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ADAPTIVE DESIGN IN CLINICAL DEVELOPMENT OF NEXT-IN-CLASS DRUGS

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Abstract

Introduction: The next-in-class drugs are the original drugs that by chemical structure and mode of action similar to their predecessors of the same pharmacological group. The clinical development of the next-in-class drugs usually follows the same path as for innovative drugs including all phases. Since the effects of the next-in-class drugs can be predicted with certain accuracy, there is a potential for optimizing their clinical program in terms of duration and costs. Adaptive design represents the innovative approach that allows for efficiency and acceleration of drug development.

Objectives: The study objective was to assess the perspectives of the adaptive design methods in clinical development of the next-in-class drugs of different pharmacological groups including hypoglycemic agents, anticoagulants and anti-HIV drugs.

Methods: The adaptive designs were developed and implemented in phase II-III studies of three next-in-class drugs. The seamless two-stage design was used for sequential assessment of two dosing schemes of gosogliptin (DPP-4 inhibitor), as well as for the dose selection and its further efficacy and safety assessment in phase II/III studies of tearxaban (factor Xa inhibitor) and elsulfavirine (NNRTI). The measures necessary to control a type I error and avoid biases were assumed at all stages.

Results and discussion: In three conducted trials the non-inferiority of the next-in-class drugs to the standards of care was demonstrated as well as comparative or improved safety profiles. The adaptive designs allowed for combining two trials/phases in one study providing efficient use of resources and expedited market access.

Conclusion: The adaptive design can be successfully implemented in clinical programs of next-in-class drugs.

Keywords: clinical trials, adaptive design, next-in-class drugs, non-inferiority, type 2 diabetes mellitus, prevention of venous thromboembolism, HIV, DPP-4 inhibitor, factor Xa inhibitor, NNRTI, gosogliptin, tearxaban, elsulfavirine.

Introduction

The development of similar in pharmacotherapeutic effect or improved analogues of innovative drugs is one of the main focuses for the development of the Russian pharmaceutical industry in 2013-2020. The mechanisms of the government support of this area include the Federal target program "Development of the pharmaceutical and medical industry of the Russian Federation for the period till 2020 and further perspective", including the rules for obtaining the subsidies for the next-in-class drugs development [1, 2].

The next-in-class drugs are original patented candidates that affect upon the known biological targets and in structure or mode of action similar to existing drugs. The development of a next-in-class drug can be considered a low-risk R&D strategy due to higher predictability of its effects in humans (i.e. similar to drugs of the same group), as well as possibly better efficacy and safety profiles due to "refining" of the original molecule.

The classic approach to the development of a next-in-class drug is the repetition of the clinical program of its innovative prototype that imposes similar expenses and timelines. Due to high volume of investments needed, the scientific and practical rationale for such drugs might be of question. Hence the pharmaceutical companies require effective planning of the clinical trials of the next-in-class drugs to ensure their reasonable price and expedited market access.

The adaptive design is one of the innovative approaches that allows for conducting clinical trials more efficiently (e.g. shorter duration, less patients, etc.) or with a higher probability of the demonstration of the drug's effects. The trials that use the adaptive design have a predefined possibility of modification of some of the design or hypothesis aspects based on the results of the interim analysis. The data analysis is performed according to the predefined plan at preliminary specified time points; it may be blinded or unblinded, with or without testing of the formal statistical hypothesis.

The first foreign publication describing the concept of the adaptive design appeared at the end of the 1980s (P. Bauer, K. Köhne, M. Posch, J. Wittes, E. Brittain, R.J. Simes) [3, 4, 5, 6, 7]. The enthusiasm towards the possibilities of implementation of the adaptive design came across the critical assessment of the complexity of the proposed statistical models. On the other hand, during the recent decades the regulatory requirements to safety and efficacy assessment have been reinforced that made the clinical programs more complicated, extended the time for the market access, and diminished every possibility for optimization of the clinical trial design.

Nevertheless in the 2000s the regulators of different countries indicated the slowdown of the innovative sector of the pharmaceutical industry that induced some stimulating initiatives such as the national US strategy for implementation of the innovative approaches to drug development, assessment and manufacturing (FDA, 2004). The adaptive design was suggested among other methods for optimization and acceleration of drug development [8, 9].

Despite the obvious advantages of the adaptive design, this approach might increase the risk of biases and misinterpretation of the clinical trial results. The choice of statistical methods to ensure integrity and validity of study data poses a certain difficulty. These aspects are described in the EU and US guidelines for the adaptive design in clinical trials (EMEA, 2007; FDA, 2010) [10, 11, 12, 13].

In our country the use of the adaptive design is limited to the two-stage approach in bioequivalence studies, as well as few phase II-III trials that altogether are less than 1% of all clinical trials in Russia [14, 15, 16].

Thus the feasibility assessment of implementation of the adaptive design in clinical trials of the next-in-class drugs is important for the pharmaceutical science and industry.

Objectives

The objective of this study was to assess the perspectives of the adaptive design methods in clinical development of the next-in-class drugs of different pharmacological groups including hypoglycemic agents, anticoagulants and anti-HIV drugs.

Three clinical trial designs were developed in order to meet the objective: a phase III clinical trial of dipeptidyl peptidase-4 (DPP-4) inhibitor gosogliptin in patients with diabetes mellitus (DM) type 2, a phase II clinical trial of factor Xa inhibitor tearxaban in patients undergoing knee replacement surgery, and a phase II-III clinical trial of non-nucleoside reverse transcriptase inhibitor (NNRTI) elsulfavirine in patients with HIV-infection. Upon the trials completion, a comparative analysis and economic efficiency assessment of the adaptive designs was performed.

Methods

The clinical trials were conducted in 2012-2016 in the framework of the technologies transfer program financed by the Ministry of Industry and Trade of Russia. The study documents were reviewed and approved by the Ministry of Health of Russia: approval #136 of gosogliptin clinical trial dated March 01, 2013 (27

sites), approval #485 of tearxaban clinical trial dated August 01, 2013 (7 sites), and approval #219 of elsulfavirine clinical trial dated April 21, 2014 (12 sites).

The studies were conducted in compliance with the Guideline for Good Clinical Practice (International Conference for Harmonization, 1996), ethical principles outlined in the Declaration of Helsinki (World Medical Association, 2013), Russian legislation and applicable regulatory requirements (Federal law #61, 2010; National industry standard P 52379-2005) [17, 18, 19].

Study designs. The clinical trials were prospective multicenter randomized studies with active control and two-stage data analysis (the adaptive seamless design). In the gosogliptin study, the two-stage analysis was used to assess the efficacy and safety of the monotherapy at Period 1 and then the combination therapy with metformin at Period 2 in the same patients' population. In the tearxaban and elsulfavirine studies, the interim analysis was used to choose the optimal dose of the investigational product (Stage 1); then additional patients were enrolled in the study in order to assess the efficacy and safety of the selected dose (Stage 2) [20].

Original marketed drugs listed in the national standards of care and the Register of vital and pivotal drugs of Russia were used as comparators: DPP-4 inhibitor vildagliptin (Galvus®, Novartis Pharma Stein AG, Switzerland) was used in the gosogliptin study; low molecule weight heparin enoxaparin (Clexane®, Sanofi-Winthrop Industry, France) was used in the tearxaban study; NNRTI efavirenz (Stocrin®, Merck Sharp & Dohme B.V., the Netherlands) was used in the elsulfavirine study.

The primary efficacy endpoint (PE) in the gosogliptin study was the mean change of HbA1c at Week 12 (period of monotherapy) and at Week 36 (period of combination therapy); in the tearxaban study it was the composite of all venous thromboembolism (VTE) within 6 weeks of the knee replacement surgery; in the elsulfavirine study it was the rate of achievement of the viral load < 400 copies/mL at Week 12 (the surrogate endpoint for the interim analysis) and the undetectable HIV RNA level at Week 24 (the final analysis).

In the gosogliptin trial, the study treatment was not blinded (open study); in the tearxaban and elsulfavirine studies the doses of the investigational products were blinded at the first stage of the studies (partially-blinded study). The credibility of the PE assessment was ensured by its analysis in the central laboratory or by the independent central reviewer; the dose selection based on the interim data analysis in the tearxaban and elsulfavirine studies was performed based on the decision of the Data Monitoring Committee (DMC).

Patients' population and study procedures. Treatment naïve patients with DM type 2 aged 18 to 78 with body mass index (BMI) of 22 to 40 kg/m^2, HbA1c from 7.5 to 11.0%, fasting plasma glucose (FPG) < 15 mmol/L, glomerular filtration rate (GFR) ≥ 60 mL/min/1.73m^2, with no severe acute of chronic complications of DM, significant and/or poorly controlled diseases, were enrolled in the gosogliptin study. A total of 299 patients were randomized to one of two treatment groups: gosogliptin or vildagliptin (at 1:1 ratio). The duration of the patients' participation in the study was about 42 weeks, including screening (1 week), diabetes education and run-in (1 week), randomization and the monotherapy period (12 weeks), the combination therapy period (24 weeks), and follow-up (4 weeks). The following parameters were controlled during the study: the state of systems and organs based on the physical examination, electrocardiography (ECG), and ultrasound; body weight, BMI, blood pressure (BP), heart rate (HR), respiratory rate (RR), and body temperature; HbA1c, FPG and safety laboratory parameters based on hematology, biochemistry and urinalysis in the central laboratory; pregnancy based on the urine pregnancy test; glycemia and hypoglycemic episodes based on glucometer and patients' diary data; adverse events (AE).

Patients aged 18 and older scheduled for the planned primary total knee replacement (TKR) surgery, with normal coagulation parameters, no history of thrombosis or coagulopathy, with no active bleeding, significant and/or poorly controlled diseases were enrolled in the tearxaban study. A total of 200 patients were randomized in one of four treatment groups: tearxaban 50 mg, 100 mg, 150 mg or enoxaparin (at 1:1:1:1 ratio at Stage 1 and at 1:1 ratio at Stage 2 after the dose

selection). The duration of the patients' participation in the study was about 8 weeks, including screening (2 weeks), randomization, surgery and study treatment (2 weeks: 12 ± 2 days) and follow-up (4 weeks). The following parameters were controlled during the study: the state of systems and organs based on the physical examination and ECG; wound assessment, VTE and bleeding symptoms; duplex ultrasound scanning, multislice computed tomography (MSCT); body weight, BP, HR, RR, and body temperature; safety laboratory parameters based on hematology, biochemistry, coagulation, and urinalysis in the central laboratory; pregnancy based on the urine pregnancy test; AE.

Patients aged 18 and older with serologically confirmed stable HIV-1 infection (Stage 1-2), HIV-1 RNA in plasma ≥ 5 000 copies/mL and CD4+ T-lymphocytes count > 200 cells/mm^3, with no hepatitis B and C, tuberculosis, acute infection, significant, and poorly controlled diseases, who meet the criteria for starting the antiretroviral therapy (ART), were enrolled in the elsulfavirine study. A total of 150 patients were randomized in one of three treatment groups: elsulfavirine 20 mg, 40 mg or efavirenz (at 1:1:1 ratio at Stage 1 and at 1:1 ratio at Stage 2 after the dose selection). The duration of the patients' participation in the study was about 54 weeks, including screening (2 weeks), randomization and study treatment (48 weeks) and follow-up (4 weeks). During the study the following parameters were controlled: state of systems and organs based on the physical examination and ECG; body weight, BP, HR, RR, and body temperature; HIV-1 RNA load by polymerase chain reaction (PCR); CD4+ and CD8+ T-lymphocytes count, HIV resistance mutations by PCR, safety laboratory parameters based on hematology, biochemistry, coagulation, and urinalysis in the central laboratory; pregnancy based on the urine pregnancy test; AE including AE of special interest in central nervous system (CNS).

Statistical analysis. The sample size for each trial was calculated based on the non-inferiority hypothesis to compare two means taking into account the standard deviation (the gosogliptin study) or to compare proportions taking into account the expected results in the study groups (the tearxaban and elsulfavirine studies); at the significance level of α = 2.5% (one-sided), power of 80%, and predefined non-inferiority margin [21, 22, 23].

The number of patients required for the interim analysis was calculated based on the Simon's MiniMax statistical model in the tearxaban study and based on the non-inferiority hypothesis for the surrogate endpoint in the elsulfavirine study. None of the studies assumed any repeated testing of the same hypothesis. The two-stage statistical analysis didn't require a type I error correction since the null hypothesis should have been rejected at both stages of the studies. The power of the clinical trials was controlled by the algorithm of the patients' recruitment; the power correction was not performed.

The PE analysis was performed in the full analysis set of patients who received at least one dose of the study drug and who had at least one post-dosing assessment of the PE; in the two-stage design the patients from both stages were included in the analysis. Additional analysis was conducted in the per protocol population. The safety analysis was conducted in the population of patients who received at least one dose of the study drug (safety population).

The statistical analysis was performed in the SPSS Statistics and R programs. The 95% confidence interval (CI) was calculated for the PE and its lower bound was compared to the non-inferiority margin; based on this comparison it was concluded whether the null hypothesis should have been confirmed or rejected. The Simon's model was used for the interim analysis in the tearxaban study. The differences between the means were assessed with the Student's t-test and singe factor ANOVA analysis. The comparison of proportions was performed with the Fisher's exact test. The Wilcoxon test was performed for non-parametric data. The significance of the parameter distribution between the treatment groups was assessed with the χ^2 criteria. AE were coded using the MedDRA dictionary [24, 25].

Results and discussion

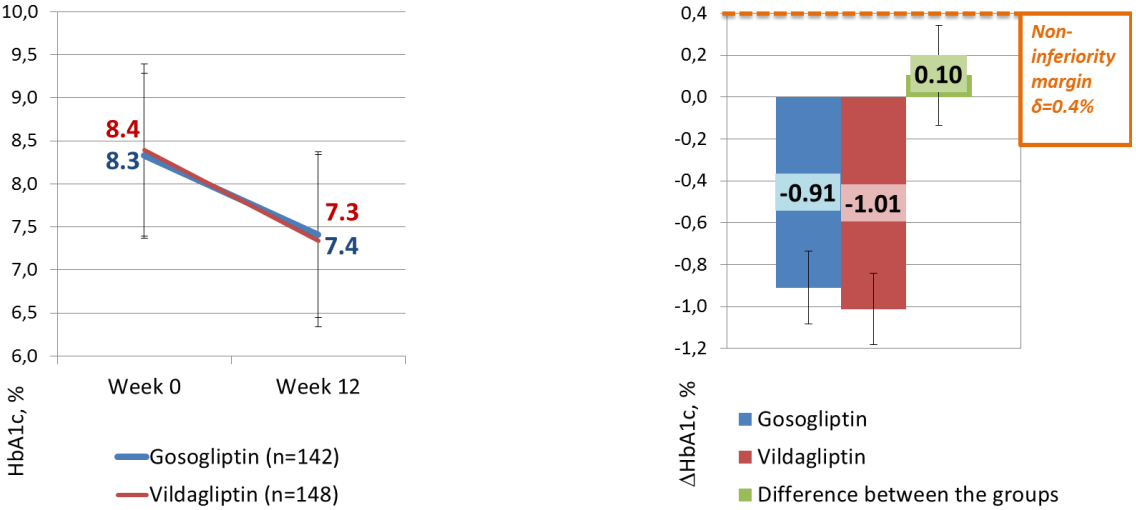
1) Study results of DPP-4 inhibitor gosogliptin in patients with DM type 2

299 patients were randomized in the study including 149 patients in gosogliptin group and 150 patients in vildagliptin group. The treatment groups were similar in demographic parameters and main baseline characteristics ($p > 0.05$): sex (F 57.7% + M 42.3% vs. F 48.7% + M 51.3%), age (55.7 ± 10.0 years vs. 56.7 ± 9.7 years), race (Caucasian 98.7%), duration on DM type 2 (1.7 ± 2.6 years vs. 2.1 ± 3.8 years), baseline HbA1c (8.3 ± 1.0% vs. 8.4 ± 1.1%), FPG (9.5 ± 2.5 mmol/L vs. 9.5 ± 2.8 mmol/L), body weight (90.6 ± 14.8 kg and 91.7 ± 15.6 kg), and BMI (32.1 ± 4.3 kg/m^2 vs. 31.8 ± 4.3 kg/m^2).

a) Period 1 – Assessment of efficacy and safety of monotherapy

The population for the efficacy assessment of the monotherapy consisted of 144 patients on gosogliptin and 148 patients on vildagliptin; the per protocol population consisted of 134 and 140 patients; the safety population consisted of 149 and 150 patients, respectively.

Upon completion of the monotherapy period, the mean change of HbA1c at Week 12 was – 0.93% in gosogliptin group (decrease from 8.3% to 7.4%) and – 1.03% in vildagliptin group (decrease from 8.4% to 7.3%); the difference between the groups in mean change of HbA1c was 0.1% (fig. 1). The null hypothesis that gosogliptin was inferior to vildagliptin with respect to the PE was rejected and its non-inferiority was established since the 95% CI upper bound of 0.342% was below the non-inferiority margin (< 0.4%). The result was confirmed in the per protocol population.



a) HbA1c change during 12 weeks of monotherapy with DPP-4 inhibitors

b) Difference between the groups in HbA1c change (upper bound of 95% CI < 0.4%)

Fig. 1. HbA1c change at Week 12 for monotherapy

The analysis of the secondary endpoints after 12 weeks of monotherapy demonstrated that there were no statistically significant differences between the groups:

- the proportion of patients who achieved HbA1c ≤ 7.0% was 41.0% on gosogliptin and 44.5% on vildagliptin ($p = 0.52$);
- the FPG decrease was -0.70 mmol/L on gosogliptin and -0.89 mmol/L on vildagliptin ($p = 0.44$);
- the mean change of post-prandial plasma glucose was -1.05 mmol/L on gosogliptin and -1.39 mmol/L on vildagliptin ($p = 0.09$);
- the body weight change was -0.54 kg on gosogliptin and -0.78 kg on vildagliptin ($p = 0.44$).

During monotherapy, AE were reported in 37 (24.8%) patients on gosogliptin and in 25 (16.7%) patients on vildagliptin. All AE were mild or moderate; there were no severe AE. One serious adverse event (SAE) not related to the study treatment was registered in each group (i.e. carcinoma of the pancreas and furuncle, respectively).

AE related to the study treatment were reported in 4 (2.7%) patients on gosogliptin (i.e.

constipation, allergic dermatitis, increase of transaminase levels, asthenia, and dizziness) and in 2 (1.3%) patients on vildagliptin (i.e. constipation, dizziness, headache).

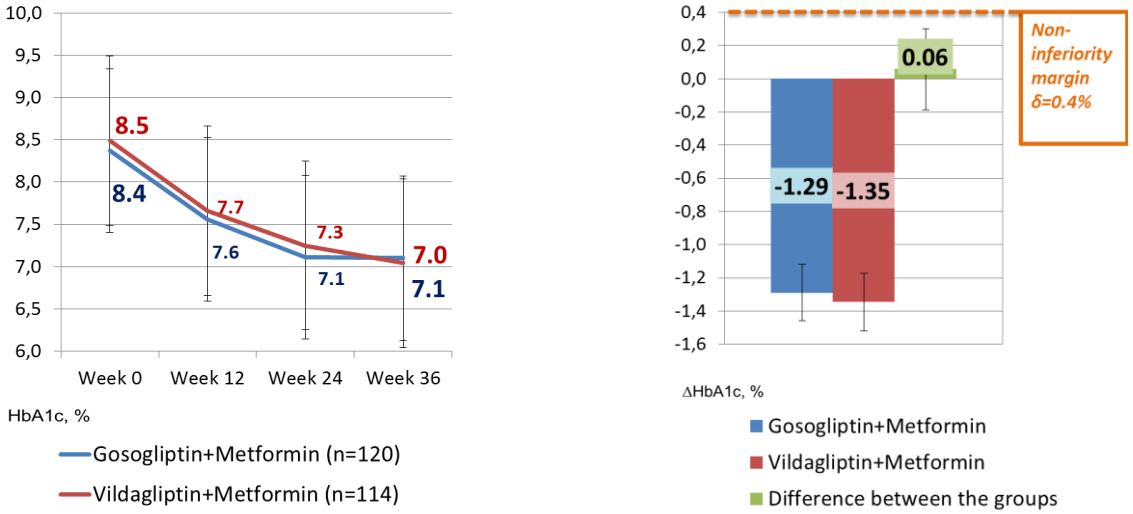
During 12 weeks of monotherapy, hypoglycemic episodes were registered in 7 (4.7%) patients on gosogliptin and in 5 (3.3%) patients on vildagliptin; those included symptomatic episodes in 4 (2.7%) and 2 (1.3%) patients, respectively. There were no severe hypoglycemic episodes.

It was concluded that gosogliptin was non-inferior in efficacy and similar in safety profile to vildagliptin while prescribed as monotherapy during 12 weeks to patients with DM type 2. The patients in both groups who didn't achieve the target glucose parameters by Week 12 rolled-over to the combination therapy with metformin and continued the treatment for additional 24 weeks.

b) Period 2 – Assessment of efficacy and safety of combination therapy

The population for the efficacy assessment of the combination therapy with metformin consisted of 120 patients on gosogliptin and 114 patients on vildagliptin; the per protocol population consisted of 104 and 105 patients; the safety population consisted of 122 and 114 patients, respectively.

Upon completion of the combination therapy with metformin, the mean change of HbA1c at Week 36 was -1.29% in gosogliptin group and -1.35% in vildagliptin group; the difference between the groups in mean change of HbA1c was 0.06% (fig. 2). The null hypothesis that gosogliptin was inferior to vildagliptin with respect to the PE was rejected and its non-inferiority was established since the 95% CI upper bound of 0.3% was below the non-inferiority margin (< 0.4%). The result was confirmed in the per protocol population.



a) HbA1c change during 36 weeks of tretment with DPP-4 inhibitors and metformin

b) Difference between the groups in HbA1c change (upper bound of 95% CI < 0.4%)

Fig. 2. HbA1c change at Week 36 for combination therapy

The analysis of the secondary endpoints at Week 36 demonstrated that there were no statistically significant differences between the groups:

- the proportion of patients who achieved HbA1c ≤ 7.0% was 57.5% on gosogliptin and 54.4% on vildagliptin (p = 0.74);
- the FPG decrease was -1.62 mmol/L on gosogliptin and -1.64 mmol/L on vildagliptin (p = 0.93);
- the mean change of post-prandial plasma glucose was -2.30 mmol/L on gosogliptin and -2.51 mmol/L on vildagliptin (p = 0.38);
- the body weight change was -1.02 kg on gosogliptin and -1.35 kg on vildagliptin (p = 0.48).

During the combination therapy with metformin, AE were reported in 29 (23.8%) patients on gosogliptin and in 30 (26.3%) patients on vildagliptin. All AE were mild or moderate; there were no severe AE. SAE not related to the study treatment were registered in 1 (0.8%) patient on gosogliptin (i.e. stroke) and in 3 (2.6%) patients on vildagliptin (i.e. lumbar osteochondrosis, pneumonia, and diabetic neuropathy).

AE related to the study treatment were reported in 4 (3.3%) patients on gosogliptin (i.e. dyspepsia, diarrhea, polyposis of gall bladder, pancreatitis, cholecystitis, and steatohepatitis with increase of total bilirubin and aspartate aminotransferase) and in 2 (1.8%) patients on vildagliptin (i.e. ventricular extrasystole and increase of transaminase).

Hypoglycemic episodes were registered in 5 (4.1%) patients on gosogliptin and in 12 (10.5%) patients on vildagliptin (p = 0.065); those included symptomatic episodes in 3 (2.5%) and 7 (6.1%) patients, respectively. There were no severe hypoglycemic episodes.

It was concluded that gosogliptin was non-inferior in efficacy and similar in safety profile to vildagliptin while prescribed in combination with metformin during 24 weeks to patients with DM type 2 [26].

2) Study results of factor Xa inhibitor tearxaban in orthopedic surgery

92 patients were enrolled in the study at Stage 1 including 23 patients in tearxaban 50 mg group, 22 patients in 100 mg group, 23 patients in 150 mg group, and 24 patients in enoxaparin group. 108 patients were additionally enrolled at Stage 2 including 54 patients in tearxaban 100 mg group and 54 patients in enoxaparin group. Thus the total number of patients randomized in tearxaban 100 mg group was 76 and in enoxaparin group was 78 (both stages).

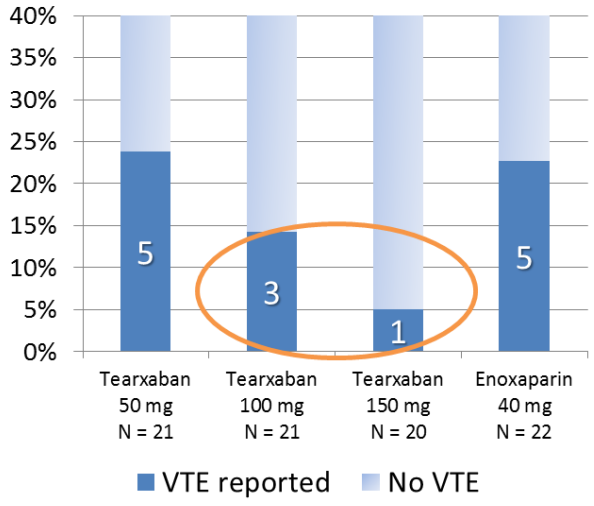
The treatment groups were similar in demographic parameters and main baseline characteristics (p > 0.05): sex (F 95.2% + M 4.8%, F 83.6% + M 16.4%, F 90.0% + M 10.0% vs. F 81.6% + M 18.4%), age (67.0 ± 8.2 years, 65.9 ± 7.4 years, 64.3 ± 7.7 years vs. 63.9 ± 8.3 years), race (Caucasian 100.0%), body weight (85.1 ± 13.9 kg, 86.4 ± 13.7 kg, 87.5 ± 11.3 kg vs. 85.8 ± 13.4 kg) and BMI (32.8 ± 5.1 kg/m^2, 32.1 ± 4.5 kg/m^2, 32.5 ± 4.8 kg/m^2 vs. 31.8 ± 4.1 kg/m^2).

a) Stage 1 – Dose selection

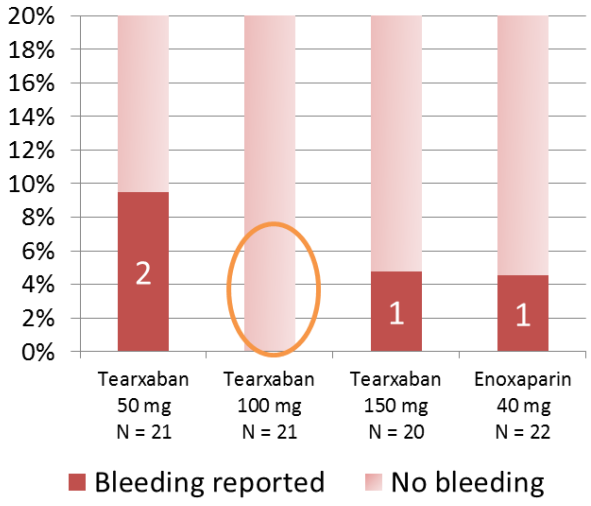
The population for the efficacy assessment at Stage 1 consisted of 21 patients on each tearxaban 50 mg and 100 mg, 20 patients on tearxaban 150 mg and 22 patients on enoxaparin; the safety population consisted of 21 patients in each group of tearxaban and 22 patients on enoxaparin, respectively.

The number of VTE on tearxaban 50 mg exceeded the predefined limit (i.e. > 4 VTE in 20 patients) and was similar to the number of VTE in the control group (23.8% and 22.7%, respectively). In tearxaban groups of 100 mg and 150 mg the number of VTE was within the predefined limit (14.3% and 5.0%, respectively), and the dose of 150 mg showed the best efficacy comparing to other doses of tearxaban and enoxaparin (fig. 3a).

Major and clinically relevant non-major bleeding within 6 weeks of surgery were reported in 2 (9.5%) patients on tearxaban 50 mg, 0 (0.0%) patients on tearxaban 100 mg, 1 (4.8%) patient on tearxaban 150 mg and in 1 (4.5%) patient on enoxaparin (fig. 3b).



a) Total VTE (target rate of VTE ≤ 4 in 20 patients)



b) Major and clinically relevant non-major bleeding rate

Fig. 3. Risk/benefit analysis for tearxaban dose selection at Stage 1

It was concluded that Tearxaban 100 mg had the lowest risk of hemorrhage that on top of the efficacy results was the reason for choosing this dose for further study.

b) ***Stage 2 – Assessment of efficacy and safety***

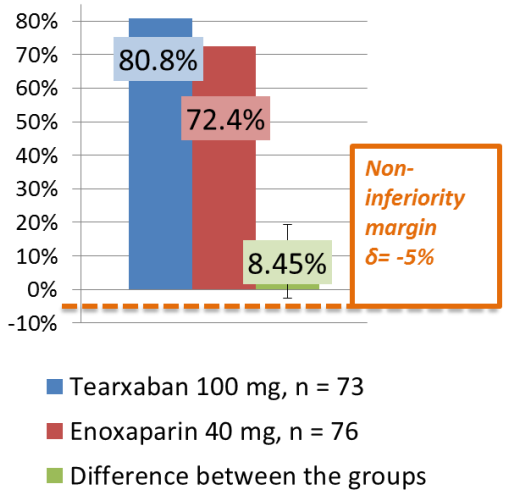
The population for the efficacy and safety assessment consisted of 73 patients on tearxaban 100 mg and 76 patients on enoxaparin; the per protocol population consisted of 63 and 64 patients, correspondingly.

The absence of VTE was confirmed in 59 (80.8%) patients on tearxaban 100 mg and 55 (72.4%) patients on enoxaparin; the difference between the groups was 8.45% (fig. 4a) The null hypothesis that tearxaban 100 mg was inferior to enoxaparin with respect to the PE was rejected and its non-inferiority was established since the 95% CI lower bound of -3.01% was above the non-inferiority margin (> -5%). The result was confirmed in the per protocol population.

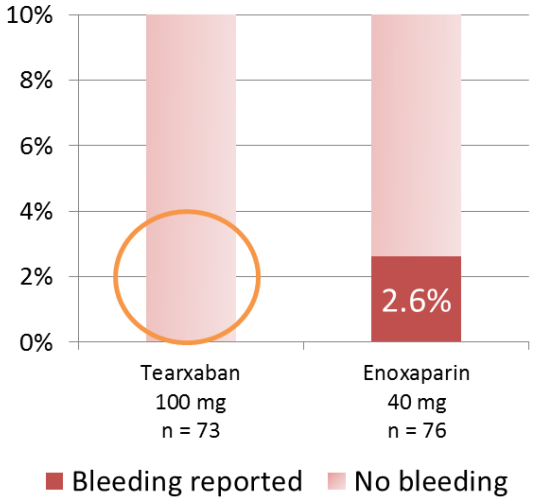
There were no fatal events during the study. Symptomatic VTE were registered in 2 (2.6%) patients on enoxaparin, including 1 (1.3%) case of non-fatal pulmonary embolism (PE) that was confirmed by MSCT. No symptomatic or proximal VTE were registered on tearxaban.

AE were registered in 21 (28.8%) patients on tearxaban 100 mg and 33 (43.4%) patients on enoxaparin (p = 0.0629). All AE were mild and moderate, not related to the study drug. Cases of early discontinuation (ED) of the study treatment were related to the surgery complications. SAE not related to the study drug were registered in 2 (2.7%) patients on tearxaban 100 mg and 5 (6.6%) patients on enoxaparin.

Hemorrhage was reported in 1 (1.4%) patient on tearxaban 100 mg and 2 (2.6%) patients on enoxaparin. Whereas major and clinically relevant non-major bleedings were registered in 2 (2.6%) patients on enoxaparin and were absent in patients on tearxaban 100 mg (fig. 4b).



a) Efficacy – absence of VTE (lower bound of 95% CI > -5%)



b) Major and clinically relevant non-major bleeding rate

Fig. 4. Efficacy and safety analysis of tearxaban 100 mg and enoxaparin at Stage 2

It was concluded that tearxaban 100 mg was non-inferior in efficacy and had lower risk of bleeding than enoxaparin when used for prevention of VTE in patients undergoing TKR surgery [27].

3) Study results of NNRTI elsulfavirine in patients with HIV-infection

90 treatment-naïve patients with HIV-infection were enrolled in the study at Stage 1 including 30 patients in each group of elsulfavirine 20 mg, 40 mg and efavirenz. 60 patients were additionally enrolled at Stage 2 including 30 patients in elsulfavirine 20 mg group and 30 patients in efavirenz group. Thus the total number of patients randomized in each group of elsulfavirine 20 mg and efavirenz was 60 patients (both stages).

The treatment groups were similar in demographic parameters and main baseline characteristics (p > 0.05): sex (F 39.7% + M 60.3%, F 44.8% + M 55.2% vs. F 35.1% + M 64.9%), age (35.8 ± 8.7 years, 35.7 ± 9.7 years vs. 33.4 ± 8.3 years), race (Caucasian 98.3-100.0%), as well as duration of

HIV-infection from the time the diagnosis was established (2.6 ± 2.8 years, 2.4 ± 2.5 years vs. 2.1 ± 2.6 years), viral load at baseline (4.7 ± 0.6 log10 copies/mL, 4.9 ± 0.6 log10 copies/mL vs. 4.8 ± 0.8 log10 copies/mL), body weight (72.1 ± 15.1 kg, 70.5 ± 14.0 kg vs. 71.2 ± 13.3 kg) and BMI (24.3 ± 4.1 kg/m^2, 23.7 ± 3.4 kg/m^2 vs. 23.7 ± 2.9 kg/m^2).

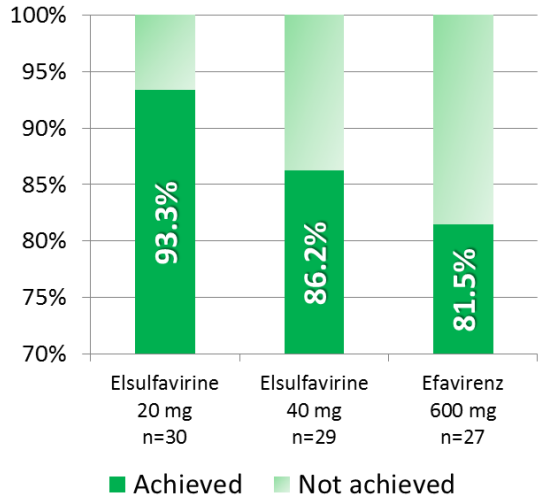
a) Stage 1 – Dose selection

The population for the efficacy assessment at Stage 1 consisted of 30 patients in elsulfavirine 20 mg group, 29 patients in elsulfavirine 40 mg group and 27 patients in efavirenz group; the per protocol population consisted of 29, 28 and 24 patients; the safety population consisted of 30, 29 and 28 patients, respectively.

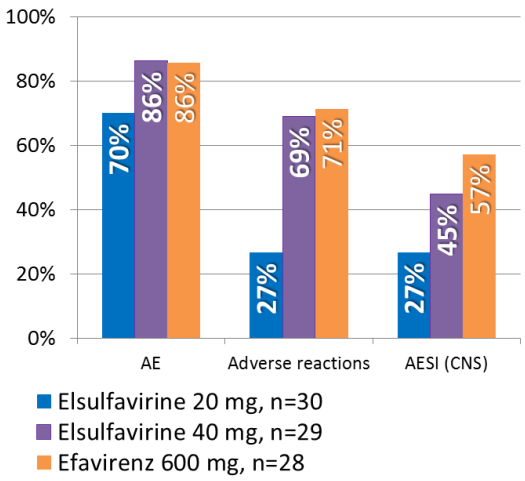
The HIV-1 RNA < 400 copies/mL at Week 12 was achieved by 28 (93.3%) patients on elsulfavirine 20 mg, 25 (86.2%) patients on elsulfavirine 40 mg and 22 (81.5%) patients on efavirenz (fig. 5a). The null hypothesis that elsulfavirine 20 mg and 40 mg were inferior to efavirenz with respect to the PE was rejected and the non-inferiority thereof was established since the 95% CI lower bounds of -2.59% and -11.50% (respectively) were above the non-inferiority margin (> -15%). The result was confirmed in the per protocol population.

AE were reported in 21 (70.0%) patients on elsulfavirine 20 mg, 25 (86.2%) patients on elsulfavirine 40 mg, and 24 (85.7%) patients on efavirenz. AE related to the study treatment were reported in 8 (26.6%), 20 (69.0%) and 20 (71.4%) patients, respectively. The frequency of adverse reactions in patients on elsulfavirine 20 mg was 2.5 times lower than in patients on elsulfavirine 40 mg or efavirenz ($p < 0.005$). AE that caused early discontinuation of treatment were registered in 1 (3.4%) patient on elsulfavirine 40 mg (rash) and in 2 (7.1%) patients on efavirenz (rash and allergic reaction).

AE in CNS were registered in 8 (26.7%) patients on elsulfavirine 20 mg, 13 (44.8%) patients on elsulfavirine 40 mg and 16 (57.1%) patients on efavirenz (fig. 5b).



a) Rate of achievement of viral load < 400 copies/mL at Week 12 (lower bound of 95% CI > -15)



b) AE, adverse reactions and AE of special interest (CNS)

Fig. 5. Risk/benefit analysis for elsulfavirine dose selection at Stage 1

It was concluded that elsulfavirine 20 mg had the lowest risk of adverse reactions that on top of the efficacy results was the reason for choosing this dose for further study.

b) Stage 2 – Assessment of efficacy and safety

The population for the efficacy assessment of the selected dose consisted of 58 patients on elsulfavirine 20 mg and 57 patients on efavirenz; the per protocol population consisted of 47 and 39 patients; the safety population consisted of 60 and 58 patients, respectively.

The undetectable level of HIV-1 RNA at Week 24 was achieved by 49 (84.5%) patients on elsulfavirine 20 mg and 38 (66.7%) patients on

efavirenz (fig. 6a); the difference between the groups was 17.8% (p = 0.031). The null hypothesis that elsulfavirine 20 mg was inferior to efavirenz with respect to the PE was rejected and its non-inferiority was established since the 95% CI lower bound of 2.4% was above the non-inferiority margin (> -15%). The result was confirmed in the per protocol population.

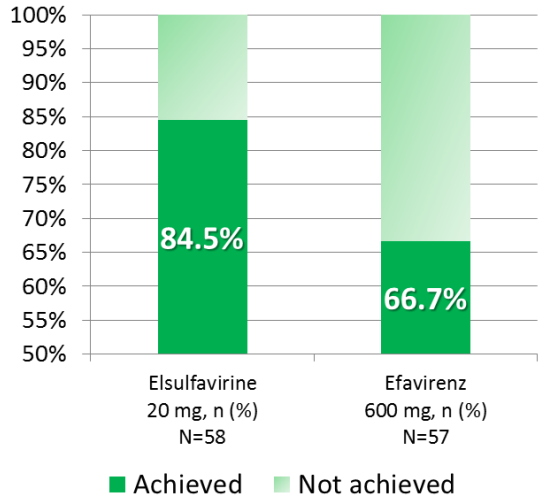
The analysis of the secondary efficacy endpoints demonstrated that there were some statistically significant differences between the groups:

- the decrease of the viral load (log10 copies/mL) by Week 12 was -2.8 ± 0.7 on elsulfavirine 20 mg and -2.7 ± 1.0 on efavirenz; by Week 24 it was -3.3 ± 0.7 and -3.3 ± 0.8; by Week 48 it was -3.3 ± 0.7 and -3.4 ± 0.7, respectively;
- the 10-fold decrease of the viral load by Week 4 was achieved by 56 (96.6%) patients on elsulfavirine 20 mg and 49 (86.0%) patients on efavirenz (p = 0.053);
- 48 weeks of the study treatment were successfully completed by 55 (91.7%) patients on elsulfavirine 20 mg and 47 (78.3%) patients on efavirenz (p = 0.041);
- the increase of CD4+ T-lymphocytes by Week 12 was 112.9 ± 127.6 on elsulfavirine 20 mg and 78.0 ± 135.8 on efavirenz; by Week 24 it was 145.0 ± 159.5 and 115.6 ± 168.0; by Week 48 it was 179.3 ± 156.3 and 182.6 ± 149.1, respectively;
- the decrease of CD8+ T-lymphocytes by Week 12 was -60.5 ± 348.2 on elsulfavirine 20 mg and -143.5 ± 372.9 on efavirenz; by Week 24 it was -166.9 ± 346.3 and -175.3 ± 402.6; by Week 48 it was -214.2 ± 330.1 and -267.5 ± 401.4, respectively;
- the HIV-1 drug resistance was not established during the trial.

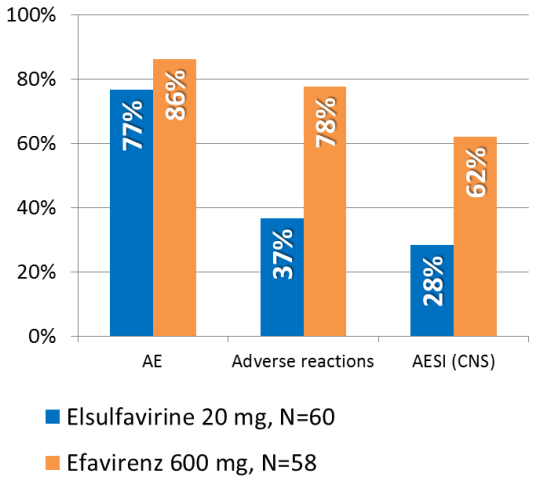
AE were reported in 46 (76.7%) patients on elsulfavirine 20 mg and 50 (86.2%) patients on efavirenz. AE related to the study treatment were reported in 22 (36.7%) patients on elsulfavirine 20 mg and 45 (77.6%) patients on efavirenz (fig. 6b). The frequency of adverse reactions on elsulfavirine 20 mg was twice lower than on efavirenz (p < 0.0001). In elsulfavirine 20 mg group the following adverse reactions were reported in 5-15% patients: headache, increase of gamma-glutamyltransferase, mild proteinuria, sleep disorder, asthenia, dizziness, and nausea.

AE of grade 3 and 4 (severe and potentially life-threatening) were reported in 5 (8.3%) patients on elsulfavirine 20 mg and in 9 (15.5%) patients on efavirenz. SAE not related to the study drug were reported in 5 (8.3%) patients on elsulfavirine 20 mg; among patients on efavirenz, SAE were reported in 7 (12.1%) patients, including severe allergic reactions and cytolysis in 4 (6.9%) patients that were related to the study drug.

AE in CNS were reported in 17 (28.3%) patients on elsulfavirine 20 mg and in 36 (62.1%) patients on efavirenz (p < 0.001).



a) Rate of achievement of undetectable viral load at Week 24 (lower bound of 95% CI > -15; p = 0.031)



b) AE, adverse reactions and AE of special interest (CNS)

Fig. 6. Efficacy and safety of elsulfavirine 20 mg and efavirenz at Stage 2

It was concluded that elsulfavirine 20 mg was non-inferior in efficacy and had lower risk of adverse reactions and AE in CNS comparing to efavirenz in patients with HIV-infection [28].

4) Comparative analysis and economic efficiency assessment of the adaptive designs

The adaptive seamless design was implemented in three clinical trials. In the gosogliptin study, the adaptive seamless design for two treatment regimens allowed assessing the efficacy and safety of the monotherapy (Period 1) and then the combination therapy with metformin (Period 2) in the same patients' population (fig. 7). In a classic clinical trial model, this would require two independent studies with recruitment of more patients.

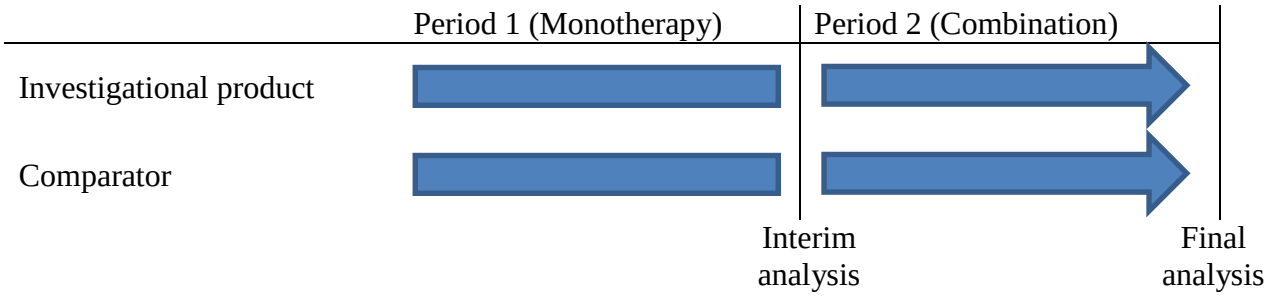


Fig. 7. Seamless design for two treatment regimens

The adaptive seamless design of phase II/III was used in the tearxaban and elsulfavirine studies (fig. 8). The optimal dose of the study drug was chosen based on the interim analysis (Stage 1); then additional patients were enrolled in the study to assess the efficacy and safety of the selected dose in the overall patients' population (Stage 2). In a classic clinical trial model, this would take longer and require recruitment of more patients.

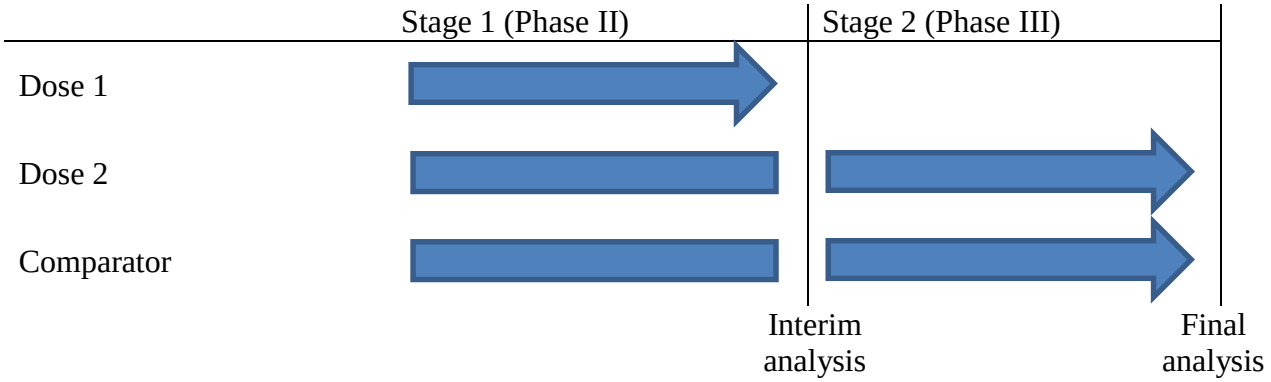


Fig. 8. Seamless phase II/III design

The comparative analysis of the clinical trial designs is presented in Table 1 [29].

The implementation of the adaptive design methods in the clinical trials of gosogliptin, tearxaban, and elsulfavirine provided the average decrease of the study budgets by 36% and the study duration by 27% (i.e. 9 months) as opposed to the classic late-stage clinical development program.

As a result, gosogliptin and elsulfavirine have been registered in Russia: Saterex (registration certificate No. LP-003598 dated May 04, 2016) and Elpida® (registration certificate No. LP-004360 dated June 30, 2017).

Table 1

Comparative analysis of clinical trial designs

	Gosogliptin, DPP-inhibitor	**Tearxaban, factor Xa inhibitor**	**Elsulfavirine, NNRTI**
Design	Multicenter open randomized, Phase III	Multicenter partially blinded randomized, Phase II	Multicenter partially blinded randomized, Phase II-III
Adaptation type Period 1/ Stage 1	Seamless design for 2 treatment regimens • Efficacy and safety of monotherapy • Gosogliptin / Vildagliptin • PE ΔHbA1c (W12-W0) • α = 2.5% (1-sided), power 80% • non-inferiority, SD = 1.1, δ = 0.4% (95% CI), n = 238 (1:1)	Seamless phase II/III design • Dose selection • Tearxaban 50 mg, 100 mg, and 150 mg / Enoxaparin 40 mg • PE % of VTE (W6) • α = 5% (2-sided), power 80% • Simon's MiniMax, p_0 = 60%, p_1 = 85%, r ≤ 4/20, n = 80 (1:1:1:1)	Seamless phase II/III design • Dose selection • Elsulfavirine 20 mg, and 40 mg / Efavirenz 600 mg • PE % of < 400 copies/mL (W12) • α = 5% (1-sided), power 80% • non-inferiority, p_0 = 80%, p_1 = 90%, δ = 15% (95% CI), n = 75 (1:1:1)
Interim analysis and adaptation	• Open • Central laboratory • Increased ED rate to control power • No change of design or statistical assumptions	• Unblinded • Central reviewer • Simon's model analysis • Dose selection based on DMC decision • No change of design or statistical assumptions	• Unblinded • Central laboratory • Analysis of the surrogate endpoint • Dose selection based on DMC decision • No change of design or statistical assumptions
Period 2/ Stage 2	• Efficacy and safety of combination therapy • Gosogliptin / Vildagliptin • PE ΔHbA1c (W36-W0) • α = 2.5% (1-sided), power 80% • non-inferiority, SD = 1.1, δ = 0.4% (95% CI), n = 238 (1:1)	• Efficacy and safety • Tearxaban (selected dose) / Enoxaparin • PE % of VTE (W6) • α = 2.5% (1-sided), power 80% • non-inferiority, p_0 = 60%, p_1 = 85%, δ = 5% (95% CI), n = 132 (1:1)	• Efficacy and safety • Elsulfavirine (selected dose) / Efavirenz • PE % < 50 copies/mL (W24) • α = 2.5% (1-sided), power 80% • non-inferiority, p_0 = 67%, p_1 = 77%, δ = 15% (95% CI), n = 102 (1:1)
Estimated number of patients per trial	ED 20% (considering 2 periods) Period 1: 300 (150+150), *out of which* Period 2: ~264 (132+132) Total: 300 (150+150) **-46.4%**	ED 15% (at each stage) Stage 1: 92 (23+23+23+23) Stage 2: 108 (54+54) Total: 200 (23+77+23+77) **-20.0%**	ED 15% (at each stage) Stage 1: 90 (30+30+30) Stage 2: 60 (30+30) Total: 150 (60+30+60) **-27.9%**
Study duration	Approval: 01.03.2013 Report Period 1: 02.07.2014 Report Period 2: 27.11.2014 1.7 years (21 months) **-0 months**	Approval: 01.08.2013 Report Stage 1: 02.10.2014 Report Stage 2: 26.10.2015 2.2 years (27 months) **-14 months**	Approval: 21.04.2014 Report Stage 1: 29.05.2015 Report Stage 2: 31.05.2016 2.1 years (25 months) **-13 months**

Conclusion

The work demonstrated that the effects of the next-in-class drugs in development can be predicted with high accuracy due to known characteristics of the efficacy and safety of the drugs of the same pharmacological group. This allows minimizing the risks of using the adaptive design methods in clinical programs of the next-in-class drugs.

The adaptive design method for two treatment schemes can be used in assessment of the efficacy and safety of drugs that require dose titration and/or stepwise adding of other components of the combination therapy.

The preliminary assessment of efficacy using Simon's statistical model or surrogate endpoint prevents from testing the primary hypothesis during the interim analysis (for dose selection) and provides additional control of the type I error in clinical trials with the adaptive seamless phase II/III design.

The results of the study open a new perspective for further implementation of the adaptive design methods in clinical trials of next-in-class drugs that will allow for the optimization of the development programs and the accelerated market access for new drugs.

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Tearxaban study was sponsored by TeaRx LLC (Russia) that reserves all rights for the drug.

Elsulfavirine study was sponsored by Viriom LLC (Russia) that reserves all rights for the drug.

Conflicts of interest

The authors have no conflict of interest to declare.

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