Multicenter observational program AIVARIX

Protocol N° IC4-05682-071-RUS

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A study to evaluate a accuracy of the AIVARIX AI-based application in detecting signs C 1-2 classes of CVD in outpatients seeking consultancy of phlebologists in the Russian Federation.

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Protocol of the Observational Clinical Study
Sponsor: JSC "Servier"
Protocol number: IC4-05682-071-RUS

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Rationale

Chronic venous disease (CVD) is widespread, underdiagnosed, and can progress to chronic venous insufficiency and venous ulcers, which can require extensive treatment and hospitalization. The global burden of CVD and its treatment are already enormous, consuming approximately 2% of national healthcare budgets.[1]

Clinical signs of CVD of lower limbs may include superficial femoral vein dilation or varicose veins, leg weakness, feeling of heaviness and/ or tenderness, edema, skin changes, venous ulcers. In addition, CVD can involve the superficial veins, traffic veins, and deep veins or even the entire lower limb venous system. This disease can be caused by primary or secondary factors, and venous reflux or proximal obstruction are the main hemodynamic changes. Due to the diversity of clinical manifestations and the complexity of pathophysiological changes, correct and timely diagnosis is the foundation to provide accurate treatment as earlier as it could be initiated. [2]

On the other hand, many patients, specifically at earlier stages of the disease, often postpone visit to a doctor. As a result, it leads to uncontrolled disease progression and further disabilities. It also can lead to trophic ulcers and other potentially dangerous complications including bleeding from varicose nodes or thromboembolic events.

Artificial Intelligence based (AI) or Neural Networks (NN) technologies have become one of the exiting areas of the scientific research and most studies in this field have been aimed at using these technologies to analyse a big massive of data to diagnose and differentiate between a large scope of conditions.[3] In diagnosis, it was shown in several studies that AI based/ NN tools demonstrated comparable with conventional methods accuracy in analysing/ diagnosing medical images, including those in the fields of dermatology and ophthalmology.[4]

Despite vast majority of studies in the mentioned field, currently there are few data available in which AI&NNs were used to segment CVD images, test them on large datasets and suggest the presence of CVD. The AIVARIX application is an AI based tool that uses machine learning in teaching the app accurately detect signs of early stages of CVD of lower limbs by photos. It has been recently published that the app is characterized by a very good interobserver agreement with conclusions (concordance score) made by experts – phlebologists in detection of $C0_s$ -C_2 classes in patients with CVD. [5] However, to our knowledge no validating clinical studies have yet been done to accurately describe Sensitivity (Sn) and Specificity (Sp) of the app in outpatients so we decided to explore the accuracy (Sn and Sp) of this application in detection of early stages of CVD (C1 and C2) by CEAP in patients seeking consultancy of phlebologists for signs and symptoms indicative to mentioned conditions.

References:

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Design

This study is a multicenter observational study, which is carried out in frame of routine clinical practice in Russia. The program will include patients suggestive to chronic venous diseases (CVDs) including but not limited to those with C1 and C2 classes by CEAP classification, who will be seeking professional phlebologists' consultation. Study conduction is scheduled in Russia in 2022-2023. The planned number of patients is 414.

Program milestones:

First Patient First Visit	Q4\2022
Last Patient Last Visit	Q3\2023
Completion of statistical analysis	Q4\2023
Clinical study report	Q4\2023

Aim of the program

The main goal of this study is to describe the AIVARIX app accuracy in detecting C1 and C2 classes by CEAP classification of chronic venous disease (CVD) in patients who are consulted by phlebologists on symptoms and signs suggestive to CVD.

Primary goal(s):
The primary goal of the study is to estimate Sensitivity (Sn) and Specificity (Sp) of the AI-based AIVARIX app in detecting C1 and C2 classes of CVD in patients who are seeking for professional advice from a phlebologist regarding symptoms and signs suggestive to CVD.

- Sensitivity is defined as the ratio of the number of positive cases of detection of signs of C1 or C2 CVD, identified using the AIVARIX tool, to the total number of truly positive cases of C1 or C2 CVD in the study population, confirmed by phlebologists using objective / instrumental examinations.
- Specificity is defined as a proportion of the number of negative cases of signs C1 or C2 classes of CVD identified by the AIVARIX tool divided to overall truly negative cases of C1 or C2 in the study population confirmed by phlebologists by means of objective/ instrumental examination.

Once Sn and Sp of the application is estimated, positive and negative likelihood ratios (LR) will be calculated.

Secondary goal(s):
Secondary objectives are to calculate the positive and negative predictive values (PPV and NPV, respectively) of AIVARIX in detecting signs of C1 and C2 classes of chronic venous disease.
PPV is defined as the proportion of true positive cases of class C1 or C2 CVD detected using AIVARIX as a proportion of the number of true positive and false positive cases of class C 1 or C 2 identified using the AIVARIX application and confirmed by phlebologists.
The NPV is defined as the ratio of the number of true negative cases of C 1 or C 2 CVD detected using AIVARIX to the true negative and false negative cases of C 1 or C 2 CVD detected using AIVARIX and confirmed by phlebologists.

Primary Variables:
- Sensitivity and specificity of the AIVARIX app in detecting C 1 class of CVD.
- Sensitivity and specificity of the AIVARIX app in detecting C 2 class of CVD.

Secondary Variables
- PPV, NPV, LR+ and LR- of the AIVARIX app in detecting C 1 class of CVD
- PPV, NPV, LR+ and LR- of the AIVARIX app in detecting C 2 class of CVD

Methodology

This is a cross sectional multicenter prospective observational study. It will include patients seeking phlebologist's consultation with any signs and symptoms suggestive to CVD including but not limited to C1 and C2 classes as well as patients without CVD who have other skin pathologic conditions of lower extremities that require differential diagnosis with CVD. Twenty-one phlebologists consulting in outpatient clinics across the country will be participating in the study.
The total number of patients as well as the number of patients with CVD C1 and C2 classes, the number of patients with other classes of CVD and the number of patients with other skin pathologic conditions of lower extremities are estimated given data on prevalence of CVD classes in general population available for Russia and other countries. This estimation is described in the "Sample size calculation and justification" paragraph. According to the mentioned estimation a distribution of patients to be enrolled in the study by each participating phlebologist should be as following:

- 20 subjects overall of whom:
    - 6 patients with CVD C1 class
    - 4 patients with CVD C2 class;
    - 2 patients with CVD with classes other than C1-C2 (C4-C6);
    - 8 patients with either $C0_s$ CVD or with skin pathologic conditions of lower extremities other than CVD;

Patients will be screened by a phlebologist and if meet inclusion/ non-inclusion criteria and provide written consent to participate in the study will be included in the study. Phlebologist will evaluate patients' status locales in accordance to routine clinical practice to objectively confirm or exclude presence of CVD and to define a class of the disease if present. Presence of CVD and associated class by C will be confirmed based on results of diagnostic methods used in routine clinical practice (presumably with use of objective examination, anamnesis morbi and ultrasonography of veins of lower extremities and/ or by venography of lower extremities, if necessary).
Once the clinical evaluation is made, investigating physician will take one photo of the locus with spider veins in patients present with C1 class, or with varicose veins for patients present with C2, or locus with either no signs of pathology or with pathologic condition of the skin of lower extremities other than CVD in accordance to the distribution split described herein above, and then will upload the picture to the cloud storage. Phlebologists participating in the study will also record results of the clinical evaluation for each enrolled patient in the eCRF with imputing the information on presence or absence of CVD with obligatory indication of class by C as well as presence or absence of other skin pathologic condition(s) of lower limbs that required consultation and differentiation by phlebologist. If a patient has CVD simultaneously present with signs of C1 and C2 as well as with other classes of CVD a phlebologist will have to decide which locus of pathology to picture in accordance to the given distribution of patients to be enrolled. In case a patient has no CVD but any other skin pathologic condition of lower extremities of different nature a phlebologist will take one photo of the locus with a corresponding pathologic sign(s) and then upload it to the cloud. In any cases investigating phlebologist will record information on presence or absence of CVD indicating its class or other pathologic condition in the eCRF.
Each uploaded photo must be deindividualized and should have a unique ID code assigned to each patient.
In order to fulfill minimum requirements for technical characteristics of smartphones/ pictures to be taken, following criteria are to be satisfied:

- Smartphone is to be manufactured in 2015 or later but not earlier.
- Area of the interest is to occupy not less than 30% of the picture. To fulfill this requirement a smartphone has to be positioned so that the distance from the skin area of interest to smartphone's camera is in range of 30-50 cm.
- Plain background (a picture is to be taken at the background of plain/ monochromic wall/ surface without any additional subjects in focus including additional parts of the body, furniture or people, etc.).
- Smartphone is to be positioned in parallel to the skin area of interest.

Once required number of patients is achieved and all images uploaded to the cloud storage they will be downloaded and analyzed by the AIVARIX application. For each photo the app will make a conclusion regarding possible presence or absence of CVD C1 or C2 that will be then compared with the conclusion made by an investigating physician. Eventually, based on obtained results, the Sensitivity and Specificity of the app will be established.

Additionally, to validate the tool with established Sensitivity and Specificity, a concordance between the confirmed diagnosis and signs of the app will be assessed. The Cohen's Kappa and Percentage agreement will be calculated for this purpose.

Patient management

The study does not implicate to routine management of patients with chronic venous disease (CVD). In particular, in this study the parameters that are usually evaluated during the examination of patients with classes C0-6 of CVD (C) will be gathered and evaluated in accordance to routine clinical practice, standards and measures.

Inclusion criteria:

- Age over 18 years
- Written informed consent is provided
- Symptoms and signs of CVD or any other skin pathologic condition (s) of lower extremities for which a patient seeks for phlebologist's consultation
- Ability to fulfil the technical requirements for smartphones/ images

Non-inclusion criteria:

- Patients with mental/ psychiatric disabilities who are not able to understand objectives of the study and therefore provide a signed consent to participate in the study.

Exclusion criteria:

- Patient's decision to withdraw his/her consent to participate in the study at any moment of the study conduction.

Data collection during the study

At single visit, investigating physicians (phlebologists) will be assessing and collecting parameters of interest which they should input in eCRF.

Following data will be collected at the visit: a signed consent form from a patient, demographic characteristics (age, sex), eligibility of a patient to the inclusion/ non-inclusion criteria, 1 (one) image of skin area of interest, conclusion on presence or absence of CVD or any other pathologic condition(s) made as a result of objective/ instrumental examination. In case there will be any information related to safety of a Servier drug provided, investigating physician will also collect the information and fill in the PV form (Appendix 1).

Investigating phlebologist will inform patients about their participation in this program using the Informed consent form . eCRFs filled by an investigating physician will be available for Servier medical affairs personal accountable for the study conduction. Personal data of each patient consented to participate in the study will be protected in accordance to the local legislation.

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DATA COLLECTION DURING THE STUDY

Type of data obtained	V1 visit (inclusion)

Informed consent form signed	+
Inclusion/ Non-inclusion criteria	+
Demographic data	+
Presence or absence of CVD with clinical class (CEAP) or presence or absence of any other pathologic condition associated with skin disorder of lower extremities (if applicable)	+
1 Image	+
Safety information (AE/ADR/SADR, if applicable)	+

Safety considerations.

1. Definitions

1.1 Pharmacovigilance information

Pharmacovigilance data include any unintended or adverse event associated with the use of a medicinal product in humans, whether or not considered drug related, including the following **special situations** (situations where no adverse event occurred but information needs to be collected):

- exposure during pregnancy or breastfeeding;

- overdose, abuse, misuse, off-label uses, medication error, occupational exposure (including professional one);

- suspected transmission of an infectious agent via a medicinal product;

- unexpected beneficial action of the drug;

- lack of the treatment efficiency of drug.

1.2. Adverse Event (AE)

Adverse event is any untoward medical occurrence in a patient or a clinical-trial subject who received the medicinal product, which does not necessarily have a causal relationship with the use of this medicinal product.

An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

1.3. Adverse (drug) reaction (ADR)

Adverse reaction (synonyms: Adverse drug reaction, suspected adverse (drug) reaction, Adverse effect, Undesirable effect) is a response to a medicinal product which is noxious and unintended.

“Response” in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

1.4. Serious adverse (drug) reaction (SADR)

Serious adverse reaction is an adverse reaction, which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

“Life threatening” in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

2. Responsibilities

2.1. Events to be reported

All available information about the following reported events occurring during the study will be recorded:

- All serious adverse drug reactions related to a Servier drug used for the disease/condition subject of the present study
- All non-serious adverse drug reactions related to a Servier drug used for the disease/condition subject of the present study
- All reports about special situations (see 1.1)
- All adverse events

2.2. Responsibilities of the treating physician

In prospective studies, at medical visits, the treating physician will ask the patient participating in the study to indicate whether or not an adverse event (serious or not) has occurred.

The treating physician has to assess the causal relationship between an adverse event and a drug intake, as well as the seriousness criteria and later on the outcome of the event.

In case of Adverse Events, Adverse Drug Reactions or special situations that occurs during the study (both serious and non-serious), the treating physician must complete the **"Adverse event / Adverse drug reaction / Special Situation Reporting Form" (Appendix 1)** without waiting for the clinical outcome or the results of additional investigations.

If the event is serious, it will be notified immediately (same or next working day at the latest) to Servier company in Russia via e-mail to address pvmail.ru@servier.com or by fax to number (495) 937-47-66. The anonymized copies of all the available and relevant laboratory findings, hospitalisation reports or other investigation results performed in connection with the adverse event should be attached to the form.

All other events should be reported by a treating physician within 2 working days.

The same rules apply for the transferring of additional information about the event.

The treating physician must ensure the appropriate follow-up of the patient depending on the nature of event, until it resolves. The treating physician will continue to notify follow up data according to timeframes defined above.

If a treating physician does not follow-up a patient anymore (i.e. in case of hospitalisation followed by the treatment by specialist or the participant's general practitioner,…), he/she will do every effort to contact the specialist or department in charge of follow-up of the patient, so as to have additional information and report it to Servier company in Russia.

2.3. Responsibilities of the Sponsor

Independently of the regulatory obligations of the treating physician, the sponsor must report the pharmacovigilance data to the appropriate authorities in accordance with the Good Vigilance Practice and local regulations.

Cases are closed when an adverse event has recovered or patient's condition was stabilised and the report is deemed sufficiently detailed for adequate medical analysis of the case.

Statistical parameters

1.1 Statistical design and analysis

Statistical analysis will be performed using validated statistical software that will be selected and approved by the Sponsor no later than the date of database lock. Examples of validated statistical software include, but not limited to, licensed versions of SAS (9.4 or higher), SPSS (21 or higher), NCSS (2019 or later), etc. Adverse events will be coded using Medical dictionary for regulatory affairs (MedDRA), MedDRA version (24.0 or higher) will be chosen at the time of data base lock.

1.2 Analysis populations

Full analysis set (FAS) will be the main analysis population for all statistical descriptions and testing. This analysis set will include all study subjects that were included into the study without major deviation from entry (inclusion and exclusion) criteria and successfully accomplished it (data and images met inclusion/ no inclusion and exclusion criteria and therefore are taken into analysis by the app).

No imputation methods will be applied for any data that is missing from the FAS due to non-comparative nature of the study.

FAS will be used for all additional sensitivity analyses, if such analyses are required.

1.3 Descriptive statistics

Continuous (quantitative) data will be presented as number of valid observations, arithmetic mean, standard deviation, median, interquartile range (presented as 1st and 3rd quartiles), minimum and maximum.

Categorical (quantitative) data will be presented as number of valid observations, number of observations falling into each category (absolute frequency), relative frequency (presented as % values).

95% confidence intervals will be presented for all types of data to measure the precision of sample estimate. Confidence intervals will be based on t-distribution for quantitative data, and on the binomial distribution (exact Clopper-Pearson method or Agresti-Coull method) for qualitative data.

Concurrent conditions and adverse events will be classified using the current version (at the time of database lock) of MedDRA (Medical Dictionary for Regulatory Activities). Concomitant medications will be classified using the most up-to-date version (at the time of database lock) of ATC (anatomical, therapeutical and chemical) classification system.

1.4 Baseline information

Due to non-comparative nature of the study, baseline data will be presented descriptively, without any statistical testing of comparisons (as detailed in section 1.3 above). Yet, as the study will test the performance for C 1 and C 2 classes separately, baseline data will be presented by C class on top of general sample data.

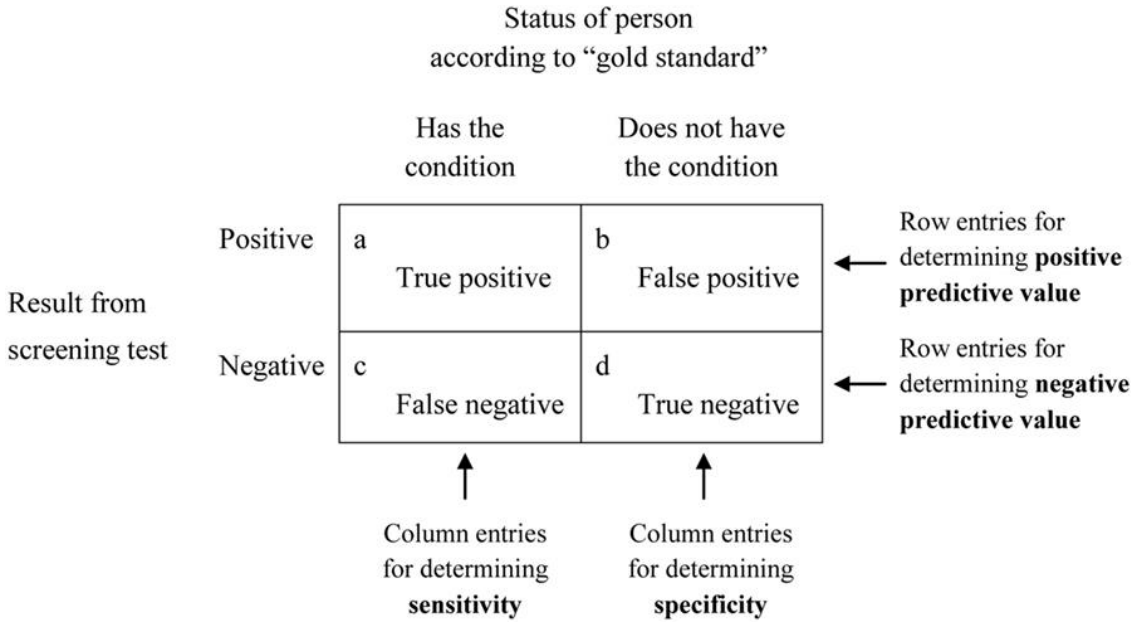
1.5 Primary endpoints

The following primary parameters will be assessed in this study:

1. Sensitivity and specificity of the AIVARIX tool in detecting C 1 class of CVD.
2. Sensitivity and specificity of the AIVARIX tool in detecting C 2 class of CVD.

Calculation of all performance parameters will be based on the two-way table as follows (where “gold standard” stands for the current approach and “screening test” stands for AIVARIX-based approach; “positive” stands for signs

of C1 class of CVD or C2 class of CVD, “negative” stands for non-signs C1 class of CVD or non-C2 class of CVD, respectively):



Primary (operational) parameters of the AIVARIX method will be calculated as follows (presented as percentages):

$$Sensitivity=[a/(a+c)]\times 100$$

$$Specificity=[d/(b+d)]\times 100$$

95% exact binomial confidence intervals calculated using the Clopper-Pearson or Agresti-Coull method will be calculated for both sensitivity and specificity.

1.6 Secondary endpoints

The following secondary parameters will be assessed in this study:

1. PPV, NPV, LR+ and LR- of the AIVARIX tool in detecting C 1 class of CVD
2. PPV, NPV, LR+ and LR- of the AIVARIX tool in detecting C 2 class of CVD

Based on the same table as mentioned in the section 1.4, the following formulas will be used to calculate the parameters of interest:

$$Positive\ predictive\ value(PPV)=[a/(a+b)]\times 100$$

$$Negative\ predictive\ value(NPV)=[d/(c+d)]\times 100.$$

$$Positive\ likelihood\ ratio\ (LR+) = \frac{Sensitivity}{100 - Specificity}$$

$$Negative\ likelihood\ ratio\ (LR-) = \frac{100 - Sensitivity}{Specificity}$$

95% confidence intervals will be calculated using the normal approximation (Wald’s) method for PPV, NPV, LR+ and LR- parameters.

1.7 Additional validation analysis

To validate the tool with established Sensitivity and Specificity, a concordance between the confirmed diagnosis and signs of the app will be assessed. The diagnoses “CVD C 1”, “CVD C 2”, “not CVD C 1-2” confirmed by

phlebologists will be compared with the corresponding signs corresponding stages of CVD made by the app. The Cohen's Kappa and Percentage agreement will be calculated to compare this data and estimate the concordance.

1.8 Safety reporting

The following events will be reported as safety parameters:

1. All serious adverse drug reactions related to any Servier drug used for the disease/condition subject of the present study
2. All non-serious adverse drug reactions related to any Servier drug used for the disease/condition subject of the present study
3. All reports about special situations
4. All adverse events

For each type of event, overall event frequency to be reported; additionally, events will be reported by grade, by relation to Servier drug and by MedDRA system-organ-class (SOC) and preferred term (PT).

This data will be presented descriptively only as detailed in sectioned 1.2.

1.9 Interim analysis

No interim analysis is planned for this study.

1.10 Significance level

Significance level alpha = 0.05 will be used for all two-sided tests. All confidence intervals will be 95% two-sided.

1.11 Sample size calculation and justification

Sample size calculation for studies sensitivity and specifisity is primarily based on two parameters: prevalence of true-positive cases in the population under study (disease prevalence) and acceptable sensitivity and specificity levels and precision of estimate.

According to the global data presented in the systematic review with pooled prevalence analysis of Salim S. et al., 2021 [1], pooled estimates for different CVD classes were: C0 s: 9%, C1: 26%, C2: 19%, C3: 8%, C4: 4%, C5: 1%, C6: 0.42%. Probably, the rest 32.58% corresponds for the absence of any sign of CVD.

According to the data for the Russian Federation presented by Zolotukhin I.A. et al., 2017 [2], about 30.8% of examined participants had no any sign of CVD; the prevalence of C0 were 5.4%, C1 – 34.3%, C2 – 21.3%, C3-6 – 8.2%. In the abstract of Cand. Sci. (Med.) Dissertation of Avakiants I.P., 2019 [3], the prevalence of C1 were estimated as 30.9%, of C2 – 19.3%.

So, we could estimate the summary prevalence for C 1 plus C 2 as approximately 50%, and the proportion "C2 : C1" as about 2 : 3.

Among the rest 50% of the population (without C 1 or C 2) we could roughly estimate the proportion of persons without any signs of CDV or with C0 class to the persons with C3-6 classes as 4 : 1.

Finally, persons without any signs of CDV or with C0 class could have some other (non-CVD) diagnosed and documented lower extremities skin conditions or they could be without any skin conditions of lower extremities at all. We do not estimate any proportions for this category.

With regards to the acceptable sensitivity and specificity, the estimates were based on the publication by Navarro T.P. Et al, 2002 [4], where targeted sensitivity is about 80% and higher while acceptable specificity should be 70% or above. Unacceptable level of both sensitivity and specificity is set to 60% based on the width of the 95% confidence intervals from the publication [4].

Accordingly, the following assumptions were made when calculating the sample size:

$H_0: Se = Se_0$ $\quad$ $H_0: Sp = Sp_0$

$H_A: Se \neq Se_0$ $\quad$ $H_A: Sp \neq Sp_0$

where

- *Se* – target sensitivity
- Se_0 – null hypothesis (i.e. not acceptable) sensitivity
- *Sp* – target specificity
- Sp_0 – null hypothesis (i.e. not acceptable) specificity

1) Null hypothesis (not acceptable) levels of both sensitivity and specificity are set to 60% (0,6), i.e. such level of effectiveness of detecting signs of early stages of CVD will be too low for screening purposes
2) Expected (detectable) level of sensitivity and specificity:
    a. Target (expected) sensitivity – 80% or higher
    b. Target (expected) specificity – 70% or higher
3) Power of analysis is set to 80% (accordingly, type II error is equal to 0,20)
4) Significance level is set to 5% (accordingly, type I error is equal to 0,05)
5) Expected prevalence is set to 70% (0,70)
6) Exact binomial distribution approach and the Agresti-Coull approach will be used
7) Up to 10% of cases can be lost for statistical analysis (due to loss of absence of reliable data for both reference standard and test under study)

Calculations results:

For Se:

- exact binomial distribution approach: a total sample size is 90 pts, the amount of patients with C 1-2 is 45;
- Agresti-Coull approach: total sample size is 88 pts, the amount of patients with C 1-2 is 44.

For Sp:

- exact binomial distribution approach: a total sample size is 362 pts, the amount of patients with C 1-2 is 181;
- Agresti-Coull approach: a total sample size is 372 pts, the amount of patients with C 1-2 is 186.

In accordance with generally accepted approach, we must choose the largest estimation among the estimation for Se and Sp, so we chose the result for Sp, the total sample size estimation is 372, and the amount of patients with C 1-2 is 186.

Taking possible 10% loss of data (41 cases), a total of 413 patients (or more, 414 for example) should be enrolled in the study.

A half of them (207 patients) are patients with C1 or C2 class (namely, 3/5 of the patients with C1 (n= 124) and 2/5 of the patients with C2 (n = 83)).

Another half of patients (n=207) will include either persons without any signs of CDV (or with C0 class) or with C3-6 classes (namely, 4/5 of these patients are without CVD or with C0 (n= 166), and 1/5 of the patients with C3-6 classes (n= 41 cases)).

1.12 Management of bias and confounding

Due to non-comparative nature of this study, management of bias and confounding factors is not applicable on the analytical level, however, any deviations from the entry criteria as well as deviations from the protocol identified during the collection of the study data should be carefully assessed for possible interaction with any parameter under study.

1.13 Subgroup analysis and multiplicity correction

No subgroup analysis is planned; all tests will be performed as one-group tests; thus, no multiplicity corrections will be introduced. Accuracy testing for C 1 and C 2 classes will be considered as independent analysis of the same data.

1.14 Multicenter study

This study is planned to be conducted in multiple investigational sites; thus, all data will be presented descriptively by site on top of the data in the general sample. If the endpoints will be substantially different across the sites, the primary data will be compared across the sites using chi-square test. It should be noted that all p-values for such comparisons will be nominal as the study was not powered for the formal conduct of site-by-site analysis.

1.15 Deviations from the planned analysis

Any deviations from the planned statistical analysis as described in this protocol should be noted, documented and reported in either statistical analysis plan or in the final study report. Any changes in the methods of statistical analysis or approach to the definition and calculation of any endpoint variables should be explained, and the rationale should be focused at the maintenance of the scientific integrity of the study.

1.16 References

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Ethical considerations:

The study will be conducted in accordance with the principles set out in the Declaration of Helsinki (version adopted in Fortaleza, Brazil, in 2013).

Participants will be fully informed about the program and provide their written consent to participate in it. Treating physician is obliged to indicate in the CRF that the informed consent has been obtained from the patient. The

"informed consent" also means that individual discussion with a participant concerning nature of the program and necessity of examinations and evaluations used in the study took place.

The confidentiality of patient data will be guaranteed using identification code numbers (IDs). The relation between the ID and the patient identity will be known only to a treating physician, so that will ensure the anonymity of patient's data.

Results:

The obtained data will be used to generate a study report under the supervision of independent scientific experts and biostatisticians.

Appendix 1.

Adverse event / Adverse drug reaction / Special Situation Form*

IC4-05682-071-RUS *Please send this form immediately by fax (495) 937-47-66 or by email to pvmail.ru@servier.com, or pass to the associate of the company.*

Year of birth or Age	**Gender**	**Height**	**Weight**	**Patient's ID:**
_____ or _____	M / F	_____	_____	_____

Description of adverse event/reaction/special situation:	**Date of event onset**	**Date of event termination (in case of recovery)**
	_____	_____

Criteria of seriousness: ☐ NO ☐ YES (please, specify from stated below) ☐ Death ☐ Life threatening ☐ Hospitalization or prolongation of existing hospitalisation ☐ Persistent or significant disability or incapacity ☐ Congenital anomaly/birth defect ☐ Medically significant	**Outcome:** ☐ Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Not recovered ☐ Fatal ☐ Unknown

General disease(s) / Concomitant disease(s) (please indicate year when first diagnosed).

Course adverse event/reaction/special situation (please enclose relevant findings, e.g. laboratory, hospital reports, histology, etc.):

Causal relationship with a Servier drug used for the disease/condition subject of the present study:

☐ NO ☐ YES ☐ NOT APPLICABLE

If yes, please specify dates of treatment with the Servier drug in the table below <u>on the first line</u>:

***If «No» or «Not applicable»**, please specify whether the adverse event/special situation is related to the medication of Servier company (which is specified in the table below)*:

☐ NO ☐ YES *Please indicate the name of the medication of Servier company:* ……

List of current medications	**Daily dose / route of administration**	**Dates of intake: from to**	**Indication**
		-	
		-	
		-	

Name (last, first, patronymic) of doctor:
Speciality:
Work address:
Phone number: _____
(city code)

Date:

Stamp

Signature: (whenever possible)

**Special situations are cases when adverse event was not observed, but the information should be collected: the impact of the drug during pregnancy/breastfeeding, abuse, misuse, medication error, overdose, off-label use, occupational exposure, treatment failure, suspected transmission of infectious agents via a medicinal product, or unexpected beneficial action of the drug.*