Stroke

ORIGINAL CONTRIBUTION

Thrombolysis With the Nonimmunogenic Staphylokinase for Acute Ischemic Stroke in FORPI Registry: An Observational Study

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BACKGROUND: The nonimmunogenic staphylokinase is a recombinant staphylokinase with low immunogenicity, high thrombolytic activity, and fibrin selectivity approved in Russia for the acute ischemic stroke (AIS) thrombolytic therapy within 4.5 hours after symptom onset. We evaluated safety and efficacy outcomes of the nonimmunogenic staphylokinase usage in patients with AIS in the Fortelyzin Population Investigation registry.

METHODS: Between March 2021 and October 2024, patients with AIS treated with the nonimmunogenic staphylokinase were enrolled in the prospective, open-label, internet-based, monitored, observational Fortelyzin Population Investigation registry. Demographics, risk factors, baseline stroke severity (defined by National Institutes of Health Stroke Scale), and onset to treatment time were recorded. Safety outcomes included symptomatic intracerebral hemorrhage (according to the ECASS III [European Cooperative Acute Stroke Study III] and SITS-MOST [Safe Implementation of Thrombolysis in Stroke—Monitoring Study] criteria) within 36 hours and all-cause mortality on day 90. Efficacy outcome was evaluated by functional independence using of modified Rankin Scale score of 0 to 2 on day 90.

RESULTS: A total of 17 636 patients with AIS were treated with the nonimmunogenic staphylokinase in 329 centers participated in the Fortelyzin Population Investigation registry during the study period (median age 68 [60–75]; 56% male; median baseline National Institutes of Health Stroke Scale score, 11 [8–16] points; median onset to treatment time, 2.4 hours [1.8–3.1]). The rate of symptomatic intracerebral hemorrhage according to the ECASS III criteria was 2% (356/17 636; 1.8–2.2), to the SITS-MOST criteria, 2% (330/17 636; 1.8–2.1). All-cause mortality on day 90 was 9% (1588/17 636; 8.6–9.4). The number of patients with a modified Rankin Scale score of 0 to 2 on day 90 was 61% (10 799/17 636; 60.5–61.9). These safety and efficacy outcomes were comparable with FRIDA (Fortelyzin Randomized Investigation Compared With Alteplase) randomized clinical trial results.

CONCLUSIONS: The presented data suggest that intravenous thrombolysis with the nonimmunogenic staphylokinase is safe and effective in routine clinical practice when used within 4.5 hours of AIS symptoms onset. These findings should encourage the wider usage of thrombolytic therapy with the nonimmunogenic staphylokinase for suitable patients.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT06707987.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cause of death ■ fibrin ■ ischemic stroke ■ risk factors ■ tenecteplase

Stroke is the second leading cause of death in people around the world.[1] Assessment of the prognostic outcomes in patients with acute ischemic stroke (AIS) receiving intravenous thrombolytic therapy is an important task. Recently, several new studies of tenecteplase as a thrombolytic agent for AIS treatment compared with

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ORIGINAL CONTRIBUTION

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
ECASS III	European Cooperative Acute Stroke Study III
FORPI	Fortelyzin Population Investigation
FRIDA	Fortelyzin Randomized Investigation Compared With Alteplase
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
SAE	serious adverse event
sICH	symptomatic intracranial hemorrhage
SITS-MOST	Safe Implementation of Thrombolysis in Stroke—Monitoring Study

alteplase were completed: in TRACE-2[2] and ATTEST-2[3] trials, tenecteplase was noninferior to alteplase; in the TASTE study,[4] tenecteplase was also noninferior in the per-protocol population, but not in the intention-to-treat population. In the PROST-2 trial, recombinant human prourokinase was shown to be noninferior to alteplase.[5]

Staphylokinase is a thrombolytic agent with high biological activity.[6] The unique fibrin selectivity of staphylokinase made it a candidate for use as a first-line treatment of patients with ST-segment–elevation myocardial infarction and AIS. Amino acid substitutions, including Lys74Ala, Glu75Ala, and Arg77Ala, resulted in a >200× reduction in titers of neutralizing antistaphylokinase IgGs in patients with ST-segment–elevation myocardial infarction.[7]

A recent advanced kinetic analysis of staphylokinase demonstrated that its catalytic activity is 1000-fold higher than that of alteplase.[8]

In the FRIDA trial (Fortelyzin Randomized Investigation Compared With Alteplase), the nonimmunogenic staphylokinase was shown to be an effective and safe thrombolytic agent for the treatment of patients with AIS within 4.5 hours of the symptoms onset and was easy to administer with a rapid single bolus administration without having to weigh the patient. Mortality, symptomatic intracranial hemorrhage (sICH) according to the ECASS III (European Cooperative Acute Stroke Study III) definition, and serious adverse events (SAEs) did not differ significantly between treatment groups.[9] In December 2020, the nonimmunogenic staphylokinase was approved in Russia for AIS thrombolytic therapy within 4.5 hours of symptom onset.[10]

The safety and efficacy of the nonimmunogenic staphylokinase in patients with AIS in routine clinical practice have been previously reported in a few small observational studies and case reports.[11–14] FORPI (Fortelyzin Population Investigation) is an observational monitoring registry that includes a cohort of patients treated with the nonimmunogenic staphylokinase within 4.5 hours from symptom onset, not only in clinical centers with previous experience in randomized clinical trials, but also in centers with less experience, but highly qualified in general AIS care.

The aim of this study was to evaluate the safety and efficacy of the thrombolytic treatment with the nonimmunogenic staphylokinase in routine clinical practice, outside the conditions of a clinical trial, and to compare these results with the FRIDA randomized clinical trial.

METHODS

The authors declare that all data are available within the article and its Supplemental Material. The funder of the study is committed to the responsible sharing of data from the FORPI registry. Data will be provided to any qualified investigator on reasonable request. Deidentified participant data will be available after the publication of the results of the completed study on request to the corresponding author. Proposals will be reviewed and approved by the funder, investigators, and the ethics committee of the Federal Center for Brain and Neurotechnology of the Federal Medical and Biological Agency. Once the proposal has been approved, data can be transferred through a secure online platform after the signing of a data access agreement and a confidentiality agreement.

The FORPI is an ongoing, prospective, academic-driven registry for centers using the nonimmunogenic staphylokinase for AIS treatment. The design of the FORPI registry was based on the principles of the world's largest stroke registries.[15] This trial is reported according to the STROBE requirements.

Description of the Registry

To become a FORPI center, certain criteria must be fulfilled. Potentially participating centers must have appropriate facilities for the inclusion; in particular, they must be able to provide an acute care setting and a staff of physicians specialized in neurological care and experienced in the AIS diagnosis and management. These facilities are presented in Stroke units, which were established in all district and regional hospitals throughout Russia according to the national program «Stroke».

Centers entered their data in the FORPI, which is an internet-based monitoring registry started as an initiative by FRIDA investigators. The FORPI registry is available from any internet-connected computer. Registered centers could enter data online[16] via an electronic case record form through a secure internet connection. The register includes a data entry section, a database, and a report section. Data entry is quick and easy to perform by answering the specified questions. The users can log into the registration form by using the special login and the password assigned to them by the regional coordinator, and then change it. The first page allows the investigator to enter a new patient, who receives an identification log for subsequent entries of additional data. To be included in the FORPI registry, all baseline data entry had to be confirmed by the investigator. After confirming and saving the page for 1 patient, it was locked, and the investigator had no possibility to enter and correct data.

Investigators included consecutive patients. Eligibility was restricted by the terms of the nonimmunogenic staphylokinase

conditional licensing approval to those individuals aged 18 years and older who presented symptoms within 4.5 hours of AIS onset. Patients with contraindications for AIS thrombolysis as National Institutes of Health Stroke Scale (NIHSS) >25 with neuroimaging signs of intracranial hemorrhage, with glucose blood below 2.7 and above 22.0 mmol/L, platelet count <100 000/mm^3, uncontrolled hypertension, and other conditions according to the National and American Heart Association/American Stroke Association Guidelines for the early management of patients with AIS were not eligible for the registry.[17,18] The nonimmunogenic staphylokinase (Fortelyzin, LLC SuperGene, Russia) was administered as a single bolus in a dose of 10 mg regardless of body weight for 10 s.

Procedures within the FORPI registry were focused on time onset in management, baseline characteristics and risk factors, demographic data, and stroke severity at admission (NIHSS score, modified Rankin Scale [mRS] score). mRS score, as well as NIHSS score, were assessed in Stroke units at admission by certified neurologists. According to the inclusion criteria in the registry, before stroke, all patients had an mRS score of 0 to 1. NIHSS was assessed at 3 different times: before treatment, 24 hours after treatment, and on discharge; mRS score was determined at 4 points: before treatment, on discharge, on day 30, and on day 90 after treatment. Functional independence was assessed by face-to-face or telephone interview with the patient on day 30 and day 90 after stroke onset.

Patients with bridging therapy (thrombolysis followed by mechanical thrombectomy) were registered separately and were excluded from further analysis.

National and regional coordinators have the opportunity to use the database for the objectives defined by their role.

Ethics Approval and Data Monitoring

Ethics approval was obtained from the Federal Center for Brain and Neurotechnology of the Federal Medical and Biological Agency (protocol no. 1 dated February 25, 2021). The FORPI regional coordinators monitored entered data online and checked individual patient data monthly to identify errors or inconsistencies. Sample source data verification was done by professional monitors working with regional coordinators. A minimum of 10% of patients included in the FORPI registry were monitored.

Outcome Measurements

Safety outcomes were sICH and all-cause mortality on day 90. sICH was assessed according to the ECASS III definition as any intracranial hemorrhage with neurological deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death. In addition, the hemorrhage must have been identified as the predominant cause of the neurological deterioration.[19] Additionally, sICH was assessed according to SITS-MOST (Safe Implementation of Thrombolysis in Stroke—Monitoring Study) definition as a local or remote parenchymal hematoma type 2 on the imaging scan obtained 22 to 36 hours after treatment, plus neurological deterioration, as indicated by a score on the NIHSS that was higher by 4 points or more than the baseline value or the lowest value between baseline and 24 hours, or hemorrhage leading to death.[20]

Efficacy outcome was defined as functional independence with an mRS score of 0 to 2 on day 90 after drug administration. Additional outcome measures were the median of mRS on discharge, on day 30, and on day 90; median of NIHSS after 24 hours and on discharge; Barthel index on discharge. The proportion of patients with mRS scores of 0 to 6 on day 90 was also calculated.

According to the International Conference on Harmonization Good Clinical Practice, SAE is defined as any adverse drug reaction that results in death, is immediately life-threatening, in persistent or significant disability/incapacity, or requires or prolongs a patient's hospitalization. SAEs that were recorded in the FOPRI registry were as follows: ICH, sICH, any major bleedings, and death. All SAEs were reported via a report form to the regulatory authorities.

FORPI compared the proportion of safety and efficacy outcomes with the corresponding proportions in the nonimmunogenic staphylokinase group of the FRIDA clinical trial.

Statistical Analysis

All statistical analyses were performed using R (version 4.2). Descriptive univariate statistical analysis for baseline clinical and imaging data, as well as outcomes, was performed. Continuous variables are presented as mean (SD) or as median (interquartile range). Categorical variables excluding missing or unknown cases are presented as n/N (%;95% CI). In the independent groups, the Mann-Whitney *U* test was used to compare continuous variables, and the 2-sided Fisher exact test was used to compare categorical variables. In the dependent groups, the Wilcoxon test was used to compare continuous variables, and the NcNemar test was used to compare categorical variables. The differences were considered statistically significant when the *P* value was <0.05.

Role of the Funding Source

The study protocol was drafted by the Federal Center for Brain and Neurotechnology of the Federal Medical and Biological Agency and developed in close collaboration with the Russian Academy of Sciences. All data collection and analysis were done independently by the Federal Center for Brain and Neurotechnology. Source data verification was done by the Federal Center for Brain and Neurotechnology in collaboration with FORPI regional coordinators. The Federal Center for Brain and Neurotechnology was responsible for SAEs reporting to the regulatory authority. As the chairman of the FORPI registry, N.A.S. had full access to all data in this study and had the final responsibility for the preparation of this article and its submission for publication.

RESULTS

Twenty-three thousand two hundred fifty patients were enrolled in the FORPI registry between March 1, 2021, and October 31, 2024, at 329 centers in 72 regions of Russia. Eighteen centers had participated in the FRIDA trial and enrolled patients in the FORPI registry; 311 centers that did not participate in the FRIDA trial were designated as new. FORPI registry regions, number of patients, and local investigators are presented in the Supplemental Material (Table S1).

3566 (15%) of patients had missing data: 2050 (8.8%) of patients had no designated time from symptom onset, 1127 (4.8%) of patients had no stroke subtype according to TOAST classification, 331 (1.4%) and 407 (1.8%) of patients had no data on day 30 and day 90 respectively due to loss of contact. All these patients were excluded from the analysis.

457 (2%) patients died during transportation before admission without performing thrombolysis, 383 (2%) patients who underwent off-label thrombolysis beyond 4.5 h stroke symptom onset, 92 (0.4%) patients who did not meet the inclusion criteria, and 1116 (5%) patients with thrombolysis followed by thrombectomy were also excluded from the analysis. Thus, 17 636 patients (76%) comprised the study cohort (Figure 1).

The median number of patients treated per center was 35 (interquartile range, 15–93). Nine centers treated >300 patients, 79 centers treated at least 100 patients, and 33 centers treated <5.

Baseline demographic data, clinical characteristics, and comorbidities for patients in the FORPI registry and in the nonimmunogenic staphylokinase group of the FRIDA randomized trial are shown in Table 1.

In the FORPI registry, median age was 68 (60–75) years; 56% of patients were men (9924/17696). 77% (13 553/17636) of patients were older than 60 years, 16% (2866/17636) were older than 80 years. In the FRIDA trial, median age was 65 (59–70) years (P<0.001), and only 3% (5/168) of patients older than 80 years were included after the amendment in the trial protocol (P<0.001).

In FORPI registry, the number of patients with hypertension, myocardial infarction, atrial fibrillation and chronic heart failure were less than in FRIDA trial (73% versus 95% P<0.001; 8% versus 38%, P<0.001; 24% versus

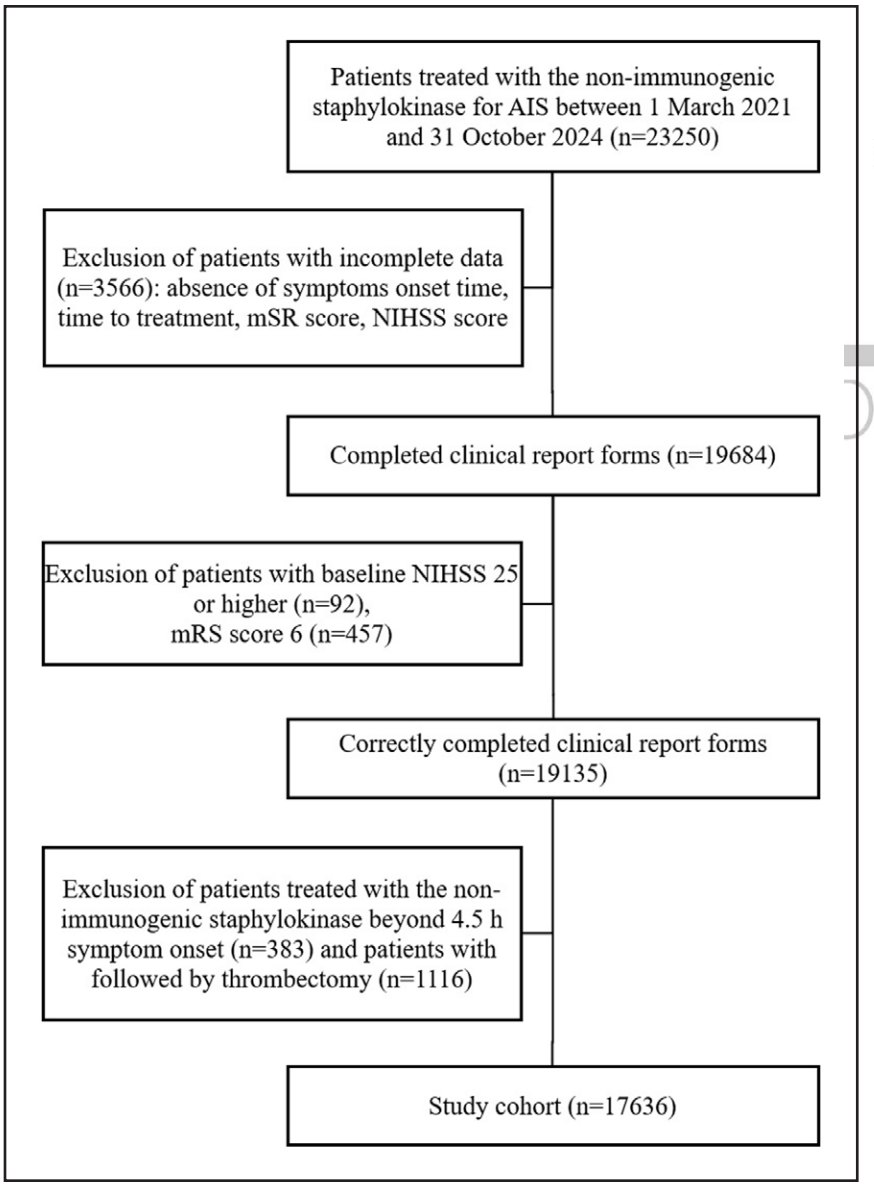

Figure 1. Trial profile.
AIS indicates acute ischemic stroke; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

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Table 1. Baseline Demographic Data, Clinical Characteristics, and Comorbidities

	Non-immunogenic staphylokinase		
	FORPI registry (n=17 636)	FRIDA trial (n=168)	*P* value
Male	9924 (56%)	106 (63%)	0.085
Age, y	68 (60–75)	65 (59–70)	<0.001
Patients older than 60 years	13 553 (77%)	125 (74%)	0.462
Patients older than 80 years	2866 (16%)	5 (3%)	<0.001
Bodyweight, kg	81.7±12.9	82.5±13.8	0.656
Body mass index, kg/m^2	28.3±4.1	28.2±4.9	0.200
Cardiovascular history			
Previous stroke	1913 (11%)	22 (13%)	0.321
Previous myocardial infarction	1416 (8%)	63 (38%)	<0.001
Stroke risk factors			
Hypertension	12 814 (73%)	159 (95%)	<0.001
Atrial fibrillation	4204 (24%)	65 (39%)	<0.001
diabetes	2569 (15%)	16 (10%)	0.077
Chronic heart failure	4444 (25%)	63 (38%)	<0.001
Onset to treatment time			
Onset to treatment time, h	2.4 (1.8–3.1)	2.9 (2.4–3.5)	<0.001
<3 h	2.1 (1.7–2.5)	2.5 (2.1–2.8)	<0.001
3–4.5 h	3.6 (3.3–4.0)	3.6 (3.3–4.0)	0.868
Number of patients with thrombolysis 0–3 h	12 947 (73%)	85 (51%)	<0.001
Number of patients with thrombolysis 3–4.5 h	4689 (27%)	83 (49%)	<0.001
Stroke characteristics			
NIHSS score	11 (8–16)	11 (8–14)	0.261
mRS score at admission	4 (4–5)	4 (4–5)	0.206
ASPECT score	9 (9–10), n=15 726	10 (10–10) n=154	0.154
Stroke localization			
Right middle cerebral artery	8709 (49%)	74 (44%)	0.187
Left middle cerebral artery	7017 (40%)	80 (48%)	0.047
Basilar artery	1910 (11%)	14 (8%)	0.381
TOAST classification			
Atherothrombotic	4813 (27%)	44 (26%)	0.794
Cardioembolic	5744 (33%)	60 (36%)	0.408
Lacunar	1255 (7%)	6 (4%)	0.094
Undetermined	4920 (28%)	58 (34%)	0.069
Other	904 (5%)	0 (0%)	<0.001
Clinical characteristics			
Systolic blood pressure, mm Hg	152±18	156±18	0.003
Diastolic blood pressure, mm Hg	89±10	89±11	0.271
Heart rate, beats per min	81±11	79±13	0.005
Hemoglobin, g/L	136 (125–146)	142 (132–152)	<0.001
Platelets, ×10^9/L	226 (192–275)	212 (168–250)	<0.001
Blood glucose level, mmoL/l	6.1 (5.3–7.2)	6.2 (5.4–7.8)	0.235

Data are presented as mean (SD), n/N (%/95% CI), or median (IQR). ASPECT, Alberta Stroke Program Early CT; FORPI, Fortelyzin Population Investigation; FRIDA, Fortelyzin Randomized Investigation Compared With Alteplase; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

39%, *P*<0.001; 25% versus 38%, *P*<0.001, respectively); the number of patients with diabetes was similar with FRIDA trial (15% versus 10%, *P*=0.077).

Median of onset to treatment time in the FORPI registry was 2.4 (1.8–3.1) hours compared with 2.9 (2.4–3.5) hours in the FRIDA trial (*P*<0.001). Median

of onset to treatment time before 3 hours in FORPI registry was 2.1 (1.7–2.5) hours compared with 2.5 (2.1–2.8) hours in FRIDA trial (*P*<0.001); between 3 and 4.5 hours—3.6 (3.3–4.0) hours versus 3.6 (3.3–4.0) hours (*P*=0.868).

In the FORPI registry, 73% (12947/17636) of patients received thrombolytic therapy during the first 3 hours after symptom onset, while 27% (4689/17636) of patients received it during 3 to 4.5 hours after symptom onset. In the FRIDA trial, there were significantly fewer patients with thrombolysis 0 to 3 hours (51%, 85/168; *P*<0.001) and higher with thrombolysis 3 to 4.5 hours (49%, 83/168; *P*<0.001).

At admission, median of NIHSS in FORPI registry was 11 (8–16) compared with 11 (8–14) in FRIDA trial (*P*=0.26), mRS was 4 (4–5) versus 4 (4–5; *P*=0.206), ASPECT score was 9 (9–10) versus 10 (10–10; *P*=0.154), respectively.

In the FORPI registry, 49% (8709/17636) of patients had a right middle cerebral artery occlusion, 40% (7017/17636) of patients had a left middle cerebral artery occlusion, 11% (1910/17636) had—basilar artery occlusion. In the FRIDA trial, there were significantly more patients with the left middle cerebral artery occlusion (48%, *P*=0.047); however, the number of patients with the right middle cerebral artery occlusion (44%, *P*=0.187) and basilar artery occlusion (8%, *P*=0.381) was similar.

According to TOAST classification, 27% (4813/17636) of patients had atherothrombotic stroke, 33% (5744/17636)—cardioembolic stroke, 7% (1255/17636)—lacunar stroke, 28% (4920/17636)—undetermined stroke. The proportion of stroke localization subtypes in patients included in the FORPI registry was similar in the FRIDA trial. 5% (904/17636) of patients in FORPI had stroke of other determined cause; in the FRIDA trial, there were no patients with other determined cause stroke (*P*<0.001).

Safety and efficacy outcomes are presented in Table 2.

In the FORPI registry, the number of patients with ICH was 16% (2839/17636; 15.6–16.6) compared with 18% (31/168; 12.9–25.2) in the FRIDA trial (*P*=0.399). The rate of sICH according to the ECASS III definition was 2% (356/17636; 1.8–2.2), compared with 3% (5/168; 0.97–6.81) in the FRIDA trial (*P*=0.397). The number of patients with sICH according to the SITS-MOST definition was 2% (330/17636; 1.8–2.1); results from the FRIDA randomized trial according to this definition are not available.

In the FORPI registry, 8% (1450/17636) of patients had died during hospitalization. 0.7% (138/17636) of patients had died after discharge. Total all-cause mortality on day 90 was 9% (1588/17636; 8.6–9.4), and it was comparable with the mortality rate in the FRIDA trial, 10% (17/168; 6.0–15.7; *P*=0.588).

Table 2. Safety and Efficacy Outcomes

	Nonimmunogenic staphylokinase		
	FORPI registry (n=17 636)	FRIDA trial (n=168)	*P* value
Safety outcomes			
Any ICH	2839 (16%)	31 (18%)	0.399
SICH			
According to the ECASS III definition*	356 (2%)	5 (3%)	0.397
According to the SITS-MOST definition†	330 (2%)	n/a	
In-hospital mortality	1450 (8%)	13 (8%)	0.999
All-cause mortality on day 90	1588 (9%)	17 (10%)	0.588
Efficacy outcomes			
Patients with mRS score 0–2 on day 90	10 799 (61%)	115 (68%)	0.056
mRS score on discharge	3 (2–4)	2 (1–3)	<0.001
mRS score on day 30	2 (1–3)	2 (1–3)	0.404
mRS score on day 90	2 (1–3)	1 (1–2)	<0.001
NIHSS score 24 h after thrombolysis	7 (4–11)	6 (3–11)	0.034
NIHSS score on discharge	5 (2–9)	4 (2–7)	0.014
Barthel index on discharge	80 (60–91)	83 (54–100)	0.034

Data are presented as mean (SD), n/N (%/95% CI), or median (IQR). ECASS indicates European Cooperative Acute Stroke Study; FORPI, Fortelyzin Population Investigation; FRIDA, Fortelyzin Randomized Investigation Compared With Alteplase; ICH, intracranial hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; n/a, non-applicable; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke—Monitoring Study.

*The ECASS III definition of symptomatic intracranial hemorrhage was any hemorrhage with neurological deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death. In addition, the hemorrhage must have been identified as the predominant cause of the neurological deterioration.

†The SITS-MOST definition was local or remote parenchymal hematoma type 2 on the imaging scan obtained 22 to 36 h after treatment, plus neurological deterioration, as indicated by a score on the NIHSS that was higher by 4 points or more than the baseline value or the lowest value between baseline and 24 h, or hemorrhage leading to death.

Functional independence (mRS score of 0–2) on day 90 was reached in the FORPI registry in 61% (10799/17636; 60.5–61.9) of patients compared with 68% (115/168; 60.9–75.4) in the FRIDA trial (*P*=0.056). The distribution of mRS scores on day 90 in the FORPI registry in comparison with FRIDA trial results is shown in Figure 2.

In Table 3, all registered SAEs are presented.

As it was noted previously, there were no significant differences in the number of all-cause mortality, any ICH, and sICH in the FORPI registry compared with the FRIDA trial. The number of major bleedings (type 3 and 5 according to Bleeding Academic Research Consortium classification), blood transfusion, as well as the incidences of acute myocardial infarction and pulmonary embolism, also did not differ significantly between the FORPI registry and FRIDA trial.

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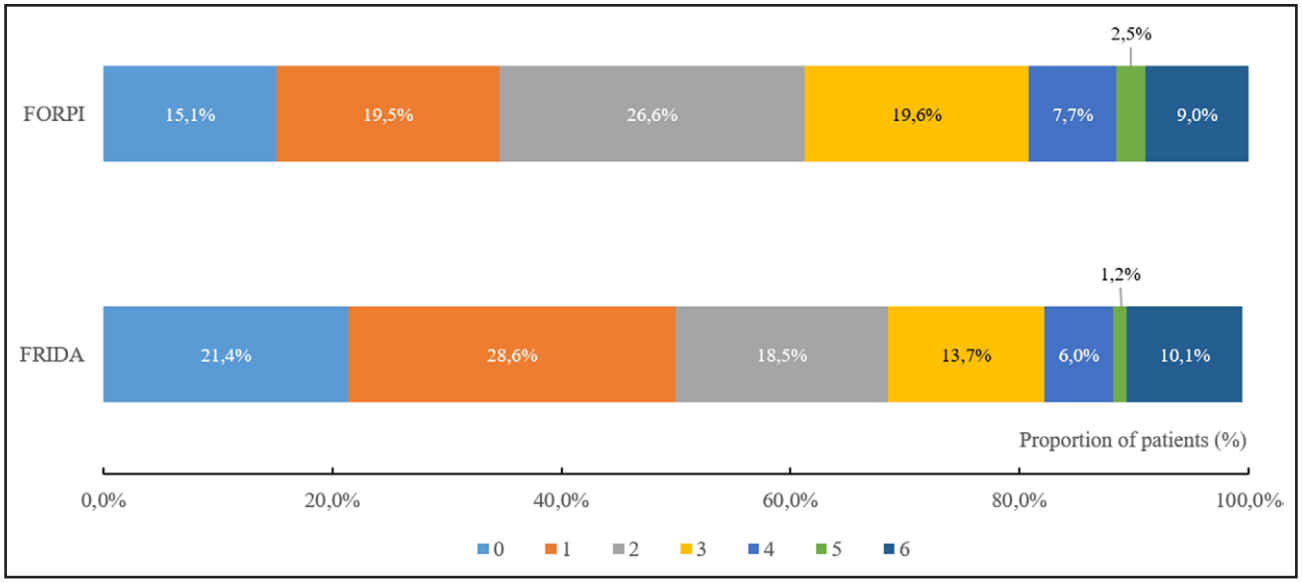

Figure 2. Distribution of modified Rankin Scale (mRS) scores on day 90 in Fortelyzin Population Investigation (FORPI) registry compared with FRIDA (Fortelyzin Randomized Investigation Compared With Alteplase) trial.

DISCUSSION

We presented the first large observational FORPI registry of outcomes following the nonimmunogenic staphylokinase treatment for AIS. The main idea of the article is that the safety and efficacy of the nonimmunogenic staphylokinase was shown in a wide range of patients, >100× greater than that in the FRIDA randomized clinical trial in 300 medical centers throughout Russia.

It should be noted that several significant differences in the baseline characteristics between the FORPI registry and the FRIDA trial were identified. Patients in the FORPI registry were older than in the FRIDA trial (P<0.001), and the number of patients older than 80 years was significantly higher (16% versus 3%; P<0.001), which could have negatively affected the safety outcomes. In contrast, in the FORPI registry, there were fewer patients with hypertension, myocardial infarction, atrial fibrillation, and chronic heart failure than in the FRIDA trial (P<0.001). In the FORPI registry, the number of patients with thrombolysis performed 0 to 3 hours from symptom onset was significantly higher than that in the FRIDA trial, and the median of the symptom onset to treatment time was shorter (P<0.001). These factors may positively affect the safety and efficacy outcomes.

Significant differences in the efficacy outcomes, such as mRS median on discharge and on day 90, as well as the NIHSS score 24 hours after thrombolysis and on discharge, and the Barthel index on discharge in the FORPI registry, were found in favor of the FRIDA trial. However, there were no differences in the safety outcomes, such as sICH rate and all-cause mortality on day 90. Taken together, the results of the FORPI registry suggest the desirable safety and efficacy profile of the nonimmunogenic staphylokinase in routine clinical practice.

Several large observational prospective registries of AIS thrombolytic therapy have been previously reported.[20–22] Despite the fact that different populations were treated with different therapeutic protocols, a few parameters that can be clearly defined were selected for analysis. The main baseline characteristics, such as median age, onset to treatment time, and NIHSS score of the patients included in the FORPI registry, were similar to the SITS-MOST and SITS-ISTR registries (Table 4).[20,21] However, in SITS-MOST and SITS-ISTR registries, patients up to 80 years old were only included, while in the FORPI registry, there were 16% (2866/17636) of elderly patients over 80 years old. In the control group of the Global COVID-19 Stroke Registry median of NIHSS was twice less that of the FORPI

Table 3. Serious Adverse Events

	Nonimmunogenic staphylokinase		
	FORPI registry (n=17 636)	FRIDA trial (n=168)	*P* value
All serious adverse events on day 90	5020	55	…
All-cause mortality on day 90	1588 (9%)	17 (10%)	0.588
Any ICH	2839 (16%)	31 (18%)	0.399
sICH (ECASS III)	356 (2%)	5 (3%)	0.397
Major bleedings (BARC 3 and 5 type)	27 (0%)	0 (0%)	0.99
Blood transfusion	16 (0%)	0 (0%)	0.99
Acute myocardial infarction	63 (1%)	1 (1%)	0.46
Pulmonary embolism	131 (1%)	1 (1%)	0.99

BARC indicates Bleeding Academic Research Consortium; ECASS III, European Cooperative Acute Stroke Study III; FORPI, Fortelyzin Population Investigation; FRIDA, Fortelyzin Randomized Investigation Compared With Alteplase; ICH, intracranial hemorrhage; and sICH, symptomatic intracranial hemorrhage

Table 4. Key Parameters of the FORPI, SITS-MOST, SITS-ISTR, and Global COVID-19 Stroke Registries

	FORPI	SITS-MOST	SITS-ISTR		Global COVID-19 Stroke Registry, control group
			Within 3 h	3–4.5 h	
Number of patients	17 636	6483	11 865	664	5519
Age, y	68 (60–75)	68 (59–75)	68 (58–74)	65 (55–73)	72.2 (14.0)
Number of patients over 80 years	2866 (16%)	0	0	0	n/a
Onset to treatment time, h	2.4 (1.8–3.1)	2.3 (1.9–2.8)	2.3 (1.9–2.8)	3.3 (3.1–3.5)	2.2 (2.2)
NIHSS score	11 (8–16)	12 (8–17)	12 (8–17)	11 (7–16)	6 (4–11)
Patients with an mRS score of 0–2 on day 90	61% (60.5–61.9)	55% (53.5–56.0)	56% (55.3–57.2)	58% (53.8–62.2)	62% (60.2–62.8)
sICH (according to SITS-MOST definition)	2% (1.8–2.1)	2% (1.4–2.0)	2% (1.4–1.8)	2% (1.2–3.7)	n/a
All-cause mortality on day 90	9% (8.6–9.4)	11% (10.5–12.1)	12% (11.6–12.8)	13% (10.1–15.8)	13% (12.4–14.2)

Data are presented as mean (SD), n/N (%/95% CI), or median (IQR). FORPI indicates Fortelyzin Population Investigation; IQR, interquartile range; mRS, modified Rankin scale; n/a, non-applicable; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke—Monitoring Study.

registry (6 (4–11) versus 11 (8–16)); the number of patients over 80 years old is unknown.[22]

The sICH level, according to the SITS-MOST definition in the FORPI registry, was similar to the SITS-MOST and SITS-ISTR registries. All-cause mortality on day 90 was comparable between all registries. The number of patients with functional independence (mRS score, 0–2) in FORPI was also similar to the above-mentioned registries (Table 4).

The use of an internet-based data FORPI registry ensured a high degree of compliance in data collection and completion. Data entries were fully completed in 19 227 (83%) of cases, including follow-up data on day 90. The difficulty with a treatment registry is to ascertain that all patients treated have been included in the data set and that no biased reporting has occurred. Independence auditing at least 10% of the centers' data in the FORPI registry did not reveal any indication of biased reporting.

The FORPI registry was created to measure the safety and efficacy of thrombolytic therapy with the nonimmunogenic staphylokinase in routine clinical practice. The obtained results showed low levels of sICH and all-cause mortality on day 90, which should encourage the wider usage of thrombolytic therapy with the nonimmunogenic staphylokinase for suitable patients.

Actually, alteplase and the nonimmunogenic staphylokinase are registered in Russia for AIS thrombolytic therapy. A 5 mg vial of the nonimmunogenic staphylokinase costs 175 USD (fixed price established by order of the Ministry of Health of the Russian Federation), and overall, per-patient cost (10 mg) is 350 USD. At the same time, a 50 mg vial of alteplase costs 255 USD, per-patient cost is 510 USD. Thus, treatment with the nonimmunogenic staphylokinase is 45% less than with alteplase and helps to save 160 USD per patient. Taking into account the safety and efficacy of the nonimmunogenic staphylokinase, it might be generalizable to countries other than Russia.

An important aspect of the FORPI registry was the monitoring of treatment safety by clinical centers without substantial previous experience of AIS thrombolytic therapy with the nonimmunogenic staphylokinase. Lyden et al[23] have previously commented on the uncertainty shown by less experienced practitioners of thrombolysis about incorporating the technique into their routine practice.

The limitations of the present study need to be addressed. The FORPI registry does not capture all district stroke units in Russia treating patients with AIS with the nonimmunogenic staphylokinase. Investigators did not collect the time elapsed from hospital admission to the thrombolytic administration (door-to-needle time). It should be noted that there may be a potential risk of selection bias given that data for all potentially eligible patients treated with the nonimmunogenic staphylokinase are not provided from participating centers. The outcomes in the FORPI registry are self-reported, and this may introduce sources of bias. 15% of clinical report forms in the FORPI registry were incomplete; however, the sample size of 17 636 patients is enough for statistical analysis. The authors focused on fully completed forms to improve the accuracy and reliability of the study results and suggested that more careful monitoring of clinical report form completion in the future is necessary to minimize data loss. Finally, given the limited availability of endovascular reperfusion therapies, we did not report separate outcomes in patients treated with bridging therapy in the presented analysis, which will be done soon.

ARTICLE INFORMATION

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Author Contributions

Drs Shamalov, Martynov, Chefranova, and Gusev contributed to conceptualization. Drs Shamalov, Martynov, and Gusev contributed to writing—original draft and writing—review and editing. Drs Yarovaya and Kutsenko contributed to the formal analysis. Drs Semenov, Ivanov, Semenov, and Markin contributed to project administration. All authors have read and commented on the first draft of this article with regard to interpretation of the data and editing, and have seen and approved the final version and revisions.

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Disclosures

Dr Shamalov participated in clinical trials by Bayer, Sanofi, Ever Neuro Pharm, AstraZeneca, and Pharmasoft and has received lecture fees from Sanofi, Ever Neuro Pharm, AstraZeneca, Pharmasoft, Nutricia, Boehringer Ingelheim, Generium, Geropharm, Euroservis, and Pfizer. Drs Gusev, Martynov, Semenov, Semenov, and Markin declare a patent issued for a method for the treatment of ischemic stroke. Drs Semenov, Ivanov, Semenov, and Markin are employees of SuperGene. The other authors report no conflicts.

Supplemental Material

Table S1

APPENDIX

FORPI study group

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