Clinical trial results:
A randomized, double-blind, placebo-controlled, adaptive-design study to assess the safety and efficacy of daily 200 mg fluvoxamine as add-on therapy to standard of care in moderate severity COVID-19 patients

Summary

EudraCT number	2020-002299-11
Trial protocol	HU
Global end of trial date	31 May 2022

Results information

Result version number	v1 (current)
This version publication date	01 February 2023
First version publication date	01 February 2023
Summary attachment (see zip file)	SD-COVID19-01 - Final Report 2022-10-26 synopsis (SD-COVID19-01 - Final Report 2022-10-26 synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	SD-COVID19-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04718480
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SigmaDrugs Research Ltd.
Sponsor organisation address	Attila út 117. V. em. 4., Budapest, Hungary, 1012
Public contact	CEO, Andrea Fekete MD PhD, SigmaDrugs Research Ltd., 0036 309472333, andrea.fekete@sigmadrugs.com
Scientific contact	CEO, Andrea Fekete MD PhD, SigmaDrugs Research Ltd., 0036 309472333, andrea.fekete@sigmadrugs.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2022
Global end of trial reached?	Yes
Global end of trial date	31 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess efficacy of fluvoxamine administration in moderate SARS-CoV-2 infected patients on short term healing.

Protection of trial subjects:

Patient Information Sheets and Informed Consent Forms were used to confirm the subjects' informed consent to participate in the trial. After the subject has read the Information Sheet and received verbal information about the trial, participation in the study was confirmed by signing and dating the Informed Consent Form.
The Investigator (according to applicable regulatory requirements), or a medically qualified person designated by the Investigator, and under the Investigator's responsibility, informed fully the subject on all pertinent aspects of the clinical study, including the written information giving approval/favorable opinion by the Regulatory Authority / Ethics Committee, as appropriate. All participants were informed to the fullest extent possible about the study, in language and terms they were able to understand.
Prior to a subject's participation in the clinical study, the written Informed Consent Form and any other local applicable documents in accordance with local laws and regulations, have been signed, the name completed and personally dated by the subject, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form and Information Sheet were provided to the subject.
The Informed Consent Form used by the Investigator for obtaining the subject's informed consent were reviewed and approved by the Sponsor prior to submission to the Regulatory Authority / Ethics Committee, as appropriate, for approval / favorable opinion.

Background therapy:

All patients received a base therapy, as per standard of care – the actual proposed therapy of moderate and severe SARS-CoV-2 infected patients according to the „Magyar Koronavírus Kézikönyv" (Hungarian Coronavirus Handbook).

Evidence for comparator:

NA Placebo controlled study.

Actual start date of recruitment	27 November 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 66
Worldwide total number of subjects	66
EEA total number of subjects	66

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	50
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Hospitalized patients with confirmed SARS-CoV-2 infection by polymerase chain reaction (PCR) or known contact of confirmed case with syndrome consistent with coronavirus disease (COVID-19) with PCR pending were enrolled to the study. (Moderate or severe cases).
The recruitment took place in Hungary between November 2020 and January 2022

Pre-assignment

Screening details:

Screening period was up to 48 hours. Preferably, after diagnosing the COVID-19, treatment was to be started on the following day (D1).
A total of 90 patients were screened at 6 Hungarian study centers.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Double-blind, placebo controlled study.
Placebo tablets matched active ingredients in looks and packaging.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description:

Patients received fluvoxamin treatment in addition to standard-of-care.

Arm type	Experimental
Investigational medicinal product name	Fluvoxamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The following dosing schedule will be used during the study to ensure careful dose escalation, 54 days treatment at the proposed 200 mg dose-level and tapering-off.

- Day 1-2: 50 mg bedtime (2 days on this dose level)
- Day 3-4: 100 mg bedtime (2 days on this dose level)
- Day 5-6: 150 mg bedtime (2 days on this dose level)
- Day 7-60: 2 x 100 mg (BID: morning and bedtime) (54 days on this dose level)
- Day 61-65: 150 mg bedtime (5 days on this dose level)
- Day 66-70: 100 mg bedtime (5 days on this dose level)
- Day 71-74: 50 mg bedtime (4 days on this dose level)

Whenever stop of treatment is required earlier the above tapering-off schedule should be followed if possible to reduce withdrawal symptoms. If this is not possible the patient should be closely monitored during the withdrawal period.

Arm title	Placebo

Arm description:

The patients received placebo treatment matching the active arm.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

- Day 1-2: 50 mg bedtime (2 days on this dose level)
- Day 3-4: 100 mg bedtime (2 days on this dose level)
- Day 5-6: 150 mg bedtime (2 days on this dose level)
- Day 7-60: 2 x 100 mg (BID: morning and bedtime) (54 days on this dose level)
- Day 61-65: 150 mg bedtime (5 days on this dose level)
- Day 66-70: 100 mg bedtime (5 days on this dose level)
- Day 71-74: 50 mg bedtime (4 days on this dose level)

Number of subjects in period 1	Active	Placebo
Started	34	32
Completed	23	20
Not completed	11	12
Adverse event, serious fatal	-	1
Consent withdrawn by subject	9	5
Adverse event, non-fatal	1	3
Lost to follow-up	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Active
Reporting group description:	
Patients received fluvoxamin treatment in addition to standard-of-care.	
Reporting group title	Placebo
Reporting group description:	
The patients received placebo treatment matching the active arm.	

Reporting group values	Active	Placebo	Total
Number of subjects	34	32	66
Age categorical			
Units: Subjects			
Adults (18-64 years)	28	22	50
From 65-84 years	6	10	16
Age continuous			
Baseline age data			
Units: years			
arithmetic mean	51.3	55	
standard deviation	± 14.3	± 13.1	-
Gender categorical			
Units: Subjects			
Female	10	14	24
Male	24	18	42
COVID19 High rik			
Patients will be stratified based on one criteria: belonging to the group at high risk for COVID-19 (comorbidities of hypertension, diabetes mellitus, chronic cardiovascular or chronic respiratory diseases) or not.			
Units: Subjects			
High-risk	19	16	35
Not high-risk	15	16	31
Somker			
Strong smokers were excluded from the study at screening			
Units: Subjects			
Smoker	3	2	5
Non-smoker	31	30	61

End points

End points reporting groups

Reporting group title	Active
Reporting group description:	
Patients received fluvoxamin treatment in addition to standard-of-care.	
Reporting group title	Placebo
Reporting group description:	
The patients received placebo treatment matching the active arm.	

Primary: Time to achieve a score of 0-2 WHO

End point title	Time to achieve a score of 0-2 WHO
End point description:	
Time to achieve a score of 0-2 (ambulatory state) on the WHO Ordinal Scale for Clinical Improvement This is a secondary enpoint, there were no primary endpoints specified for the trial, endpoint type was added to allow reporting.	
End point type	Primary
End point timeframe:	
D1-D75	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	27		
Units: days				
arithmetic mean (inter-quartile range (Q1-Q3))	10.5 (6 to 13)	13.6 (8 to 20)		

Statistical analyses

Statistical analysis title	Logrank
Statistical analysis description:	
Time to recovery (days) was assessed using Kaplan-Meyer methods. Median time to recovery in treatment groups were compared by log-rank and Wilcoxon tests. Cox regression model was applied to investigate possible significant factors influencing the time to recovery. Belonging to the high-risk group was included in the Cox regression model as independent factors. The model indicated no significant factors for the endpoint.	

Comparison groups	Active v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.032
Method	Logrank

Confidence interval	
sides	2-sided
Variability estimate	Standard deviation
Dispersion value	0.032

Statistical analysis title	Wilcoxon

Statistical analysis description:

Time to recovery (days) was assessed using Kaplan-Meyer methods. Median time to recovery in treatment groups were compared by log-rank and Wilcoxon tests.
Cox regression model was applied to investigate possible significant factors influencing the time to recovery. Belonging to the high-risk group was included in the Cox regression model as independent factors. The model indicated no significant factors for the endpoint.

Comparison groups	Active v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0352
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
sides	2-sided
Variability estimate	Standard deviation
Dispersion value	0.0352

Secondary: Time to clinical improvement

End point title	Time to clinical improvement

End point description:

Time to clinical recovery after treatment, defined as days from randomization (Day 1) to ANY THREE items of the following four:
1.) resolution from fever: oral or tympanic (core body) temperature ≤ 37.5 °C, axillary, forehead or wrist (surface body) temperature ≤ 37.0 °C for at least 48 hours without antipyretics
2.) return of respiratory rate to normal (≤ 20 / min)
3.) normalization of SpO2 (≥95% without oxygen support)
4.) cough remission (any reduction in cough-burden Visual Analogue Scale, compared to Day 1 baseline)

End point type	Secondary

End point timeframe:

D1-D75

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	30		
Units: days				
arithmetic mean (standard deviation)	2.1 (± 1.24)	2.3 (± 3.6)		

Statistical analyses

Statistical analysis title	Kaplan-Meyer method ITT

Statistical analysis description:

Time to recovery (days) was assessed using Kaplan-Meyer methods. Median time to recovery in treatment groups were compared by log-rank and Wilcoxon tests. Time to recovery was also characterized using descriptive statistical methods including the calculation of the 95% confidence intervals.

Comparison groups	Active v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8845
Method	Logrank

Statistical analysis title	Copy of Kaplan-Meyer method

Statistical analysis description:

Time to recovery (days) was assessed using Kaplan-Meyer methods. Median time to recovery in treatment groups were compared by log-rank and Wilcoxon tests. Time to recovery was also characterized using descriptive statistical methods including the calculation of the 95% confidence intervals.

Comparison groups	Active v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3577
Method	Wilcoxon (Mann-Whitney)

Secondary: Time course of cough burden

End point title	Time course of cough burden

End point description:

Assessed by a cough burden visual analogue scale (VAS) completed by the patient during study visits.

End point type	Secondary

End point timeframe:

D1-D75

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	17		
Units: VAS value				
arithmetic mean (inter-quartile range (Q1-Q3))	0.2 (0 to 0.2)	0.9 (0 to 1.3)		

Statistical analyses

Statistical analysis title	Mixed linear models

Statistical analysis description:

Variable was assessed using mixed linear models including the treatment, time, time*treatment interaction, belonging to the high-risk group as independent factors and baseline values as a covariate. The model was also re-fitted without factors that turned to be non-significant.

Comparison groups	Active v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.713
Method	Mixed models analysis

Notes:

[1] - VAS values decreased during the study in both treatment groups. It must be noted that baseline VAS values were higher in the Placebo group. The mixed model indicated significant difference between treatment groups even with the baseline VAS value included in the model.

Secondary: Time to negative COVID-19 nucleic acid results

End point title	Time to negative COVID-19 nucleic acid results

End point description:

PCR testing was performed at visit days and according to standard-of-care and not due to study considerations, therefore time to PCR negativity can be biased. In a few cases PCR negativity was never confirmed as it was no longer clinically indicated after the clinical signs have resolved.

End point type	Secondary

End point timeframe:

D1-D75

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: days				
arithmetic mean (standard deviation)	24.6 (± 23.27)	15.2 (± 15.89)		

Statistical analyses

Statistical analysis title	Logrank

Statistical analysis description:

The endpoint was assessed using Kaplan-Meyer methods. Median time to negative COVID-19 nucleid

acid were compared by log-rank and Wilcoxon tests. Endpoint was also characterized using descriptive statistical methods including the calculation of the 95% confidence intervals.
Cox regression model was applied to investigate possible significant factors influencing the time to recovery. Belonging to the high-risk group was included in the Cox regression model as independent factor.

Comparison groups	Active v Placebo
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1641
Method	Logrank

Statistical analysis title	Wilcoxon

Statistical analysis description:

The endpoint was assessed using Kaplan-Meyer methods. Median time to negative COVID-19 nucleid acid were compared by log-rank and Wilcoxon tests. Endpoint was also characterized using descriptive statistical methods including the calculation of the 95% confidence intervals.
Cox regression model was applied to investigate possible significant factors influencing the time to recovery. Belonging to the high-risk group was included in the Cox regression model as independent factor.

Comparison groups	Active v Placebo
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0946
Method	Wilcoxon (Mann-Whitney)

Secondary: Rate of patients with native chest CT recovery

End point title	Rate of patients with native chest CT recovery

End point description:

Rate of patients with native chest CT recovery from the acute stage of COVID-19 by Day 45 visit

End point type	Secondary

End point timeframe:

D45

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	21		
Units: patients				
native chest CT recovery	14	12		
No native chest CT recovery	10	9		

Statistical analyses

Statistical analysis title	Fisher’s exact test

Statistical analysis description:

Rates were compared by two-sample chi-square tests. Number of cases and ratios by treatment groups were also calculated together with the 95% Clopper-Pearson confidence intervals.

Comparison groups	Active v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Rate of patients requiring oxygen supplementation

End point title	Rate of patients requiring oxygen supplementation

End point description:

Rate of patients requiring oxygen supplementation.
Those patients who required oxygen supplementation during the study; required oxygen supplementation at baseline already.

End point type	Secondary

End point timeframe:

D1-D75

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	32		
Units: patients				
Patient requiring O2 supplementation	30	30		
Patient not requiring O2 supplementation	4	2		

Statistical analyses

Statistical analysis title	Fisher’s exact test

Statistical analysis description:

Rates were compared by two-sample chi-square tests. Number of cases and ratios by treatment groups were also calculated together with the 95% Clopper-Pearson confidence intervals.

Comparison groups	Active v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6733
Method	Fisher exact

Secondary: Long-term efficacy of fluvoxamine in preventing pulmonary pathology (fibrosis)

End point title	Long-term efficacy of fluvoxamine in preventing pulmonary pathology (fibrosis)

End point description:

Long-term efficacy of fluvoxamine in preventing pulmonary pathology (fibrosis), as monitored by native chest CT - Presence / quantification (e.g. percentage) / absence of:
1.) Reticular abnormality,
2.) Traction bronchiectasis and bronchiolectasias,
3.) Honeycombing.

End point type	Secondary

End point timeframe:

6 Months

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	20		
Units: Patients				
Pulmonary fibrosis present	6	6		
No pulmonary fibrosis detected	19	14		

Statistical analyses

Statistical analysis title	LTP generalized linear model

Statistical analysis description:

Rate was analysed using generalized linear models including treatment, belonging to the high risk group as fix factors. Only presence of pulmonary fibrosis was analysed this way as for the other parameters the model did not converge.

Comparison groups	Active v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3617
Method	Generelised linear model

Secondary: Rate of patients treated with antiviral and immunmodulant therapy or reconvalescent plasma against COVID-19 disease

End point title	Rate of patients treated with antiviral and immunmodulant therapy or reconvalescent plasma against COVID-19 disease

End point description:

Rate of patients treated with antiviral and immunmodulant therapy or reconvalescent plasma against COVID-19 disease

End point type	Secondary

End point timeframe:

D1-D75

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	32		
Units: patients				
Antiviral therapy Yes	30	28		
Antiviral therapy No	4	4		
Immunmodulant therapy Yes	3	2		
Immunmodulant therapy No	31	30		
Reconvalescent plasma Yes	0	1		
Reconvalescent plasma No	34	31		

Statistical analyses

Statistical analysis title	ITT Antiviral Fisher's test

Statistical analysis description:

Rates was compared by two-sample chi-square tests. Number of cases and ratios by treatment groups were also calculated together with the 95% Clopper-Pearson confidence intervals. General linear models were not fitted (with logit link) as only 1 patient received reconvalescent plasma therapy, 5 patients received immunmodulant therapy and almost all (58 of 67 patients) received antiviral therapy.

Comparison groups	Active v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact

Statistical analysis title	ITT Immunomdulant Fisher's test

Statistical analysis description:

Rates was compared by two-sample chi-square tests. Number of cases and ratios by treatment groups were also calculated together with the 95% Clopper-Pearson confidence intervals. General linear models were not fitted (with logit link) as only 1 patient received reconvalescent plasma therapy, 5 patients received immunmodulant therapy and almost all (58 of 67 patients) received antiviral therapy.

Comparison groups	Active v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact

Statistical analysis title	ITT Reconvlescent plasma Fisher's test

Statistical analysis description:

Rates was compared by two-sample chi-square tests. Number of cases and ratios by treatment groups

were also calculated together with the 95% Clopper-Pearson confidence intervals. General linear models were not fitted (with logit link) as only 1 patient received reconvalescent plasma therapy, 5 patients received immunmodulant therapy and almost all (58 of 67 patients) received antiviral therapy.

Comparison groups	Active v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4848
Method	Fisher exact

Secondary: Time to achieve a WHO score of 0-1

End point title	Time to achieve a WHO score of 0-1

End point description:

Time to achieve a score of 0-1 (No limitation of activities) on the WHO Ordinal Scale for Clinical Improvement

End point type	Secondary

End point timeframe:

D1-D75

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	22		
Units: days				
arithmetic mean (inter-quartile range (Q1-Q3))	18.4 (13 to 22)	23.1 (14 to 29)		

Statistical analyses

Statistical analysis title	ITT WHO<=1 Logrank

Statistical analysis description:

Time to WHO score of 0-1 was assessed using Kaplan-Meyer methods. Median time to recovery in treatment groups were compared by log-rank and Wilcoxon tests. Time to recovery was also characterized using descriptive statistical methods including the calculation of the 95% confidence intervals.
Cox regression model was applied to investigate possible significant factors influencing the time to recovery. Belonging to the high-risk group was included in the Cox regression model as independent fac

Comparison groups	Active v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.066
Method	Logrank

Statistical analysis title	ITT WHO<=1 Wilcoxon

Statistical analysis description:

Time to WHO score of 0-1 was assessed using Kaplan-Meyer methods. Median time to recovery in treatment groups were compared by log-rank and Wilcoxon tests. Time to recovery was also characterized using descriptive statistical methods including the calculation of the 95% confidence intervals.
Cox regression model was applied to investigate possible significant factors influencing the time to recovery. Belonging to the high-risk group was included in the Cox regression model as independent fac

Comparison groups	Active v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0393
Method	Wilcoxon (Mann-Whitney)

Secondary: Time to achieve a score of 0 WHO

End point title	Time to achieve a score of 0 WHO

End point description:

Time to achieve a score of 0 (Uninfected) on the WHO Ordinal Scale for Clinical Improvement

End point type	Secondary

End point timeframe:

D1-D75

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: days				
arithmetic mean (standard deviation)	37.4 (± 17.63)	44.5 (± 21.55)		

Statistical analyses

Statistical analysis title	ITT WHO=0 Logrank

Statistical analysis description:

Time to WHO=0 was assessed using Kaplan-Meyer methods. Median time to recovery in treatment groups were compared by log-rank and Wilcoxon tests. Time to recovery was also characterized using descriptive statistical methods including the calculation of the 95% confidence intervals.
Cox regression model was applied to investigate possible significant factors influencing the time to recovery. Belonging to the high-risk group was included in the Cox regression model as independent factor.

Comparison groups	Active v Placebo

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.577
Method	Logrank

Statistical analysis title	ITT WHO=0 Wilcoxon

Statistical analysis description:

Time to WHO=0 was assessed using Kaplan-Meyer methods. Median time to recovery in treatment groups were compared by log-rank and Wilcoxon tests. Time to recovery was also characterized using descriptive statistical methods including the calculation of the 95% confidence intervals.
Cox regression model was applied to investigate possible significant factors influencing the time to recovery. Belonging to the high-risk group was included in the Cox regression model as independent factor.

Comparison groups	Active v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5327
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in the total score of PHQ-9 questionnaire from baseline

End point title	Change in the total score of PHQ-9 questionnaire from baseline

End point description:

Endpoint was measured by Patient Health Questionnaire (PHQ-9)

End point type	Secondary

End point timeframe:

D1-D75

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: points				
arithmetic mean (standard deviation)	1.1 (± 1.65)	0.8 (± 1.51)		

Statistical analyses

Statistical analysis title	ITT applied mixed model

Statistical analysis description:

Change in the total score of PHQ-9 questionnaire from baseline.
Visit*treatment interaction was assessed.

Comparison groups	Active v Placebo

Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7467
Method	Mixed models analysis

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were reported from screening to end-of-study visit.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25

Reporting groups	
Reporting group title	Active
Reporting group description:	
Patients received fluvoxamin treatment in addition to standard-of-care.	
Reporting group title	Placebo
Reporting group description:	
The patients received placebo treatment matching the active arm.	

Serious adverse events	Active	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 34 (8.82%)	3 / 32 (9.38%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
cholecystolithiasis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatomegaly			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			

subjects affected / exposed	0 / 34 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 34 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 34 (2.94%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Active	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 34 (88.24%)	29 / 32 (90.63%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 34 (11.76%)	7 / 32 (21.88%)	
occurrences (all)	4	7	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 34 (8.82%)	1 / 32 (3.13%)	
occurrences (all)	3	1	
Chest pain			
subjects affected / exposed	3 / 34 (8.82%)	0 / 32 (0.00%)	
occurrences (all)	3	0	
Fatigue			

subjects affected / exposed	5 / 34 (14.71%)	3 / 32 (9.38%)	
occurrences (all)	5	3	
Oedema peripheral			
subjects affected / exposed	2 / 34 (5.88%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 34 (5.88%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Dyspnoea			
subjects affected / exposed	1 / 34 (2.94%)	3 / 32 (9.38%)	
occurrences (all)	1	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 34 (8.82%)	1 / 32 (3.13%)	
occurrences (all)	3	1	
Insomnia			
subjects affected / exposed	4 / 34 (11.76%)	1 / 32 (3.13%)	
occurrences (all)	4	1	
Investigations			
Blood glucose increased			
subjects affected / exposed	2 / 34 (5.88%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Electrocardiogram repolarisation abnormality			
subjects affected / exposed	2 / 34 (5.88%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 34 (2.94%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 34 (8.82%)	3 / 32 (9.38%)	
occurrences (all)	3	3	
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 34 (5.88%)	2 / 32 (6.25%)	
occurrences (all)	2	2	
Hypoaesthesia			
subjects affected / exposed	2 / 34 (5.88%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Tremor			
subjects affected / exposed	3 / 34 (8.82%)	1 / 32 (3.13%)	
occurrences (all)	3	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 34 (5.88%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 34 (5.88%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	0 / 34 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	2 / 34 (5.88%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	2 / 34 (5.88%)	3 / 32 (9.38%)	
occurrences (all)	2	3	
Night sweats			
subjects affected / exposed	2 / 34 (5.88%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Renal and urinary disorders			
Renal pain			
subjects affected / exposed	0 / 34 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	2 / 34 (5.88%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Back pain			
subjects affected / exposed	0 / 34 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 34 (2.94%)	4 / 32 (12.50%)	
occurrences (all)	1	4	
Clostridium difficile infection			
subjects affected / exposed	1 / 34 (2.94%)	3 / 32 (9.38%)	
occurrences (all)	1	3	
Nasopharyngitis			
subjects affected / exposed	2 / 34 (5.88%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Pneumonia			
subjects affected / exposed	1 / 34 (2.94%)	3 / 32 (9.38%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	3 / 34 (8.82%)	2 / 32 (6.25%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2021	◦ Amended inclusion-exclusion criteria: clarification regarding mild-moderate-severe COVID disease state as per Hungarian Coronavirus Handbook ◦ Malignancy exclusion criterion limited to the past 5 years ◦ Clarification of oxygen saturation, smoking, timing of first dose, start of AE collection period, CT imaging ◦ Age range: 18-80 years ◦ Implementation of flexible visit windows at Day 7, 14 and 21 visits ◦ Rationalization of temperature measurements ◦ Reduction of mandatory hospitalization period according to current standard of care ◦ Visit details for patients quarantined at home ◦ Determination of patient compliance ◦ Instruction of concurrent administration of fluvoxamin with benzodiazepins
02 November 2021	• Protocol v 4.0 implemented adaptive changes to the study based on the interim analysis, and also streamlined study flow to be in line with standard COVID care, based on study sites feedback ◦ Amended inclusion criteria to enrol severe but not critical state patients and to exlcude patients who undervent >10 days of COVID care previously ◦ Primary endpoint was reclassified as efficacy endpoint (SEC 00) ◦ New secondary endpoint of achievement of 1 or 0 score using WHO ordinal scale ◦ Rationalization of biomarkers: extension of biomarker follow-up to Day 30 and deleting IL-8 from the determinations ◦ Setting target patient number to 100

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported