SUMMARY INFORMATION ON INTERIM RESULTS OF PHASE III CLINICAL STUDY OF CORONAVIR

Clinical study "Randomized open-label multicenter parallel-group study of efficacy and safety of CORONAVIR vs. conventional therapy in subjects with mild and moderate coronavirus infection (SARS-CoV-2/COVID-19)" was planned to investigate efficacy and safety of CORONAVIR (INN: favipiravir) 200 mg film-coated tablets (internal code - TL-FVP-t) in subjects with COVID-19 coronavirus infection in outpatient and hospital cohorts vs. standard etiotropic therapy.

Authorization of the Ministry of Health of Russia for this clinical study (No. 201) was obtained on May 20, 2020. Currently, the recruitment to the study is completed; a total of 168 subjects were randomized in this the study, most of them being outpatient subjects with mild to moderate COVID-19 coronavirus infection.

The data obtained for ITT (Intent-to-Treat) population were analyzed in interim analysis; the efficacy and safety of the study treatment within 14-days period was evaluated. The ITT population includes 60 outpatient subjects (40 patients in CORONAVIR group and 20 patients in control group). The patients in the control group received standard therapy.

The main inclusion criteria were a new onset of mild or moderate COVID-19 coronavirus infection confirmed by positive PCR test of oro-/nasopharyngeal swab for SARS-CoV-2 virus. Disease duration, from the first symptoms or sampling (such as oro-/nasopharyngeal swabs for PCR-based detection of SARS-CoV-2) to the randomization was no more than 6 days. The subjects who received any etiotropic therapy for treatment of COVID-19 infection, were not included in this study.

Overall, 4 subjects prematurely discontinued the participation in study due to withdrawal of informed consent (IC): 3 subjects in CORONAVIR group (before the first dose of the study drug) and 1 subject in the control group (on the next day after the first dose of the comparator drug). Mean age of the subjects in CORONAVIR group was 39.8 years, in the control group – 42.2 years. In CORONAVIR group, 57.5 % were females, in control group 40.0 % were females. The distribution of the patients in the treatment groups based on severity of the main disease was the same in both groups: mild disease in 45.0 % of subjects, moderate disease in 55.0 % of subjects.

The subjects in CORONAVIR group received CORONAVIR orally according to the following treatment regimen: on day 1 - 1800 mg (nine 200 mg tablets) with a 12-hour interval (i.e. twice daily), on days 2-10 at 800 mg (four 200 mg tablets) with a 12-hour interval (i.e. twice daily). The subjects randomized to CORONAVIR group received the recommended standard etiotropic therapy according to the current version of Temporary Methodological Guidelines of the Ministry of Health of Russian Federation on prevention, diagnosis and therapy of coronavirus infection (COVID-19) that was valid at the time of the study conduct (versions 6 and 7). The patients (n=60) included into interim analysis received only the combination of umifenovir, 200 mg capsules 4 times a day orally for 5 days + recombinant interferon alpha-2b, nasal drops 10,000 IU/mL, 3 drops into each nasal passage 5 times a day for 5 days. Also, in addition to the study drug and conventional etiotropic therapy the subjects in both groups received the concomitant therapy at the investigator's decision and based on the subject's condition: palliative treatment, curative treatment and antibacterial therapy, in accordance with the Guidelines of the Ministry of Health of Russian Federation that was mentioned above.

Efficacy of CORONAVIR

Efficacy was evaluated based on the data on combined primary endpoint including the time to clinical improvement (at least 1-point reduction in Clinical Improvement Score assessed using

WHO Ordinal Scale) and time required to reach the undetectable viral load of SARS-CoV-2. The viral load was assessed by 2 consecutive PCR tests for swabs obtained with at least 24-hours interval.

Analysis of efficacy (in ITT population) demonstrated the statistically significant superiority of 3 days based on time to clinical improvement for CORONAVIR vs. standard therapy. Mean time to clinical improvement assessed by WHO Ordinal Scale for Clinical Improvement score was 6.95 (4.55) days in CORONAVIR group and 10.4 (5.0) days in the control group, respectively. This difference between the treatment groups was statistically significant (see Fig. 1).

Mean time to reduction in viral load to undetectable level was 4.51 (2.89) days in CORONAVIR group and 5.53 (3.42) days in control group, respectively. The difference in time to undetectable viral load is about 1 day.

Therefore, based on the analysis of primary endpoints, faster recovery of the patients in CORONAVIR group vs. standard therapy was obvious: the reduction in viral load to undetectable level occurred 1 day earlier and significant clinical improvement was achieved 3 days earlier (average values). In CORONAVIR group, the time to undetectable viral load was 4 days; this result is consistent with the literature data (Cai Q. et al., 2020).

Table 1. Summary data on primary efficacy endpoints (mean, SD) (n=60).

Parameter	**Group 1: CORONAVIR (n = 40)**	**Group 2: Standard therapy (n = 20)**	**p-value**
Time to clinical improvement according to WHO scale (days)	**6.95 (4.55)**	**10.4 (5.0)**	**0.016***
Time to reduction in viral load of SARS-CoV-2 to undetectable level (days)	4.51 (2.89)	5.53 (3.42)	0.278
Note: * the difference is statistically significant			

Among the secondary endpoints, the special attention should be paid to proportion of subjects with clinical improvement according to WHO Ordinal Scale for Clinical Improvement on study day 7 which was statistically higher in CORONAVIR group compared to the control group: 55.0 % and 20.0 %, respectively (p = 0.013) suggesting that more than half of the subjects who received CORONAVIR had better medical condition after one week of the study treatment.

The proportion of subjects reaching clinical improvement on study day 14 post-baseline is also an important parameter. In CORONAVIR group, the improvement was demonstrated in 77.5 % subjects (31 from 40 patents included into interim analysis) vs. 40 % in the control group (8 from 20). The difference in proportion of subjects with clinical improvement on days 7 and 14 were statistically significant (p=0.013 and p=0.009, respectively) and, therefore, were more prominent, as compared to day 7. These differences are presented in Fig. 2.

Figure 1. Kaplan-Meier curves: clinical improvement vs. time

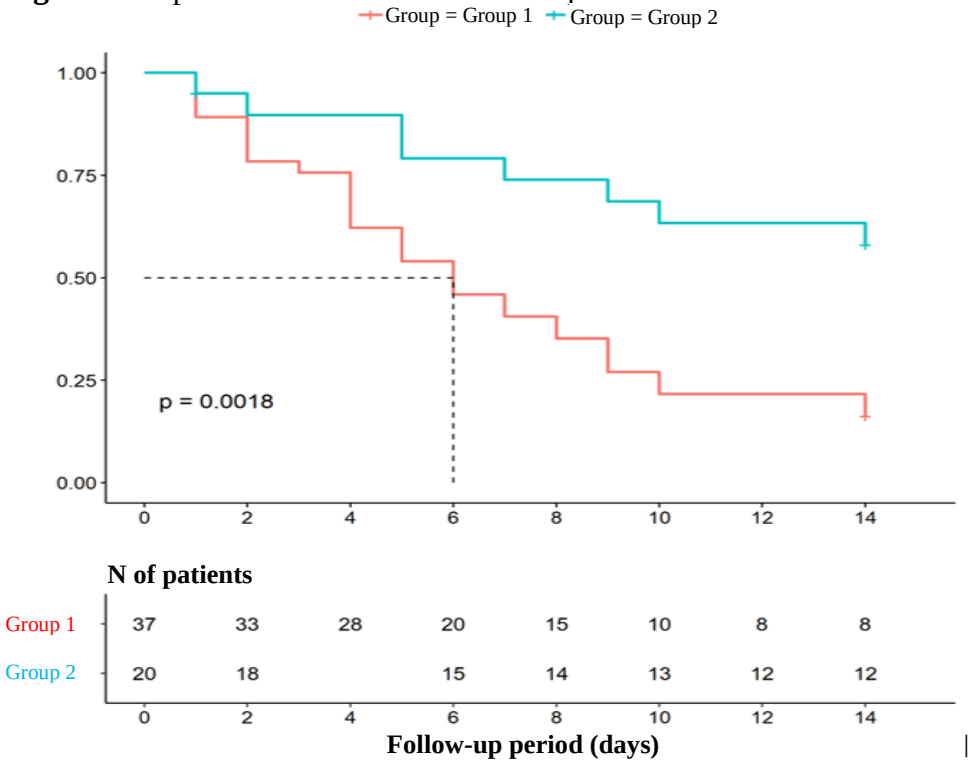
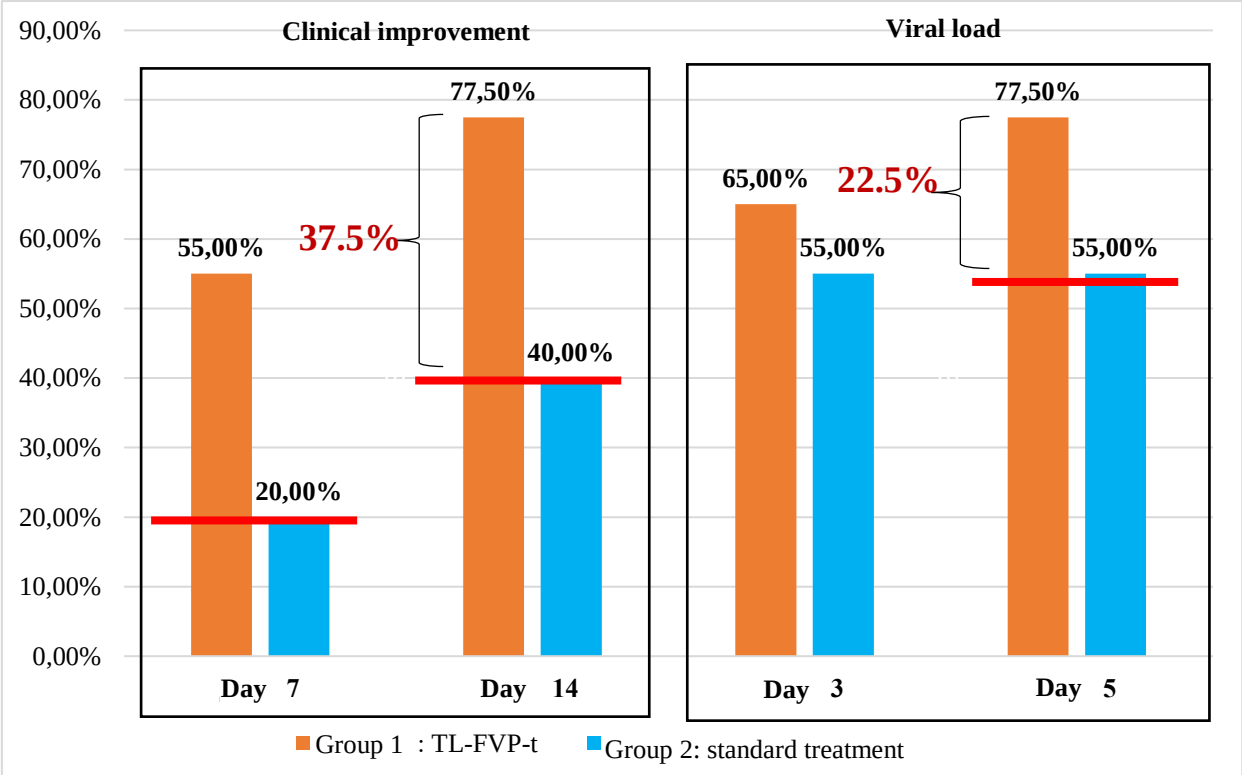


Figure 2. Proportions of subjects (%) with the improvement based on WHO Ordinal Scale for Clinical Improvement and reduction in viral load to undetectable level (n = 60).



TL-FLP-t means CORONAVIR

Analysis of these changes by days (study days 3, 5, 7 and 10) demonstrated that the most prominent differences in proportion of the subjects with undetectable viral load were observed on study days 3 and 5. On day 3, the undetectable viral load was achieved in 65 % (26 out of 40) subjects in CORONAVIR group and 55 % (11 out of 20) in control group, on day 5 in 77.5 % (31 out of 40) subjects in CORONAVIR group and 75 % (15 out of 20) in control group, while starting from day 7 the difference was mitigated, so that by day 10 the proportions of subjects with undetectable viral load were similar in both groups: 90 % (36 out of 40) subjects in CORONAVIR group and 90 % (18 out of 20) in the control group. No significant differences between the groups in proportion of subjects with undetectable viral load at the specified time points were observed; this can be explained by small sample size. However, obvious differences on day 5 demonstrate that the treatment with CORONAVIR allows to achieve undetectable viral load as soon as by day 5 in most subjects (77.5 %) and, therefore, prevents further propagation of the virus.

Table 2. Summary data on secondary efficacy endpoints available at the time of interim analysis (n=60).

Parameter	Group 1: CORONAVIR (N = 40)	Group 2: standard therapy (N = 20)	p-value
Proportion of subjects with clinical improvement on day 7	**22 (55.0 %)**	**4 (20.0 %)**	**0.013***
Proportion of subjects with undetectable viral load on day 5	31 (77.5 %)	11 (55.0 %)	0.134
Proportion of subjects with undetectable viral load on day 7	31 (77.5 %)	15 (75.0 %)	1.000
Proportion of subjects with lung recovery based on CT findings on day 14	8 (20.0 %)	3 (15.0 %)	0.736
Note: * statistically significant difference			

CT assessment demonstrated that recovery (with/without residual changes) on day 14 occurred in 20.0 % subjects in CORONAVIR group and in 15.0 % subjects in control group; furthermore, in 3 subjects (7.5 %) from CORONAVIR group, the recovery without any residual changes was observed; there were no such cases in the control group. Noteworthy, CT data showed that on day 5, the progression of the disease was less frequent in CORONAVIR group: 20.0 % vs. 30.0 % in the control group; however, this difference was not statistically significant.

There were no cases of hospitalization of outpatient subjects within 14 days of treatment in CORONAVIR group, while in the control group 10 % subjects (2 out of 20) were hospitalized; however, this difference was not statistically significant.

There were no clinical data for evaluation of the exploratory endpoints, such as the rate of transfer to ICU, rate of mechanical ventilation or number of deaths.

Therefore, the interim analysis demonstrated statistically significant superiority of CORONAVIR vs. standard therapy, assessed by clinical improvement. However, the decisive conclusion on superiority based on viral load data still cannot be made; this can be explained by the small sample size of population used in the interim analysis. More prominent difference between the treatment groups in proportion of patients with undetectable viral load is expected to be seen in final analysis. In this case, statistically significant superiority of CORONAVIR over the standard therapy will be additionally confirmed using virological data. Noteworthy, the superiority of CORONAVIR over conventional therapy was also observed for the other parameters .

Therefore, statistically significant superiority in terms of proportion of subjects with clinical improvement on day 7 was demonstrated in this study (despite the small sample size).

Safety of CORONAVIR

According to the literature data, the risk of CORONAVIR (favipiravir) use is predominantly associated with the adverse drug reactions that were already reported in clinical studies of the original drug, favipiravir, including the following: blood and lymphatic system disorders (reduced neutrophil and lymphocyte count), risk of skin rash, increased uric acid and triglyceride levels; gastrointestinal disorders (diarrhea, nausea, abdominal pain), hepatobiliary disorders (predominantly increased blood AST and ALT, γ-GTP, AP and bilirubin); increased creatine kinase level, hematuria and urine discoloration (see table 3).

Table 3. Adverse reactions based on the data provided in Global Data Sheet for Avigan, at November 2017.[1]

System organ class	Incidence		
	>1 %	0.5-<1 %	<0.5 %
Blood and lymphatic system disorders	Neutrophil count decreased Lymphocytes count decreased		Lymphocytes, monocytes count increased Reticulocytes count decreased
Immune system disorders		Rash	Eczema, pruritus
Metabolism and nutrition disorders	Increased blood uric acid level increased triglycerides level	Glucosuria	Hypokalemia
Nervous system disorders			Dizziness
Eye disorders			Blurred vision, eye pain
Respiratory, thoracic and mediastinal disorders			Asthma, sore throat, rhinitis, nasopharyngitis
Gastrointestinal disorders	Diarrhea	Nausea, vomiting, abdominal pain.	Abdominal discomfort, duodenal ulcer, hematochezia, gastritis
Hepatobiliary disorders	AST increased ALT increased γ-GTP increased		Blood alkaline phoshatase and bilirubin increased
Miscellaneous			Creatine kinase increased, hematuria, Urine discoloration

The most common adverse effects of CORONAVIR (favipiravir) in the published studies of the original drug were: diarrhea, signs of hepatic impairment including increased hepatic enzyme levels, reduced blood neutrophil count and increased blood uric acid. All adverse events

[1] [Taisho Toyama Pharmaceutical Co., Ltd. Avigan® (favipiravir) tablets prescribing information [English translation]. Tokyo, Japan; 2017 Nov. Accessed 2020 Apr 14. Available at: https:// www.cdc.gov.tw/File/Get/ht8jUiB_MI-aKnlwstwzvw

were moderate, did not lead to early treatment discontinuation and resolved rapidly after discontinuation of the treatment.

In a study of favipiravir (1600 mg twice a day on day 1 and 600 mg on days 2-14) for treatment of coronavirus infection (35 subjects), adverse drug reactions were identified in 11.43 % (4 subjects); it was markedly lower than 55,56 % (25 subjects) in the comparator (lopinavir) group. Two subjects had diarrhea, one developed hepatic effects and another one had the lack of appetite. All adverse events were mild (Q. Cai, 2020).

In another comparative study of favipiravir vs. umifenovir, the increased blood uric acid level was observed in favipiravir group was more common, as compared to umifenovir group. Furthermore, the cases of increased liver enzyme levels, mental disorders and gastrointestinal disorders were reported in favipiravir and umifenovir groups, statistically significant differences were not observed. All these abnormalities resolved by the end of therapy, at the time of patient's discharge from hospital (Chang Chen, 2020).

Therefore, according to the clinical studies of favipiravir, the following adverse reactions can be expected: diarrhea, nausea, vomiting, dysgeusia, pruritus, rash, increased transaminase levels (ALT, AST, AP, GGT increased), increased C-reactive protein level, increased blood triglyceride levels, increased blood uric acid level, hyperuricemia, increased APTT, changes in neutrophil count, reduced urinary uric acid level.

According to nonclinical studies, potential risks of favipiravir include increased total bilirubin level, increased albumin level, increased blood sodium level, decreased potassium level, increased fibrinogen level, phototoxicity, hair discoloration and nail discoloration.

In this interim analysis, evaluation of safety was carried out on a population of 57 subjects (those who received at least one dose of study drug or standard therapy). This analysis demonstrated that CORONAVIR has favorable safety and tolerability profile consistent with the literature data. As described in the literature, the most common adverse reactions to CORONAVIR were hyperuricemia (increased blood uric acid level) (62.2 % vs. 10.0 %, statistically significant difference vs. control group); this laboratory abnormality was not associated with any clinical manifestation. Statistically significant difference in frequency (vs. the control group) was observed only for this adverse event. Other favipiravir-specific AEs, such as nausea, diarrhea, abdominal pain, increased ALT and AST were also more common in favipiravir group; however, statistically significant differences vs. control group were not observed. All adverse events were mild; all AEs resolved during the follow-up period without sequelae.

Throughout the study, both the study drug, CORONAVIR, and the standard therapy were well tolerated. A total of 41 AEs have been reported during the study. Generally, AEs were recorded in most subjects in both groups: 78.4 % subjects in CORONAVIR group and in 60.0 % subjects in control group. Despite the notable difference in total frequency of AEs, this difference was not statistically significant ($p=0.216$) and was explained mainly by the high number of hyperuricemia episodes in CORONAVIR group. This result matches to the expectations.

All AEs were mild (grade 1 acc. to CTCAE 5.0) except for one case of grade 3 wrist fracture (grade 3; SAE with hospitalization as the criterion of seriousness), which, in the opinion of the Investigator was not related to the study drug. Most AEs were self-limiting and resolved without any sequelae based on the follow-up on day 14.

There were no early withdrawals or discontinuations of the study treatment due to adverse events. No deaths were recorded during the study.

The data on frequency of the AEs described above are consistent with the safety profile of favipiravir found in the scientific literature.

Table 4. Summary table of AE incidence by groups (n=57).

Adverse event	Group 1: CORONAVIR (N = 37)	Group 2: control group (N = 20)	p[1] value
Metabolism and nutrition disorders			
Hyperuricemia	**23 (62.2 %)**	**2 (10.0 %)**	**0.000***
Hyperglycemia	5 (13.5 %)	4 (20.0 %)	0.705
Hepatobiliary disorders			
Increased ALT	8 (21.6 %)	4 (20.0 %)	1.000
Increased AST	6 (16.2 %)	2 (10.0 %)	0.699
Hyperbilirubinemia	1 (2.7 %)	2 (10.0 %)	0.279
LDH increased	1 (2.7 %)	0 (0.0 %)	1.000
Gastrointestinal disorders			
Diarrhea	7 (18.9 %)	3 (15.0 %)	1.000
Nausea	2 (5.4 %)	0 (0.0 %)	0.536
Epigastric pain	2 (5.4 %)	0 (0.0 %)	0.536
Investigations			
Increased creatine kinase	5 (13.5 %)	3 (15.0 %)	1.000
Blood ferritin increased	1 (2.7 %)	0 (0.0 %)	1.000
Skin and subcutaneous tissue disorders			
Skin rash	3 (8.1 %)	1 (5.0 %)	1.000
Foot sweating increased	1 (2.7 %)	0 (0.0 %)	1.000
Renal and urinary disorders			
Hematuria	1 (2.7 %)	0 (0.0 %)	1.000
Increased creatinine level	0 (0.0 %)	1 (5.0 %)	0.351
Proteinuria	0 (0.0 %)	1 (5.0 %)	0.351
Nervous system disorders			
Skin hyperesthesia	0 (0.0 %)	1 (5.0 %)	0.351
Headache	1 (2.7 %)	0 (0.0 %)	1.000
Hand weakness	1 (2.7 %)	0 (0.0 %)	1.000
Foot chill	1 (2.7 %)	0 (0.0 %)	1.000
Vascular disorders			
Exacerbation of chronic hemorrhoids	0 (0.0 %)	1 (5.0 %)	0.351
Infections and infestations			
Exacerbation of chronic sinusitis	0 (0.0 %)	1 (5.0 %)	0.351
Injury, poisoning and procedural complications			
Radius fracture	1 (2.7 %)	0 (0.0 %)	1.000

Note: 1 – p-value for group comparison was calculated using exact Fisher's test; * statistically significant difference.

Therefore, the results of interim analysis demonstrated that CORONAVIR has the statistically significant effect, assessed by the time to clinical improvement **in outpatient subjects with a new coronavirus infection and, therefore, is significantly more effective compared to the standard etiotropic therapy.** The values obtained in this study are similar to the literature data where the improvement on treatment day 7 has been achieved in more than 50 % of subjects (Chen C. et al., 2020). The data on time required for reduction in viral load to undetectable level (4 days) observed in CORONAVIR group are also consistent with corresponding literature data (Cai Q. et al., 2020). CORONAVIR also demonstrated the favorable safety profile. The study treatment was well tolerated in all subjects; the cases of study treatment discontinuation due to adverse events were not reported. The data obtained in the interim analysis are consistent with available results of COVID-19 studies. We expect that the final data analysis in this study will additionally confirm the high efficacy and safety of CORONAVIR in the treatment of COVID-19 in both outpatient and hospitalized patients.