Clinical trial results:
Stopping ACE-inhibitors in COVID-19 - a randomized, controlled clinical trial

Summary

EudraCT number	2020-001206-35
Trial protocol	AT DE
Global end of trial date	31 December 2021

Results information

Result version number	v1 (current)
This version publication date	29 January 2023
First version publication date	29 January 2023

Trial information

Trial identification

Sponsor protocol code	ACEI-COVID-19

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04353596
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University Innsbruck
Sponsor organisation address	Christoph-Probst-Platz 1, Innrain 52, Innsbruck, Austria, 6020
Public contact	Univ.-Prof. Dr. Axel Bauer, University Hospital for Internal Medicine III, Anichstrasse 35, 6020 Innsbruck, +43 51250425621, kks-regulatory@i-med.ac.at
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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	31 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2021
Global end of trial reached?	Yes
Global end of trial date	31 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Patients with coronary artery disease, arterial hypertension or diabetes are often treated with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). Treatment with ACEI and ARB may be of great relevance for the course of COVID-19: Similar to SARS-CoV (epidemic 2002-2003), the novel SARS-CoV2 is also absorbed into human cells via angiotensin converting enzyme 2 (ACE2). Treatment with ACEI and ARB leads to a significant upregulation of the SARS-CoV2 receptor ACE2. An increased expression of ACE2 in turn correlates with a higher intake of SARS-CoV2 and possibly promotes a faster spread of the virus in the organism of infected patients.
The primary aim of the study is to test whether discontinuing chronic ACEI or ARB therapy in patients with proven SARS-CoV2 infection leads to a more favorable course of the disease of COVID-19 than the continuation of the ACEI or ARB therapy.

Protection of trial subjects:

After randomisation, the treating physicians were asked to follow the respective treatment strategy. Treating physicians could stop or initiate ACEI or ARB therapy at any time for clinical indications. Participants discharged from hospital were contacted daily by telephone by the local study teams to obtain clinical and medical information.

Background therapy:

Patients received treatment due to their medical history.

Evidence for comparator:

Patients were randomly assigned 1:1 to discontinuation or continuation of RAS inhibition for 30 days.

Actual start date of recruitment	09 April 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 89
Country: Number of subjects enrolled	Austria: 127
Worldwide total number of subjects	216
EEA total number of subjects	216

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	148
85 years and over	18

Subject disposition

Recruitment

Recruitment details:

The Stopping ACE-inhibitors in Covid-19 (ACEI-COVID) trial was a prospective, parallel group, randomised, controlled, open-label study done at 35 centres, including 19 university clinics and 16 large referral hospitals, in Austria and Germany.

Pre-assignment

Screening details:

Eligible patients were aged 18 years or older, had had a recent symptomatic SARS-CoV-2 infection confirmed by a positive RT-PCR test result within the last 5 days and were on chronic treatment with ACEIs or ARBs for at least 1 month. Admission to hospital was no requirement for study inclusion.

Period 1

Period 1 title	Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Discontinuation group

Arm description:

Patients were randomly assigned to discontinuation of RAS inhibition for 30 days. If participants were randomly assigned to a discontinuation strategy, a substitution with an alternative substance class was at the discretion of the treating physician.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Continuation group

Arm description:

Patients were randomly assigned to continuation of RAS inhibition for 30 days.

Arm type	Active comparator
Investigational medicinal product name	ACE Inhibitor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Depends on medical history of patient.

Investigational medicinal product name	Angiotensin II Rezeptor Blocker
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Depends on medical history of patient.

Number of subjects in period 1	Discontinuation group	Continuation group
Started	109	107
Completed	74	64
Not completed	35	43
Adverse event, serious fatal	8	12
Consent withdrawn by subject	6	2
No evidence of recent SARS-CoV-2 infection	1	3
Did not complete follow-up	15	18
Lost to follow-up	1	4
Never received intervention per protocol	4	4

Baseline characteristics

Reporting groups	
Reporting group title	Discontinuation group
Reporting group description:	
Patients were randomly assigned to discontinuation of RAS inhibition for 30 days. If participants were randomly assigned to a discontinuation strategy, a substitution with an alternative substance class was at the discretion of the treating physician.	
Reporting group title	Continuation group
Reporting group description:	
Patients were randomly assigned to continuation of RAS inhibition for 30 days.	

Reporting group values	Discontinuation group	Continuation group	Total
Number of subjects	109	107	216
Age categorical 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)	27	23	50
From 65-84 years	73	75	148
85 years and over	9	9	18
Age continuous Units: years			
arithmetic mean	71.80	73.42	
full range (min-max)	38 to 93	51 to 93	-
Gender categorical Units: Subjects			
Female	41	39	80
Male	68	68	136

End points

End points reporting groups

Reporting group title	Discontinuation group
Reporting group description:	
Patients were randomly assigned to discontinuation of RAS inhibition for 30 days. If participants were randomly assigned to a discontinuation strategy, a substitution with an alternative substance class was at the discretion of the treating physician.	
Reporting group title	Continuation group
Reporting group description:	
Patients were randomly assigned to continuation of RAS inhibition for 30 days.	

Primary: Maximum median (IQR) SOFA score

End point title	Maximum median (IQR) SOFA score
End point description:	
The primary outcome measure was the composite of the maximum sequential organ failure assessment (SOFA) score and death within 30 days.The score is calculated from six different components, each of which reflects the status of an organ system, including respiratory function, cardiovascular integrity, liver function, coagulation, renal function and neurological status. The score can range from 0 (best) to 24 (worst).	
End point type	Primary
End point timeframe:	
20.04.20202-20.01.2021	

End point values	Discontinuation group	Continuation group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	100		
Units: number				
median (inter-quartile range (Q1-Q3))	0.00 (0.00 to 2.00)	0.00 (0.00 to 3.00)		

Statistical analyses

Statistical analysis title	Maximum median (IQR) SOFA score
Comparison groups	Discontinuation group v Continuation group
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.12
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - The primary endpoint of our study, the maximum median (IQR) SOFA score, did not significantly differ between treatment groups.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

20.04.2020-20.01.2021

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups

Reporting group title	Intervention

Reporting group description:

Patients were randomly assigned to discontinuation of RAS inhibition for 30 days. If participants were randomly assigned to a discontinuation strategy, a substitution with an alternative substance class was at the discretion of the treating physician.

Reporting group title	Control

Reporting group description:

Patients were randomly assigned to continuation of RAS inhibition for 30 days.

Serious adverse events	Intervention	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 109 (25.69%)	31 / 107 (28.97%)	
number of deaths (all causes)	8	12	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
General deterioration			
subjects affected / exposed	3 / 109 (2.75%)	5 / 107 (4.67%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 2	
Respiratory, thoracic and mediastinal disorders			
Respiratory deterioration			
subjects affected / exposed	14 / 109 (12.84%)	10 / 107 (9.35%)	
occurrences causally related to treatment / all	0 / 24	0 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory exhaustion			
subjects affected / exposed	1 / 109 (0.92%)	4 / 107 (3.74%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 109 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 109 (1.83%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Intervention	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 109 (60.55%)	65 / 107 (60.75%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	66 / 109 (60.55%)	65 / 107 (60.75%)	
occurrences (all)	131	131	
Fever			
subjects affected / exposed	42 / 109 (38.53%)	39 / 107 (36.45%)	
occurrences (all)	81	81	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	9 / 109 (8.26%)	3 / 107 (2.80%)	
occurrences (all)	12	12	
Diarrhoea			
subjects affected / exposed	15 / 109 (13.76%)	15 / 107 (14.02%)	
occurrences (all)	30	30	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	38 / 109 (34.86%)	43 / 107 (40.19%)	
occurrences (all)	81	81	
Cough			
subjects affected / exposed	53 / 109 (48.62%)	54 / 107 (50.47%)	
occurrences (all)	107	107	
Musculoskeletal and connective tissue disorders			

Myalgia subjects affected / exposed occurrences (all)	24 / 109 (22.02%) 60	36 / 107 (33.64%) 60	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34126053