АНАЛИЗ ЭФФЕКТИВНОСТИ И БЕЗОПАСНОСТИ ЭВОГЛИПТИНА ПО СРАВНЕНИЮ С СИТАГЛИПТИНОМ ПРИ ДОБАВЛЕНИИ К МОНОТЕРАПИИ МЕТФОРМИНОМ В РУССКО-КОРЕЙСКОЙ ПОПУЛЯЦИИ. РЕЗУЛЬТАТЫ ИССЛЕДОВАНИЯ ЭВОКОМБИ

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ОБОСНОВАНИЕ. Ингибиторы дипептидилпептидазы 4 типа (иДПП-4), обладая инкретиновой активностью, воздействуют на один из основных патогенетических механизмов сахарного диабета 2 типа (СД2). Эвоглиптин является новым препаратом класса иДПП-4 с уникальными для класса характеристиками фармакокинетики, эффективность и безопасность которого в монотерапии была изучена ранее в плацебо-контролируемых испытаниях.

ЦЕЛЬ. Оценить эффективность и безопасность эвоглиптина в сравнении с ситаглиптином в международном двойном слепом рандомизированном контролируемом испытании у больных СД2 с неудовлетворительным контролем гликемии на монотерапии метформином. Сравнить полученные результаты в российской и корейской популяциях.

МЕТОДЫ. Нами была использована база данных исследования ЭВО-КОМБИ, в которой содержались данные российских и корейских участников исследования (в соотношении 1:4). Всего в исследование 1:1 были рандомизированы пациенты (n=281), получавшие монотерапию метформином в дозе не менее 1000 мг/сут (142 – в группу эвоглиптина 5 мг, 139 – в группу ситаглиптина, 100 мг). Исследование имело параллельный дизайн, продолжительность терапии составила 24 нед. Первичной конечной точкой было абсолютное изменение уровня гликированного гемоглобина (HbA_{1c}) через 24 нед по сравнению с исходным значением. Для доказательства не меньшей эффективности эвоглиптина по сравнению с ситаглиптином было необходимо, чтобы верхняя граница 95% двустороннего доверительного интервала (ДИ) для средней разницы между группами изменения уровня HbA_{1c} на 24-й неделе по сравнению с исходными значениями не превышала 0,35%. Дополнительно проводился анализ подгрупп.

РЕЗУЛЬТАТЫ. В группе пациентов, принимавших эвоглиптин, изменение уровня HbA_{1c} составило -0,58±0,70% (p<0,001), а в группе принимавших ситаглиптин – -0,61±0,66% (p<0,001). Межгрупповое различие эффективности составило 0,03% [95% ДИ: -0,14; 0,19%], что ниже установленной границы 0,35% и доказывает не меньшую эффективность эвоглиптина по сравнению с ситаглиптином. Наблюдалась тенденция к большей эффективности обоих препаратов в южно-корейской субпопуляции (p=0,030), однако снижение HbA_{1c} было сопоставимым (p=0,657). Оба препарата хорошо переносились. Нежелательные явления при приеме обоих препаратов наблюдались преимущественно со стороны желудочно-кишечного тракта (ЖКТ), при этом количество нежелательных явлений (НЯ) было сопоставимо (p>0,05) между препаратами, а НЯ со стороны ЖКТ регистрировались чаще у пациентов из Южной Кореи (p=0,014). Тяжелых гипогликемических эпизодов зарегистрировано не было. Частота развития легких гипогликемических эпизодов, зарегистрированных в течение 24 нед, была сопоставима между группами (p=0,365) и составила 0,7% в группе эвоглиптина и 5,2% в группе ситаглиптина.

ЗАКЛЮЧЕНИЕ. В настоящем исследовании продемонстрированы не меньшая эффективность и сопоставимая безопасность препарата эвоглиптин в дозе 5 мг один раз в день по сравнению с ситаглиптином 100 мг один раз в день. Профиль эффективности и безопасности эвоглиптина был сопоставим в российской и корейской популяциях.

КЛЮЧЕВЫЕ СЛОВА: иДПП-4; эвоглиптин; ситаглиптин; HbA_{1c}

EFFICACY AND SAFETY OF EVOGLIPTIN VERSUS SITAGLIPTIN AS ADD ON TO METFORMIN ALONE IN A COMBINED RUSSIAN-KOREAN POPULATION. EVO-COMBI TRIAL

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BACKGROUND: Dipeptidyl-peptidase-4 inhibitors (iDPP-4) are pathogenically targeted drugs for diabetes mellitus type 2 (T2DM). Evogliptin is a new member of iDPP-4 class. The drug has the longest half-elimination period among the class, and its efficacy and safety as monotherapy have been already studied in placebo-controlled randomized clinical trials.

AIMS: To study efficacy and safety of evogliptin as compared to sitagliptin in T2DM patients with unsatisfying glycemic control with metformin monotherapy via a multinational double blind randomized controlled trial. To compare the study results in Russian and Korean subpopulations.

Received: 24.02.2018. Accepted: 06.08.2018.

MATERIALS AND METHODS: We used a combined Russian-Korean database (1:4) of EVO-COMBI trial. 281 adult T2DM patients administered metformin alone (at least 1000 mg/day) were randomized 1:1 to add on evogliptin (142 patients) or sitagliptin (139 patients) for 24 weeks once daily. The primary endpoint was change in glycated hemoglobin (HbA1c) level at Week 24 as compared to baseline. Non-inferiority was concluded if the upper limit of the 2-sided 95% confidence interval for the HbA1c difference between treatments was < 0.35 %. Subgroup analysis for between-subpopulation difference in treatment effect was also conducted.

RESULTS: The mean between-group difference was 0.03 % [95 % CI: -0.14; 0.19 %], that confirms non-inferiority of evogliptin (mean HbA1c decrease -0.58 ± 0.70 %, p<0.001) to sitagliptin (mean HbA1c decrease -0.61 ± 0.66 %, p<0.001). Evogliptin and sitagliptin both tend to be more effective in South Korean subpopulation in terms of fasting plasma glucose lowering (p=0.030), however HbA1c decrease in subpopulations was comparable (p=0.657). Both drugs were well tolerated in both subpopulations. Adverse effects were associated mostly with gastrointestinal disorders, and the frequency was comparable between treatment groups (p>0.05). Gastrointestinal adverse effects were registered more often in Korean patients (p=0.014). There were no severe hypoglycemia. Frequency of mild hypoglycemia was comparable between evogliptin and sitagliptin (0.7 % and 5.2 %, respectively, p=0.365).

CONCLUSIONS: Evogliptin 5 mg/day is non-inferior to sitagliptin 100 mg/day in T2DM patients with unsatisfying glycemic control with metformin monotherapy. Safety profile is also comparable. Efficacy-safety profile of evogliptin is comparable in Russian and South Korean subpopulations.

KEYWORDS: iDPP-4; evogliptin; sitagliptin; HbA_{1c}

BACKGROUND

The contemporary treatment protocols for type 2 diabetes mellitus (T2DM) include an intensification of the early combination of metformin drug and early therapy for patients with HbA1c < 7.5%, which comprise important options to maintain glycaemic control. These treatment combinations were recognised as optimal as they influence the main pathogenetic mechanisms of T2DM, namely insulin resistance (metformin) [1] and insulin/glucagon secretion disorder. The latter is optimally affected by drugs and incretin therapy, especially dipeptidyl peptidase type 4 inhibitors (iDPP-4) [2].

Several iDPP-4 are currently registered in the Russian Federation, including Sitagliptin, Saxagliptin, Vildagliptin, Linagliptin and Alogliptin. Therefore, sufficient information on the efficacy and safety of individual drugs is crucial to optimise the treatment selection. Although clinical studies evaluating the efficacy of abovementioned treatment options, a combination of both monotherapy [3-7] and other drugs treatment options [8-12], direct comparative studies of the various gliptins are required. Meta-analyses are used for drug comparisons to demonstrate extent Sitagliptin and Vildagliptin provide higher efficacy than other iDPP-4, both in monotherapy [13] and in combination with metformin [14].

Craddy et al. performed a meta-analysis to compare the efficacy of the iDPP-4 (Alogliptin, Linagliptin, Saxagliptin, Sitagliptin and Vildagliptin) (Table 1) [15] and found that all produced an absolute decrease of 0.45–0.59% in the HbA1c level, which carried a similar risk of a hypoglycaemic episode. A comparative analysis is also carried out for the efficacy of different iDPP-4 when combined with metformin (see Table 1). Moreover, iDPP-4 administration as second-line therapy, in addition to metformin, led to an additional HbA1c reduction of 0.48–0.70% as compared with metformin monotherapy. The same study also revealed that iDPP-4, both in monotherapy and in combination with metformin, did not affect body weight (see Table 1) [15]. However, these results are limited because the severity of the hypoglycaemic effect exerted by iDPP-4 correlates directly with the HbA1c baseline level because of the glucose-dependent effects of the preparations on insulin secretion, (i.e. an absolute decrease of HbA1c depends both on its baseline value and on the patient's body mass index (BMI)) [16]. The aforementioned meta-analysis included patients with different median body weight (see Table 1).

The complexity of indirect comparisons on the efficacy of individual drugs is caused by the influence of several factors, such as ethnicity [17], patient's age [18, 19], duration of diabetes [20], the severity of insulin resistance [21] among others. All these evidences support a need for direct comparative studies of Sitagliptin and Saxagliptin [22], Sitagliptin and Vildagliptin [23]). Such direct comparisons demonstrated either comparable [23] or better [22] efficacy of Sitagliptin and Vildagliptin as compared with other iDPP-4, leading to a conclusion that these two drugs were considered as reference drugs, especially sitagliptin registered in most countries.

Evogliptin is a new selective DPP-4 inhibitor, similar to Sitagliptino (>80%), that inhibits the enzyme for 24 hours [24]. The peak blood concentration is 5 hours after intake and the half-life is 36–39 hours. In South Korea, a study was performed to compare the efficacy and safety of Evogliptin monotherapy using different doses (2.5 mg, 5 mg, 10 mg once per day) with placebo in the T2DM patient population. Patient's average fasting glycaemia levels were 8.28 mmol/l, and the average HbA1c was 7.6%. The treatment period was 12 weeks, after which the endpoints were evaluated. The results showed that 2.5, 5 and 10 mg of Evogliptin doses led to a significant clinical decrease of HbA1c by 0.46%, 0.57% and 0.51%, respectively as compared with placebo. No difference was found on the effect of the three-drug concentrations. The drugs significantly improved insulin secretion and did not affect the patients' body weight [25].

Table 1. Comparative analysis of the efficacy of individual inhibitors of dipeptidyl-peptidase 4 in monotherapy and combined with metformin. All values are weighted mean (95% confidence interval). Adapted from Craddy et al. [15].

Preparation	Initial HbA1c, %*	Absolute decrease in HbA1c, %	Probability of reaching HbA1c <7%	Absolute risk of hypoglycaemia development	Initial weight, kg*	Absolute decrease in body weight, kg
In monotherapy						
Alogliptin 25 mg	8.00	-0.58 (-0.83; -0.33)	40% (34–59%)	0.13% (0.003–0.7%)	67.7	-0.17 (-0.60; 0.23)
Linagliptin 5 mg	8.13	-0.58 (-0.81; -0.35)	34% (19–53%)	0.8% (0.003–4.2%)	79.1	-0.12 (-0.62; 0.38)
Saxagliptin 5 mg	8.59	-0.45 (-0.75; -0.15)	25% (11– 44%)	0.88% (0.062–3.8%)	86.6	-
Sitagliptin 100 mg	7.96	-0.59 (-0.75; -0.43)	37% (24–51%)	0.29% (0.046–0.97%)	85.1	0.20 (-0.18; 0.60)
Vildagliptin 50 mg × 2 times	8.49	-0.52 (-0.71; -0.31)	39% (24–55%)	0.37% (0.043–1.4%)	89.5	0.33 (-0.12; 0.80)
Combined with metformin						
Alogliptin 25 mg	7.93	-1.10 (-1.38; -0.82)	56% (32–78%)	0.39% (0.028–1.7%)	-	-0.45 (-2.22; 1.31)
Linagliptin 5 mg	8.00	-0.99 (-1.17; -0.82)	41% (22–63%)	1.2% (0.36–2.8%)	83.0	-0.54 (-6.31; 5.09)
Saxagliptin 5 mg	8.43	-1.03 (-1.21; -0.85)	31% (17–50%)	1.3% (0.45–3.0%)	81.5	-
Sitagliptin 100 mg	8.34	-1.06 (-1.22; -0.91)	38% (22–57%)	2.1% (0.74–4.7%)	83.8	-0.99 (-2.38; 0.35)
Vildagliptin 50 mg x 2 times	7.86	-1.02 (-1.18; -0.86)	35% (18 – 54%)	1.2% (0.37 – 3.1%)	90.0	0.15 (-0.99; 1.28)

Note: * Weighted average value.

Oh et al. assessed the efficacy and safety of Evogliptin in T2DM patients with different renal dysfunction manifestations. Both the Evogliptin plasma concentration and the degree of DPP-4 inhibition increased with a decreasing renal function. The average area from 0 to 120 hours after a single dose of drug increased by 1.2, 1.8 and 1.98 times with mild, moderate and severe chronic renal failure, respectively as compared with the group with preserved renal function. On the other hand, no clinically significant changes in the efficacy and safety of Evogliptin were demonstrated [26].

AIM

The present study aimed to assess the efficacy and safety of Evogliptin 5 mg (Dong-A ST Co., Ltd., South Korea/GEROFARM, Russia) and metformin for the management of T2DM patients with inadequate glycaemic control. The efficacy of Evogliptin (5 mg) and Sitagliptin (100 mg) in combination with metformin was first compared among patients of different ethnic groups (South Korea and the Russian Federation).

METHODS

Study design

The present study was designed as an international randomised, double-blind, multicentre study in active control parallel groups (2 groups with the ratio 1:1).

Acceptance criteria

Inclusion criteria

Inclusion criteria were as follows: (1) men and women aged 18 years and older with a confirmed diagnosis of T2DM; (2) who signed informed voluntary consent; (3) had a glycated haemoglobin screening level of 6.5–11.0%; (4) who received monotherapy with metformin at a dose of at least 1000 mg per day for at least 3 months, including the last 6 weeks before screening; (5) had a BMI with a range of 20–40 kg/m2 at screening; (6) patients who signed an agreement to adhere to barrier contraception methods from the time of signing the informed voluntary consent until the study completion.

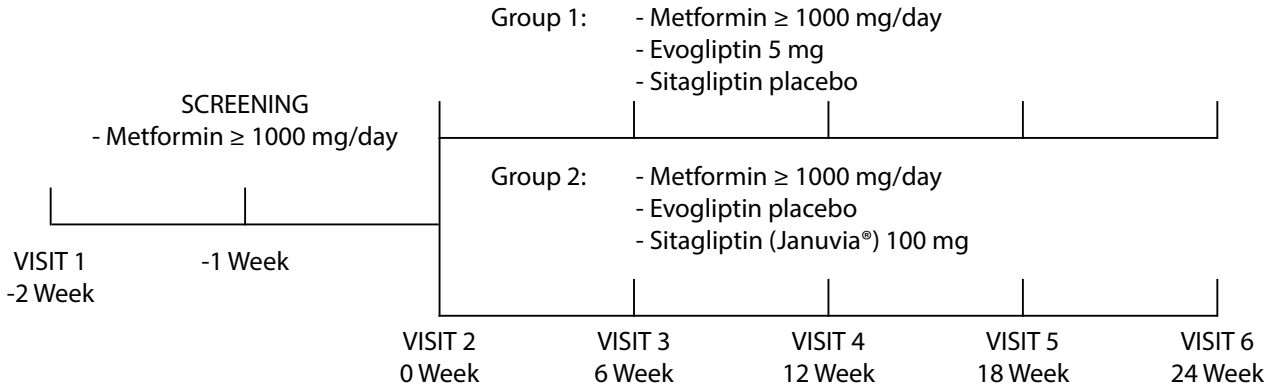

Fig. 1. Схема проведения исследования.

Exclusion criteria

Patients with one or more of the following criteria were excluded: (1) Fasting plasma glucose of 15 mmol/l or more at screening; (2) DM1, secondary diabetes mellitus, or gestational diabetes mellitus; (3) myocardial infarction or acute cerebrovascular disorder within the last 6 months; (4) Chronic heart failure of class III or IV (by NYHA), hepatic cirrhosis, gallbladder disease, acromegaly, asthma, allergic skin diseases, thyroid dysfunction with an abnormal thyroid-stimulating hormone level at screening; (5) a history of coronary bypass surgery, or gastrointestinal tract resection; (6) Indicators of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), exceeding the standard upper limit by more than 2.5 times; (7) indicator of creatine phosphokinase (CK) exceeding the standard upper limit by more than 2.5 times with symptoms of dyspnoea and chest pain; (8) level of blood serum creatinine in blood exceeding 132.6 μmol/l in men or 123.8 μmol/l in women; (9) fasting triglycerides exceeding 4.52 mmol/l; (10) patients currently taking oral contraceptives, corticosteroids, warfarin, digoxin, or CYP3A4 isoenzyme inhibitors or inducers; (11) prior therapy with insulin or glucagon-like peptide 1 (GLP-1) analogues (in exceptional cases, patients who received insulin for no more than 2 weeks after surgery or examination could be included), or thiazolidinediones or iDPP-4 for 6 months prior to screening; (12) anamnestic information of alcohol or drug abuse within 2 months prior to screening; (13) participation in a pharmacological clinical trial for 2 months prior to the study; (14) pregnant and lactating women; (15) any other conditions judged by the investigator to hinder the patient's participation in the study; (16) allergic reactions to the components of the preparation Januvia® (Sitagliptin).

Implementation conditions

The study was conducted in 33 clinical centres, among which 6 were located in the Russian Federation, and 27 were located in South Korea.

Duration of the study

The study design comprised a 2-week screening period and a 24-week treatment period. The scheme of the study is presented in Fig. 1.

Description of medical interventions

Included patients were randomised into two groups according to the glycated haemoglobin HbA1c level at screening (HbA1c < 8.5% or HbA1c ≥ 8.5%), using a stratified randomisation method. During the screening period, all patients were asked to take the same dose of metformin prior to screening. Subsequently, patients continued to take metformin, in combination with either the study drug (e.g. Evogliptin, film-coated tablets, 5 mg), or a reference preparation (Sitagliptin, film-coated tablets, 100 mg) in combination with placebo. As a follow-up, patients visited the research centre at 6-week intervals. At each visit, the medical investigator monitored patients' compliance to the recommended diet, physical activity and concomitant therapy through physical examination, BMI evaluation, measurement of vital signs (blood pressure, heart rate and respiratory rate), clinical and biochemical blood analysis, general urine analysis, HbA1c level, fasting plasma glucose concentration and occurrence of adverse events.

Conditions for early termination of therapy

Participation could be terminated prior to the end of the study if: (1) the patient requested withdrawal (recall of informed consent or refusal to visit the clinical centre); (2) the patient took a medication that was not prescribed by the principal investigator, which was expected to affect the efficacy and safety evaluation of the study drug; (3) participation in the study was hindered by serious adverse events or clinically significant laboratory test abnormalities, including the development of acute pancreatitis. Patients could also withdraw from the study if (4) after 2-week rescue therapy (Glimepiride), the fasting blood glucose exceeded 15.0, 13.3 and 11.1 mmol/l after visits 2, 4 and 5, respectively; (5) the patient underwent one episode of severe or symptomatic hypoglycaemia or two episodes of asymptomatic hypoglycaemia during treatment; (6) the investigator decided to discontinue the patient's participation in the study.

Primary study outcome

The primary endpoint of the study was a change in the level of HbA1c (%) at week 24 as compared with

the baseline values. To prove Evogliptin non-inferiority as compared with Sitagliptin, it was necessary that the 95% bilateral confidence interval (CI) upper limit for the average group difference in HbA1c level changed at week 24 in comparison with baseline values that did not exceed 0.35%.

Additional study outcomes

The secondary endpoints were: (1) change in fasting plasma glucose (FPG) concentration at week 24 as compared with initial value; (2) change in lipid profile parameters (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), free fatty acids (FFA)) at week 24 as compared with initial value; (3) proportion of patients who achieved HbA1c ≤ 6.5% at week 24; (4) number of cases requiring immediate hyperglycaemia correction; (5) changes in the level of basal insulin and C-peptide at week 24 relative to the baseline level; (6) change in insulin resistance index HOMA-IR at week 24 relative to baseline; (7) change in the index of function of pancreatic β-cells HOMA-β at week 24 relative to baseline; (8) change in the QUICKI index at week 24 relative to baseline; (9) change in body weight at week 24 as compared with baseline value; (10) change in the mean daily blood glucose level at week 24 as compared with the baseline value.

Safety assessment

The criteria for safety assessment included: (1) occurrence, frequency and severity of adverse events; (2) changes in physical examination parameters; (3) changes in vital indicators relative to the baseline level; (4) changes in instrumental indicators (ECG in 12 leads) relative to the baseline level; (5) incidence of hypoglycaemia episodes (plasma glucose level < 3.9 mmol/l); (6) changes in the clinical indices, biochemical blood tests and general urinalysis relative to the baseline level.

Subgroup analysis

Subgroup analysis was performed for the primary efficacy point (i.e. change in HbA1c level), and the secondary efficacy point (i.e. changes in the FPG level; changes in FA as assessed by: HbA1c level at screening (HbA1c < 8.5% and 8.5%), gender, age (up to 65 years, 65 years and older at the time of screening), BMI (≤ 25, > 25 at the time of screening) and study country (Russia, South Korea)).

Methods of outcome registration

Physical examination and laboratory and instrumental testing of patients were conducted according to standard protocols. The average daily blood glucose was determined using patient self-monitoring of blood glucose levels. The average daily glucose level were corresponded to the average of the 7 daily glucose (i.e. prior to meals, 2 hours after meals and at bedtime), using a glucometer in one of the 7 days prior to the hospital visit. In the data analysis, all the 7 glucose levels at Week 0 and Week 24 were measured.

The HOMA-IR index was calculated using the formula:

$$\text{HOMA-IR} = \frac{\text{fasting glucose}\left(\frac{\text{mmol}}{\text{l}}\right) * \text{fasting insulin}\left(\frac{\mu\text{U}}{\text{ml}}\right)}{22{,}5}.$$

The NOMA-B index was calculated using the formula:

$$\text{HOMA-B} = \frac{20 * \text{fasting insulin}\left(\frac{\mu\text{U}}{\text{ml}}\right)}{\text{fasting glucose}\left(\frac{\text{mmol}}{\text{l}}\right) - 3{,}5}.$$

The QUICKI index was calculated using the formula:

$$\text{HOMA-B} = \frac{1}{\log(\text{fasting insulin}\left(\frac{\mu\text{U}}{\text{ml}}\right)) + \log(\text{fasting glucose}\left(\frac{\text{mmol}}{\text{l}}\right) * 18)}$$

Ethical approval

In the Russian Federation, all the study documents (i.e. protocol, investigator's brochure, informed consent, patients' life and health insurance documents) were approved by the Ethics Council (Conclusion of the Ethics Council meeting No. 118 of 02.02.2016). In South Korea, the study was approved by the Ministry of Food and Drug Safety and received on 4 November 2013 (Resolution No. 11953). Additionally, the study was approved by the Independent Ethical Committees at each participating research centre.

Statistical analysis

Principles of calculating the sample size. The sample size was calculated using the results of the previous studies focusing on the 24-week iDPP-4 administration. The required number of patients were calculated under the following assumptions: a standard deviation of HbA1c level changed relative to the baseline of 0.9; a boundary of non-inferiority of 0.35%; a significance level of 2.5% (α, unilateral); a power of 80% (1-β).

Methods of the statistical data analysis. To compare the non-inferiority of Evogliptin with the active control Sitagliptin preparation, the 95% bilateral CI was calculated for the average difference between groups with the HbA1c change at 24 weeks as compared with the baseline level.

To analyse the efficacy and safety indicators, the significant changes at week 24 relative to baseline was assessed in each group. Depending on the type of data collected, the Student's t-test for coupled aggregates, the non-parametric Wilcoxon test, or the non-parametric Mann–Whitney test was performed. Depending on the type of data for group comparisons, the Student's t-test for independent groups, the non-parametric Mann–Whitney test, the Fisher exact test, or the Pearson $\chi 2$ criterion was performed.

Efficacy was analysed using the primary endpoint on a set of randomised patients who took the study drug, and for which the primary point value of efficacy (Full Analysis Set, FA-set) was estimated at least once. A secondary analysis was performed in patients who completed the study, did not receive the salvage therapy (Glimepiride) and did not have any serious protocol deviations (Per Protocol Set, PP-set). Safety assessment was performed in patients who took at least one dose of the study drug and underwent at least one safety indicator assessment.

Table 2. Initial demographic, anthropometric and anamnestic characteristics of patients

Indicator (mean ± standard deviation)	Evogliptin (n=142)	Sitagliptin (n=139)	p-value
Age, years	57.43±9.50	57.86±9.23	0.703
≤34 years, n (%)	3 (2.1)	1 (0.7)	
35–44 years, n (%)	9 (6.3)	10 (7.2)	
45–54 years, n (%)	39 (27.5)	42 (30.2)	
55–64 years, n (%)	55 (38.7)	47 (33.8)	0.652
65–74 years, n (%)	34 (23.9)	35 (25.2)	
75–84 years, n (%)	1 (0.7)	4 (2.9)	
≥85 years, n (%)	1 (0.7)	0 (0.0)	
Gender			
male, n (%)	65 (45.8)	66 (47.5)	0.867
female, n (%)	77 (54.2)	73 (52.5)	
Body weight, kg	71.55±15.87	70.87±14.96	0.880
Height, cm	163.51±8.80	162.94±9.38	0.432
BMI, kg/m2	26.58±4.35	26.49±3.83	0.779
≤25	59 (41.5)	55 (39.6)	0.829
>25	83 (58.5)	84 (60.4)	
DM duration, years1	8.59±5.49	7.74±4.66	0.260
HbA1c on screening	7.45±0.71	7.46±0.74	0.734
Lower than 8.5%, n (%)	122 (85.9)	123 (88.5)	0.600
8.5% and more	20 (14.1)	16 (11.5)	
Diabetic retinopathy, n (%)	8 (5.8)	14 (9.9)	0.245
Diabetic neuropathy, n (%)	25 (18.0)	26 (18.3)	0.933
Diabetic nephropathy, n (%)	6 (4.3)	5 (3.5)	1.00
Disorders in the cardiovascular system in the history, n (%)			
Arterial hypertension	58 (41.7)	61 (43.0)	0.693
Myocardial infarction	3 (2.2)	1 (0.7)	0.630
IHD. Angina	3 (2.2)	1 (0.7)	0.630
IHD. Unstable angina	1 (0.7)	2 (1.4)	0.985
Atrial fibrillation	4 (2.9)	1 (0.7)	0.380
Chronic heart failure	1 (0.7)	2 (1.4)	0.990

Notes: 1Since several participants could not provide the exact diagnosis date, diabetes duration was calculated using the following formula: (screening visit year - the year of diagnosis + 1). Five participants had no information on the date of diagnosis establishment (n=138 for this indicator in each of the groups).

RESULTS

Objects (participants) of the study

A total of 208 patients (104 patients in each group) demonstrated the non-inferiority of Evogliptin as compared with Sitagliptin. Following a withdrawal of 35% of the patients, a total of 320 patients (160 patients in each group) were included. The screening was performed in 348 patients, among whom 67 did not pass the screening test. This remained a total of 281 participants randomised for the clinical study. Among the randomised patients, 142 patients received Evogliptin and metformin (group 1), and 139 received Sitagliptin and metformin (group 2). However, a total of 256 patients (131 patients from group 1 (93.0%) and 125 patients from group 2 (89.9%)) were able to complete the test. The reason for early withdrawal included 'patient's refusal' (n=8), the occurrence of 'adverse event' (n=8), deviation from the study protocol (n=5) and 'investigator's decision' (n=3). Information regarding the patients randomised is presented in Table 2.

At the start of the treatment, subjects in Russia had a higher fasting glucose level (p = 0.039), and a

higher concentration of blood C-peptide (p = 0.002) than those in South Korea. Russian patients also had higher BMI (p < 0.0001), and dyslipidaemia (p = 0.0003 for total cholesterol concentration, p < 0.0001 for LDL concentration) than South Korean patients. However, the two subpopulations did not differ in the level of HbA1c and insulin resistance index. Russian patients had a higher glomerular filtration rate (p = 0.013) and arterial hypertension (p = 0.016) than South Korean patients. Thus South Korean patients received angiotensin-converting enzyme inhibitor therapy (p < 0.0001). Blood pressure was satisfactory and similar in both subpopulations (p = 0.316 for systolic blood BP and p = 0.568 for diastolic BP).

Primary study results

The results of this study are presented for the first time in the clinical research environment.

Efficacy analysis at the primary endpoint included data of 274 patients (140 subjects in the Evogliptin group and 134 subjects in the Sitagliptin group). The remaining 7 patients were excluded from the Full Analysis Set due to missing data.

Compared to baseline, HbA1c (%) changed after 24 weeks of treatment. The mean ± standard deviation of patients taking Evogliptin were 0.58 ± 0.70 and −0.61 ± 0.66 of patients taking Sitagliptin (both p < 0.0001). In the group difference in the HbA1c, the mean values changed at week 24 by 0.03% [95% CI: −0.14; 0.19%]. Post-hoc covariate analysis of the primary endpoint, considering the drug treatment of the ethnic the 0.35% limit separation group of non-inferiority, proved non-inferiority of the Evogliptin preparation in relation with the Sitagliptin group and the research group. This showed that none of the listed covariates was statistically significant (p > 0.05). Changes in the level of HbA1c during treatment are shown in Fig. 2.

Additional results of the study

Proportion of patients who reached a HbA1c level of 6.5% or lower. Results from the PP-set showed that the 31,67% in the Evogliptin group (38 of 120), and 36.61% in the Sitagliptin group (41 of 112) exhibited an HbA1c level below 6.5% after 24 weeks of treatment. No significant differences were observed between the two groups (p = 0.345).

Number of cases requiring immediate hyperglycaemia correction. Immediate hyperglycaemia correction with the subsequent prescription of salvage therapy (Glimepiride) was required for two patients taking Evogliptin and for no patients taking Sitagliptin. The risk of hyperglycaemic conditions did not differ between the groups (p = 0.497).

Laboratory indicators. Initial values and changes in the laboratory indices of secondary endpoints are provided in Table 3. The analysis was performed on the patients of PP-set. A statistical significant decrease in both fasting and daily glycaemia levels, and an increase in the HOMA-β index after 24 weeks of treatment (p < 0.0001) were recorded. Moreover, patients receiving Sitagliptin underwent a decrease in the total concentration of FFA (p = 0.021). No significant changes were observed for other indicators and no significant differences were found between the two groups, regarding the secondary endpoints.

Subgroup analysis

Subgroup analysis revealed no statistically significant differences in the efficacy of Evogliptin and Sitagliptin. Results (median, CI) concerning HbA1c change are presented in Table 4 and those concerning fasting glycaemia are presented in Table 5.

Considering the previously evidence supporting a greater efficacy of iDPP-4 in the Mongoloid race [17], an additional comparison of Evogliptin efficacy was performed between the Russian and South Korean subpopulations. A slightly greater reduction in fasting glycaemia was found for the South Korean subpopulation (p = 0.030), whereas both subpopulations exhibited similar HbA1c level (p = 0.657). Similar results were obtained for Sitagliptin efficacy, which was consistent with previously published data.

Adverse events

For safety analysis, the incidence of adverse events (AE) and adverse drug reactions (ADR) was assessed separately. No serious adverse events (SAE) were observed in association with the study drug. Patients taking Evogliptin exhibited more ADRs (p = 0.015) significantly, although most were mild. Only 2 cases presented moderate severity (1 patient receiving Evogliptin and 1 patient receiving Sitagliptin). Severe ADRs were not observed in either group. Regarding the incidence of ADRs, no significant differences were found between the groups. Information about the frequency of AEs, SAEs, ADRs and the most frequent AEs and ADRs is presented in Table 6.

In the study, 1 episode of angina (severity level is mild AE), 1 episode of unstable angina (severe AE) and 1 case of acute myocardial infarction (severe AE) were observed among patients taking Evogliptin, although none was associated with the treatment. Among the patients receiving Sitagliptin, 1 presented a cardiac rhythm disorder (mild AE) and 1 presented a complete atrioventricular blockade (severe AE), none was associated with the treatment. Since gastrointestinal disorders are expected during the intake of incretin

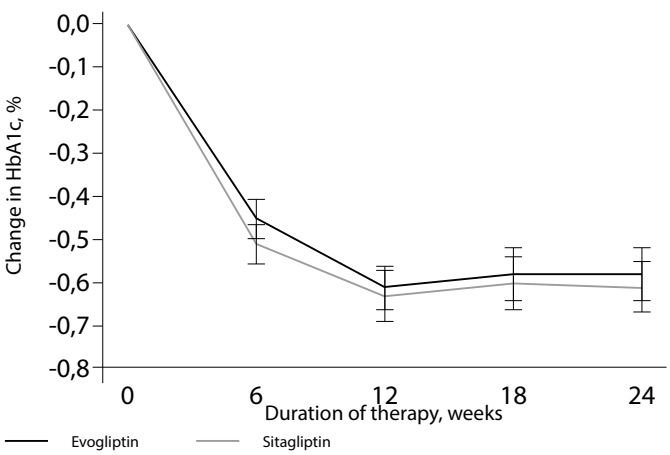

Fig. 2. Change in HbA1c when treatment (mean ± standard error)

Table 3. Changes in the indicators of secondary endpoints

Indicator#(mean ± standard deviation)	Evogliptin (n = 120)	Sitagliptin (n = 112)	p-value (between groups)
Fasting glycaemia level, mmol/l			
Week 0	7.54±1.67	7.91±1.75	ns
Change after 24 weeks	-0.54±1.55	-0.75±1.33	ns
p -value	<0.0001	<0.0001	
Fasting insulin level, μU/ml			
Week 0	8.68±6.55	8.74±4.54	ns
Change after 24 weeks	0.83±5.51	0.50±3.88	ns
p-value	ns	ns	
Fasting C-peptide level, ng/ml			
Week 0	2.30±1.21	2.40±1.01	ns
Change after 24 weeks	0.06±0.86	0.16±1.02	ns
p-value	ns	ns	
HOMA-B index, %			
Week 0	47.64±32.25	45.45±30.45	ns
Change after 24 weeks	11.60±28.55	13.98±26.13	ns
p-value	< 0.0001	< 0.0001	
HOMA-IR index			
Week 0	2.94±2.56	3.10±1.84	ns
Change after 24 weeks	0.10±2.31	-0.09±1.62	ns
p-value	ns	ns	
QUICKI index			
Week 0	0.15±0.01	0.14±0.01	ns
Change after 24 weeks	0.00±0.01	0.00±0.01	ns
p-value	ns	ns	
Average daily glycaemia level, mmol/l			
Week 0	8.90±1.92	9.20±2.00	ns
Change after 24 weeks	-0.95±1.51	-1.32±1.56	ns
p-value	<0.0001	<0.0001	
Body weight, kg			
Week 0	71.26±15.48	70.55±15.38	ns
Change after 24 weeks	0.33±1.98	0.29±2.18	ns
p-value	ns	ns	
Total cholesterol, mmol/l			
Week 0	4.51±1.09	4.43±1.07	ns
Change after 24 weeks	-0.10±0.81	-0.01±0.64	ns
p-value	ns	ns	
LDL, mmol/l			
Week 0	2.75±1.02	2.68±0.97	ns
Change after 24 weeks	-0.10±0.67	-0.04±0.56	ns
p-value	ns	ns	
HDL, mmol/l			
Week 0	1.35±0.29	1.31±0.35	ns
Change after 24 weeks	0.01±0.22	0.00±0.24	ns
p-value	ns	ns	

Table 3. Changes in the indicators of secondary endpoints

Indicator#(mean ± standard deviation)	Evogliptin (n = 120)	Sitagliptin (n = 112)	p-value (between groups)
Triglycerides, mmol/l			
Week 0	1.56±0.80	1.65±0.74	ns
Change after 24 weeks	-0.03±0.82	0.09±0.85	ns
p-value	ns	ns	
Free fatty acids, μEq/l1			
Week 0	673.86±252.98	688.21±278.12	ns
Change after 24 weeks	-25.46±269.96	-67.85±276.32	ns
p-value	ns	0.021	

Notes: 'ns'= 'non-significant'–no statistically significant differences were revealed (p > 0.05).
1 For several patients, the laboratory analysis of FFA was performed by determining the FFA through gas chromatography in selected ion mode (GC-SM). Precise concentrations of saturated and monounsaturated fatty acids were determined separately, without the overall FFA index. In this case, the results do not seem to be correct; the table presents the results of FFA determination in the PP-set of 182 patients (95 patients of group 1 and 87 patients of group 2).

Table 4. Subgroup analysis for indicators of HbA1c change after 24 weeks of treatment, %.

Subgroup	n	Evogliptin	n	Sitagliptin	p-value
HbA1c <8.5%	119	-0.47 [-0.82; -0.14]	118	-0.56 [-0.90; -0.20]	0.322
HbA1c ≥8.5%	19	-1.21 [-1.78; -0.56]	16	-1.34 [-1.88; -1.02]	0.679
Men	63	-0.60 [-1.02; -0.19]	64	-0.69 [-1.11; -0.30]	0.558
Women	75	-0.47 [-0.82; -0.14]	70	-0.56 [-0.82; -0.21]	0.481
Under 65 years	103	-0.52 [-0.91; -0.23]	97	-0.66 [-1.00; -0.20]	0.643
65 years or more	35	-0.44 [-0.77; -0.10]	37	-0.56 [-0.83; -0.37]	0.168
BMI <25 kg/m2	59	-0.52 [-0.90; -0.21]	54	-0.56 [-1.02; -0.24]	0.573
BMI ≥25 kg/m2	79	-0.47 [-0.93; -0.12]	80	-0.64 [-0.93; -0.27]	0.460
Russia	27	-0.50 [-1.00; -0.05]	28	-0.45 [-1.02; 0.05]	0.711
South Korea	111	-0.52 [-0.90; -0.18]	106	-0.64 [-0.97; -0.34]	0.702

Table 5. Subgroup analysis for indicators of fasting glycaemia level change after 24 weeks of treatment, mmol/l

Subgroup	n	Evogliptin	n	Sitagliptin	p-value
HbA1c <8.5%	119	-0.33 [-1.12; 0.16]	118	-0.50 [-1.19; 0.10]	0.387
HbA1c ≥8.5%	19	-0.78 [-2.02; 1.06]	16	-1.08 [-2.21; -0.61]	0.707
Men	63	-0.72 [-1.45; 0.04]	64	-0.53 [-1.27; 0.00]	0.619
Women	75	-0.16 [-0.78; 0.33]	70	-0.56 [-1.19; 0.28]	0.075
Under 65 years	103	-0.50 [-1.32; 0.14]	97	-0.56 [-1.27; 0.05]	0.717
65 years or more	35	-0.19 [-0.72; 0.27]	37	-0.61 [-1.33; 0.06]	0.098
BMI <25 kg/m2	59	-0.39 [-1.14; 0.08]	54	-0.89 [-1.39; 0.00]	0.126
BMI ≥25 kg/m2	79	-0.33 [-1.26; 0.21]	80	-0.44 [-1.17; 0.17]	0.738
Russia	27	0.07 [-0.94; 1.06]	28	-0.69 [-1.22; 0.33]	0.104
South Korea	111	-0.50 [-1.25; 0.06]	106	-0.50 [-1.28; 0.06]	0.702

mimetics, a comparative analysis was performed between the Russian and South Korean subpopulations regarding the incidence of AEs. The percentage of patients with gastrointestinal AEs (i.e. dyspepsia, diarrhoea, constipation, nausea, vomiting, discomfort in the epigastric region and others) was lower in the Russian than South Korean subpopulation, both of which used Evogliptin (4% and 14 %, respectively, p = 0.014), and Sitagliptin (3% and 9%, respectively, p = 0.014).

The frequency of hypoglycaemic episodes was separately analysed. No statistically significant differences were found between the groups with the hypoglycaemia (p = 0.365) incidence and its types: exactly defined symptomatic hypoglycaemia (p = 0.242); asymptomatic hypoglycaemia (p = 0.618) and

Table 6. Most frequent adverse events and adverse drug reactions observed during the study

Event	Evogliptin, n (%) (140 patients)	Sitagliptin, n (%) (136 patients)	p-value
Total AEs	61 (43.6)	51 (37.5)	ns
Total SAEs	5 (3.6)	6 (4.4)	ns
DT disorders	17 (12.1)	11 (8.1)	ns
Infectious and parasitic diseases	16 (11.4)	15 (11.0)	ns
Disorders in the musculoskeletal and connective tissue	8 (5.7)	10 (7.4)	ns
Disorders in the skin and subcutaneous tissue	8 (5.7)	< 5%	ns
Total ADRs	24 (17.1)	7 (5.1)	0.015
DT disorders	5 (3.6)	3 (2.2)	ns
Disorders in the skin and subcutaneous tissue	5 (3.6)	2 (1.5)	ns

Notes: 'ns' = 'non-significant'–no statistically significant differences were revealed ($p > 0.05$).
AE–adverse event–any clinical event detected in a subject of a clinical study after taking the medicinal product, which is adverse from a medical point of view, which may not have a causal relationship with its use.
SAE–serious adverse event–any AE that, irrespective of the dose of the medicinal product, caused death, life-threatening, required hospitalisation or its prolongation, resulted in persistent or significant incapacity for work or disability, constituted a congenital abnormality or birth defect.
ADR–adverse drug reaction–AE, for which the causal relationship with the drug intake cannot be ruled out.
DT - digestive tract.

probably symptomatic hypoglycaemia ($p = 0.493$). In total, 1 hypoglycaemic episode was observed in the Evogliptin group (asymptomatic hypoglycaemia), whereas 7 episodes were observed in the Sitagliptin group (3 exactly defined symptomatic hypoglycaemia, 1 probable symptomatic hypoglycaemia, 3 asymptomatic hypoglycaemia). All episodes of hypoglycaemia observed in South Korean patients. No episodes of severe hypoglycaemia were observed during the study.

DISCUSSION

Summary of the study's primary result

The primary result of the randomised phase III, active-controlled and double-blind study was the non-inferiority of the new highly selective iDPP-4 Evogliptin as compared with the reference preparation Sitagliptin. One important aspect of this study was the inclusion of patients from different ethnic groups. As stated above, previous studies demonstrated a greater iDPP-4 efficacy in the Asian population [17], which was confirmed by the subgroup analysis performed in the present study (the role of confounding differences in BMI at the start of therapy was not excluded). Comparing the efficacy of Evogliptin and Sitagliptin within the Russian and Korean subpopulations, we demonstrated a similar efficacy and non-inferiority of Evogliptin in relation to Sitagliptin for both subpopulations.

Discussion of the study's primary result

The present study demonstrated an improvement in β-cell function, as estimated by the HOMA-β index, in both groups. The parameters to evaluate insulin resistance (insulin and fasted C-peptide level, HOMA-IR index and QUICKI index) remained unchanged in both groups and the patient's body weight. These results were expected, given that the primary point of iDPP-4 administration was the secretory function of pancreatic endocrine cells (α- and β-cells).

Effects of other metabolic parameters, such as blood lipid levels and blood pressure, were statistically insignificant and comparable in both groups. The only observed difference was a decrease in the FFA level during Sitagliptin therapy. An increase in the circulation FFA level is often detected in obese patients and may contribute to the peripheral (muscle) insulin resistance. [27]. It is suggested that their reduction can improve the sensitivity of tissues to insulin. However, no significant differences were observed in the dynamics of the insulin resistance parameters measured in this study. Additional studies, with a longer observation period, are required to clarify the clinical role of a change in FFA concentration associated with iDPP-4 therapy.

In the present study, a comparative subgroup analysis with patient distribution to strata was performed, according to the already known predictors of iDPP-4 efficacy (baseline HbA1c, patient's gender, age, BMI, ethnicity). However, significant differences in stratification were only observed for the initial level of HbA1c. Both groups exhibited similar tolerability and safety. The total

number of AE was slightly higher in the Evogliptin group, but all adverse effects in all the groups were mild. No SAE were reported in any of the groups. There were also no significant differences in the hypoglycaemia incidence.

CONCLUSION

This study demonstrates that a dose of 5 mg of Evogliptin is non-inferior and comparably safe as compared to Sitagliptin 100 mg.

ADDITIONAL INFORMATION

Source of financing. This analysis was performed with the grant provided by the Russian Science Foundation (project No. 17-75-30052) and co-financing provided under this project by Gerofarm.

Conflict of interest. I.E. Makarenko and V.V. Leusheva are employees of the company Gerofarm.

A. Yu. Babenko, A.A. Mosikyan, E.V. Shlyakhto declare no obvious and potential conflicts of interest related to the publication of this article.

Participation of authors. A.Yu. Babenko is a coordinating investigator of a double-blind, randomised clinical study to compare the efficacy and safety of Evogliptin 5 mg and Sitagliptin 100 mg, the principal investigator of the Almazov National Medical Research Centre. Proofreading and reviewing of the original text of the manuscript; A.A. Mosikyan–statistical analysis of the submitted data (analysis of subgroups), writing of the original text of the manuscript; V.V. Leusheva–statistical analysis of the research results, preparation of a statistical report;

I.E. Makarenko–provision of a double-blind, randomised clinical study to compare the efficacy and safety of Evogliptin 5 mg and Sitagliptin 100 mg, the preparation of a study protocol, control of its conduct at the centres, proofreading and reviewing the original text of the manuscript; E.V. Shlyakhto–proofreading and reviewing of all versions of the manuscript.

Acknowledgements. The authors are grateful to the investigators and research centres involved in the EVOKOMBI study.

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4. National Medical Research Centre of Endocrinology. The principal investigator is Alexander Yuryevich Mayorov, MD, PhD, head of the Department of diabetes prognosis and innovation.
5. The branch of the non-governmental private public health institution Scientific Clinical Center of the company Russian Railways. The principal investigator is Emma Anatolievna Voichik, PhD, the head of the Endocrinology center of the Scientific Clinical Center of the company Russian Railways.
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ЦИТИРОВАТЬ:

Бабенко А.Ю., Мосикян А.А., Макаренко И.Е., Леушева В.В., Шляхто Е.В. Анализ эффективности и безопасности эвоглиптина по сравнению с ситаглиптином при добавлении к монотерапии метформином в русско-корейской популяции. Результаты исследования ЭВОКОМБИ // *Сахарный диабет*. — 2018. — Т. 21. — №4. — С. 241-254. doi: 10.14341/DM9586

TO CITE THIS ARTICLE:

Babenko AY, Mosikian AA, Makarenko IE, Leusheva VV, Shlyakhto EV. Efficacy and safety of evogliptin versus sitagliptin as add on to metformin alone in a combined russian-korean population. Evo-combi trial. *Diabetes Mellitus*. 2018;21(4):241-254. doi: 10.14341/DM9586