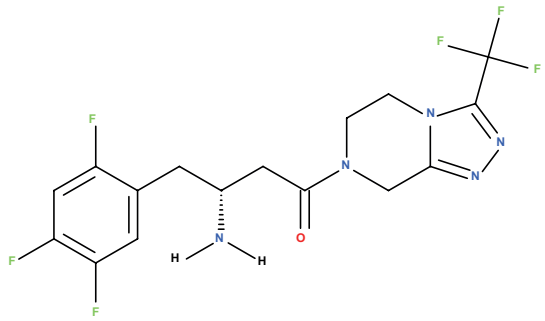
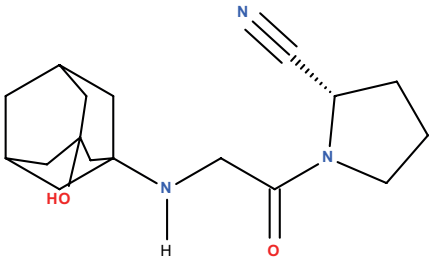
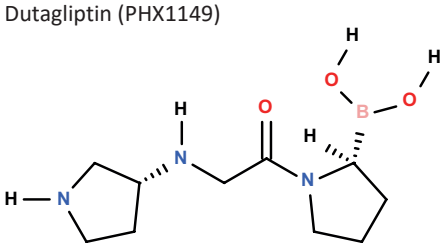
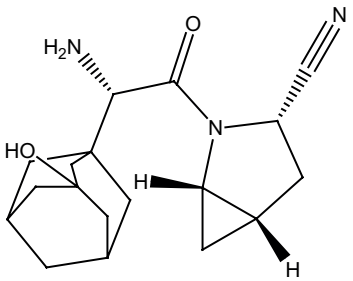
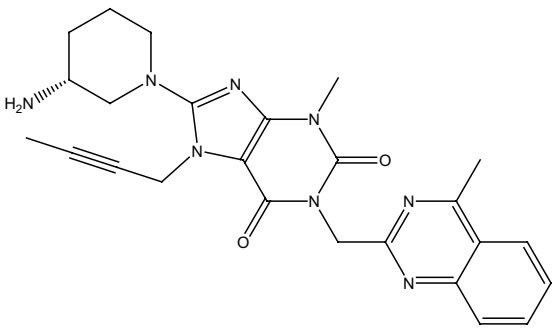
Table 1 – DPP-4 inhibitors, general information

Drugs	General information
Sitagliptin (MK-0431, Januvia®) 	IC_{50}=18 nM; manufactured by Merck, registered in more than 40 countries, including the US and EU countries; bioavailability is 87%; after a single dose of 25 mg its DPP-4 enzyme activity is inhibited by 80% and 47% at 2 and 24 h, respectively; selectivity for related enzymes: DPP-8 and DPP-9 >2 600 times; $T_{1/2}$ – 12 h; it reduces the content of glycated hemoglobin at the dose of 100 mg per day 0.8%; a small part of the drug is metabolized; the enzymes CYP3A4 and CYP2C8 are involved in the process. There are six metabolites found out, they do not have any DPP-4 inhibitory activity [22, 60].
Vildagliptin (LAF-237, Galvus®) 	IC_{50}=3.5 nM; manufactured by Novartis, registered in more than 78 countries, including the US and EU countries; bioavailability is 85%; after taking a single dose of 100 mg, the activity of the DPP-4 enzyme is inhibited by 80% within 7 h and retains 40% after 24 h; selectivity for natural enzymes: DPP-8 >250 times and DPP-9 by 23 times; $T_{1/2}$ – 3 h; it reduces the content of glycated hemoglobin at the dose of 25 mg per day – 0.6%; 69% of the drug dose undergoes biotransformation, the main metabolite, LAY151 (57% of the dose), is pharmacologically inactive and is hydrolysis product of the cyanocomponent [22].
Dutagliptin (PHX1149) 	IC_{50}=25 nM; manufactured by Phenomix Corp, passes the 3rd stage of CTs; the activity of the DPP-4 enzyme is inhibited by 90% when using the drug at the dose of 400 mg for 24 h, and by 50% – within 24 h if the dose is 100 mg; its selectivity for related enzymes: DPP-8 and DPP-9 >400 times; $T_{1/2}$ – 10–13 h; reduces the content of glycated hemoglobin at the dose of 400 mg after 12 weeks – 0.52%, at the dose of 200 mg – -0.35%; it is excreted unchanged through the kidneys [72, 73].
Saxagliptin (BMS-477118, Onglyza®) 	IC_{50}=26 nM; manufactured by Bristol-Myers Squibb, registered in 56 countries including the US, Canada, Mexico, 30 EU countries, Chile, India, Brazil, Argentina and Switzerland; bioavailability is 67%; it inhibits DPP-4 activity by 80 and 57% for up to 90 min and 24 h, respectively, at a single dose of 10 mg. At a single dose of 100 mg, it inhibits the DPP-4 activity by more than 95%; selectivity for related enzymes: DPP-8 >390 times and DPP-9 >77 times; it reduces the content of glycated hemoglobin at the dose of 2.5–10 mg ~ 1%; metabolized to the active metabolite M_2. $T_{1/2}$ – 2–4 h for saxagliptin and 3–7 h for the M_2 metabolite [13].
Linagliptin (BI-1356, Tradjenta®) 	IC_{50}=1.0 nM; manufactured by Boehringer Ingelheim, registered in Austria, Australia, Brazil, Great Britain, Greece, Spain, India, Canada, Korea, Mexico, USA, Singapore, Japan, Russia; bioavailability is 30%; at a single dose of 10.0 mg/kg, the inhibition of plasma DPP-4 is ≥80% within 24 h; selectivity for related enzymes: DPP-8 and DPP-9 >10 000 times; $T_{1/2}$ – 113–131 h; it reduces the content of glycated hemoglobin at the dose of 5 mg after 24 weeks 0.69%; it is practically not metabolized in the body, one main metabolite of linagliptin which does not have a pharmacological activity, is known [83].

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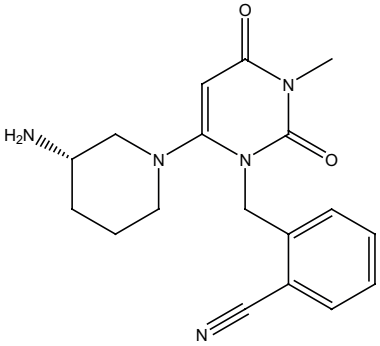
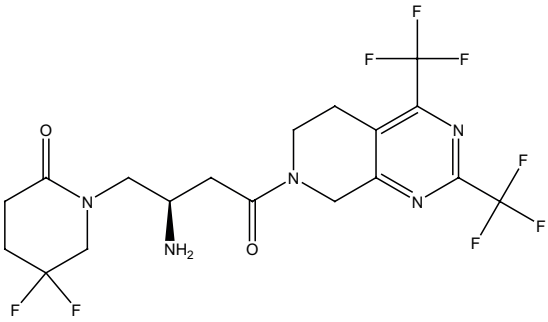
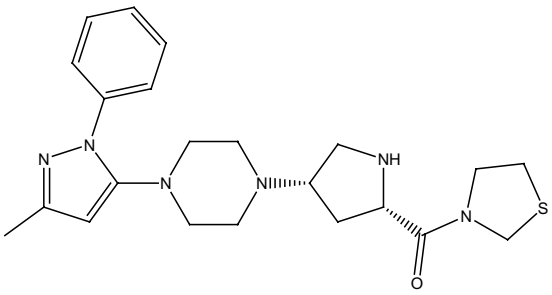
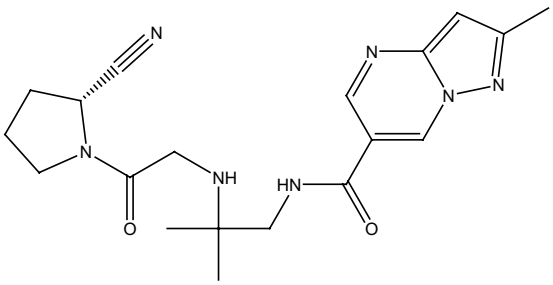
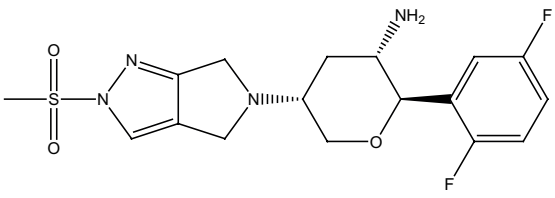
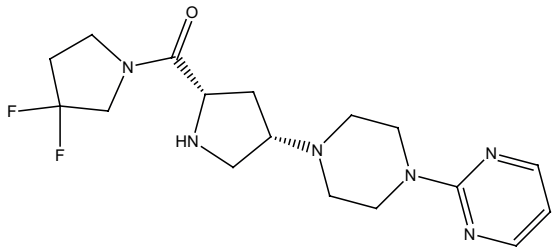
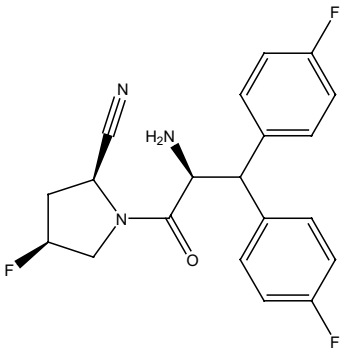
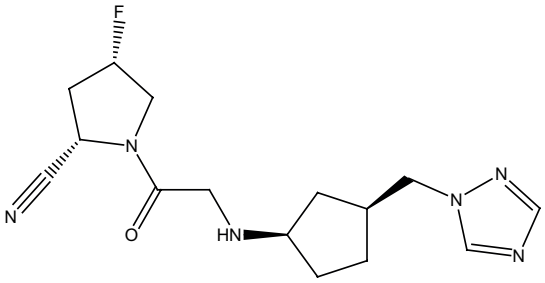
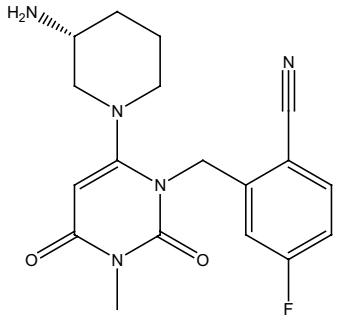
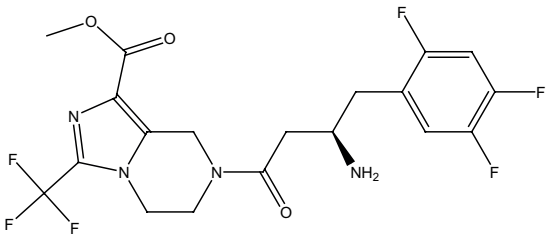
Drugs	General information
Alogliptin (SYR-322, Nesina® in the US and Vipidia® in Europe) 	IC_{50}=7.0 nM; manufactured by Takeda, registered in the USA, EU countries, Russia, China, Japan, Korea; bioavailability is 100%; its application causes more than 90% inhibition of DPP-4 for 24 h at the dose of 25 mg per day; highly selective (>10 000 times) against DPP-4 compared with other isoenzymes (DPP-2, DPP-8, DPP-9, etc.; $T_{1/2}$ – 21 h; at the dose of 25 mg after 26 weeks – 0.6%; it is not extensively metabolized, 60–71% of alogliptin is excreted unchanged by the kidneys. There are two minor metabolites – N-demethylated alogliptin (less than 1% of the original compound) and N-acetylated alogliptin (less than 6% of the original compound). N-demethylated metabolite is active, it is an inhibitor of DPP-4. About 10-20% of the dose of the drug is metabolized in the liver under the influence of cytochromes CYP3A4 and CYP2D6 [89].
Gemigliptin (LC15-0444, Zemiglo®) 	IC_{50}=6.3 nM; manufactured by LG Life Sciences, registered in Korea, India, Colombia, Costa Rica, Panama and Ecuador; its bioavailability is more than 63%; at the dose of 200 mg it inhibits the activity of DPP-4 in plasma by more than 80% within 24 h, at the dose of 400 mg – for 36 h, 600 mg for 48 h; a selectivity for related enzymes: DPP-8 >27 000 times, DPP-9 > by 23 000 times, FAP-α >41 000 times; $T_{1/2}$ – 17 h, for the active metabolite – 24 h; at the dose of 50 mg per day after 24 weeks, the decrease in glycated hemoglobin is 0.71%; about 10% of the dose is metabolized with the participation of cytochrome CYP3A4 to LC15-0636, hydroxylated gemigliptin [97].
Teneligliptin (MP-0513, Tenelia®) 	IC_{50}=1.8 nM; manufactured by Mitsubishi Tanabe, registered in Japan, Korea, India; bioavailability is 63–85%; inhibits the activity of plasma DPP-4 by more than 50% within 24 h after a single dose of 1 mg/kg; the selectivity for related enzymes: DPP-8 >703 times and DPP-9 >1 460 times; $T_{1/2}$ – 8–16 h; the decrease in glycated hemoglobin is 0.9 at the doses of 10 and 20 mg, by 1% at 40 mg after 12 weeks; about 65.6% of the dose is metabolized [100].
Anagliptin (SK-0403, Suiny®) 	IC_{50}=3.8 nM; manufactured by Sanwa Kagaku Kenkyusho, registered in Japan, Korea; bioavailability is 73%; inhibits DPP-4 activity by 95% at the dose of 3 mg/kg; the selectivity for related enzymes: DPP-8 and DPP-9 >10 000 times; at the dose of 100 mg after 24 weeks it causes a decrease in glycated hemoglobin by 0.5%; metabolite M_1 (carboxylate) is 29.2% of the dose, the proportion of other metabolites is about 1%. The half-life of anagliptin is 4.37 h, M_1 is 9.88 h [108].
Omarigliptin (MK-3102, Marizev®) 	IC_{50}=1.6 nM; manufactured by Merck, approved for use in Japan; bioavailability is 74%; causes inhibition of plasma DPP-4 by 77–89% up to 168 h; highly specific for other proteases including DPP-8, DPP-9, QPP, FAP, PEP; $T_{1/2}$ – 68 h; at the dose of 25 mg/week after 54 weeks it causes a decrease in glycated hemoglobin by 0.3%; not metabolized, excreted unchanged mainly through the kidneys, through the intestine – about 3% [113].

Drugs	General information
Gosogliptin (PF-00734200, Saterex®, SatRx® or Saterex®) 	IC_{50}=13 nM; developed by Pfizer, registered in Russia in 2016; bioavailability is over 99%; it causes inhibition of DPP-4 by 75% after 24 h; selectivity is more than 100-fold for DPP-2, DPP-3, DPP-8 and DPP-9; $T_{1/2}$ – 2.7 h; at the dose of 10 mg per day after 12 weeks it causes a decrease in glycated hemoglobin by 0.7%. The main metabolic pathway of gosogliptin in humans it is associated with hydroxylation of the pyrimidine group (M_5). Other metabolites are associated with amide hydrolysis, carbamoyl glucuronidation, formamide conjugation, glucose conjugation, and creatinine conjugation. Withdrawal: 48.5% – unchanged. It has 8 metabolites, with 17.9% of the dose being metabolite M_5 [117].
Denagliptin (GSK-823093, GW823093) 	IC_{50}=22 nM; manufactured by GlaxoSmithKline, undergoing stage 3 of CTs; a maximum inhibition of DPP-4 is after 30 min and it is more than 85% after 24 h at the dose of 25 mg; at the dose of 45 mg at week 12 of the treatment it causes a decrease in glycated hemoglobin by 0.84%; it has hepatic and extrahepatic metabolism; there are 13 metabolites [22].
Melogliptin (GRC 8200, EMD-675992) 	IC_{50}=1.61 nM; manufactured by Glenmark, passes the 3rd stage of CTs; bioavailability is 60, 90, and 94% in rats, dogs, and monkeys, respectively (5 mg/kg). Data on humans are not published; the drug causes more than 90% inhibition of DPP-4 within 1 h; selectivity for related enzymes: DPP-8 and DPP-9 >10 000 times; it reduces the content of glycated hemoglobin by 0.75 and 0.60% at the dose of 50 mg bid and at the dose of 100 mg per day [22].
Trelagliptin (SYR-472, SYR111472, TAK-472, Zafatec®) 	IC_{50}=4.2 nM; manufactured by Takeda/Furiex, approved for use in Japan and Korea; bioavailability in rats is 50.3%; taking 100 mg causes a 70% inhibition of plasma DPP-4 activity, which persists after 168 h; selectivity for related enzymes: DPP-8 and DPP-9 >10 000 times; $T_{1/2}$ – 72–168 h; at the dose of 100 mg/week after 52 weeks it reduces the content of glycated hemoglobin by 0.57%; metabolized by cytochrome P450 (CYP2D6), excreted mainly through the kidneys [22].
Retagliptin (SP-2086) 	IC_{50}=8 nM; manufactured by Jiangsu Hengrui Medicine, passes the 3rd stage of CTs; selectivity for related enzymes: DPP-8 >3 263 times and DPP-9 >9 438 times; $T_{1/2}$ – 1.5 h [22].

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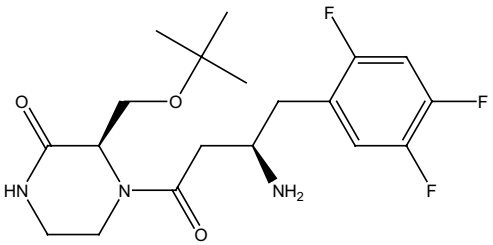
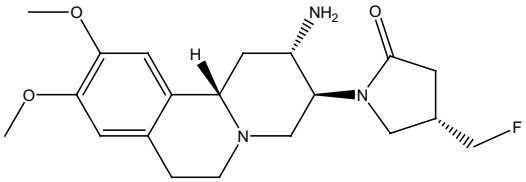
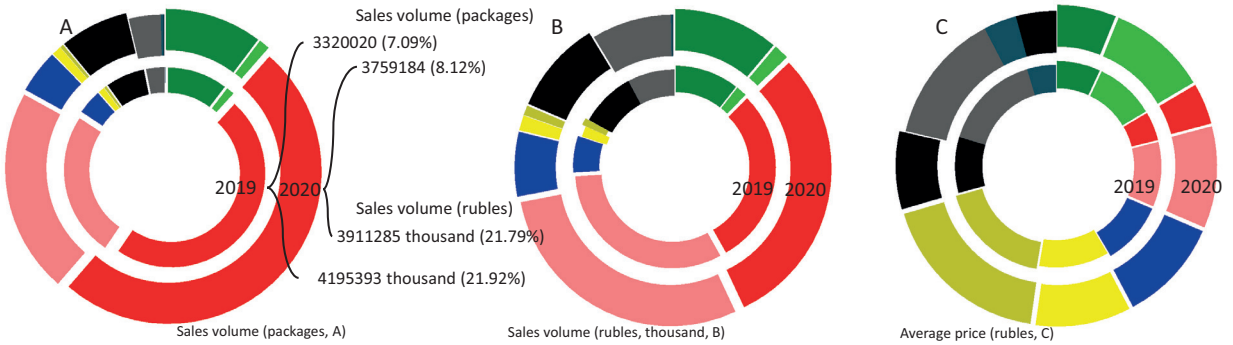
Drugs	General information
Evogliptin (DA-1229, Suganon®, Evodine® or Evodin®) 	IC_{50}=0.98 nM; manufactured by Dong-A Pharmaceutical, registered in South Korea, the drug is sold in Russia; bioavailability is 50.2%; causes inhibition of DPP-4 by more than 80% after a single dose of 5 mg; its selectivity for related enzymes: DPP-8 and DPP-9 >6 000 times; $T_{1/2}$ – 30 h; reduces the level of HbA1c by 0.56% at the dose of 2.5 mg and by 0.61% at the dose of 5 mg. It is metabolized by the processes of oxidation, glucuronization and sulfation. It has four metabolites [22].
Carmegliptin (R-1579) 	IC_{50}=6.8 nM; manufactured by F. Hoffmann-La Roche Ltd, passes the 3rd stage of CTs; bioavailability is 33% at 1 mg/kg in monkeys, 28% in rats, there are no data on humans; it reduces the activity of plasma DPP-4 by 40 and 60% after 24 and 48 h, respectively, after a single oral dose of 3 mg/kg; its selectivity for related enzymes: DPP-8 and DPP-9 >10 000 times, DPP-2 >2 000 times; $T_{1/2}$ – 6.8 h. It is not metabolized; it is excreted unchanged through the liver and kidneys [129].



	Sales volume (packages, A)		Sales volume (rubles, thousand, B)		Average price (rubles, C)	
	2019	2020	2019	2020	2019	2020
Alogliptin	344901 (10.39%)	386596 (10.28%)	415665 (10.63%)	468604 (11.17%)	1090.31 (6.95%)	1027 (6.15%)
Alogliptin + metformin	45844 (1.38%)	43585 (1.16%)	70568 (1.,80%)	67604 (1.61%)	1494.12 (9.53%)	1732.54 (10.38%)
Vildagliptin	1584690 (47.73%)	1876337 (49.91%)	1150815 (29.42%)	1267789 (30.22%)	723.23 (4.61%)	719 (4.31%)
Vildagliptin + metformin	824156 (24.82%)	814582 (21.67%)	1259694 (32.21%)	1214527 (28.95%)	1623.7 (10.36%)	1774.82 (10.64%)
Linagliptin	140976 (4.25%)	174160 (4.63%)	235270 (6.02%)	285992 (6.82%)	1576.83 (10.06%)	1799.83 (10.78%)
Saxagliptin	36965 (1.11%)	37853 (1.01%)	69293 (1.77%)	67458 (1.61%)	1754.28 (11.19%)	1669.22 (10.00%)
Saxagliptin + metformin	14636 (0.44%)	14084 (0.37%)	46093 (1.18%)	43739 (1.04%)	2826.98 (18.03%)	3037.6 (18.20%)
Sitagliptin	222278 (6.7%)	272118 (7.24)	357402 (9.14%)	414779 (9.89%)	1395.99 (8.90%)	1355.08 (8.12%)
Sitagliptin + metformin	104762 (3.16%)	126716 (3.37%)	305884 (7.82%)	354919 (8.46%)	2464.31 (15.72%)	2291.16 (13.73%)
Gosogliptin	812 (0.02%)	11675 (0.31%)	599 (0.02%)	8697 (0.21%)	729.67 (4.65%)	578.31 (3.47%)
Evogliptin	–	1478 (0.04%)	–	1284 (0.03%)	–	703.72 (4.22%)

Figure 1 – Some indicators of iDPP-4 domestic market (according to DSM Group)[1]

Note: the data are presented in Russian rubles, as of 1 Aug 2022, 1 US dollar (USD) corresponded to 61.3 Russian rubles (RUB).

[1] The data was officially purchased from DSM Group. Calculations were made on their basis, diagrams were presented.

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3.3. Dutogliptin (PHX1149, Phenomix Corp)

Dutogliptin is a derivative of boric acid and a representative of the second generation of iDPP-4s. It is active (IC_{50}=25 nM) and highly selective for DPP-4 (unlike DPP-8 and DPP-9 (400 times). It inhibits the enzyme action up to 50% and 80% in dogs and monkeys, respectively, even when measured after 24 h at a single dose of 9 mg/kg. In humans, at the dose of 400 mg, a 90% inhibition of the enzyme is observed within 24 h; at the dose of 100 mg, a 50% inhibition is observed within 24 h [72]. It is excreted unchanged through the kidneys; its half-life is 10–13 h [73]. Currently, it is in Phase III of the clinical trials (CTs).

Pattzi H.M. et al. [74] determined the efficacy and tolerability of dutogliptin in type 2 diabetes patients in a 12-week, multicenter, randomized, double-blind, placebo-controlled study. The patients with a body mass index of 25–48 kg/m^2 and an initial HbA1c level of 7.3–11.0% were randomized to the following groups: dutogliptin – 200 or 400 mg per day, or placebo in addition to taking metformin, thiazolidinedione, or their combinations. After 12 weeks, the use of dutogliptin at the both dosages made it possible to achieve a decrease in the level of HbA1c by 0.52 and 0.35% in the groups treated at the doses of 400 mg (p <0.001) and 200 mg (p=0.006, placebo-corrected values), respectively. The proportion of patients who additionally received 400 and 200 mg of dutogliptin or placebo and achieved the target level of HbA1c <7%, was 27, 21 and 12%, respectively. The fasting plasma glucose levels were significantly lower in both the combination treatment groups compared with placebo: a placebo-adjusted difference of -1.00 mmol/l (p <0.001) for the 400 mg dutogliptin group and -0.88 mmol/ L (p=0.003) for the 200 mg group. Dutogliptin caused a significant decrease in *postprandial* glucose AUC0-120 in both 400 and 200 mg groups (the placebo-corrected values were -2.58 and -1.63 mmol/l/h, respectively). The authors conclude that the treatment with dutogliptin in the combination therapy with metformin and/or thiazolidinedione for 12 weeks improved a glycemic control in the type 2 diabetes patients.

Garcia-Soria G. et al. [75] determined the efficacy and tolerability of dutogliptin (PHX1149) in the type 2 diabetes patients in a multicenter, randomized, double-blind, placebo-controlled 4-week study. The patients with a baseline HbA1c level of 7.3 to 11% were randomized into 4 groups: dutogliptin at the doses of 100, 200, or 400 mg per day, or placebo against the background of a continuous metformin therapy, or metformin+glitazone. In all the groups treated with dutagliptin, there was a significant decrease in glucose AUC0-120 (approximately by 20%). *Postprandialiy,* there was an increase in $AUC_{0–120}$ GLP-1 by 3.90±2.83 pmol/l/h in the placebo group, 11.63±2.86 pmol/l/h in the 100 mg group, 16.42±2,72 pmol/l/h in the 200 mg group and 15.75±2.71 pmol/l/h in the 400 mg dutogliptin group. HbA1c levels were reduced in all the groups treated with dutogliptin; the placebo-corrected change in the 400 mg group was 0.28%. The frequency of adverse events did not differ between the dutogliptin and placebo groups. The authors conclude that the addition of dutogliptin to the chronic metformin or metformin+glitazone therapy in type 2 diabetes patients is well tolerated and improves a glycemic control.

Schenk R. and Nix D. [76] studied the effect of dutogliptin separately and in combination with a granulocyte colony-stimulating factor (G-CSF), which mobilizes stem cells from the bone marrow into the peripheral circulation. According to the authors, dutogliptin prevents the cleavage of the SDF-1 factor of stem cells. The administration of a high/low dose of dutogliptin (the exact doses of dutogliptin are not specified by the authors) in combination with G-CSF for 28 days after a simulated myocardial infarction significantly improved the animal survival and a myocardial remodeling reduced an infarct size compared with dutogliptin and G-CSF used separately. The authors report a planned CT to evaluate the effect of dutogliptin in combination with G-CSF in patients with myocardial infarction.

3.4. Saxagliptin (BMS-477118, Onglyza®, Bristol-Myers Squibb)

Saxagliptin is the first methanopyrrolidine-based iDPP-4. Compared to DPP-8 and DPP-9, saxagliptin is selective and highly active (IC_{50}=26 nM). Saxagliptin inhibits a DPP-4 activity by 80% and 57% for up to 90 min and 24 h, respectively, when taken once at the dose of 10 mg, and at a single dose of 100 mg, it reduces the DPP-4 activity by more than 95%. A bioavailability is about 67% [13]. It is metabolized to active metabolite (M_2). The apparent elimination half-life ($T_{1/2}$) for saxagliptin is 2–4 h, and $T_{1/2}$ for the M_2 metabolite is 3–7 h. The use of the drug significantly reduces the concentration of HbA1c. The drug was approved by the US FDA in 2009.

Rosenstock J. et al. [77] conducted a 12-week, multicenter, randomized, double-blind, placebo-controlled study in type 2 diabetes patients (HbA1c=6.8–9.7%). The patients received saxagliptin at the doses of 2.5, 5, 10, 20, or 40 mg once-daily for 12 weeks (a low dose group). In the second group, the patients received saxagliptin at the dose of 100 mg once-daily for 6 weeks (a high dose group). In all the treatment groups, saxaglipin significantly reduced HbA1c by 0.7–0.9% from the mean baseline compared with placebo (-0.3%). The effect did not depend on the dose. Saxagliptin significantly reduced the concentration of glucose measured on an empty stomach (0.8–1.4 mmol/l). 60 minutes after a meal, the glucose

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levels were lower than in the placebo group by 1.33–1.28 mmol/l. Saxagliptin improved a β-cell function (HOMA) at all the doses. The side effects (hypoglycemia, headache, dyspepsia) were similar to placebo in all the treatment groups.

Matthaei S. et al. [78] studied the efficacy of the saxagliptin administration at the dose of 5 mg per day (compared with placebo) in type 2 diabetes patients (the mean HbA1c was 7.9%) treated with dapagliflozin 10 mg per day and metformin for 52 weeks. The adjusted mean change in HbA1c from the baseline at week 52 was greater in the saxagliptin group than in the placebo one (-0.38% *vs.* 0.05%). The number of patients who achieved the target HbA1c <7% in the group treated with saxagliptin compared with placebo (29% *vs.* 13%), was also higher. The weight loss (≤1.5 kg) was observed in the both groups. A comparable number of patients reported one or more adverse events (58%). The authors conclude that a triple therapy with saxagliptin in addition to dapagliflozin and metformin for 52 weeks improved a glycemic control without any weight gain or an increased risk of adverse events.

Chacra A.R. et al. [79] evaluated the efficacy and safety of saxagliptin in combination with glyburide versus monotherapy in type 2 diabetes patients. The patients received saxagliptin at the doses of 2.5 or 5 mg in combination with glyburide (7.5 mg), while the control group received only glyburide (10 mg) for 24 weeks. In the saxagliptin groups, a more pronounced decrease in the HbA1c concentration was observed (-0.54% in the 2.5 mg group, -0.64% in the 5 mg group *vs.* +0.08% in the glyburide group; p <0.0001) and glucose measured on an empty stomach (-0.389, -0.556 *vs.* +0.056 mmol/L). The number of patients who achieved the target level of HbA1c <7% in the saxagliptin group (2.5 and 5 mg) was greater compared with the glyburide one (22.4 and 22.8% *vs.* 9.1%; p <0.0001).

In a safety study of saxagliptin, in the patients who had taken it at the dose of 5 mg per day for 2 years, the number of patients who were hospitalized for a heart failure in the saxagliptin group was more than in the placebo group (3.5 *vs.* 2.8%). In the absence of an effect on the incidence of ishemia, the rate of hospitalization for a heart failure was not significantly higher. In 2016, the FDA, referring to this study, reported that saxagliptin may increase the risk of developing a heart failure, especially in the patients who had already had heart or kidney diseases. Therefore, the FDA recommends that healthcare professionals consider discontinuing saxagliptin-containing products in the patients who have developrd or are developing a heart failure [80].

In the review research on saxagliptin [81] by Petunina N.A. and Brashchenkova A.V., a number of foreign studies on this drug were summarized. The authors report not only the effectiveness of saxagliptin, but also its high safety. Thus, the subscription of saxagliptin to the patients with type 2 diabetes and a chronic kidney disorder is possible at any stage of the disease, including terminal. The use of saxagliptin is also justified in case of an impaired liver function, including any degree of a liver failure. A very important advantage of saxagliptin can be also considered its cardiovascular safety, confirmed by the results of a meta-analysis of 8 clinical trials.

Kosaraju J. et al. [82] studied the effect of saxagliptin in rats with streptozocin-induced Alzheimer's disease (AD). Three months after the induction of AD, the animals were administered with saxagliptin *p.o.* (0.25, 0.5 and 1 mg/kg) for 60 days. Saxagliptin minimized cognitive deficits, which can be associated with a decrease in the amyloid concentration, tau protein phosphorylation and neuroinflammation, and also showed neuroprotective properties.

3.5. Linagliptin (BI-1356, Tradjenta®, Boehringer Ingelheim)

Linagliptin is a second-generation xanthine-based DPP-4 inhibitor. One of the most highly active (IC_{50}=1.0 nM) and selective for DPP-4 (compared to DPP-8 and DPP-9 by >10 000 times). A bioavailability is approximately 30%, a half-life is 113–131 h. At a single dose of 10 mg/kg, the inhibition of plasma DPP-4 is ≥80% and it persists for 24 h. It was approved by the FDA in the USA in 2011. Unlike other inhibitors, it actively binds to plasma proteins (>80%) and is practically not metabolized. Linagliptin is excreted mainly in the bile (84.7% after the oral administration and 58.2% after the intravenous administration) and less through the kidneys (5.4% after the administration *p.o.* and 30.8% after the intravenous administration). Thus, a dose adjustment for a renal insufficiency is practically not required, which can be an important advantage for the patients with type 2 diabetes and nephropathy [83].

The study by del Prato S. et al. [84] reported the results of a phase 3 multicenter randomized trial of linagliptin. The dosage of the drug was 5 mg per day for the patients with type 2 diabetes who had received the drug for 24 weeks. The average decrease in the concentration of HbA1c, compared with the initial values, was -0.69% (p <0.0001). The severity of the hypoglycemic effect depended on the initial level of HbA1c. So, for the group with the initial level of HbA1c <7.5%, its decrease after the treatment was -0.57%, with HbA1c=7.5–8% – -0.55% (p <0.005), with HbA1c 8–9% – -0.71% (p <0.0001), and with HbA1c ≥9%, the decrease was 1.1% (p <0.0001). In the group treated with linagliptin, there was also a more significant decrease in the glucose concentration measured on an empty stomach (1.3 mmol/l; p <0.0001) and 2 h after a meal (3.2 mmol/l; p <0.0001). The proportion of the patients

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achieving HbA1c <7% after 24 weeks of treatment was 25.2% in the linagliptin group and only 11.6% in the placebo group (p=0.0006).

Taskinen M.R. et al. [85] studied the effect of lingaliptin (5 mg per day) in patients with the uncompensated type 2 diabetes treated with metformin at the dose of ≥1500 mg per day for 24 weeks. In the patients receiving linagliptin in addition to metformin, there was a greater decrease in HbA1c compared with placebo adjusted mean changes from the baseline (-0.49 *vs.* 0.15% placebo), fasting glucose (-0.59 *vs.* 0.58 mmol/l placebo) and glucose levels 2 h after a meal (-2.7 vs. 1.0 mmol/l in the placebo group); p <0.0001. The episodes of hypoglycemia were observed in 3 patients (0.6%) treated with linagliptin and 5 patients (2.8%) in the placebo group. The authors conclude that the addition of linagliptin 5 mg once-daily to the patients with type 2 diabetes resulted in a clinically significant improvement in the glycemic control without increasing the risk of hypoglycemia.

Forst T. et al. [86] compared the effects of linagliptin at the doses of 1, 5 and 10 mg once-daily, glimepiride (1–3 mg once-daily) and placebo in the type 2 diabetes patients with an inadequate glycemic control (HbA1c ≥7.5–10%) with metformin monotherapy. After 12 weeks of treatment, the placebo-corrected mean change in HbA1c levels in the group treated with linagliptin 1 mg was -0.40%, 5 mg -0.73%, 10 mg -0.67%. For glimepiride, the change in mean placebo-adjusted HbA1c from the baseline was –0.9%. The frequency of adverse events was low and comparable in all groups. There were no episodes of hypoglycemia in the linagliptin or placebo groups, in contrast to the glimepiride group (5%).

Owens D.R. et al. [87] reported the results of a multicenter, 24-week, randomized, double-blind clinical trial conducted in type 2 diabetes patients treated with linagliptin at the dose of 5 mg per day or placebo when added to the main therapy with metformin or a sulfonylurea drug. At week 24, a change in the mean placebo-adjusted HbA1c from the baseline was -0.62% (p <0.0001). More patients with the baseline HbA1c ≥7.0% achieved HbA1c <7.0% in the linagliptin group compared with placebo (29.2% *vs.* 8.1%; p <0.0001). The fasting plasma glucose concentration was lower in the linagliptin group compared with placebo (p <0.0001). In addition to metformin or a sulfonylurea, linagliptin also showed significant improvements in the β-cell function (p <0.001). The proportion of patients with serious adverse effects was low in both groups (linagliptin 2.4%, placebo 1.5%). The episodes of hypoglycemia were observed in 16.7 and 10.3% of patients in the linagliptin and placebo groups, respectively. Hypoglycemia was mostly mild to moderate; severe hypoglycemia was noted in 2.7 and 4.8% of participants in the linagliptin and placebo groups, respectively. The authors note that in type 2 diabetes patients, the addition of linagliptin to the combination therapy with metformin and sulfonylurea drugs significantly improved the glycemic control and was well tolerated.

In the course of a two-year study of the linagliptin efficacy (5 mg per day) and glimepiride (1–4 mg per day) in combination with metformin in patients with the uncompensated type 2 diabetes, the average reduction in HbA1c with linagliptin was -0.16%, and glimepiride -0.36%. HbA1c levels less than 7% at week 104 of the treatment were observed in 30% of patients in the linagliptin group and 35% in the glimepiride group. In the linagliptin group, there were fewer episodes of hypoglycemia compared with glimepiride (7 and 36%, respectively) [88].

Kosaraju J. et al. [15] studied the efficacy of linagliptin in 3xTg-AD mice (a transgenic line of mice with AD). The mice were administered with linagliptin *p.o.* (5, 10 and 20 mg/kg) for 8 weeks. The authors found out that the treatment with linagliptin for 8 weeks dose-dependently reduced cognitive deficits, increased the concentration of incretins in the brain, and reduced the tau-phosphorylation, neuroinflammation, and β-amyloidization processes. The authors noted that linagliptin has nootropic properties, which can be explained by the passage of more GLP-1 and GIP through the BBB and an increase in the concentration of incretins in the brain.

3.6. Alogliptin (SYR-322, Nesina® in the US and Vipidia® in Europe, Takeda)

Alogliptin is a third generation DPP-4 inhibitor based on pyrimidinedione (IC_{50}=7 nM) [89]. It is highly selective (>10 000 times) for DPP-4 (compared to other isoenzymes such as DPP-2, DPP-8, DPP-9, etc.), inhibits DPP-4 by more than 90%. The effect persists for 24 h when used at the dose of 25 mg per day. Alogliptin is not extensively metabolized: 60–71% of it is excreted unchanged by the kidneys. There are two minor metabolites, N-demethylated alogliptin (less than 1% of the parent compound) and N-acetylated alogliptin (less than 6% of the parent compound). The N-demethylated metabolite is active and is an inhibitor of DPP-4. About 10–20% of the drug dose is metabolized in the liver under the influence of cytochromes CYP3A4 and CYP2D6. The bioavailability of alogliptin is approximately 100%. It has been approved by the FDA since 2013.

DeFronzo R.A. et al. [90] conducted a 26-week, double-blind, placebo-controlled study in patients with the uncompensated type 2 diabetes and an average initial level of HbA1c=7.9%. The authors found out that the use alogliptin at the doses of 12.5 mg, 25 mg, or placebo 1 once-daily, led to a significant decrease in the

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concentration of HbA1c and glucose, measured on an empty stomach compared with placebo. In the patients receiving 25 mg of alogliptin, a decrease the in HbA1c concentration by 0.6% was observed. At the same time, at week 26 of the treatment, 44% of patients reached the level of HbA1c ≤7%. Significant changes in the fasting glucose concentration and HbA1c were noted as early as week 1. The incidence of side effects (67.4–70.3%) and hypoglycemia (1.5–3.0%) was similar in all the treatment groups. The authors concluded that monotherapy with alogliptin in patients with type 2 diabetes is well tolerated and significantly improves a glycemic control without increasing the incidence of hypoglycemic conditions.

Rosenstock J. et al. [91] also studied the effects of alogliptin in patients with the uncompensated type 2 diabetes with an HbA1c level of about 8.8% in a 26-week, double-blind study. The patients received alogliptin 25 mg per day, pioglitazone 30 mg per day, alogliptin/pioglitazone 12.5/30 mg, or alogliptin/pioglitazone 25/30 mg per day. A combination therapy with alogliptin/pioglitazone (25/30 mg) caused a more significant decrease in the HbA1c concentration (-1.7±0.1%) compared with other groups (alogliptin 25 mg – -1.0±0.1%; p <0.001, pioglitazone 30 mg – -1.2±0.1%, p <0.001 and fasting glucose (-2.8±0.2 mmol/l) *vs.* alogliptin 25 mg group (-1.4±0.2 mmol/l; p<0.001) or pioglitazone 30 mg (-2.1±0.2 mmol/l; p=0.006). The combination of alogliptin (25 mg) and pioglitazone (30 mg) when taken once a day led to a more significant (than monotherapy) decrease in the plasma HbA1c concentration (1.7%) and fasting glucose (-24 mg/dl, which corresponds to 1.33 mmol/l).

Chen X.W. et al. [92] reported the results of a multicenter, randomized, double-blind, placebo-controlled, 26-week use of alogliptin in patients with type 2 diabetes (the mean baseline HbA1c=8.4%). The patients were randomized to the following groups: placebo; metformin 500 or 1000 mg bid; alogliptin 12.5 mg bid; alogliptin 25 mg once-daily; alogliptin 12.5 mg with metformin 500 mg bid or alogliptin 12.5 mg with metformin 1000 mg bid. Both combination therapy options (alogliptin 12.5 mg and metformin 500 or 1000 mg) produced statistically significant improvements in HbA1c and fasting glucose compared with monotherapy. In the groups receiving a combination therapy, the number of patients who achieved the target levels of HbA1c (compared with monotherapy) – 47 and 59% *vs.* 20–34% – was also higher. The authors concluded that alogliptin in combination with metformin significantly improved a glycemic control in patients with type 2 diabetes.

Pratley R.E. et al. [93] presented the results of a 26-week placebo-controlled study in patients with the uncompensated type 2 diabetes who had received pioglitazone separately or in combination with metformin or sulfonylurea (10 mg) (the baseline HbA1c=8%). The addition of alogliptin 25 mg per day to the pioglitazone therapy resulted in statistically significant improvements from the baseline HbA1c and decreased fasting glucose compared to placebo. A clinically significant decrease in HbA1c levels was observed in combination with alogliptin compared with placebo, regardless of the fact whether the subjects simultaneously received metformin or sulfonylurea (0.2% placebo *vs.* 0.9% alogliptin) or pioglitazone (0% placebo *vs.* 0.52% alogliptin).

The safety of alogliptin was studied in patients with type 2 diabetes associated with an acute coronary syndrome (ACS). The patients received alogliptin or placebo in addition to hypoglycemic therapy for 18 months. Mortality from cardiovascular diseases was 4.1% in the alogliptin group and 4.9% in the placebo group. Hospitalization for a heart failure was required in 3.9% of the patients treated with alogliptin compared with 3.3% in the placebo group [94]. Referring to this study, the FDA reported in 2016 that alogliptin (as well as saxagliptin) can increase the risk of a heart failure, especially in the patients who had already had a heart or kidney disease. As a result, the FDA recommended that healthcare professionals consider discontinuing the use of the drugs containing alogliptin in the patients who have a risk of developing a heart failure.

Mkrtumyan A.M., the Head of the Department of Endocrinology and Diabetology, the Faculty of Medicine, Moscow State Medical and Dental University named after A.I. Evdokimov, published a number of review articles on the efficacy and safety of alogliptin, both in monotherapy and in combination with other antidiabetic drugs [95, 96]. It was concluded that the use of alogliptin in patients at a high risk of a cardiovascular failure is not associated with the development of new events, and after a recent ACS, the risk of death from cardiovascular complications during the treatment with alogliptin is not higher than in the patient's taking placebo.

3.7. Gemigliptin (LC15-0444, Zemiglo®, LG Life Sciences)

Gemigliptin is a structural analog of sitagliptin, it has a long inhibitory effect on DPP-4 (IC_{50}=6.3 nM), with a high selectivity against isoenzymes DPP-8 (more than 27 000 times), DPP-9 (more than 23 000 times), FAP-α (over 41 000 times). After the oral administration, about 10% of the dose is metabolized to the active metabolite LC15-0636, which is twice as potent as gemigliptin. Its absolute bioavailability is more than 63%, it inhibits the activity of DPP-4 by more than 80%, and the effect persists for 24 h. The drug has been approved for the treatment of type 2 diabetes in the South Korea [97].

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Rhee E.J. and co-authors studied the effect of different doses of gemigliptin (50, 100 and 200 mg per day) in a double blind, randomized study for 12 weeks [98]. All the three doses of gemigliptin significantly reduced HbA1c from the baseline (-0.06 in the placebo group *vs.* -0.98, -0.78, and -0.74% in the 50, 100, and 200 mg groups, respectively), with no significant differences between the doses. The patients with higher baseline HbA1c levels (≥8.5%) experienced greater reductions. After 12 weeks of treatment, the insulin sensitivity and secretion improved significantly, and the concentrations of total cholesterol and low-density lipoprotein decreased in the 50 and 200 mg per day groups compared to the placebo group. The authors conclude that the treatment with gemigliptin (50 mg per day) for 12 weeks reduces HbA1c and fasting glucose, improves an insulin sensitivity and a β-cell function, and is well tolerated by patients.

A randomized, double-blind, phase III study evaluated the efficacy of gemigliptin in combination with metformin [99]. The patients had been randomized to receive gemigliptin 50 mg per day, metformin (long-acting) or a combination of the two once-daily. The mean daily dose of metformin at week 24 was 1.7 mg in combination with gemigliptin and 1.9 mg in the metformin monotherapy group, respectively. The mean change in HbA1c from the baseline was -2.1% in the gemigliptin+metfomin group compared to -1.2% in the gemigliptin group and -1.5% in the metformin group, respectively (p <0.0001). The differences in achieving the target HbA1c level of 6–7% were also statistically significant (p <0.0001) between the groups receiving combined and monotherapy. The authors conclude that gemigliptin and metformin are effective treatments for type 2 diabetes.

3.8. Teneligliptin (MP-0513, Tenelia®, Mitsubishi Tanabe)

Teneligliptin is a bicyclic derivative of heteroarylpiperazine. It has high activity (IC_{50}=1.8 nM) and selectivity for DPP-4 in comparison with DPP-8 more than 700 times, and DPP-9 – more than 1460 times. The half-life in rats is 8–16 h, a bioavailability at the dose of 0.1–1.0 mg/kg *p.o.* is 63–85%. 65.6% of the drug dose is metabolized. It inhibits the activity of plasma DPP-4 by more than 50% within 24 h after a single dose of 1 mg/kg and significantly reduces the concentration of glucose in the blood in a dose-dependent manner [100]. Teneligliptin was approved for the treatment of type 2 diabetes in Japan in 2012.

Kadowaki T. and Kondo K. [101] studied various doses of teneligliptin (10, 20 and 40 mg per day) *vs.* placebo in the patients with uncompensated type 2 diabetes in monotherapy for 12 weeks. In all the groups, with the exception of placebo, there was a decrease in the concentration of HbA1c and fasting glucose. The difference in the HbA1c reduction was not significant between the groups receiving different doses of teneligliptin, and it was -0.9% for the doses of 10 and 20 mg, and -1.0% for 40 mg. The difference in fasting glucose declines between placebo and teneligliptin 10, 20, and 40 mg was -17.8 mg/dL (0.9 mmol/l), -16.9 mg/dl (0.9 mmol/l) and -20.0 mg/dl (1.1 mmol/l), respectively (p <0.001).

Otsuki H. et al. [102] studied the effects of teneligliptin at the dosage of 20 mg per day in patients with type 2 diabetes and a terminal stage of the renal disease. After 4 weeks of treatment, the plasma glucose concentration decreased by 36.7 mg/dL (2.0 mmol/l), and at week 24, the difference in HbA1c between the teneligliptin and control groups was -3.1% (p <0.05) and -0.57% (p=0.057), respectively. These parameters were also reduced in the patients who had started teneligliptin instead of voglibose 0.2 mg tid or vildagliptin 50 mg/day due to a poor glycemic control. The authors concluded that teneligliptin (20 mg per day) was well tolerated, safe, significantly improved a glycemic control, and was more effective than either voglibose or vildagliptin.

Hasikata T. et al. [103] studied the effect of teneligliptin on the endothelial and left ventricular function in patients with type 2 diabetes who had been taking the drug at the doses of 20 or 40 mg per day for 3 months. Compared to the baseline levels, HbA1c decreased (from 7.6±1.0 to 6.9±0.7%; p <0.01). 3 months after the end of treatment, there was an improvement in the systolic and diastolic function of the left ventricle, an improvement in the endothelial function: RH-PAT index (Reactive Hyperemia Peripheral Arterial Tonometry) increased from 1.58±0.47 to 2.01±0.72%; p <0.01). In addition, the concentration of circulating adiponectin increased from 27.0±38.5 to 42.7±33.2 pg/mL, which corresponds to 0.09±0.13 and 0.15±0.12 nmol/l, respectively (p <0.01) without changes in patients' body weight. The authors conclude that the teneligliptin treatment improved a left ventricular and endothelial function and also increased serum adiponectin concentrations. These results confirm the cardioprotective effects of teneligliptin in patients with type 2 diabetes.

Kadowaki T. and Kondo K. [104] reported the results of a double-blind, placebo-controlled study in which patients with type 2 diabetes had received teneligliptin at the dose of 20 mg per day in combination with glimepiride (1–4 mg per day). After 12 weeks of treatment in the group receiving combination therapy, the concentration of HbA1c glucose measured on an empty stomach and 2 h after a meal, decreased (the difference with the group receiving placebo and glimepiride was -1.0% HbA1c, -1.5 mmol/l glucose measured on an empty stomach and -2.7 mmol/l after a meal). The entire study lasted 52

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weeks, by the end of this period there was a significant (p <0.001) decrease in HbA1c levels compared to the baseline, and the improvement in the glycemic control (p <0.05).

In another study, Kadowaki T. and Kondo K. [105] investigated the effectiveness of the combined use of teneligliptin 20 mg per day and pioglitazone (15–30 mg per day) in patients with type 2 diabetes for 12 weeks. In the group receiving a combination therapy, there was a decrease in the concentration of HbA1c, fasting glucose and 2 h after a meal (the difference with the placebo and pioglitazone group was -0.7% HbA1c, -16.4 (or 0.911 mmol/l) and -51.3 mg/dl (or 2.85 mmol/l) for fasting and 2 h *postprandial* glucose, respectively).

When studying the combination therapy efficacy with teneligliptin (20 mg per day) and metformin (≥1000 mg per day) in patients with type 2 diabetes for 16 weeks, a difference was notified between the teneligliptin and placebo groups in terms of changes in the HbA1c concentration and glucose measured on an empty stomach (-0.78% and -1.24 mmol/l (22.42 mg/dl), respectively [106].

Tanaka K. et al. [107] studied the effects of teneligliptin (20 mg/day) and linagliptin (5 mg per day) in patients with type 2 diabetes and a chronic renal failure (CRF) in a 12-day crossover study. The patients took teneligliptin or linagliptin for 6 days, and then changed the drug. The average amplitude of changes in the glucose concentration was 83.8±34.0 mg/dl (4.7±1.9 mmol/l) in the linagliptin group and 82.6±32.6 mg/dl (4.6±1.8 mmol/l) in the teneligliptin group. The both drugs reduced the average 24-hour glucose concentration comparablely; there was no significant difference in the maximum and minimum glucose concentrations between them. The authors concluded that in the patients with type 2 diabetes and a chronic renal failure, teneligliptin or linagliptin reduce blood glucose concentrations comparable, having the same safety profile.

3.9. Anagliptin (SK-0403, Suiny®, Sanwa Kagaku Kenkyusho)

Anagliptin is a 2-methyl-pyrazolopyrimidine derivative of cyanopyrrolidine, it has a high activity (IC_{50}=3.8 nM) and a selectivity for DPP-4 compared to DPP-8 and DPP-9 (more than 10 000 times), its bioavailability is about 73%. Metabolite M_1 (carboxylate) is 29.2% of the dose, the share of other metabolites is about 1%. The half-life of anagliptin is 4.4 h, for M_1 it is 9.9 h [108]. The drug dose-dependently inhibits the activity of DPP-4 by 95% at the dose of 3 mg/kg, increases the level of GLP-1 insulin and improves the glycemic control. Anagliptin was approved for the treatment of type 2 diabetes in Japan in 2013.

Kaku K. et al. [109] published the data on the results of a multicenter, randomized, double blind, and placebo-controlled study of anagliptin in patients with type 2 diabetes. The patients received anagliptin (25 to 200 mg bid) or placebo for 12 weeks. In the anagliptin groups, the HbA1c concentration was significantly and dose-dependently lower (25–100 mg), and the difference between the 100 and 200 mg groups was only 0.07%. In the subgroup with the initial HbA1c level of 8.4% or more, the decrease in the HbA1c concentration was significantly greater in the 200 mg group than in the 100 mg bid group. However, the authors conclude that the optimal dose is 100 mg bid, and in the patients with high HbA1c levels, a dose of 200 mg bid can be also used.

Yang H.K. et al. [110] reported the results of a double blind, randomized, placebo-controlled trial in which patients took anagliptin 100 or 200 mg bid or placebo for 24 weeks. At the end of the study, the concentration of HbA1c was significantly lower in the groups treated with anagliptin at the dose of 100 mg (-0.50±0.45%) and 200 mg (-0.51±0.55%). In the placebo group, the concentration of HbA1c increased over the same period (0.23±0.62%). Both doses of anagliptin significantly reduced both fasting plasma glucose (-0.53±1.25 and -0.72±1.25 mmol/l, respectively) and the proinsulin/insulin ratio (-0.04±0.15 and -0.07±0.18 mmol/l, respectively) compared with placebo. No significant change in the body weight from the baseline was observed in all 3 groups. After 24 weeks of treatment with anagliptin, the plasma DPP-4 activity was significantly lower and it was >75% for 100 mg and >90% for 200 mg. The authors concluded that anagliptin at the doses of 100 and 200 mg bid, effectively improves a glycemic control in patients with type 2 diabetes.

Kakuda H. et al. [111] studied the effect of anagliptin on glucose and lipid metabolism, as well as the development of the oxidative stress in patients with type 2 DM. The patients received 200 mg of anagliptin per day *p.o.* for 12 weeks; after that, they were observed for another 12 weeks (the total study lasted 24 weeks). At week 12 of the study, an increase in the early phase insulin secretion, a decrease in HOMA-R and fasting glucose concentrations were found out, indicating a positive effect of anagliptin on the insulin resistance and insulin secretion. After 12 weeks of the treatment, anagliptin reduced the concentration of plasma glucose, triglycerides, atherogenic lipoproteins and LDL, which returned to the level at week 24 (after the drug withdrawal). The authors summarize that since postprandial (alimentary) lipidemia promotes the production of pro-inflammatory cytokines, the development of the oxidative stress and, as a result, the occurrence of the endothelial dysfunction, the use of anagliptin can slow down the development of these conditions.

Kaku K. et al. [112] studied the effects of anagliptin in the combination therapy with an α-glucosidase

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inhibitor, metformin, sulfonylurea drugs (glimepiride, glibenclamide) or thiazolidinedione (pioglitazone) in patients with uncompensated type 2 diabetes (HbA1c=6.9–10.4%) for 52 weeks. An additional 200 mg of anagliptin per day (100 mg bid) or placebo was added to the patients' main therapy. The authors noted an improvement in glycemic parameters (HbA1c) comparable between the groups treated with anagliptin and significantly different from placebo as early as the 12th week.

3.10. Omarigliptin (MK-3102, Marizev®, Merck)

Omarigliptin was developed by Merck and approved for use in Japan in 2015. The drug is an analogue of sitagliptin based on aminotetrahydropyran, in which the central basis of sitagliptin is changed to rigid cyclohexylamine. It is highly active (IC_{50}=1.6 nM) and selective for DPP-4 isoenzymes. Omarigliptin has a unique pharmacokinetic profile with a half-life of about 68 h, once-weekly dosing, and a bioavailability of about 74% [113]. During a 12-week study, it was shown that its use at the dose of 25 mg reduces the concentration of blood glucose and HbA1c. It inhibits plasma DPP-4 by 77–89% for up to 168 h after a single dose and increases the concentration of GLP-1 almost twice. The drug is highly specific for other proteases (IC_{50}>67 μM), including DPP-8, DPP-9, QPP, FAP, PEP; it has a biphasic pharmacokinetic profile, phase I α (40–50 h) and phase I β (93-116 h). The drug is excreted mainly through the kidneys unchanged, through the intestines – about 3%. C_{max}=750 nmol/l, the half-life is about 68 h, T_{max}=0.75–4 h [113].

Sheu W. et al. [114] studied the effects of omarigliptin at the doses of 0.25, 1, 3, 10 and 25 mg per week for 78 weeks compared with placebo in patients with type 2 diabetes. 12 weeks after starting the treatment, omarigliptin reduced HbA1c levels in a dose-dependent manner (the dose of 0.25 mg was minimally effective). Omarigliptin also reduced the concentration of glucose measured on an empty stomach (-1.3 mmol/l) and 2 h after a meal (-2.5 mmol/l). All doses of the drug were well tolerated, and the incidence of adverse effects did not depend on the dose. The authors note that the level of an inhibitory activity of omarigliptin at the dose of 25 mg per week differed little from that of sitagliptin taken at the dose of 100 mg (the measurements were made 168 h after taking omarigliptin and 24 h after taking sitagliptin) and amounted to more than 90%.

Evans R. and Bain S. [115] showed that the use of omarigliptin at the doses of 10–100 mg in healthy volunteers led to a more than twofold increase in the level of GLP-1. At the same time, a comparable increase in GLP-1 was observed in individuals with obesity, diabetes or without it. The authors report that in a 24-week study in the patients with poorly controlled type 2 diabetes who received metformin, omarigliptin at the dose of 25 mg per week, HbA1c reduced at the level comparable to sitagliptin (-0.47% omarigliptin and -0.43% sitagliptin). The authors also report a 54-week comparative study of omarigliptin (25 mg/weekly) and glimepiride (6 mg per day) in the patients with uncompensated type 2 diabetes receiving metformin. Glimepiride was more effective at lowering HbA1c levels (omarigliptin -0.30%, glimepiride -0.48%), as well as fasting glucose levels (omarigliptin -0.15 mmol/l, glimepiride -0.46 mmol/l); however, hypoglycemia was significantly more common in patients in the glimepiride group (26.7 and 5%, respectively).

Tan X. [116] reports the result of a 12-week study of omarigliptin at the doses of 0.25, 1, 3, 10, or 25 mg or placebo in patients with type 2 diabetes. The administration of omarigliptin at the dose of 25 mg per week *p.o.* demonstrated a significant reduction in HbA1c compared with placebo (p <0.001) as early as week 12 of treatment. A significantly higher proportion of patients treated with omarigliptin at the dose of 25 mg achieved the target HbA1c levels compared with placebo (<7% 33.6% *vs.* 21.8% placebo and <6.5% 13.6% *vs.* 4.5% placebo), which is due to a decrease in the plasma DPP-4 activity by 80.7% after 12 weeks of treatment.

3.11. Gosogliptin (PF-00734200, Saterex®, SatRx® or Saterex®, Pfizer)

The drug was developed by Pfizer, which subsequently transferred the exclusive molecule rights to the Russian Chemical Diversity Research Institute (CDRI) "Himrar", which is currently registered (at the end of 2016) and approved for use in the Russian Federation as a hypoglycemic drug. Gosogliptin is a diprolyl-derivative of piperazine with a high activity (IC_{50}=13 nM) and selectivity for DPP-4 in contrast to DPP-2 and DPP-8 (100 times), has a half-life of 2.7 h, its bioavailability is more than 99 %. The drug inhibits DPP-4 by 75% after 24 h. The main metabolic pathway of gosogliptin in humans is associated with the hydroxylation of the pyrimidine group, with the formation of the M5 metabolite (17.9% of the dose). The other 8 metabolites [117] are associated with amide hydrolysis, carbamoyl glucuronization, formamide conjugation, glucose conjugation, and creatinine. After the administration *p.o.*, about 77% of the gosogliptin dose is excreted by the kidneys, with 48.5% unchanged, another 10.5% is excreted through the intestines, with a significant proportion coming from gosogliptin metabolites. A half-life after the administration *p.o.* is about 20 h.

According to Muto S. et al. [118], in healthy volunteers, gosogliptin doubled the level of GLP-1 at the dose of 10 mg/kg and inhibited a DPP-4 activity by 75%, even after 24 h.

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Rosenstock J. et al. [119] investigated the effects of gosogliptin at the doses of 20 and 30 mg in patients with uncompensated type 2 diabetes who had already been treated with metformin for 12 weeks (a placebo-controlled, double-blind, randomized, multicenter study). In the patients treated with gosogliptin, a glycemic control improved significantly: compared with placebo, the concentration of HbA1c decreased by -0.79% (corresponding to 8.6 mmol/mol) in the group of the patients taking gosogliptin at the dose of 20 mg, and by -0.92% (corresponding to 10.1 mmol/mol) in the 30 mg group. The positive effects of gosogliptin did not depend on the dose, in contrast to the side ones. The authors conclude that the 20 mg dose of gosogliptin is preferred.

Terra S.G. et al. [120] studied a gosogliptin effect in patients with uncompensated type 2 diabetes (HbA1c=7–11%) in a multicenter, randomized, double-blind, placebo-controlled study. For 12 weeks, patients received metformin and placebo or gosogliptin at the doses of 2, 5, 10, or 20 mg per day. At the dose of 5 mg per day separately, gosogliptin caused a statistically significant decrease in HbA1c compared with placebo. Reductions in HbA1c were observed at -0.31% (2 mg), -0.74% (5 mg), -0.70% (10 mg), and -0.75% (20 mg). The authors note that the 20 mg per day dose provides a better glycemic control compared to the other doses and placebo.

In Russia, the efficacy and safety of gosogliptin was evaluated compared with vildagliptin as monotherapy in patients with type 2 diabetes in 26 clinical centers involving 299 patients [121]. The participants received gosogliptin 20 mg per day (titrated to 30 mg per day) or vildagliptin 50 mg per day (titrated to 100 mg per day) for 36 weeks. After 12 weeks of gosogliptin monotherapy, a mean decrease in HbA1c was 0.93% (p <0.05) and 1.03% (p <0.05) in the vildagliptin group. Side effects and episodes of hypoglycemia were infrequent and differed little between the groups. The authors concluded that gosogliptin has a comparable efficacy and safety profile to vildagliptin.

3.12. Denagliptin (GSK-823093, GW823093C, GlaxoSmithKline)

Since 2010, GlaxoSmithKline (UK) has been conducting denagliptin clinical trials. This compound is a member of the cyanofluoropyrrolidine class, it significantly inhibits DPP-4 (IC_{50}=22 nM), and is more than 100-fold selective to other DPP-4 isoforms. The maximum inhibition of DPP-4 is observed 30 minutes after thhhe administration at the dose of 25 mg and more than 85% persists after 24 h. It increases the levels of GLP-1/insulin and reduces the concentration of glucagon in the blood plasma. It has hepatic and extrahepatic metabolism and 13 metabolites [22].

As reported by Lotfy M. et al. [73], the pharmacokinetic profile, side effects and clinical effects of denagliptin are similar to those of vildagliptin and saxagliptin, but no study data (no reference sources) have been published. The clinical studies are ongoing.

3.13. Melogliptin (GRC 8200, GlenMark)

Melogliptin is a triazole-containing inhibitor of DPP-4 (IC_{50}=1.61 nM), it has a high selectivity for isoenzymes (10 000 times). Its half-life is 1.28, 4.31 and 2.15 h; a bioavailability (at the dose of 5 mg/kg) is 60, 90 and 94% in rats, dogs and monkeys, respectively [22].

According to Kushwaha R.N. et al. [22] when administered to mice db/db, melogliptin causes a decrease in the glucose concentration by 30% and increases insulin levels twice (in a single dose of 3 mg/kg administered *p.o.*). A single dose of 5 mg/kg completely inhibits a DPP-4 activity in dogs within 1 h and more than 90% when analyzed 6 h later. The clinical trials of melogliptin are ongoing.

3.14. Trelagliptin (SYR-472, Zafatec®, Takeda/Furiex)

Trelagliptin is a pyrimidinedione-based DPP-4 inhibitor (IC_{50}=4.2 nM), highly selective for isoenzymes (10 000 times). A bioavailability in rats is 50.3%, in dogs – 29.8%; the data on humans have not been published [22]. Like omarigliptin, trelagliptin is taken once a week and has a similar pharmacological profile. The drug has been approved for the type 2 diabetes treatment in Japan since 2015.

McKeage K. [122] reported that in healthy volunteers, 7 days after a single dose of trelagliptin (100 mg, 30 min before meals), the average maximum plasma concentration (C_{max}) after 1.3 h was 619.4 ng/mL. A mean half-life is 72–168 h; trelagliptin binds to plasma proteins by 22–28%, it is metabolized by cytochrome P450 (CYP2D6) and excreted mainly through the kidneys.

Grimshaw S.E. et al. [123] report that after 168 h of the 100 mg dose administration, the trelagliptin plasma concentration is sufficient to maintain its pharmacodynamic effect, the inhibition of the plasma DPP-4 activity occurs by 70%. The authors found out that trelagliptin has a slower dissociation rate compared to alogliptin (8 times), and also, unlike saxagliptin and vildagliptin (which are covalent inhibitors of DPP-4), trelagliptin binds to DPP-4 non-covalently.

In 2016, Inagaki N. et al. [124] studied the effects of trelagliptin 100 mg/weekly in patients with the uncompensated type 2 diabetes who had previously received hypoglycemic agents *p.o.* (a combination with sulfonylureas, glinide, α-glucosidase inhibitor, biguanide, or thiazolidinedione), and in monotherapy for 52 weeks. At the end of the treatment, the mean change in HbA1c from the baseline was -0.57% in the trelagliptin

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monotherapy group and -0.37, -0.25, -0.67, -0.31, and -0.74% in the combination therapy groups with sulfonylurea, glinide, α-glucosidase inhibitor, biguanide and thiazolidinedione, respectively. The proportion of the patients achieving HbA1c <7.0% at the end of the treatment was 36% for the trelagliptin monotherapy, 22.7, 34.4, 35.0, 46.9 and 44.6% for the combination therapy with sulfonylurea, glinide, α-glucosidase inhibitor, biguanide and thiazolidinedione, respectively. The inhibition of the DPP-4 activity was measured 7 days after the drug administration. It was found out that at the end of treatment, it persisted for 52 weeks and was 76.48–79.6%. The authors conclude that trelagliptin is a highly effective drug for the treatment of type 2 diabetes in monotherapy and in combination with existing hypoglycemic drugs, and once a week the administration is effective and reasonable.

3.15. Retagliptin (SP-2086, Jiangsu Hengrui Medicine)

Retagliptin is a tetrahydroimidazolo derivative [1,5-a]pyrazine (IC_{50}=8 nM), highly selective for DPP-4 compared to DPP-8 (3 263 times) and DPP-9 (9 438 times) [22]. Its half-life is 1.5 h. The drug reduces the concentration of glucose and its change during the oral glucose tolerance test. The clinical studies are ongoing.

Yong X. et al. studied a combined use of retagliptin and metformin in healthy volunteers (retagliptin 100 mg, metformin 1500 mg or retagliptin 100 mg+ metformin 1500 mg). The authors found out that the combination of retagliptin + metformin did not lead to clinically significant changes in the pharmacokinetics of retagliptin or metformin, compared with their use separately. $AUC_{0-\infty}$ and C_{max} of retagliptin used in combination, were 16.49% and 25.88% higher than for retagliptin in monotherapy; $AUC_{0-\infty}$ of metformin in combination with retagliptin was 22.06% more than in the metformin monotherapy. The authors conclude that the combined use of these drugs does not require a dose adjustment of any of them [125].

3.16. Evogliptin (DA-1229, Suganon®, Evodine® or Evodin®, Dong-A Pharmaceutical)

Evogliptin is a β-aminoamide derivative (IC_{50}=0.98 nM) and is highly selective for isoenzymes (6000-fold). The adminisration of the drug inhibits DPP-4 by more than 80% after a single dose of 5 mg, significantly reduces the level of HbA1c by 0.56% at the dose of 2.5 mg and by 0.61% at the dose of 5 mg. Its half-life is about 30 h and it does not depend on food intake, the bioavailability is 50.2% [22]. It is metabolized by the processes of oxidation, glucuronization and sulfation and has 4 metabolites. The drug was approved for the treatment of type 2 diabetes in Korea in 2015. The Russian pharmaceutical company GeroPharm has received a permission to conduct an international multicenter clinical trial (phase III) and is selling this drug in Russia.

Chae Y.N. et al. [126] investigated the effect of evogliptin in the model of diet-induced obesity in mice. After 2 weeks of treatment at the doses of 20, 60 and 200 mg/kg, it caused a dose-dependent decrease in fat mass and reduced the average size of adipocytes. The authors suggest that a part of the evogliptin-induced fat loss may be due to the acecelerated metabolism, which is not only associated with an increase in GLP-1.

Cho J.M. et al. [127] studied the effects of evogliptin with streptozotocin-induced diabetes (100 mg/kg streptozotocin ip) in C57BL/6 mice after 1 week without treatment, the mice received evogliptin at the dose of 300 mg/kg. An intraperitoneal glucose tolerance test (IPGTT) was performed 10 weeks after the treatment with evoligliptin by intraperitoneal (rather than oral, unlike the oral test) administration of 1 g/kg fasting glucose. In contrast to the control group, a significant decrease (p <0.05–0.005) in the blood glucose concentration was observed in the mice treated with evogliptin. Relatively low glucose concentrations were maintained in the animals even 6 weeks after the evogliptin treatment. Plasma insulin levels before (0 min) and 15 min after glucose administration were significantly higher in the mice treated with evogliptin compared to the controls (p <0.005). In addition, in the group treated with evogliptin, the mass of pancreatic β-cells, their proliferation and neogenesis was higher.

Gu N. et al. [128] studied evogliptin in healthy volunteers. At the dose of 5–20 mg, it inhibited a DPP-4 activity by more than 80% for 24 h in all groups, regardless of the dose, and increased postprandial GLP-1 levels by 1.5–2.4 times compared with placebo.

3.17. Carmegliptin (R-1579, F. Hoffmann-La Roche)

Carmegliptin (IC_{50}=6.8 nM) has a tricyclic base, its selectively inhibits DPP-4 compared to DPP-8, DPP-9 (more than by 100 times) and DPP-2 (more than by 2000 times). Its half-life is 6–8 h, and the bioavailability at 1 mg/kg is 33% in monkeys and 28% in rats [134 Mattei]. The drug is not metabolized, excreted unchanged through the liver and kidneys. Its use (once *p.o.* at the dose of 3 mg/kg) significantly reduces the concentration of glucose in the blood, inhibits the activity of plasma DPP-4 by 40 and 60% after 24 and 48 hours, respectively.

After the administration of 10 mg/kg carmegliptin in ZFR rats, in the course of the oral glucose tolerance test, Mattei R. et al. [129] observed an improvement in the glucose tolerance (30% compared with the control). In the db/db mice, there was a significant (p ≤0.05) decrease in the glucose concentration measured on an empty stomach 2 h after its administration compared

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with the control group. The authors also investigated the carmegliptin efficacy in the ZFR rats at the dose of 20 mg/kg administered for 7 days in the euglycemia model (Euglycemic Hyperinsulinemic Clamp). In this experiment, carmegliptin increased the insulin sensitivity, which was manifested by the maintenance of the normal blood glucose concentration after the administration *p. o.,* compared with the control group.

Kuhlmann O. et al. [130] noted that after the administration of carmegliptin in healthy volunteers, the plasma glucose concentration measured on an empty stomach and after a meal decreased, the secretion of GLP-1 and insulin increased, and the body weight decreased, lipid metabolism and the state of β-cells improved.

CONCLUSION

Despite a fairly large number of registered iDPP-4s, the interest of researchers in this therapeutic target does not fade away. The above DPP-4 ibids have different chemical structures, but they share a moderate hypoglycemic activity, which is expressed in a decrease in the level of HbA1c and AUC of glucose after a meal or an oral glucose tolerance test. For the drugs of this group, there is a high safety use, no effect on the body weight of patients and the possibility of the effective combination with other hypoglycemic drugs. Many of them are already used for the treatment of type 2 diabetes; others are in different phases of clinical trials. The drugs differ in the DPP-4 isoform selectivity, metabolism and pharmacokinetic profile. These factors determine their individual advantages in specific clinical situations.

Serious obstacles, due to which new DPP-4 inhibitors under development can fail in clinical trials, are the pharmacokinetic profile, inhibition of cytochrome P450 enzymes, and selectivity for DPP-4 isoenzymes, which depend on the chemical structure of a particular compound. This class of drugs is promising both in monotherapy for type 2 diabetes and when combined with other hypoglycemic drugs. The interest in the development of such drugs is fueled by the results of the studies that reveal the breadth of their pleiotropic effects due to the spectrum of biological effects of this enzymes group.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Denis V. Kurkin – idea, structure planning, graphic design; Dmitry A. Bakulin, Yuliya V. Gorbunova, Valeria B. Saparova – materials collecting, manuscript draft writing; Evgeniy I. Morkovin, Andrey V. Strygin, Elena V. Volotova – final version of the manuscript editing; Igor E. Makarenko, Roman V. Drai, Vladimir I. Petrov – consultations on highly specialized problems, editing and approval of the manuscript final version.

REFERENCES

1. Dedov II, Shestakova MV, Mayorov AYu, Mokrysheva NG, Vikulova OK, Galstyan GR, Kuraeva TL, Peterkova VA, Smirnova OM, Starostina EG, Surkova EV, Sukhareva OY, Tokmakova AY, Shamkhalova MS, Jarek-Martynova IR, Artemova EV, Beshlieva DD, Bondarenko ON, Volevodz NN, Gomova IS, Grigoryan OR, Dzhemilova ZN, Esayan RM, Ibragimova LI, Kalashnikov VY, Kononenko IV, Laptev DN, Lipatov DV, Melnikova OG, Mikhina MS, Michurova MS, Motovilin OG, Nikonova TV, Rozhivanov RV, Sklyanik IA, Shestakova EA. Standards of specialized diabetes care. Edited by Dedov II, Shestakova MV, Mayorov AYu. 10th edition. Diabetes mellitus. 2021;24(1S):1–148. DOI:10.14341/DM12802. Russian
2. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, Pavkov ME, Ramachandaran A, Wild SH, James S, Herman WH, Zhang P, Bommer C, Kuo S, Boyko EJ, Magliano DJ. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022 Jan;183:109119. DOI:10.1016/j.diabres.2021.109119
3. Hu Y, Chen Y. Overview of Type 2 Diabetes Drugs on the Market. J Biosci Med. 2020;8(8):1–14. DOI:10.4236/jbm.2020.88001
4. Röhrborn D, Wronkowitz N, Eckel J. DPP4 in Diabetes. Front Immunol. 2015 Jul 27;6:386. DOI:10.3389/fimmu.2015.00386
5. Drucker DJ. Dipeptidyl peptidase-4 inhibition and the treatment of type 2 diabetes: preclinical biology and mechanisms of action. Diabetes Care. 2007 Jun;30(6):1335–43. DOI:10.2337/dc07-0228
6. Nabeno M, Akahoshi F, Kishida H, Miyaguchi I, Tanaka Y, Ishii S, Kadowaki T. A comparative study of the binding modes of recently launched dipeptidyl peptidase IV inhibitors in the active site. Biochem Biophys Res Commun. 2013 May 3;434(2):191–6. DOI:10.1016/j.bbrc.2013.03.010
7. Matteucci E, Giampietro O. Dipeptidyl peptidase-4 (CD26): knowing the function before inhibiting the enzyme. Curr Med Chem. 2009;16(23):2943–51. DOI:10.2174/092986709788803114
8. Saisho Y. Incretin-based therapy and pancreatitis: accumulating evidence and unresolved questions. Ann Transl Med. 2018 Apr;6(7):131. DOI:10.21037/atm.2018.02.24

ISSN 2307-9266 e-ISSN 2413-2241

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9. Kubota S, Haraguchi T, Kuwata H, Seino Y, Murotani K, Tajima T, Terashima G, Kaneko M, Takahashi Y, Takao K, Kato T, Shide K, Imai S, Suzuki A, Terauchi Y, Yamada Y, Seino Y, Yabe D. Association of dipeptidyl peptidase-4 inhibitor use and risk of pancreatic cancer in individuals with diabetes in Japan. J Diabetes Investig. 2023 Jan;14(1):67–74. DOI:10.1111/jdi.13921
10. Dicembrini I, Montereggi C, Nreu B, Mannucci E, Monami M. Pancreatitis and pancreatic cancer in patientes treated with Dipeptidyl Peptidase-4 inhibitors: An extensive and updated meta-analysis of randomized controlled trials. Diabetes Res Clin Pract. 2020 Jan;159:107981. DOI:10.1016/j.diabres.2019.107981
11. Shao S, Xu Q, Yu X, Pan R, Chen Y. Dipeptidyl peptidase 4 inhibitors and their potential immune modulatory functions. Pharmacol Ther. 2020 May;209:107503. DOI:10.1016/j.pharmthera.2020.107503
12. Mentlein R. Mechanisms underlying the rapid degradation and elimination of the incretin hormones GLP-1 and GIP. Best Pract Res Clin Endocrinol Metab. 2009 Aug;23(4): 443–52. DOI:10.1016/j.beem.2009.03.005
13. Duez H, Cariou B, Staels B. DPP-4 inhibitors in the treatment of type 2 diabetes. Biochem Pharmacol. 2012 Apr 1;83(7):823–32. DOI:10.1016/j.bcp.2011.11.028
14. Uto A, Miyashita K, Endo S, Sato M, Ryuzaki M, Kinouchi K, Mitsuishi M, Meguro S, Itoh H. Transient Dexamethasone Loading Induces Prolonged Hyperglycemia in Male Mice With Histone Acetylation in Dpp-4 Promoter. Endocrinology. 2021 Dec 1;162(12):bqab193. DOI:10.1210/endocr/bqab193. Erratum in: Endocrinology. 2022 Oct 11;163(11).
15. Kosaraju J, Holsinger RMD, Guo L, Tam KY. Linagliptin, a Dipeptidyl Peptidase-4 Inhibitor, Mitigates Cognitive Deficits and Pathology in the 3xTg-AD Mouse Model of Alzheimer's Disease. Mol Neurobiol. 2017 Oct;54(8):6074–84. DOI:10.1007/s12035-016-0125-7
16. Avogaro A, Fadini GP. The pleiotropic cardiovascular effects of dipeptidyl peptidase-4 inhibitors. Br J Clin Pharmacol. 2018 Aug;84(8):1686–95. DOI:10.1111/bcp.13611
17. Biryukova EV, Shinkin MV. The practice of hypoglycemic therapy: choosing the optimal drug from the group of Dipeptidyl Peptidase 4 Inhibitors. Effective Pharmacotherapy. 2022;18(6):20–30. DOI:10.33978/2307-3586-2022-18-6-20-30. Russian
18. Lazareva NB. Dipeptidyl Dipeptidase-4: view of the clinical pharmacologist. Meditsinskiy sovet=Medical Council. 2016;(19):114–21. DOI:10.21518/2079-701X-2016-19-114-121. Russian
19. Korbut AI, Klimontov VV. Incretin-based therapy: renal effects. Diabetes mellitus. 2016;19(1):53–63. DOI:10.14341/DM7727. Russian
20. Gasbjerg LS, Bergmann NC, Stensen S, Christensen MB, Rosenkilde MM, Holst JJ, Nauck M, Knop FK. Evaluation of the incretin effect in humans using GIP and GLP-1 receptor antagonists. Peptides. 2020 Mar;125:170183. DOI:10.1016/j.peptides.2019.170183
21. Neumiller JJ, Wood L, Campbell RK. Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes mellitus. Pharmacotherapy. 2010 May;30(5):463-84. DOI:10.1592/phco.30.5.463
22. Kushwaha RN, Haq W, Katti SB. Discovery of 17 Gliptins in 17-Years of Research for the Treatment of Type 2 Diabetes: A Synthetic Overview. Chemistry & Biology Interface. 2014;4:137–62.
23. Goldenberg R, Gantz I, Andryuk PJ, O'Neill EA, Kaufman KD, Lai E, Wang YN, Suryawanshi S, Engel SS. Randomized clinical trial comparing the efficacy and safety of treatment with the once-weekly dipeptidyl peptidase-4 (DPP-4) inhibitor omarigliptin or the once-daily DPP-4 inhibitor sitagliptin in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Diabetes Obes Metab. 2017 Mar;19(3):394–400. DOI:10.1111/dom.12832
24. Stoimenis D, Karagiannis T, Katsoula A, Athanasiadou E, Kazakos K, Bekiari E, Matthews DR, Tsapas A. Once-weekly dipeptidyl peptidase-4 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Expert Opin Pharmacother. 2017 Jun;18(9):843–51. DOI:10.1080/14656566.2017.1324848
25. Zou H, Zhu N, Li S. The emerging role of dipeptidyl-peptidase-4 as a therapeutic target in lung disease. Expert Opin Ther Targets. 2020 Feb;24(2):147–53. DOI:10.1080/14728222.2020.1721468
26. Anderluh M, Kocic G, Tomovic K, Kocic H, Smelcerovic A. DPP-4 inhibition: A novel therapeutic approach to the treatment of pulmonary hypertension? Pharmacol Ther. 2019 Sep;201:1–7. DOI:10.1016/j.pharmthera.2019.05.007
27. Zhang S, Li P, Xin M, Jin X, Zhao L, Nan Y, Cheng XW. Dipeptidyl peptidase-4 inhibition prevents lung injury in mice under chronic stress via the modulation of oxidative stress and inflammation. Exp Anim. 2021 Nov 10;70(4):541–52. DOI:10.1538/expanim.21-0067
28. Patel PM, Jones VA, Kridin K, Amber KT. The role of Dipeptidyl Peptidase-4 in cutaneous disease. Exp Dermatol. 2021 Mar;30(3):304–18. DOI:10.1111/exd.14228
29. Tasic T, Bäumer W, Schmiedl A, Schwichtenhövel F, Pabst R, Raap U, von Hörsten S, Stephan M. Dipeptidyl peptidase IV (DPP4) deficiency increases Th1-driven allergic contact dermatitis. Clin Exp Allergy. 2011 Aug;41(8):1098-107. DOI:10.1111/j.1365-2222.2011.03778.x
30. Kridin K, Bergman R. Association of Bullous Pemphigoid With Dipeptidyl-Peptidase 4 Inhibitors in Patients With Diabetes: Estimating the Risk of the New Agents and Characterizing the Patients. JAMA Dermatol. 2018 Oct 1;154(10):1152–8. DOI:10.1001/jamadermatol.2018.2352
31. Huang J, Liu X, Wei Y, Li X, Gao S, Dong L, Rao X, Zhong J. Emerging Role of Dipeptidyl Peptidase-4 in Autoimmune Disease. Front Immunol. 2022 Mar 4;13:830863. DOI:10.3389/fimmu.2022.830863
32. Guo Q, Zhang S, Huang J, Liu K. Alogliptin inhibits IL-1β-induced inflammatory response in fibroblast-like synoviocytes. Int Immunopharmacol. 2020 Jun;83:106372. DOI:10.1016/j.intimp.2020.106372
33. Han CK, Lee WF, Hsu CJ, Huang YL, Lin CY, Tsai CH, Huang CC, Fong YC, Wu MH, Liu JF, Tang CH. DPP4 reduces proinflammatory cytokine production in human rheumatoid arthritis synovial fibroblasts. J. Cell Physiol. 2021;236(12):8060–9. DOI:10.1002/jcp.30494
34. Jackson EK. Context-dependent effects of dipeptidyl peptidase 4 inhibitors. Curr Opin Nephrol Hypertens. 2017 Mar;26(2):83–90. DOI:10.1097/MNH.0000000000000303
35. Gupta S, Sen U. More than just an enzyme: Dipeptidyl peptidase-4 (DPP-4) and its association with diabetic kidney remodelling. Pharmacol Res. 2019 Sep;147:104391. DOI:10.1016/j.phrs.2019.104391

36. Allada R, Ren J, Restrepo R, Nistala R. Role of Dipeptidyl Peptidase 4 and Effects of a Western Diet in Renal Sodium Transport and Tubular Injury. FASEB. 2022;36(S1). DOI:10.1096/fasebj.2022.36.s1.r5683
37. Min HS, Kim JE, Lee MH, Song HK, Kang YS, Lee MJ, Lee JE, Kim HW, Cha JJ, Chung YY, Hyun YY, Han JY, Cha DR. Dipeptidyl peptidase IV inhibitor protects against renal interstitial fibrosis in a mouse model of ureteral obstruction. Lab Invest. 2014 Jun;94(6):598–607. DOI:10.1038/labinvest.2014.50
38. O'Leary H, Ou X, Broxmeyer HE. The role of dipeptidyl peptidase 4 in hematopoiesis and transplantation. Curr Opin Hematol. 2013 Jul;20(4):314–9. DOI:10.1097/MOH.0b013e32836125ac
39. Bae JC. DPP-4 Inhibitor in Type 2 Diabetes Mellitus Patient with Non-Alcoholic Fatty Liver Disease: Achieving Two Goals at Once? Endocrinol Metab (Seoul). 2022 Dec;37(6):858–60. DOI:10.3803/EnM.2022.605
40. Jung E, Kim J, Kim CS, Kim SH, Cho MH. Gemigliptin, a dipeptidyl peptidase-4 inhibitor, inhibits retinal pericyte injury in db/db mice and retinal neovascularization in mice with ischemic retinopathy. Biochim Biophys Acta. 2015 Dec;1852(12):2618–29. DOI:10.1016/j.bbadis.2015.09.010
41. Avogaro A, Fadini GP. The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications. Diabetes Care. 2014 Oct;37(10):2884-94. DOI:10.2337/dc14-0865
42. Bazhin AA, Chambon M, Vesin J, Bortoli J, Collins JW, Turcatti G, Chou CJ, Goun EA. A Universal Assay for Aminopeptidase Activity and Its Application for Dipeptidyl Peptidase-4 Drug Discovery. Anal Chem. 2019 Jan 2;91(1):1098–104. DOI:10.1021/acs.analchem.8b04672
43. Méndez LR, Arrebola Y, Valdés-Tresanco ME, Díaz-Guevara L, Bergado G, Sánchez B, Charli JL, Pascual Alonso I. Bestatin and bacitracin inhibit porcine kidney cortex dipeptidyl peptidase IV activity and reduce human melanoma MeWo cell viability. Int J Biol Macromol. 2020 Dec 1;164:2944–52. DOI:10.1016/j.ijbiomac.2020.08.157
44. Chittepu VCSR, Kalhotra P, Osorio-Gallardo T, Jiménez-Martínez C, Torre RRR, Gallardo-Velazquez T, Osorio-Revilla G. New Molecular Insights into the Inhibition of Dipeptidyl Peptidase-4 by Natural Cyclic Peptide Oxytocin. Molecules. 2019 Oct 28;24(21):3887. DOI:10.3390/molecules24213887
45. Gao J, Gong H, Mao X. Dipeptidyl Peptidase-IV Inhibitory Activity and Related Molecular Mechanism of Bovine α-Lactalbumin-Derived Peptides. Molecules. 2020 Jun 30;25(13):3009. DOI:10.3390/molecules25133009
46. Huang PK, Lin SR, Chang CH, Tsai MJ, Lee DN, Weng CF. Natural phenolic compounds potentiate hypoglycemia via inhibition of Dipeptidyl Peptidase IV // Sci Rep. 2019;9(1):15585. DOI:10.1038/s41598-019-52088-7
47. Wang J, Dai G, Li W. [Berberine regulates glycemia *via* local inhibition of intestinal dipeptidyl peptidase-IV]. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2016 May 25;45(5):486–92. DOI:10.3785/j.issn.1008-9292.2016.09.06. Chinese
48. Kalhotra P, Chittepu VCSR, Osorio-Revilla G, Gallardo-Velazquez T. Phytochemicals in Garlic Extract Inhibit Therapeutic Enzyme DPP-4 and Induce Skeletal Muscle Cell Proliferation: A Possible Mechanism of Action to Benefit the Treatment of Diabetes Mellitus. Biomolecules. 2020 Feb 14;10(2):305. DOI:10.3390/biom10020305
49. Narayanan N, Naik D, Sahoo J, Kamalanathan S. Dipeptidyl peptidase 4 inhibitors in COVID-19: Beyond glycemic control. World J Virol. 2022 Nov 25;11(6):399–410. DOI:10.5501/wjv.v11.i6.399
50. Ortenberg EA, Suplotova LA. Inhibitors of dipeptidyl-peptidase-4: obvious and probable (literature review). Meditsinskiy sovet=Medical Council. 2022;(10):40–5. DOI:10.21518/2079-701X-2022-16-10-40-45. Russian
51. Vankadari N, Wilce JA. Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerg Microbes Infect. 2020 Mar 17;9(1):601–4. DOI:10.1080/22221751.2020.1739565
52. Li Y, Zhang Z, Yang L, Lian X, Xie Y, Li S, Xin S, Cao P, Lu J. The MERS-CoV Receptor DPP4 as a Candidate Binding Target of the SARS-CoV-2 Spike. iScience. 2020 Jun 26;23(6):101160. DOI:10.1016/j.isci.2020.101160. Epub 2020 May 13. Erratum in: iScience. 2020 Aug 21;23(8):101400.
53. Sebastián-Martín A, Sánchez BG, Mora-Rodríguez JM, Bort A, Díaz-Laviada I. Role of Dipeptidyl Peptidase-4 (DPP4) on COVID-19 Physiopathology. Biomedicines. 2022 Aug 19;10(8):2026. DOI:10.3390/biomedicines10082026
54. Krejner-Bienias A, Grzela K, Grzela T. DPP4 Inhibitors and COVID-19-Holy Grail or Another Dead End? Arch Immunol Ther Exp (Warsz). 2021 Feb 2;69(1):1. DOI:10.1007/s00005-020-00602-5
55. Dastan F, Abedini A, Shahabi S, Kiani A, Saffaei A, Zare A. Sitagliptin Repositioning in SARS-CoV-2: Effects on ACE-2, CD-26, and Inflammatory Cytokine Storms in the Lung. Iran J Allergy Asthma Immunol. 2020 May 17;19(S1):10–2. DOI:10.18502/ijaai.v19i(s1.r1).2849
56. Schlicht K, Rohmann N, Geisler C, Hollstein T, Knappe C, Hartmann K, Schwarz J, Tran F, Schunk D, Junker R, Bahmer T, Rosenstiel P, Schulte D, Türk K, Franke A, Schreiber S, Laudes M. Circulating levels of soluble Dipeptidylpeptidase-4 are reduced in human subjects hospitalized for severe COVID-19 infections. Int J Obes (Lond). 2020 Nov;44(11):2335–8. DOI:10.1038/s41366-020-00689-y. Epub 2020 Sep 21. Erratum in: Int J Obes (Lond). 2022 Jan;46(1):243.
57. Varin EM, Mulvihill EE, Beaudry JL, Pujadas G, Fuchs S, Tanti JF, Fazio S, Kaur K, Cao X, Baggio LL, Matthews D, Campbell JE, Drucker DJ. Circulating Levels of Soluble Dipeptidyl Peptidase-4 Are Dissociated from Inflammation and Induced by Enzymatic DPP4 Inhibition. Cell Metab. 2019 Feb 5;29(2):320–34.e5. DOI:10.1016/j.cmet.2018.10.001
58. Kifle ZD, Woldeyohanin AE, Demeke CA. SARS-CoV-2 and diabetes: A potential therapeutic effect of dipeptidyl peptidase 4 inhibitors in diabetic patients diagnosed with COVID-19. Metabol Open. 2021 Dec;12:100134. DOI:10.1016/j.metop.2021.100134
59. Soare A, Györfi HA, Matei AE, Dees C, Rauber S, Wohlfahrt T, Chen CW, Ludolph I, Horch RE, Bäuerle T, von Hörsten S, Mihai C, Distler O, Ramming A, Schett G, Distler JHW. Dipeptidylpeptidase 4 as a Marker of Activated Fibroblasts and a Potential Target for the Treatment of Fibrosis in Systemic Sclerosis. Arthritis Rheumatol. 2020 Jan;72(1):137–49. DOI:10.1002/art.41058
60. Herman GA, Bergman A, Stevens C, Kotey P, Yi B, Zhao P, Dietrich B, Golor G, Schrodter A, Keymeulen B, Lasseter KC, Kipnes MS, Snyder K, Hilliard D, Tanen M, Cilissen C, De Smet M, de Lepeleire I, Van Dyck K,

ISSN 2307-9266 e-ISSN 2413-2241

Wang AQ, Zeng W, Davies MJ, Tanaka W, Holst JJ, Deacon CF, Gottesdiener KM, Wagner JA. Effect of single oral doses of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on incretin and plasma glucose levels after an oral glucose tolerance test in patients with type 2 diabetes. J Clin Endocrinol Metab. 2006 Nov;91(11):4612–9. DOI:10.1210/jc.2006-1009

61. Hou L, Zhao T, Liu Y, Zhang Y. Efficacy and safety of sitagliptin compared with sulfonylurea therapy in patients with type 2 diabetes showing inadequately controlled glycosylated hemoglobin with metformin monotherapy: A meta-analysis. Exp Ther Med. 2015 Apr;9(4):1528–36. DOI:10.3892/etm.2015.2277
62. Hayes J, Anderson R, Stephens JW. Sitagliptin/metformin fixed-dose combination in type 2 diabetes mellitus: an evidence-based review of its place in therapy. Drug Des Devel Ther. 2016 Jul 19;10:2263–70. DOI:10.2147/DDDT.S93076
63. Fonseca V, Staels B, Morgan JD 2nd, Shentu Y, Golm GT, Johnson-Levonas AO, Kaufman KD, Goldstein BJ, Steinberg H. Efficacy and safety of sitagliptin added to ongoing metformin and pioglitazone combination therapy in a randomized, placebo-controlled, 26-week trial in patients with type 2 diabetes. J Diabetes Complications. 2013 Mar-Apr;27(2):177–83. DOI:10.1016/j.jdiacomp.2012.09.007
64. Shestakova MV. Experience with sitagliptin (the first DPP-4 inhibitor) application to the treatment of type 2 diabetes mellitus in the Russian Federation:Results of the DIA-DA observation program. Diabetes mellitus. 2010;13(3):57–60. DOI:10.14341/2072-0351-5489. Russian
65. Ametov AS, Gusenbekova DG. The role of dipeptidyl peptidase 4 inhibitors in fat metabolism in patients with type 2 diabetes and obesity. Diabetes mellitus. 2015;18(3):85–92. DOI:10.14341/DM2015385-92. Russian
66. Pavlova MG. Vildagliptin – new opportunities in the treatment of type 2 Diabetes mellitus. Farmateka. 2022;29(11/12):36–40. DOI:10.18565/pharmateca.2022.11-12.36-40. Russian
67. Azuma K, Rádiková Z, Mancino J, Toledo FG, Thomas E, Kangani C, Dalla Man C, Cobelli C, Holst JJ, Deacon CF, He Y, Ligueros-Saylan M, Serra D, Foley JE, Kelley DE. Measurements of islet function and glucose metabolism with the dipeptidyl peptidase 4 inhibitor vildagliptin in patients with type 2 diabetes. J Clin Endocrinol Metab. 2008 Feb;93(2):459–64. DOI:10.1210/jc.2007-1369
68. Odawara M, Sagara R. Effects of vildagliptin as add-on treatment in patients with type 2 diabetes mellitus: insights from long-term clinical studies in Japan. J Diabetes Metab Disord. 2016 Jul 4;15:21. DOI:10.1186/s40200-016-0240-z
69. Ametov AS. Galvus. 5 years in Russia. Endocrinology: News, Opinions, Training. 2014;(3):10–6. Russian
70. Kosaraju J, Murthy V, Khatwal RB, Dubala A, Chinni S, Muthureddy Nataraj SK, Basavan D. Vildagliptin: an anti-diabetes agent ameliorates cognitive deficits and pathology observed in streptozotocin-induced Alzheimer's disease. J Pharm Pharmacol. 2013 Dec;65(12):1773–84. DOI:10.1111/jphp.12148
71. Arruda-Junior DF, Martins FL, Dariolli R, Jensen L, Antonio EL, Dos Santos L, Tucci PJ, Girardi AC. Dipeptidyl Peptidase IV Inhibition Exerts Renoprotective Effects in Rats with Established Heart Failure. Front Physiol. 2016 Jul 12;7:293. DOI:10.3389/fphys.2016.00293
72. O'Farrell AM, van Vliet A, Abou Farha K, Cherrington JM, Campbell DA, Li X, Hanway D, Li J, Guler HP. Pharmacokinetic and pharmacodynamic assessments of the dipeptidyl peptidase-4 inhibitor PHX1149: double-blind, placebo-controlled, single- and multiple-dose studies in healthy subjects. Clin Ther. 2007 Aug;29(8):1692–705. DOI:10.1016/j.clinthera.2007.08.005
73. Lotfy M, Singh J, Kalász H, Tekes K, Adeghate E. Medicinal Chemistry and Applications of Incretins and DPP-4 Inhibitors in the Treatment of Type 2 Diabetes Mellitus. Open Med Chem J. 2011;5(Suppl 2):82–92. DOI:10.2174/1874104501105010082
74. Pattzi HM, Pitale S, Alpizar M, Bennett C, O'Farrell AM, Li J, Cherrington JM, Guler HP; PHX1149-PROT202 Study Group. Dutogliptin, a selective DPP4 inhibitor, improves glycaemic control in patients with type 2 diabetes: a 12-week, double-blind, randomized, placebo-controlled, multicentre trial. Diabetes Obes Metab. 2010 Apr;12(4):348–55. DOI:10.1111/j.1463-1326.2010.01195.x
75. Garcia-Soria G, Gonzalez-Galvez G, Argoud GM, Gerstman M, Littlejohn TW 3rd, Schwartz SL, O'Farrell AM, Li X, Cherrington JM, Bennett C, Guler HP. The dipeptidyl peptidase-4 inhibitor PHX1149 improves blood glucose control in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2008 Apr;10(4):293–300. DOI:10.1111/j.1463-1326.2008.00868.x
76. Schenk R, Nix D. TCT-180 Impact of the novel DPP-IV-inhibitor Dutogliptin in combination with G-CSF on survival rates and cardiac remodelling after acute myocardial infarction. J Am Coll Cardiol. 2016 Nov;68(Suppl 18):B74. DOI:10.1016/j.jacc.2016.09.322
77. Rosenstock J, Sankoh S, List JF. Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naive patients with type 2 diabetes. Diabetes Obes Metab. 2008 May;10(5):376–86. DOI:10.1111/j.1463-1326.2008.00876.x
78. Matthaei S, Aggarwal N, Garcia-Hernandez P, Iqbal N, Chen H, Johnsson E, Chin A, Hansen L. One-year efficacy and safety of saxagliptin add-on in patients receiving dapagliflozin and metformin. Diabetes Obes Metab. 2016 Nov;18(11):1128–33. DOI:10.1111/dom.12741
79. Chacra AR, Tan GH, Apanovitch A, Ravichandran S, List J, Chen R; CV181-040 Investigators. Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: a randomised controlled trial. Int J Clin Pract. 2009 Sep;63(9):1395–406. DOI:10.1111/j.1742-1241.2009.02143.x. Epub 2009 Jul 15. Erratum in: Int J Clin Pract. 2010 Jan;64(2):277.
80. Huang J, Jia Y, Sun S, Meng L. Adverse event profiles of dipeptidyl peptidase-4 inhibitors: data mining of the public version of the FDA adverse event reporting system. BMC Pharmacol Toxicol. 2020 Sep 16;21(1):68. DOI:10.1186/s40360-020-00447-w
81. Petunina NA, Brashchenkova AV. Saxagliptin (Onglyza®) In Conception of Effective Management of Type 2 Diabetes Mellitus. Farmateka. 2011;16 (229):12–19. Russian
82. Kosaraju J, Gali CC, Khatwal RB, Dubala A, Chinni S, Holsinger RM, Madhunapantula VS, Muthureddy Nataraj SK, Basavan D. Saxagliptin: a dipeptidyl peptidase-4 inhibitor ameliorates streptozotocin induced Alzheimer's disease. Neuropharmacology. 2013 Sep;72:291–300. DOI:10.1016/j.neuropharm.2013.04.008

83. Verspohl EJ. Novel pharmacological approaches to the treatment of type 2 diabetes. Pharmacol Rev. 2012 Apr;64(2):188–237. DOI:10.1124/pr.110.003319
84. Del Prato S, Barnett AH, Huisman H, Neubacher D, Woerle HJ, Dugi KA. Effect of linagliptin monotherapy on glycaemic control and markers of β-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. Diabetes Obes Metab. 2011 Mar;13(3):258–67. DOI:10.1111/j.1463-1326.2010.01350.x
85. Taskinen MR, Rosenstock J, Tamminen I, Kubiak R, Patel S, Dugi KA, Woerle HJ. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2011 Jan;13(1):65–74. DOI:10.1111/j.1463-1326.2010.01326.x
86. Forst T, Uhlig-Laske B, Ring A, Graefe-Mody U, Friedrich C, Herbach K, Woerle HJ, Dugi KA. Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled Type 2 diabetes. Diabet Med. 2010 Dec;27(12):1409–19. DOI:10.1111/j.1464-5491.2010.03131.x
87. Owens DR, Swallow R, Dugi KA, Woerle HJ. Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study. Diabet Med. 2011 Nov;28(11):1352–61. DOI:10.1111/j.1464-5491.2011.03387.x. Erratum in: Diabet Med. 2012 Jan;29(1):158.
88. Gallwitz B, Rosenstock J, Rauch T, Bhattacharya S, Patel S, von Eynatten M, Dugi KA, Woerle HJ. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet. 2012 Aug 4;380(9840):475–83. DOI:10.1016/S0140-6736(12)60691-6
89. Gupta R, Walunj SS, Tokala RK, Parsa KV, Singh SK, Pal M. Emerging drug candidates of dipeptidyl peptidase IV (DPP IV) inhibitor class for the treatment of Type 2 Diabetes. Curr Drug Targets. 2009 Jan;10(1):71–87. DOI:10.2174/138945009787122860
90. DeFronzo RA, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 010 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control: a randomized, double-blind, placebo-controlled study. Diabetes Care. 2008 Dec;31(12):2315–7. DOI:10.2337/dc08-1035
91. Rosenstock J, Rendell MS, Gross JL, Fleck PR, Wilson CA, Mekki Q. Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA(1C) without causing weight gain or increased hypoglycaemia. Diabetes Obes Metab. 2009 Dec;11(12):1145–52. DOI:10.1111/j.1463-1326.2009.01124.x
92. Chen XW, He ZX, Zhou ZW, Yang T, Zhang X, Yang YX, Duan W, Zhou SF. Clinical pharmacology of dipeptidyl peptidase 4 inhibitors indicated for the treatment of type 2 diabetes mellitus. Clin Exp Pharmacol Physiol. 2015 Oct;42(10):999–1024. DOI:10.1111/1440-1681.12455
93. Pratley RE, Reusch JE, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 009 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin. 2009 Oct;25(10):2361–71. DOI:10.1185/03007990903156111
94. Trujillo JM, Wettergreen SA, Nuffer WA, Ellis SL, McDermott MT. Cardiovascular Outcomes of New Medications for Type 2 Diabetes. Diabetes Technol Ther. 2016 Dec;18(12):749–58. DOI:10.1089/dia.2016.0295
95. Mkrtumyan AM. Alogliptin – effective and safe Dipeptidyl Peptidase-4 inhibitor in the therapy of type 2 Diabetes mellitus. Farmateka. 2015;5(298):20–7. Russian
96. Mkrtumyan AM, Egshatyan LV. Alogliptin – highly selective DPP-4 inhibitor with a focus on cardiovascular safety. 2016;(5):104–7. DOI:10.21518/2079-701X-2016-05-104-107. Russian
97. Kim SH, Jung E, Yoon MK, Kwon OH, Hwang DM, Kim DW, Kim J, Lee SM, Yim HJ. Pharmacological profiles of gemigliptin (LC15-0444), a novel dipeptidyl peptidase-4 inhibitor, in vitro and in vivo. Eur J Pharmacol. 2016 Oct 5;788:54–64. DOI:10.1016/j.ejphar.2016.06.016
98. Rhee EJ, Lee WY, Yoon KH, Yoo SJ, Lee IK, Baik SH, Kim YK, Lee MK, Park KS, Park JY, Cha BS, Lee HW, Min KW, Bae HY, Kim MJ, Kim JA, Kim DK, Kim SW. A multicenter, randomized, placebo-controlled, double-blind phase II trial evaluating the optimal dose, efficacy and safety of LC 15-0444 in patients with type 2 diabetes. Diabetes Obes Metab. 2010 Dec;12(12):1113–9. DOI:10.1111/j.1463-1326.2010.01303.x
99. Lim S, Han KA, Yu J, Chamnan P, Kim ES, Yoon KH, Kwon S, Moon MK, Lee KW, Kim DJ, Kim M, Wongtanate M, Kim EY, Kim SH, Lee MK; INICOM Study Group. Efficacy and safety of initial combination therapy with gemigliptin and metformin compared with monotherapy with either drug in patients with type 2 diabetes: A double-blind randomized controlled trial (INICOM study). Diabetes Obes Metab. 2017 Jan;19(1):87–97. DOI:10.1111/dom.12787
100. Maladkar M, Sankar S, Kamat K. Teneligliptin: heralding change in type 2 diabetes. J Diabetes Mellitus. 2016;6:113–31. DOI:10.4236/jdm.2016.62012
101. Kadowaki T, Kondo K. Efficacy, safety and dose-response relationship of teneligliptin, a dipeptidyl peptidase-4 inhibitor, in Japanese patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2013 Sep;15(9):810–8. DOI:10.1111/dom.12092
102. Otsuki H, Kosaka T, Nakamura K, Shimomura F, Kuwahara Y, Tsukamoto T. Safety and efficacy of teneligliptin: a novel DPP-4 inhibitor for hemodialysis patients with type 2 diabetes. Int Urol Nephrol. 2014 Feb;46(2):427–32. DOI:10.1007/s11255-013-0552-6
103. Hashikata T, Yamaoka-Tojo M, Kakizaki R, Nemoto T, Fujiyoshi K, Namba S, Kitasato L, Hashimoto T, Kameda R, Maekawa E, Shimohama T, Tojo T, Ako J. Teneligliptin improves left ventricular diastolic function and endothelial function in patients with diabetes. Heart Vessels. 2016 Aug;31(8):1303–10. DOI:10.1007/s00380-015-0724-7. Epub 2015 Aug 13. Erratum in: Heart Vessels. 2016 Aug;31(8):1311-2.
104. Kadowaki T, Kondo K. Efficacy and safety of teneligliptin added to glimepiride in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled study with an open-label, long-term extension. Diabetes Obes Metab. 2014 May;16(5):418–25. DOI:10.1111/dom.12235

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

105. Kadowaki T, Kondo K. Efficacy and safety of teneligliptin in combination with pioglitazone in Japanese patients with type 2 diabetes mellitus. J Diabetes Investig. 2013 Nov 27;4(6):576–84. DOI:10.1111/jdi.12092
106. Kim MK, Rhee EJ, Han KA, Woo AC, Lee MK, Ku BJ, Chung CH, Kim KA, Lee HW, Park IB, Park JY, Chul Jang HC, Park KS, Jang WI, Cha BY. Efficacy and safety of teneligliptin, a dipeptidyl peptidase-4 inhibitor, combined with metformin in Korean patients with type 2 diabetes mellitus: a 16-week, randomized, double-blind, placebo-controlled phase III trial. Diabetes Obes Metab. 2015 Mar;17(3):309–12. DOI:10.1111/dom.12424
107. Tanaka K, Okada Y, Mori H, Inada Y, Suzuka K, Uriu K, Tanaka Y. Efficacy of linagliptin and teneligliptin for glycemic control in type 2 diabetic patients with chronic kidney disease: assessment by continuous glucose monitoring; a pilot study. Diabetol Int. 2016 Mar 9;7(4):368–74. DOI:10.1007/s13340-016-0258-y
108. Furuta S, Smart C, Hackett A, Benning R, Warrington S. Pharmacokinetics and metabolism of [14C]anagliptin, a novel dipeptidyl peptidase-4 inhibitor, in humans. Xenobiotica. 2013 May;43(5):432–42. DOI:10.3109/00498254.2012.731618
109. Kaku K. Dose-ranging study of anagliptin in Japanese patients with type 2 diabetes: a multi-centre, randomized, placebo-controlled, double-blind, parallel-group study. Jpn Pharmacol. Ther. 2012;40:973–84
110. Yang HK, Min KW, Park SW, Chung CH, Park KS, Choi SH, Song KH, Kim DM, Lee MK, Sung YA, Baik SH, Kim IJ, Cha BS, Park JH, Ahn YB, Lee IK, Yoo SJ, Kim J, Park IeB, Park TS, Yoon KH. A randomized, placebo-controlled, double-blind, phase 3 trial to evaluate the efficacy and safety of anagliptin in drug-naïve patients with type 2 diabetes. Endocr J. 2015;62(5):449–62. DOI:10.1507/endocrj.EJ14-0544
111. Kakuda H, Kobayashi J, Kakuda M, Yamakawa J, Takekoshi N. The effect of anagliptin treatment on glucose metabolism and lipid metabolism, and oxidative stress in fasting and postprandial states using a test meal in Japanese men with type 2 diabetes. Endocrine. 2015 Apr;48(3):1005–9. DOI:10.1007/s12020-014-0376-x
112. Kaku K. Efficacy and safety of anagliptin add-on therapy in Japanese patients with type 2 diabetes. Jpn Pharmacol Ther. 2012;40(9):745–70.
113. Burness CB. Omarigliptin: first global approval. Drugs. 2015 Nov;75(16):1947–52. DOI:10.1007/s40265-015-0493-8
114. Sheu WH, Gantz I, Chen M, Suryawanshi S, Mirza A, Goldstein BJ, Kaufman KD, Engel SS. Safety and Efficacy of Omarigliptin (MK-3102), a Novel Once-Weekly DPP-4 Inhibitor for the Treatment of Patients With Type 2 Diabetes. Diabetes Care. 2015 Nov;38(11):2106–14. DOI:10.2337/dc15-0109
115. Evans PM, Bain SC. Omarigliptin for the treatment of type 2 diabetes mellitus. Expert Opin Pharmacother. 2016 Oct;17(14):1947–52. DOI:10.1080/14656566.2016
116. Tan X. Omarigliptin for the treatment of type 2 diabetes. Endocrine. 2016 Oct;54(1):24–31. DOI:10.1007/s12020-016-1011-9
117. Sharma R, Sun H, Piotrowski DW, Ryder TF, Doran SD, Dai H, Prakash C. Metabolism, excretion, and pharmacokinetics of ((3,3-difluoropyrrolidin-1-yl)((2S,4S)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone, a dipeptidyl peptidase inhibitor, in rat, dog and human. Drug Metab Dispos. 2012 Nov;40(11):2143–61. DOI:10.1124/dmd.112.047316
118. Muto C, Dai H, Teeter JG, Johnson S, Cropp AB, Chiba K, Suwa T. The pharmacokinetics and pharmacodynamics of PF-00734200, a DPP-IV inhibitor, in healthy Japanese subjects. Int J Clin Pharmacol Ther. 2012 Jul;50(7):505–9. DOI:10.5414/CP201614
119. Rosenstock J, Lewin AJ, Norwood P, Somayaji V, Nguyen TT, Teeter JG, Johnson SL, Dai H, Terra SG. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor PF-734200 added to metformin in Type 2 diabetes. Diabet Med. 2011 Apr;28(4):464–9. DOI:10.1111/j.1464-5491.2010.03181.x
120. Terra SG, Somayaji V, Schwartz S, Lewin AJ, Teeter JG, Dai H, Nguyen TT, Calle RA. A Dose-Ranging Study of the DPP-IV Inhibitor PF-734200 Added to Metformin in Subjects With Type 2 Diabetes*. Exp Clin Endocrinol Diabetes. 2011 Jul;119(7):401–7. DOI:10.1055/s-0031-1273737
121. Galstyan KO, Nedosugova LV, Petunina NA, Trakhtenberg JA, Vostokova NV, Karavaeva OV, Chasovskaya TE. First Russian DPP-4 inhibitor Gosogliptin comparing to Vildagliptin in type 2 diabetes mellitus patients. Diabetes mellitus. 2016;19(1):89–96. DOI:10.14341/DM7233. Russian
122. McKeage K. Trelagliptin: First Global Approval. Drugs. 2015 Jul;75(10):1161–4. DOI:10.1007/s40265-015-0431-9
123. Grimshaw CE, Jennings A, Kamran R, Ueno H, Nishigaki N, Kosaka T, Tani A, Sano H, Kinugawa Y, Koumura E, Shi L, Takeuchi K. Trelagliptin (SYR-472, Zafatek), Novel Once-Weekly Treatment for Type 2 Diabetes, Inhibits Dipeptidyl Peptidase-4 (DPP-4) via a Non-Covalent Mechanism. PLoS One. 2016 Jun 21;11(6):e0157509. DOI:10.1371/journal.pone.0157509
124. Inagaki N, Sano H, Seki Y, Kuroda S, Kaku K. Long-term safety and efficacy of a novel once-weekly oral trelagliptin as monotherapy or in combination with an existing oral antidiabetic drug in patients with type 2 diabetes mellitus: A 52-week open-label, phase 3 study. J Diabetes Investig. 2016 Sep;7(5):718–26. DOI:10.1111/jdi.12499
125. Yong X, Hu T, Feng S, Du X, Shi H, Feng W. Synergism in Pharmacokinetics of Retagliptin and Metformin Observed during Clinical Trials of their Combination Therapy. Trop J Pharm Res. 2015;14(8):1481–6. DOI:10.4314/tjpr.v14i8.22
126. Chae YN, Kim TH, Kim MK, Shin CY, Jung IH, Sohn YS, Son MH. Beneficial Effects of Evogliptin, a Novel Dipeptidyl Peptidase 4 Inhibitor, on Adiposity with Increased Ppargc1a in White Adipose Tissue in Obese Mice. PLoS One. 2015 Dec 3;10(12):e0144064. DOI:10.1371/journal.pone.0144064
127. Cho JM, Jang HW, Cheon H, Jeong YT, Kim DH, Lim YM, Choi SH, Yang EK, Shin CY, Son MH, Kim SH, Kim HJ, Lee MS. A novel dipeptidyl peptidase IV inhibitor DA-1229 ameliorates streptozotocin-induced diabetes by increasing β-cell replication and neogenesis. Diabetes Res Clin Pract. 2011 Jan;91(1):72–9. DOI:10.1016/j.diabres.2010.10.012
128. Gu N, Park MK, Kim TE, Bahng MY, Lim KS, Cho SH, Yoon SH, Cho JY, Jang IJ, Yu KS. Multiple-dose pharmacokinetics and pharmacodynamics of evogliptin (DA-1229), a novel dipeptidyl peptidase IV inhibitor, in healthy volunteers. Drug Des Devel Ther. 2014 Oct 6;8:1709–21. DOI:10.2147/DDDT.S65678
129. Mattei P, Boehringer M, Di Giorgio P, Fischer H, Hennig M, Huwyler J, Koçer B, Kuhn B, Loeffler BM, Macdonald A, Narquizian R, Rauber E, Sebokova E, Sprecher U. Discovery of carmegliptin: a potent and long-acting dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. Bioorg Med Chem Lett. 2010 Feb 1;20(3):1109–13. DOI:10.1016/j.bmcl.2009.12.024
130. Kuhlmann O, Carlile D, Noe J, Bentley D. Interaction potential of Carmegliptin with P-glycoprotein (Pgp) transporter in healthy volunteers. J Drug Assess. 2014 Mar 3;3(1):28–37. DOI:10.3109/21556660.2014.900065

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