Clinical trial results:
COUNTER-COVID - Oral imatinib to prevent pulmonary vascular leak in Covid19 – a randomized, double --blind, placebo controlled, clinical trial in patients with severe Covid19 disease'

Summary

EudraCT number	2020-001236-10
Trial protocol	NL BE
Global end of trial date	01 February 2021

Results information

Result version number	v1 (current)
This version publication date	22 April 2022
First version publication date	22 April 2022
Summary attachment (see zip file)	Publication 2 of EudraCT 2020–001236–10 in Lancet Respir Med 2021 (Long term outcomes Lancet Respir Med 2022.pdf) Publication of EudraCT 2020–001236–10 in Lancet Respir Med 2021 (Imatinib Lancet Respir Med 2021.pdf)

Trial information

Trial identification

Sponsor protocol code	CounterCOVID study

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	EU Clinical Trials Register : EudraCT 2020–001236–10, Netherlands Trial Register: NL8491

Notes:

Sponsors

Sponsor organisation name	Amsterdam UMC, location VUmc
Sponsor organisation address	De Boelelaan 1117, Amsterdam, Netherlands, 1081HV
Public contact	Jurjan Aman, Amsterdam UMC, +31 610738910, j.aman@amsterdamumc.nl
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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	05 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 February 2021
Global end of trial reached?	Yes
Global end of trial date	01 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test whether treatment with oral imatinib reduces disease burden and consumption of medical resources.

Protection of trial subjects:

All trial subjects underwent monitoring of clinical, biochemistry and ECG parameters.

Background therapy:

Dexamethasone, remdesivir (temporarily), oxygen suppletion

Evidence for comparator:

The comparator was the placebo group

Actual start date of recruitment	23 March 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 385
Worldwide total number of subjects	385
EEA total number of subjects	385

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)	203
From 65 to 84 years	170
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

Between March 31st 2020 and Jan 04th 2021, 805 patients were screened at 13 hospitals in the Netherlands (appendix p 2). Four hundred patients were randomised. Eleven patients withdrew consent before receiving the first gift of study medication. 2 patients left the study before receiving their first study dose, after being reallocated.

Pre-assignment

Screening details:

Patients eligible for inclusion were 18 years of age or older, were admitted to the hospital with proven SARS-CoV-2 infection (based on a reverse transcriptase PCR test), and required supplemental oxygen to maintain a peripheral oxygen saturation greater than 94%.

Period 1

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

Blinding implementation details:

Patients received oral imatinib (tablets of 400mg) or non-matching placebo distributed in sealed containers. Medical staff and investigators were not involved in dispensing of the study drug. Patients, medical staff and investigators were blinded for the intervention.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two placebo tablets one the first day, follow by one tablet each day for 9 days

Arm title	Imatinib

Arm description:

Imatinib mesylate, 400mg tablets, starting with loading dose of 800mg (Day 0), followed by 400mg once daily (Day 1-9).

Arm type	Experimental
Investigational medicinal product name	Imatinib mesylate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

800mg loading dose once (2 tablets of 400mg) followed by 400mg once daily for 9 days

Number of subjects in period 1	Placebo	Imatinib
Started	188	197
Completed	188	197

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Imatinib
Reporting group description:	
Imatinib mesylate, 400mg tablets, starting with loading dose of 800mg (Day 0), followed by 400mg once daily (Day 1-9).	

Reporting group values	Placebo	Imatinib	Total
Number of subjects	188	197	385
Age categorical			
In the placebo group 100 patiens were <= 65 years, 88 were >65 years In the imatinib group 103 patients were <= 65 years, 94 were >65 years			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	100	103	203
From 65-84 years	86	84	170
85 years and over	2	10	12
Age continuous			
Units: years			
median	64	64	
inter-quartile range (Q1-Q3)	55 to 74	57 to 73	-
Gender categorical			
Units: Subjects			
Female	70	51	121
Male	118	146	264
Current/former smoker			
Units: Subjects			
(former)smoker	76	77	153
non-smoker	112	120	232
Obesity (BMI>30)			
Units: Subjects			
BMI>30	83	53	136
BMI<30	105	144	249
Diabetes			
Units: Subjects			
Diabetes_yes	54	41	95
Diabetes_No	134	156	290
Cardiovascular disease			
Units: Subjects			
CVD_Yes	48	35	83

CVD_No	140	162	302
LMWH_initiated at admission Units: Subjects			
LMWH_yes	150	167	317
LMWH_no	38	30	68
oral anticoagulants initiated at baseline Units: Subjects			
OAC_yes	8	6	14
OAC_no	180	191	371
Antibiotics_initiated at admission Units: Subjects			
AB_yes	77	85	162
AB_no	111	112	223
Dexamethasone initiated at admission Units: Subjects			
Dexa_yes	133	143	276
Dexa_no	55	54	109
Remdesivir initiated at admission Units: Subjects			
Remdes_yes	40	40	80
Remdes_no	148	157	305
Hydroxychloroquine initiated at admission Units: Subjects			
HCQ_yes	17	15	32
HCQ_no	171	182	353
BMI Units: kg/m2			
median	29.7	27.5	
inter-quartile range (Q1-Q3)	25.6 to 32.9	25.3 to 31.1	-
Days from symptom onset Units: Days			
median	10	10	
inter-quartile range (Q1-Q3)	8 to 12	8 to 12	-
SpO2/FiO2 ratio_baseline Units: ratio			
median	323	321	
inter-quartile range (Q1-Q3)	238 to 377	265 to 380	-
Haemoglobin_baseline Units: g/dl			
median	13.7	13.5	
inter-quartile range (Q1-Q3)	12.6 to 14.7	12.6 to 14.7	-
CRP_baseline Units: mg/L			
median	95	102	
inter-quartile range (Q1-Q3)	45 to 149	47.8 to 157.5	-
NT-proBNP_baseline Units: ng/L			
median	132	147	
inter-quartile range (Q1-Q3)	50 to 352	49 to 411	-
LDH_baseline Units: U/L			

median	366	365	
inter-quartile range (Q1-Q3)	293 to 496	279 to 445	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Imatinib
Reporting group description:	
Imatinib mesylate, 400mg tablets, starting with loading dose of 800mg (Day 0), followed by 400mg once daily (Day 1-9).	

Primary: Liberation from oxygen and ventilation

End point title	Liberation from oxygen and ventilation
End point description:	
The primary outcome was the time to discontinuation of ventilation and supplemental oxygen for more than 48 consecutive hours, while being alive during a 28-day period after randomisation	
End point type	Primary
End point timeframe:	
28 days	

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	197		
Units: Subjects	143	160		

Attachments (see zip file)	All figures of first manuscript/Figuren manuscript.pptx

Statistical analyses

Statistical analysis title	Time to event analysis primary outcome
Statistical analysis description:	
The primary outcome was analysed using Kaplan-Meier curves to plot event rate over time; between group differences were expressed as a hazard ratio with 95% confidence intervals (CI) based on Cox regression analyses.	
Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.2

Secondary: Time to intubation

End point title	Time to intubation

End point description:

Time-to-event analysis for time-to-intubation

End point type	Secondary

End point timeframe:

28 days (Side note: the outcome is the same for the 90 day follow up period, since no patients were intubated after the 28 day follow up period)

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	197		
Units: Subjects				
Intubation_yes	26	30		
intubation_no	162	167		

Statistical analyses

Statistical analysis title	Kaplan Meier for intubation

Statistical analysis description:

The secondary outcomes mechanical ventilation was analysed using Kaplan-Meier curves to plot event rate over time; between group differences were expressed as a hazard ratio with 95% confidence intervals (CI) based on Cox regression analyses.

Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.8

Secondary: Mortality

End point title	Mortality

End point description:

End point type	Secondary

End point timeframe:

28 days

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	197		
Units: subjects				
Mortality_yes	27	15		
mortality_no	161	182		

Statistical analyses

Statistical analysis title	Kaplan Meier analysis for mortality

Statistical analysis description:

The secondary outcomes mortality was analysed using Kaplan-Meier curves to plot event rate over time; between group differences were expressed as a hazard ratio with 95% confidence intervals (CI) based on Cox regression analyses.

Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.95

Notes:

[1] - Uncorrected for baseline variable

Statistical analysis title	Copy of Kaplan Meier analysis for mortality

Statistical analysis description:

The secondary outcomes mortality was analysed using Kaplan-Meier curves to plot event rate over time; between group differences were expressed as a hazard ratio with 95% confidence intervals (CI) based on Cox regression analyses.

Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.068 [3]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.05

Notes:

[2] - Corrected for baseline imbalances (sex, obesity, diabetes, cardiovascular disease)

[3] - Corrected for baseline variables mentioned above

Secondary: Duration of oxygen supplementation

End point title	Duration of oxygen supplementation

End point description:

End point type	Secondary

End point timeframe:

28 days

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	197		
Units: Days				
median (inter-quartile range (Q1-Q3))	5 (3 to 11)	7 (3 to 12)		

Statistical analyses

Statistical analysis title	Duration of oxygen supplementation
Comparison groups	Imatinib v Placebo
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.23
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Notes:
[4] - Mann Whitney U test

Secondary: Duration of mechanical ventilation

End point title	Duration of mechanical ventilation

End point description:
Continuous variables were analysed using a Wilcoxon rank sum test.

End point type	Secondary

End point timeframe:
28-days

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	197		
Units: Days				
median (inter-quartile range (Q1-Q3))	12 (6 to 20)	7 (3 to 13)		

Statistical analyses

Statistical analysis title	Duration of mechanical ventilation

Statistical analysis description:
Continuous variables were analysed using a Wilcoxon rank sum test.

Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.008
Method	Wilcoxon (Mann-Whitney)

Notes:
[5] - Continuous variables were analysed using a Wilcoxon rank sum test, analysis was performed in the whole population.

Secondary: Duration of hospital admission

End point title	Duration of hospital admission

End point description:

End point type	Secondary

End point timeframe:
28 days

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	197		
Units: day				
median (inter-quartile range (Q1-Q3))	6 (3 to 11)	7 (4 to 11)		

Statistical analyses

Statistical analysis title	Median comparison - Mann Whitney U
Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %

Secondary: Duration of intensive care admission

End point title	Duration of intensive care admission
End point description:	
End point type	Secondary
End point timeframe: 28 days	

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	39		
Units: day				
median (inter-quartile range (Q1-Q3))	15 (7 to 21)	8 (5 to 13)		

Statistical analyses

Statistical analysis title	Median comparison - Mann Whitney U
Comparison groups	Placebo v Imatinib

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.025
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Post-hoc: Number of Ventilator Free Days

End point title	Number of Ventilator Free Days

End point description:

End point type	Post-hoc

End point timeframe:

28 days

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	39		
Units: Days				
median (inter-quartile range (Q1-Q3))	9 (0 to 23)	22 (14 to 26)		

Statistical analyses

Statistical analysis title	Median comparison - Mann Whitney U
Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	72
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.018
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)

Post-hoc: Mortality - Long term Follow up

End point title	Mortality - Long term Follow up

End point description:

End point type	Post-hoc

End point timeframe:
90 days

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	197		
Units: subjects	18	31		

Statistical analyses

Statistical analysis title	Cox regression - Hazard Ratio
Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	385
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.03 [6]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.94

Notes:

[6] - Adjusted for sex HR 0·50 (0·28, 0·90) p=0·021
Adjusted for obesity HR 0·47 (0·25, 0·89) p=0·020
Adjusted for diabetes HR 0·55 (0·31, 0·97) p=0·045
Adjusted for CVD HR 0·56 (0·31, 1·00) p=0·048
Adjusted for all the above HR 0·52 (0·28,0.99)p=0.045

Post-hoc: Liberation from oxygen and ventilation - Long term follow up

End point title	Liberation from oxygen and ventilation - Long term follow up

End point description:

End point type	Post-hoc

End point timeframe:
90 days

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	197		
Units: subjects	152	167		

Statistical analyses

Statistical analysis title	Cox regression - Hazard Ratio
Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	385
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.96
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.17

Post-hoc: Combined outcome: time to need for mechanical ventilation or death - Long term follow up

End point title	Combined outcome: time to need for mechanical ventilation or death - Long term follow up
End point description:	
End point type	Post-hoc
End point timeframe:	
90 days	

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	197		
Units: subjects	46	40		

Statistical analyses

Statistical analysis title	Cox regression - Hazard Ratio
Comparison groups	Placebo v Imatinib

Number of subjects included in analysis	385
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.25
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.19

Post-hoc: Duration of hospital admission - Long term follow up	
End point title	Duration of hospital admission - Long term follow up
End point description:	

End point type	Post-hoc
End point timeframe:	
90 days	

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	197		
Units: day				
median (inter-quartile range (Q1-Q3))	6.5 (3 to 11)	7 (4 to 11)		

Statistical analyses

Statistical analysis title	Median comparison - Mann Whitney U
Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	385
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.66
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Post-hoc: Duration of intensive care admission - Long term follow up

End point title	Duration of intensive care admission - Long term follow up

End point description:

End point type	Post-hoc

End point timeframe:

90 days

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	39		
Units: day				
median (inter-quartile range (Q1-Q3))	15 (7 to 21)	9 (5 to 15)		

Statistical analyses

Statistical analysis title	Median comparison - Mann Whitney U
Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	72
Analysis specification	Post-hoc
Analysis type	
P-value	= 0.098
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Post-hoc: Duration of mechanical ventilation - Long term follow up

End point title	Duration of mechanical ventilation - Long term follow up

End point description:

End point type	Post-hoc

End point timeframe:

90 days

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	30		
Units: day				
median (inter-quartile range (Q1-Q3))	12 (7 to 22)	7 (3 to 15)		

Statistical analyses

Statistical analysis title	Median comparison - Mann Whitney U
Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	56
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.026
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Post-hoc: Number of Ventilator Free Days - Long term follow up

End point title	Number of Ventilator Free Days - Long term follow up
End point description:	
End point type	Post-hoc
End point timeframe:	
90 days	

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	39		
Units: day				
median (inter-quartile range (Q1-Q3))	64 (0 to 84)	84 (54 to 88)		

Statistical analyses

Statistical analysis title	Median comparison - Mann Whitney U
Comparison groups	Placebo v Imatinib

Number of subjects included in analysis	72
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.036
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Post-hoc: Additional organ support free days - Long term follow up

End point title	Additional organ support free days - Long term follow up

End point description:

The number of additional organ support free days
was defined as the total number of days free from cardiovascular support, renal replacement therapy (RRT), and
extracorporeal mechanical oxygenation (ECMO). Patients that died before day 90 were assigned -1 additional
organ support free days.

End point type	Post-hoc

End point timeframe:

90 days

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	39		
Units: day				
median (inter-quartile range (Q1-Q3))	20 (-1 to 26)	24 (17 to 27)		

Statistical analyses

Statistical analysis title	Cox regression - Hazard Ratio
Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	72
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.11
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Post-hoc: WHO ordinal scale - Long term follow up

End point title	WHO ordinal scale - Long term follow up

End point description:

Category 1 indicates that the patient was not hospitalised, and received no oxygen supplementation; 2. was not hospitalised, but received supplemental oxygen; 3. was hospitalised, without the use of supplemental oxygen; 4. was hospitalised and received supplemental oxygen using a nasal cannula or mask ; 5. was hospitalised and received oxygen through non-invasive ventilation or high-flow devices; 6. was hospitalised and received invasive ventilation with no extra organ support ; 7. was hospitalised and received invasive ventilation plus additional organ support: vasopressors, renal replacement therapy (RRT), or extra corporal membrane oxygenation (ECMO); and 8. died.

End point type	Post-hoc

End point timeframe:

90 days

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	197		
Units: subjects				
the patient was not hospitalised, and received no	153	174		
was not hospitalised, but received supplemental ox	3	2		
was hospitalised, without the use of supplemental	0	0		
was hospitalised and received supplemental oxygen	0	1		
was hospitalised and received invasive ventilation	0	0		
invasive ventilation and additional organ support	0	0		
died	31	18		

Statistical analyses

Statistical analysis title	Linear mixed model

Statistical analysis description:

Adjusted for sex, diabetes, obesity (BMI > 30kg/m2), and cardiovascular disease.

Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	385
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.012 [7]
Method	Mixed models analysis
Parameter estimate	Estimate
Point estimate	-0.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	-0.11

Notes:

[7] - Through day 90 unadjusted HR -0·53 (-0·94, -0·11) p =0·014
Category at day 9 HR -0·54 (-0·99, -0·09) p= 0·018
Category at day 28 HR-0·52 (-0·97, -0·07) p = 0·023
Category at day 90 HR -0·51 (-0·96, -0·06) p = 0·025

Post-hoc: PaO2/FiO2

End point title	PaO2/FiO2

End point description:

End point type	Post-hoc

End point timeframe:

First 14 days after intubation

End point values	Placebo	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	30		
Units: mmHg				
number (not applicable)	26	30		

Statistical analyses

Statistical analysis title	Linear mixed model

Statistical analysis description:

Treatment with imatinib, time, and time*treatment were entered as fixed effects
Subject IDs were entered as random effect

Comparison groups	Placebo v Imatinib
Number of subjects included in analysis	56
Analysis specification	Post-hoc
Analysis type	superiority[8]
P-value	= 0.011
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	3.71

Notes:

[8] - Time*treatment estimate

Adverse events

Adverse events information

Timeframe for reporting adverse events:

28 days

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Imatinib

Reporting group description:

Imatinib mesylate, 400mg tablets, starting with loading dose of 800mg (Day 0), followed by 400mg once daily (Day 1-9).

Serious adverse events	Placebo	Imatinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 188 (32.98%)	56 / 197 (28.43%)	
number of deaths (all causes)	31	18	
number of deaths resulting from adverse events	31	18	
Vascular disorders			
Septic shock	Additional description: septic shock resulting in admission to the intensive care unit		
subjects affected / exposed	1 / 188 (0.53%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 188 (1.60%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Death	Additional description: Death from respiratory insufficiency		
subjects affected / exposed	31 / 188 (16.49%)	18 / 197 (9.14%)	
occurrences causally related to treatment / all	0 / 31	0 / 18	
deaths causally related to treatment / all	0 / 31	0 / 18	
Mechanical ventilation	Additional description: Transfer to the ICU because of mechanical ventilation due to respiratory insufficiency, no mortality (grade 4)		

subjects affected / exposed	20 / 188 (10.64%)	20 / 197 (10.15%)	
occurrences causally related to treatment / all	0 / 20	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intensive care	Additional description: transfer to the intensive care unit because of respiratory insufficiency. No intubation, no mortality		
subjects affected / exposed	4 / 188 (2.13%)	10 / 197 (5.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extracorporeal circulation	Additional description: ECMO because of respiratory insufficiency, no mortality		
subjects affected / exposed	0 / 188 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 188 (0.00%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 188 (0.53%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Placebo	Imatinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 188 (47.87%)	82 / 197 (41.62%)	
Investigations			
Liver function test abnormal	Additional description: increased blood ALT or AST grade 3 according to the CTCAE v5.0		
subjects affected / exposed	5 / 188 (2.66%)	6 / 197 (3.05%)	
occurrences (all)	5	6	
Lymphocyte count decreased	Additional description: grade 3 according to the CTCAE v5.0		
subjects affected / exposed	15 / 188 (7.98%)	20 / 197 (10.15%)	
occurrences (all)	15	20	
Vascular disorders			

thromboembolic event	Additional description: grade 3 according to the CTCAE v5.0		
subjects affected / exposed	14 / 188 (7.45%)	18 / 197 (9.14%)	
occurrences (all)	14	18	
Cardiac disorders			
prolonged QT corrected interval	Additional description: grade 3 according to the CTCAE v5.0		
subjects affected / exposed	14 / 188 (7.45%)	8 / 197 (4.06%)	
occurrences (all)	14	8	
Blood and lymphatic system disorders			
Anaemia	Additional description: Grade 3 according to the CTCAE v5.0		
subjects affected / exposed	7 / 188 (3.72%)	3 / 197 (1.52%)	
occurrences (all)	7	3	
Respiratory, thoracic and mediastinal disorders			
Lung infection (other than COVID-19)	Additional description: Grade 3 according to the CTCAE v5.0		
subjects affected / exposed	10 / 188 (5.32%)	7 / 197 (3.55%)	
occurrences (all)	10	7	
Acute respiratory distress syndrome grade 3	Additional description: grade 3 according to the CTCAE v5.0		
subjects affected / exposed	6 / 188 (3.19%)	9 / 197 (4.57%)	
occurrences (all)	6	9	
Acute respiratory distress syndrome grade 4	Additional description: grade 4 according to the CTCAE v5.0		
subjects affected / exposed	20 / 188 (10.64%)	26 / 197 (13.20%)	
occurrences (all)	20	26	
Psychiatric disorders			
Delirium	Additional description: grade 3 according to the CTCAE v5.0		
subjects affected / exposed	12 / 188 (6.38%)	2 / 197 (1.02%)	
occurrences (all)	12	2	
Infections and infestations			
Culture	Additional description: a positive throat swab culture that resulted in starting intravenous antibiotic, antifungal, or antiviral treatment grade 3 according to the CTCAE v5.0		
subjects affected / exposed	4 / 188 (2.13%)	5 / 197 (2.54%)	
occurrences (all)	4	5	
Metabolism and nutrition disorders			
Acidosis grade 3	Additional description: grade 3 according to the CTCAE v5.0		
subjects affected / exposed	8 / 188 (4.26%)	10 / 197 (5.08%)	
occurrences (all)	8	10	
Alkalosis	Additional description: grade 3 according to the CTCAE v5.0		

subjects affected / exposed	20 / 188 (10.64%)	21 / 197 (10.66%)	
occurrences (all)	20	21	
Hyperglycaemia	Additional description: grade 3 according to the CTCAE v5.0		
subjects affected / exposed	37 / 188 (19.68%)	22 / 197 (11.17%)	
occurrences (all)	37	22	
Acidosis grade 4	Additional description: grade 4 according to the CTCAE v5.0		
subjects affected / exposed	5 / 188 (2.66%)	1 / 197 (0.51%)	
occurrences (all)	5	1	
Hyperkalaemia			
subjects affected / exposed	6 / 188 (3.19%)	1 / 197 (0.51%)	
occurrences (all)	6	1	
Hypoalbuminaemia	Additional description: grade 3 according to the CTCAE v5.0		
subjects affected / exposed	5 / 188 (2.66%)	2 / 197 (1.02%)	
occurrences (all)	5	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2020	Change in: - Protocol: double blind, extra blood drawings, removal of viral swabs, pregnancy test, change in inclusion criteria oxygen saturation - informed consent form version update - added participating centers
12 May 2020	Change in protocol: hydroxychloroquine use is now exclusion criterium, prolonged QTc as exclusion criterium, changed the stop criterium for elevated liver enzymes, update of the informed consent form, english version of the informed consent form, New participating center
16 October 2020	Change in primary in endpoint definition, addition of new centers, addition of new safety point, change in principal investigator from one hospital, update of informed consent form

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A more detailed overview of the post hoc endpoints are provided only in the supplementary appendix of the long term outcome publication.
Rare adverse events (prevalence <3%) are only provided in the first publication.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35172891