Clinical trial results:
A Multicenter, Phase III Randomized, Double-Blind, Placebo-Controlled, Outpatient Study to Evaluate the Efficacy, Safety, Antiviral Activity of RO7496998 (AT-527) in Patients With Mild or Moderate COVID-19

Summary

EudraCT number	2020-005759-18
Trial protocol	DE BE DK FR PT IT RO
Global end of trial date	02 December 2021

Results information

Result version number	v1 (current)
This version publication date	15 June 2022
First version publication date	15 June 2022

Trial information

Trial identification

Sponsor protocol code	CV43043

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04889040
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002963-PIP01-21
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 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 December 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of RO7496998 (AT-527) compared with placebo

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Brazil: 17
Country: Number of subjects enrolled	Switzerland: 11
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Japan: 39
Country: Number of subjects enrolled	Mexico: 32
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Turkey: 35
Country: Number of subjects enrolled	Ukraine: 42
Worldwide total number of subjects	216
EEA total number of subjects	39

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)	3
Adults (18-64 years)	201
From 65 to 84 years	11
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were non-hospitalized, with mild to moderate COVID-19, with or without risk factors for severe disease.

Pre-assignment

Screening details:

216 subjects were enrolled in the study and 212 subjects received either AT-527 or matching placebo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

The dose and regimen of the placebo will match that of AT-527.

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

Dosage and administration details:

The dose and regimen of the placebo will match that of AT-527.

Arm title	RO7496998 (AT-527)

Arm description:

Orally administered, 550 mg twice daily (BID) for 5 days

Arm type	Experimental
Investigational medicinal product name	AT-527
Investigational medicinal product code	
Other name	RO7496998
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

550 mg twice daily (BID) for 5 days

Number of subjects in period 1	Placebo	RO7496998 (AT-527)
Started	73	143
Received Treatment	71	141
Completed	68	138
Not completed	5	5
Consent withdrawn by subject	3	3
Adverse event, non-fatal	2	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
The dose and regimen of the placebo will match that of AT-527.	
Reporting group title	RO7496998 (AT-527)
Reporting group description:	
Orally administered, 550 mg twice daily (BID) for 5 days	

Reporting group values	Placebo	RO7496998 (AT-527)	Total
Number of subjects	73	143	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)	2	1	3
Adults (18-64 years)	66	135	201
From 65-84 years	4	7	11
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	41.7	41.1	
standard deviation	± 14.9	± 13.2	-
Sex: Female, Male Units:			
Female	32	62	94
Male	41	81	122
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	6	9	15
Asian	14	26	40
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	1	3	4
White	50	105	155
More than one race	0	0	0
Unknown or Not Reported	1	0	1

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
The dose and regimen of the placebo will match that of AT-527.	
Reporting group title	RO7496998 (AT-527)
Reporting group description:	
Orally administered, 550 mg twice daily (BID) for 5 days	

Primary: Time to Alleviation or Improvement of COVID-19 Symptoms (21.5 hours)

End point title	Time to Alleviation or Improvement of COVID-19 Symptoms (21.5 hours)[1]

End point description:

COVID-19 symptoms will be evaluated using the COVID-19 Symptom Diary (questions 1-12). The severity of each COVID-19 symptom will be recorded on a Likert scale (i.e none/mild/moderate/severe).

The time to alleviation or improvement of COVID-19 symptoms is defined as follows: for new symptoms, it is defined as the length of time taken from randomization to the point at which a Score of 0 or 1 has been maintained for a duration of at least 21.5 hours. For preexisting symptoms, it is defined as the time from randomization to when a patient's symptoms have been maintained or improved (requires at least a single category improvement from baseline on the COVID-19 Symptom Diary Likert scale) for a duration of 21.5 hours.

End point type	Primary

End point timeframe:

Up to 29 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to early trial termination, the targeted enrolment numbers were not reached and no meaningful statistical analyses could be performed.

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: hours				
median (confidence interval 97.5%)	73.7 (47.1 to 105.8)	94.5 (68.1 to 131.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Alleviation or Improvement of COVID-19 Symptoms (43 hours)

End point title	Time to Alleviation or Improvement of COVID-19 Symptoms (43 hours)

End point description:

COVID-19 symptoms will be evaluated using the COVID-19 Symptom Diary (questions 1-12). The severity of each COVID-19 symptom will be recorded on a Likert scale (i.e none/mild/moderate/severe).

The time to alleviation or improvement of COVID-19 symptoms is defined as follows: for new symptoms, it is defined as the length of time taken from randomization to the point at which a Score of 0 or 1 has been maintained for a duration of at least 43 hours. For preexisting symptoms, it is defined as the time from randomization to when a patient's symptoms have been maintained or improved (requires at least a single category improvement from baseline on the COVID-19 Symptom Diary Likert scale) for a duration of 43 hours.

End point type	Secondary

End point timeframe:

Up to 29 days

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: hours				
median (confidence interval 97.5%)	79.6 (55.7 to 108.2)	109.5 (83.8 to 147.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Alleviation of COVID-19 Symptoms (21.5 hours)

End point title	Time to Alleviation of COVID-19 Symptoms (21.5 hours)

End point description:

Time from randomization to the point at which the following criterion is met and maintained for at least 21.5 hours.
- Score of 0 or 1 on Items 1-12 of the COVID-19 Symptom Diary.

End point type	Secondary

End point timeframe:

Up to 29 days

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: hours				
median (confidence interval 97.5%)	73.7 (47.1 to 105.8)	94.5 (68.1 to 131.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Alleviation of COVID-19 Symptoms (43 hours)

End point title	Time to Alleviation of COVID-19 Symptoms (43 hours)

End point description:

Time from randomization to the point at which the following criterion is met and maintained for at least 43 hours.
- Score of 0 or 1 on Items 1-12 of the COVID-19 Symptom Diary.

End point type	Secondary

End point timeframe:

Up to 29 days

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: hours				
median (confidence interval 97.5%)	79.6 (55.7 to 108.2)	109.5 (83.8 to 147.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to One-Category Improvement of Baseline Presenting COVID-19 Symptoms

End point title	Time to One-Category Improvement of Baseline Presenting COVID-19 Symptoms

End point description:

Time from randomization to the point at which symptoms (Items 1-12 of the COVID-19 Symptom Diary) have improved by at least one category from baseline on the COVID-19 Symptom Diary Likert scale, maintained for at least 21.5 hours.

End point type	Secondary

End point timeframe:

Up to 29 days

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	130		
Units: hours				
median (confidence interval 97.5%)	70.9 (41.8 to 91.8)	81.5 (60.5 to 119.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Alleviation of Individual Symptoms

End point title	Time to Alleviation of Individual Symptoms

End point description:

Time from randomization to the point at which the following criterion is met and maintained (for each individual symptom) for at least 21.5 hours.
- Score of 0 or 1 for Items 1-14 of the COVID-19 Symptom Diary

Here 99999 or 0.99999 represents values that were not evaluable due to an insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 29 days

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: hours				
median (confidence interval 97.5%)				
Nasal Congestion or Runny Nose	36.4 (23.4 to 60.6)	37.3 (23.4 to 57.6)		
Sore Throat	45.6 (23.4 to 75.1)	33.2 (20.9 to 54.3)		
Cough	37.6 (26.8 to 118.7)	49.5 (28.4 to 106.4)		
Shortness of Breath	24.0 (11.8 to 106.8)	47.5 (32.4 to 96.8)		
Muscle or Body Aches	35.3 (14.3 to 59.4)	44.9 (33.1 to 53.0)		
Fatigue	66.6 (36.5 to 118.9)	61.3 (47.1 to 108.1)		
Headache	23.2 (14.5 to 41.8)	41.4 (24.4 to 59.5)		
Chills/Sweats	36.0 (22.5 to 57.6)	39.0 (28.4 to 50.5)		
Feeling Hot or Feverish	24.6 (16.4 to 66.7)	36.2 (19.7 to 61.4)		
Nausea	31.4 (11.1 to 99999)	43.5 (22.6 to 73.4)		
Vomiting	20.1 (16.4 to 99999)	33.0 (0.99999 to 99999)		
Diarrhea	17.6 (14.9 to 73.6)	66.7 (19.8 to 107.2)		
Sense of Smell	132.6 (84.3 to 229.0)	104.9 (72.6 to 206.0)		
Sense of Taste	128.9 (84.3 to 202.2)	155.7 (52.5 to 371.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Participants Requiring Hospitalization for COVID-19

End point title	Proportion of Participants Requiring Hospitalization for COVID-19

End point description:

Hospitalizations for COVID-19 are defined as SAEs for which the investigator has cited that the suspected cause was the disease under study and where there is a non-missing hospital admission date.

End point type	Secondary

End point timeframe:

Up to Day 33 visit

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: percentage of participants				
number (confidence interval 97.5%)	10.0 (1.25 to 18.75)	2.9 (0.00 to 6.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Participants with Greater than or Equal to 1 COVID-19 Related Medically Attended Visit

End point title	Proportion of Participants with Greater than or Equal to 1 COVID-19 Related Medically Attended Visit

End point description:

Medically attended visit is defined as hospitalization, emergency room (ER) visit, urgent care visit, physician’s office visit, or telemedicine visit, with the primary reason for the visit being COVID-19.

End point type	Secondary

End point timeframe:

Up to Day 33 visit

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: percentage of participants				
number (confidence interval 97.5%)	14.3 (4.20 to 24.37)	10.2 (4.05 to 16.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Fever

End point title	Duration of Fever

End point description:

Time to return to an afebrile state (temperature ≤ 37.5°C) maintained for at least 21.5 hours in patients with a fever at baseline.

End point type	Secondary

End point timeframe:

Up to 29 days

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	20		
Units: hours				
median (confidence interval 97.5%)	47.3 (12.6 to 82.2)	55.7 (25.9 to 96.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of COVID-19 Related Complications

End point title	Frequency of COVID-19 Related Complications

End point description:

COVID-related complications are defined as death, hospitalization, pneumonia, sepsis, coagulopathy, pericarditis/myocarditis and cardiac failure.

Pneumonia, acute respiratory failure, sepsis, coagulopathy, pericarditis/myocarditis, and cardiac failure were adjudicated per blinded manual medical review of events by an internal adjudication team before study readout.

End point type	Secondary

End point timeframe:

Up to Day 33 visit

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: percentage of participants				
number (confidence interval 97.5%)	10.0 (1.25 to 18.75)	4.4 (0.10 to 8.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Participants with any Post-Treatment Infection

End point title	Proportion of Participants with any Post-Treatment Infection

End point description:

Post-treatment infections were defined as any treatment-emergent adverse event with a primary system organ class of infections and infestations.

End point type	Secondary

End point timeframe:

Up to Day 33 visit

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: percentage of participants				
number (confidence interval 97.5%)	14.3 (4.20 to 24.37)	9.5 (3.51 to 15.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Amount of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Virus RNA

End point title	Change from Baseline in the Amount of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Virus RNA

End point description:

SARS-CoV-2 virus RNA will be measured by reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR)

End point type	Secondary

End point timeframe:

Baseline and on Days 3, 5, 7 and 14

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: log10 copies/mL				
arithmetic mean (standard deviation)				
Baseline	6.49 (± 1.61)	6.59 (± 1.54)		
Day 3	-1.05 (± 1.06)	-1.07 (± 1.16)		
Day 5	-2.24 (± 1.40)	-2.01 (± 1.50)		
Day 7	-3.10 (± 1.38)	-2.98 (± 1.66)		
Day 14	-4.21 (± 1.64)	-4.25 (± 1.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cessation of SARS-CoV-2 Viral Shedding

End point title	Time to Cessation of SARS-CoV-2 Viral Shedding

End point description:

Defined as time from randomization to the first time when a negative qualitative virus RNA by RT-PCR test result is obtained.

Here 99999 represents data that were not evaluable.

End point type	Secondary

End point timeframe:

Up to 14 days

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: days				
median (confidence interval 97.5%)	13.0 (12.8 to 99999)	13.0 (13.0 to 13.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Participants Positive for SARS-CoV-2 Virus RNA at Specified Timepoints

End point title	Proportion of Participants Positive for SARS-CoV-2 Virus RNA at Specified Timepoints

End point description:

Defined as proportion of patients with a positive qualitative virus RNA by RT-PCR.

End point type	Secondary

End point timeframe:
Baseline and on Days 3, 5, 7 and 14

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	137		
Units: percentage of participants				
number (not applicable)				
Baseline	97.1	100		
Day 3	98.5	96.4		
Day 5	89.7	91.9		
Day 7	74.6	76.3		
Day 14	43.9	34.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve (AUC) in the Amount of SARS-CoV-2 Virus RNA

End point title	Area Under the Curve (AUC) in the Amount of SARS-CoV-2 Virus RNA

End point description:

End point type	Secondary

End point timeframe:
Up to 14 days

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	137		
Units: log10 copies/mL*hour				
arithmetic mean (standard deviation)	1122.39 (± 339.70)	1174.30 (± 377.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events (AEs)

End point title	Percentage of Participants with Adverse Events (AEs)

End point description:

End point type	Secondary

End point timeframe:

Up to Day 33 visit

End point values	Placebo	RO7496998 (AT-527)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	141		
Units: percentage of participants				
number (not applicable)	36.6	39.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of AT-511 at Specified Timepoints

End point title	Plasma Concentration of AT-511 at Specified Timepoints[2]

End point description:

AT-511 is the free base form of RO7496998 (AT-527).

End point type	Secondary

End point timeframe:

Up to 7 days

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Plasma concentrations were measured in subjects that received AT-527. Therefore the placebo arm was excluded from this endpoint.

End point values	RO7496998 (AT-527)			
Subject group type	Reporting group			
Number of subjects analysed	137			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Day 1, 0 hour	17.4 (± 158.6)			
Day 1, 1 hour	1456.8 (± 1757.7)			
Day 1, 2 hours	1029.3 (± 1085.5)			
Day 1, 4 hours	206.3 (± 289.5)			
Day 5, 0 hour	52.8 (± 271.0)			
Day 5, 1 hour	1659.0 (± 2213.9)			
Day 5, 2 hours	1934.5 (± 2210.6)			
Day 5, 4 hours	202.3 (± 310.7)			

Day 5, 8 hours	8.8 (± 9.5)			
Day 5, 48 hours	4.6 (± 40.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of AT-551 at Specified Timepoints

End point title	Plasma Concentration of AT-551 at Specified Timepoints[3]

End point description:

AT-511 is the free base form of RO7496998 (AT-527). Major metabolites are AT-551, AT-229, and AT-273 (a surrogate for the intracellular concentration of the active triphosphate metabolite AT-9010)

End point type	Secondary

End point timeframe:

Up to 7 days

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Plasma concentrations were measured in subjects that received AT-527. Therefore the placebo arm was excluded from this endpoint.

End point values	RO7496998 (AT-527)			
Subject group type	Reporting group			
Number of subjects analysed	137			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Day 1, 0 hour	1.9 (± 12.2)			
Day 1, 1 hour	166.9 (± 209.8)			
Day 1, 2 hours	335.7 (± 257.6)			
Day 1, 4 hours	195.0 (± 146.4)			
Day 5, 0 hour	49.1 (± 65.0)			
Day 5, 1 hour	150.2 (± 144.5)			
Day 5, 2 hours	213.6 (± 201.7)			
Day 5, 4 hours	138.8 (± 136.2)			
Day 5, 8 hours	27.5 (± 17.5)			
Day 5, 48 hours	2.6 (± 5.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of AT-229 at Specified Timepoints

End point title	Plasma Concentration of AT-229 at Specified Timepoints[4]

End point description:

AT-511 is the free base form of RO7496998 (AT-527). Major metabolites are AT-551, AT-229, and AT-273 (a surrogate for the intracellular concentration of the active triphosphate metabolite AT-9010)

End point type	Secondary

End point timeframe:

Up to 7 days

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Plasma concentrations were measured in subjects that received AT-527. Therefore the placebo arm was excluded from this endpoint.

End point values	RO7496998 (AT-527)			
Subject group type	Reporting group			
Number of subjects analysed	137			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Day 1, 0 hour	2.2 (± 18.4)			
Day 1, 1 hour	123.6 (± 172.5)			
Day 1, 2 hours	507.8 (± 497.5)			
Day 1, 4 hours	354.4 (± 259.2)			
Day 5, 0 hour	367.8 (± 259.1)			
Day 5, 1 hour	418.0 (± 257.6)			
Day 5, 2 hours	454.3 (± 331.7)			
Day 5, 4 hours	490.1 (± 296.4)			
Day 5, 8 hours	279.6 (± 176.0)			
Day 5, 48 hours	118.7 (± 127.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of AT-273 at Specified Timepoints

End point title	Plasma Concentration of AT-273 at Specified Timepoints[5]

End point description:

AT-511 is the free base form of RO7496998 (AT-527). Major metabolites are AT-551, AT-229, and AT-273 (a surrogate for the intracellular concentration of the active triphosphate metabolite AT-9010)

End point type	Secondary

End point timeframe:

Up to 7 days

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Plasma concentrations were measured in subjects that received AT-527. Therefore the placebo arm was excluded from this endpoint.

End point values	RO7496998 (AT-527)			
Subject group type	Reporting group			
Number of subjects analysed	137			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Day 1, 0 hour	0.7 (± 2.5)			
Day 1, 1 hour	15.5 (± 26.9)			
Day 1, 2 hours	135.1 (± 136.2)			
Day 1, 4 hours	173.5 (± 120.6)			
Day 5, 0 hour	149.8 (± 78.1)			
Day 5, 1 hour	141.7 (± 72.7)			
Day 5, 2 hours	108.8 (± 61.0)			
Day 5, 4 hours	172.7 (± 129.2)			
Day 5, 8 hours	118.6 (± 80.2)			
Day 5, 48 hours	48.4 (± 32.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to the Day 33 visit	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1.
Reporting groups	
Reporting group title	AT-527
Reporting group description: Orally administered, 550 mg twice daily (BID) for 5 days	
Reporting group title	Placebo
Reporting group description: The dose and regimen of the placebo will match that of AT-527.	

Serious adverse events	AT-527	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 141 (3.55%)	7 / 71 (9.86%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 141 (0.71%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 141 (0.71%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 141 (0.71%)	0 / 71 (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	2 / 141 (1.42%)	3 / 71 (4.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 141 (0.71%)	4 / 71 (5.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	1 / 141 (0.71%)	0 / 71 (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: 5 %

Non-serious adverse events	AT-527	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 141 (7.80%)	5 / 71 (7.04%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 141 (2.84%)	5 / 71 (7.04%)	
occurrences (all)	4	5	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 141 (5.67%)	0 / 71 (0.00%)	
occurrences (all)	8	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2021	The purpose of this update was to address the feedback and questions received as part of a multinational clinical trial authorization application process.
02 June 2021	Major updates included Study Rationale and Benefit-Risk Assessment, addition of 2 additional efficacy endpoints, updated number of study sites and eligibility criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 December 2021	The study was terminated with 16% of the planned sample size with enrollment initially paused on 29 October 2021. Subsequently, study CV43043 was terminated early on 07 December 2021 due to program level decisions. The LPLV was 02 December 2021.	-

Notes:

Limitations and caveats

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

The study was terminated with only 16% of the planned sample size.

Notes: