Neogliptin: a promising new DPP-4 inhibitor

Neogliptin project

Neoglipin is a promising novel DPP-4 inhibitor ("gliptin") for the treatment of type 2 diabetes mellitus. Its key advantages include high potency against the target enzyme (DPP-4) and an improved safety profile, particularly regarding cardiotoxicity. Computational screening has demonstrated that Neoglipin exhibits stronger inhibitory activity compared to sitagliptin and vildagliptin, while presenting a lower predicted cardiotoxicity risk than sitagliptin and a safety level comparable to vildagliptin.

In addition, Neoglipin demonstrates chemical stability and improved ADME characteristics compared to vildagliptin, which may have a positive impact on the drug's pharmacokinetic properties. Collectively, these attributes make this molecule an attractive candidate: in essence, **Neoglipin combines the best qualities of existing gliptins while offering reduced side effects**.

Properties:

Pharmacological group:	hypoglycemic synthetic and other agents, incretinomimetics - DPP inhibitors – 4
Mechanism of action:	inhibition of DPP-4
Dosage form:	solid dosage form with prolonged effect
Route of administration:	oral
Chemical compound:	a derivative of beta-amino acid amides

Neogliptin selectively inhibits the enzyme dipeptidyl peptidase-4 (DPP-4), which ultimately stimulates the pancreatic islets of Langerhans. Rapid and significant inhibition of DPP-4 activity causes increased secretion of glucagon-like peptide type 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) from the intestine into the systemic circulation throughout the day.

An increase in GLP-1 and GIP levels causes an increase in the sensitivity of pancreatic β-cells to glucose, which leads to an improvement in glucose-dependent insulin secretion. When using a drug based on DPP-4 in patients with type 2 diabetes mellitus, the functions of pancreatic β-cells improve. The degree of improvement in the function of β-cells depends on the degree of their initial damage; Thus, in non-diabetic individuals (with normal plasma glucose levels), the drug practically does not stimulate insulin secretion and does not reduce glucose levels.

Elevated levels of endogenous GLP-1 also increase the sensitivity of α-cells to glucose, resulting in improved glucose-dependent regulation of glucagon secretion. The decrease in excess glucagon levels during meals, in turn, causes a decrease in insulin resistance.

An increase in the insulin/glucagon ratio against the background of hyperglycemia, due to an increase in the levels of GLP-1 and GIP, causes a decrease in the production of glucose by the liver both in the prandial period and after a meal, which leads to a decrease in the level of glucose in the blood plasma.

During the development period of Neogliptin in 2016-2024, a significant set of works was done:

- the active substance was developed;
- optimization (Hit-to-Lead Optimization) of the molecule was carried out using docking (using software products: Glide, Autodoc, PV Protein Modeler, ChemBioOffice);
- developed several options for the finished dosage form.

Numerous preclinical studies have been carried out:

- evaluation of ADME parameters;
- development and validation of methods for the quantitative determination of the drug;
- ***in vitro*** and ***in vivo*** in several animal species.

A comprehensive in silico comparative study was conducted to assess the cardiotoxicity of Neoglipin alongside sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, gozogliptin, and evogliptin. Based on combined data from QSAR analysis, molecular docking, molecular dynamics, ADMET profiling, pharmacophore modeling, machine learning predictions, and others, an integrated cardiotoxicity ranking was developed. According to this ranking, Neoglipin holds a leading position in safety for patients with cardiovascular conditions, confirming its strong potential for use in populations with elevated cardiovascular risk.

At the moment, a complex of preclinical studies to assess the efficacy and safety of the finished dosage form of the drug is being completed, it is planned to enter phase I clinical trials at the middle of 2026.

The results obtained in the course of preclinical studies, as well as a comparative analysis of efficacy and safety with analogous drugs, allow us to predict a high probability of a positive completion of clinical researches and bringing the drug to the market.

Project competitive advantages

1. According to preclinical researches («Acute Toxicity») - the toxicity of Neogliptin is at the level of the best analogues available on the world market; Hodge & Sterner toxicity class 4 (LD50 = 500 - 4999 μg/kg - “non-toxic”);
2. According to preclinical researches Neogliptin is 25% more effective than Linagliptin/Trajenta (best in class);
3. According to preclinical researches Neogliptin Bioavailability is 3 times higher than that of Linagliptin/Trajenta;
4. According to preclinical researches – due to the rate of adsorption of the pharmaceutical substance, Neogliptin provides a smooth and long-term pharmacokinetics and, accordingly, the possibility of a single dose of one tablet per day;
5. According to the conducted in silico cardiotoxicity assessment, Neoglipin demonstrated one of the most favorable safety profiles compared to other gliptins, indicating its exceptional safety for patients with cardiovascular conditions;
6. High manufacturability of solid dosage form production;
7. The increase of type 2 diabetes mellitus in the world ensures an increased demand for the drug on the market and the prospects for the project’s products;
8. A strong team is involved in the implementation of the project, having all the necessary competencies for the implementation of the project (aspects of chemical synthesis, creating an effective dosage form, solving production problems, conducting preclinical and clinical studies).

Current research status on the project

To date, the following results have been obtained, confirming the exceptionally high prospects of Neogliptin:

- the technology of scalable synthesis of Neogliptin substance has been developed and tested;
- the required amount of raw materials for the synthesis of Neogliptin under GMP conditions for clinical researches has been prepared;
- research centers for preclinical studies have been chosen;
- methods for obtaining various salt forms of Neogliptin have been developed, comparative studies of the solubility and other important physico-chemical properties of various salt forms have been carried out;
- for further research, the salt form of Neogliptin tosylate was chosen, both in terms of the totality of indicators and taking into account world practice, as the safest, most effective and optimal from the point of view of technological aspects;
- pharmaceutical development of a finished dosage form with a modified release of Neogliptin active substance was carried out;
- experiments are being completed to study the efficacy and safety of the finished dosage form with a modified release of Neogliptin in the framework of preclinical studies;

The following stages of Neogliptin preclinical studies were carried out:

- the structure of the target active substance was characterized in detail and confirmed by modern physicochemical methods;
- multiple in vitro experiments established and confirmed the nanomolar activity and DPP-4 specificity of the developed substance; it was found that in both indicators the substance is equal or superior to foreign analogues;
- an assessment of the parameters (ADME panel) of absorption, distribution, metabolism and excretion of the substance was carried out;
- methods for quantitative determination of the target substance in biological fluids (blood plasma) were developed and validated;
- pharmacokinetic studies of the substance in vitro (LogD, solubility, stability in liver microsomes, stability in plasma, plasma protein binding) were carried out;
- pharmacokinetic studies of the substance in vivo (using laboratory animals) were carried out according to the required indicators - AUC, half-life (t1 / 2), bioavailability, detection of metabolites, dose-dependence, half-life T1 / 2, relative bioavailability for oral and intravenous administration, distribution by authorities);
- the mutagenic effect of the drug was studied with a single oral and multiple administration (in different doses), no mutagenic effect was detected;
- a preliminary assessment of the specific pharmacological activity in the STZ-diabetes-induced model and the model of sugar load in white outbred CD rats was carried out;
- metabolic stability in two animal species was studied;
- the development of several prototypes of the finished dosage form was carried out, the most

optimal ones (with a modified, prolonged release) were selected based on the totality of indicators;

- developed and implemented technological approaches to obtaining the finished dosage form;
- the stages of preclinical researches were carried out to identify the specific activity and chronic toxicity of the drug;
- completed studies on the chronic toxicity of the finished dosage form of Neogliptin tosylate on outbred rats with an assessment of the local irritant effect;
- to assess the cardiotoxicity of Neoglipin, a comprehensive comparative analysis with other gliptins was performed using a wide range of advanced in silico methodologies:
  - QSAR analysis of activity against the hERG channel and DPP-4;
  - molecular docking with the hERG channel and DPP-4;
  - molecular dynamics simulations of complexes with DPP-4 and hERG;
  - ADMET profiling using SwissADME, pkCSM, and other specialized databases;
  - pharmacophore modeling based on known DPP-4 inhibitors and hERG-binding data;
  - assessment of potential effects on oxidative stress and mitochondrial dysfunction using validated predictors;
  - application of machine learning models trained on open datasets to predict cardiotoxicity;
  - and others.
- patents for the active substance «Dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes mellitus, compounds (variants)» (No. 2712097 dated September 28, 2018) and finished dosage form «Pharmaceutical composition based on the active substance, a dipeptidyl peptidase-4 inhibitor» were obtained, to prevent the development and treatment of type 2 diabetes» (No. 2727898 dated July 24, 2020). The publication of PCT applications has been completed, the national application in China and India, and a patent application in the USA is in the process of formalization.

Diabetes — The epidemic of the century, key facts[1]:

- The number of people with diabetes rose from 108 million in 1980 to 830 million in 2022. Prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries;
- More than half of people living with diabetes did not take medication for their diabetes in 2022. Diabetes treatment coverage was lowest in low- and middle-income countries;
- Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation;
- Between 2000 and 2016, there was a 5% increase in premature mortality from diabetes;
- In 2021, diabetes and kidney disease due to diabetes caused over 2 million deaths. In addition, around 11% of cardiovascular deaths were caused by high blood glucose;
- A healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use are ways to prevent or delay the onset of type 2 diabetes;
- Diabetes can be treated and its consequences avoided or delayed with diet, physical activity, medication and regular screening and treatment for complications;
- More than 95% of people with diabetes have type 2 diabetes. This type of diabetes is largely the result of excess body weight and physical inactivity;
- In the EUR Region alone, it is estimated that 66 million people (9.8% prevalence) were living with diabetes in 2024;
- There are more than 107 million patients diagnosed with diabetes in the SEA region, and this number is projected to grow to 185 million by 2050;
- In May 2021, the World Health Assembly agreed a Resolution on strengthening prevention and control of diabetes
- In 2024, just over four in ten (42.8%; 251.7 million) adults living with diabetes (20–79 years ld) were undiagnosed;

1 origin : https://www.who.int/news-room/fact-sheets/detail/diabetes

Rule of halves

Evidence from one practice and from the literature suggest that approximately half of most common chronic disorders are undetected, that half of those detected are not treated, and that half of those treated are not controlled: the "rule of halves" [2].

Thus, according to the "rule of halves":

- There are more than 1 billion people in the world who suffer from diabetes;
- Of more than 500 million people who were being treated, more than 250 million didn't get positive results;
- Of the 250 million who have recovered, more than 125 million have diabetes complications.

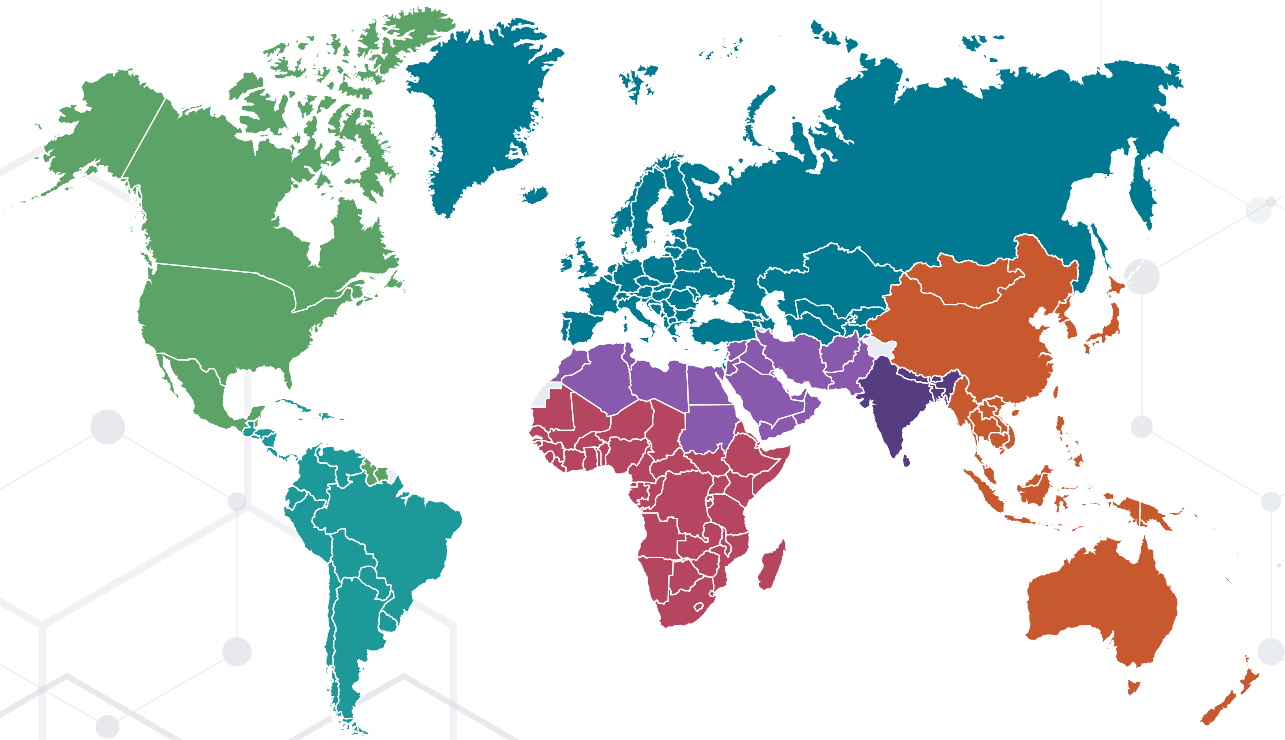
Also, important facts about the spread of diabetes:

- The 2004 predicts of diabetes statistics for the year 2030 were far below similar predicts today (by 75.683%), the incidence rate is growing more than experts expected;
- With 108 million diabetes people in 1980 and 537 million in 2021 we have 497,222% increase in 41 years. Relying on this growth we can estimate 2,6 billion diagnosed diabetes to 2060 or, taking the "Rule of halves", – in 2060th 5.2 billion people (or more than 50% of predicted in 2060 10.1 bln population) will be really suffering from diabetes;
- These facts made International Diabetes Federation to say that "Diabetes is spiralling out of control".

4 origin : https://pubmed.ncbi.nlm.nih.gov/1493028/

Summary

Map 1 Number of people with diabetes worldwide and per IDF Region, in 2024–2050 (20–79 years)



World

2050	852.5 Million
2024	588.7 Million

45% increase

Africa (AFR)

2050	59.5 Million
2024	24.6 Million

142% increase

Europe (EUR)

2050	72.4 Million
2024	65.6 Million

10% increase

Middle-East and North Africa (MENA)

2050	162.6 Million
2024	84.7 Million

92% increase

North America and Caribbean (NAC)

2050	68.1 Million
2024	56.2 Million

21% increase

South and Central America (SACA)

2050	51.5 Million
2024	35.4 Million

45% increase

South-East Asia (SEA)

2050	184.5 Million
2024	106.9 Million

73% increase

Western Pacific (WP)

2050	253.8 Million
2024	215.4 Million

18% increase