Clinical trial results:
A Phase 2 Randomized Study of the Efficacy and Safety of Acalabrutinib with Best Supportive Care Versus Best Supportive Care in Subjects Hospitalized with COVID-19

Summary

EudraCT number	2020-001644-25
Trial protocol	FR DE ES SE IT
Global end of trial date	15 November 2020

Results information

Result version number	v1 (current)
This version publication date	29 October 2021
First version publication date	29 October 2021

Trial information

Trial identification

Sponsor protocol code	D822FC00001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Acerta Pharma B.V.
Sponsor organisation address	121 Oyster Point Blvd, South San Francisco, United States, CA 94080
Public contact	Clinical Trial Call Center, Acerta Pharma B.V., acertamc@dlss.com
Scientific contact	Clinical Trial Call Center, Acerta Pharma B.V., acertamc@dlss.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	21 December 2020

Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall objective of the study is to evaluate the efficacy of adding acalabrutinib to BSC for the treatment of COVID-19

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2020
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	South Africa: 9
Country: Number of subjects enrolled	India: 33
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Brazil: 52
Country: Number of subjects enrolled	Argentina: 18
Country: Number of subjects enrolled	Peru: 18
Country: Number of subjects enrolled	Mexico: 15
Country: Number of subjects enrolled	Chile: 4
Worldwide total number of subjects	177
EEA total number of subjects	3

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)	121
From 65 to 84 years	54
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

All participants had COVID-19 pneumonia (documented radiographically) requiring hospitalization and were recruited from: South Africa; India; Turkey; Japan; Russian Federation; France; Italy; Brazil; Argentina; Peru; Mexico; Chile. The first participant was randomized on 15 June 2020 and the last participant was randomized on 17 August 2020.

Pre-assignment

Screening details:

Screening assessments were performed within the 3 days prior to randomization. Of 236 screened participants, 177 were enrolled. Of the 59 participants that were screened but not enrolled, 54 were screen failures (did not meet eligibility criteria), 1 died, 1 was withdrawn by physician decision and 3 withdrew consent.

Period 1

Period 1 title	Overall 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	Acalabrutinib + BSC

Arm description:

Participants received acalabrutinib 100mg tablet orally twice daily for 10 days, plus best supportive care per the discretion of the Investigator and institutional guidelines.

Arm type	Experimental
Investigational medicinal product name	acalabrutinib
Investigational medicinal product code	ACP-196
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100 mg twice daily for 10 days.

Arm title	BSC alone

Arm description:

Participants received best supportive care per the discretion of the Investigator and institutional guidelines.

Arm type	Standard of care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Acalabrutinib + BSC	BSC alone
Started	89	88
Completed	74	77
Not completed	15	11
Study terminated by sponsor incorrectly entered	2	-
Adverse event, serious fatal	8	9

Consent withdrawn by subject	5	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Acalabrutinib + BSC
Reporting group description:	
Participants received acalabrutinib 100mg tablet orally twice daily for 10 days, plus best supportive care per the discretion of the Investigator and institutional guidelines.	
Reporting group title	BSC alone
Reporting group description:	
Participants received best supportive care per the discretion of the Investigator and institutional guidelines.	

Reporting group values	Acalabrutinib + BSC	BSC alone	Total
Number of subjects	89	88	177
Age Categorical Units: Participants			
< 65 years	61	60	121
>= 65 years	28	28	56
Age Continuous Units: Years			
arithmetic mean	56.7	56.7	
standard deviation	± 13.3	± 14.8	-
Sex: Female, Male Units: Participants			
MALE	60	64	124
FEMALE	29	24	53
Ethnicity (NIH/OMB) Units: Subjects			
HISPANIC OR LATINO	48	47	95
NOT HISPANIC OR LATINO	41	41	82
NOT REPORTED	0	0	0
Race (NIH/OMB) Units: Subjects			
WHITE	40	48	88
BLACK OR AFRICAN AMERICAN	3	5	8
AMERICAN INDIAN OR ALASKA NATIVE	7	3	10
ASIAN	23	13	36
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0
OTHER	14	19	33
NOT REPORTED	2	0	2

End points

End points reporting groups

Reporting group title	Acalabrutinib + BSC
Reporting group description:	
Participants received acalabrutinib 100mg tablet orally twice daily for 10 days, plus best supportive care per the discretion of the Investigator and institutional guidelines.	
Reporting group title	BSC alone
Reporting group description:	
Participants received best supportive care per the discretion of the Investigator and institutional guidelines.	

Primary: Percentage of participants alive and free of respiratory failure at Day 14

End point title	Percentage of participants alive and free of respiratory failure at Day 14
End point description:	
Respiratory failure, is defined based on resource utilization of any of the following modalities: a) Endotracheal intubation and mechanical ventilation b) Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5) c) Non-invasive positive pressure ventilation or continuous positive airway pressure d) Extracorporeal membrane oxygenation	
End point type	Primary
End point timeframe:	
At Day 14	

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Percentage of participants				
number (confidence interval 95%)	83.1 (74.8 to 91.5)	90.9 (84.3 to 97.5)		

Statistical analyses

Statistical analysis title	Statistical analysis
Statistical analysis description:	
Stratified analysis of the proportion of subjects alive and free of respiratory failure at Day 28. Stratified analysis, adjusting for age (<65 vs >=65 years) and comorbidities (present vs absent).	
Comparison groups	Acalabrutinib + BSC v BSC alone
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.121
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)

Point estimate	0.48
Confidence interval	
level	95.01 %
sides	2-sided
lower limit	0.19
upper limit	1.22

Secondary: Number of participants with Adverse Events and Serious Adverse Events

End point title	Number of participants with Adverse Events and Serious Adverse Events

End point description:

Using the safety analysis set: If the participant receives at least 1 dose of acalabrutinib, they are summarized in the Acalabrutinib + BSC group. Otherwise, they are summarized in the BSC alone group. The number of participants in the BSC alone group (91) is greater than the number of participants randomized to this group (88) because three participants randomized to Acalabrutinib + BSC did not receive any acalabrutinib and therefore are included in the BSC alone group for the safety analysis set.

End point type	Secondary

End point timeframe:

Screening to 28 (+3) days after last dose of acalabrutinib (for acalabrutinib + BSC participants) or to 38 (+3) days after randomization (for BSC alone participants)

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89[1]	88[2]		
Units: Participants				
Any Adverse Event	43	37		
Any Serious Adverse Event	7	2		

Notes:

[1] - Counts are out of the safety analysis set (86 subjects)

[2] - Counts are out of the safety analysis set (91 subjects)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants alive and free of respiratory failure at Day 28

End point title	Percentage of participants alive and free of respiratory failure at Day 28

End point description:

Respiratory failure, is defined based on resource utilization of any of the following modalities: a) Endotracheal intubation and mechanical ventilation b) Oxygen delivered by highflow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5) c) Non-invasive positive pressure ventilation or continuous positive airway pressure d) Extracorporeal membrane oxygenation

End point type	Secondary

End point timeframe:

At Day 28

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Percentage of participants				
number (confidence interval 95%)	84.3 (76.1 to 92.4)	88.6 (81.4 to 95.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in C-reactive protein.

End point title	Percent change from baseline in C-reactive protein.

End point description:

Baseline is defined as the result obtained on the date of randomization. If no result was obtained on the date of randomization, the last result prior to the date of randomization is used.

Percent change from baseline at Day X is calculated by multiplying the following result by 100%: (Day X value - Baseline value)/Baseline value.
The mean of this result for all analyzed patients is taken to get the mean percent change from baseline.

End point type	Secondary

End point timeframe:

Days 3, 5, 7, 10, 14, 28

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Percent change				
arithmetic mean (standard deviation)				
Day 3	-15.06 (± 95.82)	-15.25 (± 91.61)		
Day 5	-12.48 (± 113.38)	-41.07 (± 92.59)		
Day 7	-45.71 (± 106.84)	-23.41 (± 223.06)		
Day 10/ Discharge	-16.84 (± 194.71)	-29.32 (± 166.35)		
Day 10	-35.53 (± 126.84)	-23.41 (± 203.02)		
Day 14	-12.49 (± 187.37)	-17.26 (± 256.87)		
Day 28	-30.28 (± 192.90)	-63.74 (± 75.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in ferritin

End point title	Percent change from baseline in ferritin

End point description:

Baseline is defined as the result obtained on the date of randomization. If no result was obtained on the date of randomization, the last result prior to the date of randomization is used.
Percent change from baseline at Day X is calculated by multiplying the following result by 100%: (Day X value - Baseline value)/Baseline value.
The mean of this result for all analyzed patients is taken to get the mean percent change from baseline.

End point type	Secondary

End point timeframe:

Days 3, 5, 7, 10, 14, 28

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Percent change				
arithmetic mean (standard deviation)				
Day 3	9.84 (± 92.66)	6.49 (± 40.23)		
Day 5	12.92 (± 105.09)	-12.76 (± 43.18)		
Day 7	-8.93 (± 53.52)	-8.79 (± 36.40)		
Day 10/ Discharge	-9.09 (± 58.85)	1.35 (± 125.95)		
Day 10	-5.99 (± 73.71)	6.84 (± 178.23)		
Day 14	-18.81 (± 67.85)	-26.80 (± 46.10)		
Day 28	-66.82 (± 18.24)	-66.05 (± 21.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in absolute lymphocyte count

End point title	Percent change from baseline in absolute lymphocyte count

End point description:

Baseline is defined as the result obtained on the date of randomization. If no result was obtained on the date of randomization, the last result prior to the date of randomization is used.

Percent change from baseline at Day X is calculated by multiplying the following result by 100%: (Day X value - Baseline value)/Baseline value.
The mean of this result for all analyzed patients is taken to get the mean percent change from baseline.

End point type	Secondary

End point timeframe:

Days 3, 5, 7, 10, 14, 28

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Percent change				
arithmetic mean (standard deviation)				
Day 3	31.74 (± 59.32)	36.82 (± 79.91)		
Day 5	55.79 (± 101.57)	87.25 (± 140.37)		
Day 7	51.72 (± 91.82)	79.33 (± 119.73)		
Day 10/ Discharge	78.34 (± 95.88)	99.65 (± 149.02)		
Day 10	98.55 (± 113.66)	83.08 (± 105.56)		
Day 14	74.65 (± 124.47)	91.58 (± 123.63)		
Day 28	89.35 (± 100.24)	96.62 (± 97.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Median overall survival, calculated using the Kaplan-Meier technique. Confidence interval for median overall survival (days) is derived based on Brookmeyer-Crowley method with log-log transformation.

End point type	Secondary

End point timeframe:

From randomization until 90 days after randomization.

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Days				
median (confidence interval 95%)				
Median overall survival	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants alive and discharged from ICU

End point title	Percentage of participants alive and discharged from ICU

End point description:

End point type	Secondary

End point timeframe:

At Day 14 and at Day 28

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Percentage of participants				
number (not applicable)				
At Day 14	78.7	89.8		
At Day 28	83.1	87.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from randomization to first occurrence of respiratory failure or death on study due to any cause

End point title	Time from randomization to first occurrence of respiratory failure or death on study due to any cause

End point description:

Median time to first occurrence of respiratory failure or death, calculated using the Kaplan-Meier technique. Confidence interval for median overall survival (days) is derived based on Brookmeyer-Crowley method with log-log transformation.

End point type	Secondary

End point timeframe:

From randomization to 28 days after randomization.

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Days				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Statistical analysis
Statistical analysis description:	
Stratified analysis of time to first occurrence of respiratory failure or death through Day 28	
Comparison groups	Acalabrutinib + BSC v BSC alone
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.758
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.323
upper limit	1.722

Secondary: Number of days alive and free of respiratory failure

End point title	Number of days alive and free of respiratory failure
End point description:	
Respiratory failure, is defined based on resource utilization of any of the following modalities: a) Endotracheal intubation and mechanical ventilation b) Oxygen delivered by highflow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5) c) Non-invasive positive pressure ventilation or continuous positive airway pressure d) Extracorporeal membrane oxygenation	
End point type	Secondary
End point timeframe:	
From randomization to 28 days after randomization.	

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Days				
arithmetic mean (standard deviation)	24.8 (± 8.0)	25.3 (± 7.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days with respiratory failure

End point title	Number of days with respiratory failure

End point description:

Respiratory failure, is defined based on resource utilization of any of the following modalities: a) Endotracheal intubation and mechanical ventilation b) Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5) c) Non-invasive positive pressure ventilation or continuous positive airway pressure d) Extracorporeal membrane oxygenation For participants who die (due to any cause) prior to Day 28, days from death to Day 28 are counted as days with respiratory failure. For participants in hospital and experiencing respiratory failure at the time they withdraw from the study, days from last known status to Day 28 are counted as days with respiratory failure.

End point type	Secondary

End point timeframe:

From randomization to 28 days after randomization.

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Days				
arithmetic mean (standard deviation)	3.2 (± 8.0)	2.7 (± 7.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days hospitalized

End point title	Number of days hospitalized

End point description:

For this summary, the hospitalization must be considered clinically indicated to count as a day hospitalized.
For participants who die (due to any cause) prior to Day 28, days from death to Day 28 are counted as days hospitalized.
For participants in hospital at the time they withdraw from the study, days from last known status to Day 28 are counted as days hospitalized.

End point type	Secondary

End point timeframe:

From randomization to 28 days after randomization.

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Days				
arithmetic mean (standard deviation)	12.2 (± 8.6)	10.4 (± 7.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days in ICU

End point title	Number of days in ICU

End point description:

For this summary, the ICU stay must be considered clinically indicated to count as a day in ICU.
For participants who die (due to any cause) prior to Day 90, days from death to Day 90 are counted as days in ICU.

End point type	Secondary

End point timeframe:

From randomization to 90 days after randomization.

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Days				
arithmetic mean (standard deviation)	10.4 (± 25.5)	9.7 (± 25.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days alive outside of hospital at Day 28

End point title	Number of days alive outside of hospital at Day 28

End point description:

End point type	Secondary

End point timeframe:

From randomization to 28 days after randomization.

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Days				
arithmetic mean (standard deviation)	15.1 (± 8.4)	17.0 (± 7.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days alive outside of hospital at Day 90

End point title	Number of days alive outside of hospital at Day 90

End point description:

End point type	Secondary

End point timeframe:

From randomization to 90 days after randomization.

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Days				
arithmetic mean (standard deviation)	66.8 (± 28.2)	71.3 (± 24.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in oxygenation index

End point title	Percent change from baseline in oxygenation index

End point description:

Baseline is defined as the result obtained on the date of randomization.

Percent change from baseline at Day X is calculated by multiplying the following result by 100%: (Day X value - Baseline value)/Baseline value.
The mean of this result for all analyzed patients is taken to get the mean percent change from baseline.

End point type	Secondary

End point timeframe:

Days 3, 5, 7, 10, 14, 28

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Percent change				
arithmetic mean (standard deviation)				
Day 3	11.65 (± 29.40)	12.20 (± 33.88)		
Day 5	23.94 (± 41.72)	33.09 (± 51.50)		
Day 7	30.58 (± 57.79)	54.51 (± 84.75)		
Day 10/ Discharge	54.25 (± 71.71)	62.10 (± 80.79)		
Day 10	64.44 (± 84.02)	80.52 (± 101.48)		
Day 14	70.39 (± 77.27)	83.71 (± 84.96)		
Day 28	80.93 (± 89.61)	90.68 (± 95.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from randomization to clinical improvement of at least 2 points on a 9-point category ordinal scale

End point title	Time from randomization to clinical improvement of at least 2 points on a 9-point category ordinal scale

End point description:

9-point category ordinal scale:
0. * Uninfected, no clinical or virological evidence of infection
1. Ambulatory, no limitation of activities
2. Ambulatory, limitation of activities
3. Hospitalized – mild disease, no oxygen therapy
4. Hospitalized – mild disease, oxygen by mask or nasal prongs
5. Hospitalized – severe disease, non-invasive ventilation or high flow oxygen
6. Hospitalised – severe disease, intubation and mechanical ventilation
7. Hospitalized – severe disease, ventilation and additional organ support, such as pressors, renal replacement therapy, extracorporeal membrane oxygenation
8. Death

Median time to first occurrence of respiratory failure or death, calculated using the Kaplan-Meier technique. Confidence interval for median overall survival (days) is derived based on Brookmeyer-Crowley method with log-log transformation.

End point type	Secondary

End point timeframe:

From randomization to 28 days after randomization.

End point values	Acalabrutinib + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	83		
Units: Days				
median (confidence interval 95%)	10.00 (8.00 to 12.00)	10.00 (8.00 to 11.00)		

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Stratified analysis of time from randomization to clinical improvement of at least 2 points on a 9-point category ordinal scale. Stratified analysis, adjusting for age (<65 vs >=65 years) and comorbidities (present vs absent).

Comparison groups	Acalabrutinib + BSC v BSC alone
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.967
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.353

Secondary: Pharmacokinetics of acalabrutinib

End point title	Pharmacokinetics of acalabrutinib[3]

End point description:

Summary of plasma concentrations (ng/mL) of acalabrutinib

End point type	Secondary

End point timeframe:

Day 3 and Day 7

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: This objective is to assess pharmacokinetics of acalabrutinib. This end point is not applicable to BSC alone arm as this arm does not contain acalabruinib

End point values	Acalabrutinib + BSC			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 3, Pre-dose	15.359 (± 195.1)			

Day 3, 0.5 hours post-dose	54.580 (± 139.7)			
Day 3, 1 hour post-dose	56.120 (± 141.6)			
Day 3, 2 hours post-dose	90.173 (± 104.3)			
Day 3, 4 hours post-dose	36.841 (± 179.2)			
Day 3, 6 hours post-dose	23.551 (± 205.0)			
Day 7, 1 hour post-dose	117.015 (± 60.3)			
Day 7, 4 hours post-dose	17.454 (± 108.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of ACP-5862

End point title	Pharmacokinetics of ACP-5862[4]

End point description:

Summary of plasma concentrations (ng/mL) of ACP-5862

End point type	Secondary

End point timeframe:

Day 3 and Day 7

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: This objective is to assess pharmacokinetics of acalabrutinib. This end point is not applicable to BSC alone arm as this arm does not contain acalabruinib

End point values	Acalabrutinib + BSC			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 3, Pre-dose	71.526 (± 94.8)			
Day 3, 0.5 hours post-dose	125.332 (± 109.9)			
Day 3, 1 hour post-dose	144.784 (± 95.1)			
Day 3, 2 hours post-dose	213.370 (± 72.7)			
Day 3, 4 hours post-dose	154.437 (± 70.3)			
Day 3, 6 hours post-dose	113.769 (± 82.8)			
Day 7, 1 hour post-dose	156.133 (± 68.0)			
Day 7, 4 hours post-dose	95.392 (± 69.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug until last study visit	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Acalabrutinib + BSC
Reporting group description: -	
Reporting group title	BSC alone
Reporting group description: -	

Serious adverse events	Acalabrutinib + BSC	BSC alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 86 (8.14%)	2 / 91 (2.20%)	
number of deaths (all causes)	7	10	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 86 (1.16%)	0 / 91 (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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 86 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	1 / 86 (1.16%)	0 / 91 (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	2 / 86 (2.33%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	

deaths causally related to treatment / all	0 / 2	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 86 (0.00%)	1 / 91 (1.10%)	
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 / 86 (1.16%)	0 / 91 (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			
Bacterial sepsis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mucosal infection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 86 (2.33%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	0 / 86 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Acalabrutinib + BSC	BSC alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 86 (11.63%)	2 / 91 (2.20%)	

Nervous system disorders Headache subjects affected / exposed occurrences (all)	10 / 86 (11.63%) 11	2 / 91 (2.20%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2020	Changes were implemented to address the FDA comments.
28 April 2020	The overall rationale for the amendment was to remove Part 2 of the study based on Health Authority feedback.
23 June 2020	The overall rationale for the amendment was to address feedback from global study sites that are managing local challenges around the world during the COVID-19 pandemic.
24 July 2020	The overall rationale for the amendment was to provide clarification regarding laboratory tests for hepatitis B virus (HBV) and hepatitis C virus (HCV) during screening.

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.

Improvements in BSC have reduced mortality and morbidity which in turn minimizes the impact that additional treatment regimens can have on prognosis and recovery. Variability in population and BSC performance poses challenges to demonstrate benefit.

Notes: