Clinical trial results:
A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, DOSE-FINDING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF CC-90001 IN SUBJECTS WITH NON-ALCOHOLIC STEATOHEPATITIS (NASH) AND LIVER FIBROSIS

Summary

EudraCT number	2018-004431-79
Trial protocol	GB FR ES PL
Global end of trial date	28 September 2021

Results information

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

Trial information

Trial identification

Sponsor protocol code	CC-90001-NASH-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04048876
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	28 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 September 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the effect of oral CC-90001, administered once daily (QD), compared with placebo, on liver histology in subjects with nonalcoholic steatohepatitis (NASH) and Stage 2 or Stage 3 fibrosis.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 August 2019
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	Japan: 12
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	56
EEA total number of subjects	11

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	41
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

56 Participants Randomized and Treated

Period 1

Period 1 title	Placebo Controlled Phase
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	Treatment 1

Arm description:

CC-90001 100 mg PO QD

Arm type	Experimental
Investigational medicinal product name	CC-90001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg

Arm title	Treatment 2

Arm description:

CC-90001 200 mg PO QD

Arm type	Experimental
Investigational medicinal product name	CC-90001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg

Arm title	Treatment 3

Arm description:

CC-90001 400 mg PO QD

Arm type	Experimental
Investigational medicinal product name	CC-90001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg

Arm title	Placebo

Arm description:

Placebo in placebo controlled phase. CC-90001 100mg 200mg or 400mg in active treatment extension phase

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:

Placebo

Number of subjects in period 1	Treatment 1	Treatment 2	Treatment 3
Started	13	15	13
Continuing to Follow Up	7	12	8
Completed	2	0	3
Not completed	11	15	10
Consent withdrawn by subject	1	2	-
Adverse event, non-fatal	-	1	-
Study Terminated by Sponsor	10	12	10

Number of subjects in period 1	Placebo
Started	15
Continuing to Follow Up	11
Completed	2
Not completed	13
Consent withdrawn by subject	1
Adverse event, non-fatal	-
Study Terminated by Sponsor	12

Period 2

Period 2 title	Active Treatment Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes

Arm title	Treatment 1
Arm description:	
CC-90001 100 mg PO QD	
Arm type	Experimental
Investigational medicinal product name	CC-90001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
100 mg	
Arm title	Treatment 3
Arm description:	
CC-90001 400 mg PO QD	
Arm type	Experimental
Investigational medicinal product name	CC-90001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
400 mg	
Arm title	Placebo
Arm description:	
Placebo in placebo controlled phase. CC-90001 100mg 200mg or 400mg in active treatment extension phase	
Arm type	Placebo
Investigational medicinal product name	CC-90001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
100 mg	
Investigational medicinal product name	CC-90001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
400 mg	

Number of subjects in period 2	Treatment 1	Treatment 3	Placebo
Started	2	3	2
Completed	0	0	0
Not completed	2	3	2
Study Terminated by Sponsor	2	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Treatment 1
Reporting group description:	
CC-90001 100 mg PO QD	
Reporting group title	Treatment 2
Reporting group description:	
CC-90001 200 mg PO QD	
Reporting group title	Treatment 3
Reporting group description:	
CC-90001 400 mg PO QD	
Reporting group title	Placebo
Reporting group description:	
Placebo in placebo controlled phase. CC-90001 100mg 200mg or 400mg in active treatment extension phase	

Reporting group values	Treatment 1	Treatment 2	Treatment 3
Number of subjects	13	15	13
Age categorical Units: Subjects			
Adults (18-64 years)	10	11	10
From 65-84 years	3	4	3
Age Continuous Units: Years			
arithmetic mean	52.2	58.3	52.1
standard deviation	± 12.37	± 9.92	± 11.91
Sex: Female, Male Units: Participants			
Female	8	11	6
Male	5	4	7
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	5	5	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	7	9	11
More than one race	0	0	0
Unknown or Not Reported	1	1	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	0	4
Not Hispanic or Latino	10	15	9
Unknown or Not Reported	0	0	0

Reporting group values	Placebo	Total	
Number of subjects	15	56	

Age categorical Units: Subjects			
Adults (18-64 years)	10	41	
From 65-84 years	5	15	
Age Continuous Units: Years			
arithmetic mean	60.5		
standard deviation	± 8.20	-	
Sex: Female, Male Units: Participants			
Female	12	37	
Male	3	19	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	4	15	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	9	36	
More than one race	0	0	
Unknown or Not Reported	2	5	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	9	
Not Hispanic or Latino	12	46	
Unknown or Not Reported	1	1	

End points

End points reporting groups	
Reporting group title	Treatment 1
Reporting group description: CC-90001 100 mg PO QD	
Reporting group title	Treatment 2
Reporting group description: CC-90001 200 mg PO QD	
Reporting group title	Treatment 3
Reporting group description: CC-90001 400 mg PO QD	
Reporting group title	Placebo
Reporting group description: Placebo in placebo controlled phase. CC-90001 100mg 200mg or 400mg in active treatment extension phase	
Reporting group title	Treatment 1
Reporting group description: CC-90001 100 mg PO QD	
Reporting group title	Treatment 3
Reporting group description: CC-90001 400 mg PO QD	
Reporting group title	Placebo
Reporting group description: Placebo in placebo controlled phase. CC-90001 100mg 200mg or 400mg in active treatment extension phase	

Primary: Percentage of participants who achieve a ≥1 stage improvement in liver fibrosis using the NASH CRN Histological Scoring System at Week 52

End point title	Percentage of participants who achieve a ≥1 stage improvement in liver fibrosis using the NASH CRN Histological Scoring System at Week 52[1]

End point description:

Percentage of participants who achieve a ≥1 stage improvement in liver fibrosis using the NASH CRN Histological Scoring System at Week 52. A participant with a change of ≤ -1 from baseline in fibrosis stage is considered as an improvement responder for this endpoint.

The NASH CRN Histologic Scoring System comprised:
steatosis (0 to 3)
lobular inflammation (0 to 3)
hepatocellular ballooning (0 to 2)
fibrosis disease stage (0 to 4)

· Stage 0 - None;
· Stage 1a - Mild (delicate) zone 3 perisinusoidal fibrosis;
· Stage 1b - Moderate (dense) zone 3 perisinusoidal fibrosis;
· Stage 1c - Portal/periportal fibrosis only;
· Stage 2 - Zone 3 perisinusoidal fibrosis with portal/periportal fibrosis;
· Stage 3 - Bridging fibrosis;
· Stage 4 - Cirrhosis.

End point type	Primary

End point timeframe:

at week 52

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: No Statistical Analysis done for this endpoint

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	15	13	15
Units: Percentage of Participants				
number (confidence interval 95%)	15.4 (1.92 to 45.45)	0 (0 to 21.80)	7.7 (0.19 to 36.03)	6.7 (0.17 to 31.95)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with no worsening of steatohepatitis and ≥1 stage improvement in liver fibrosis score at week 52

End point title	Percentage of participants with no worsening of steatohepatitis and ≥1 stage improvement in liver fibrosis score at week 52

End point description:

Percentage of participants with no worsening of steatohepatitis and ≥1 stage improvement in liver fibrosis score at week 52 using the NASH CRN Histological Scoring System at Week 52. A participant with a change of ≥ -1 from baseline in fibrosis stage and no worsening in steatohepatitis is considered as an improvement responder for this endpoint.

The NASH CRN Histologic Scoring System comprised:
steatosis (0 to 3)
lobular inflammation (0 to 3)
hepatocellular ballooning (0 to 2)
fibrosis disease stage (0 to 4)

· Stage 0 - None;
· Stage 1a - Mild (delicate) zone 3 perisinusoidal fibrosis;
· Stage 1b - Moderate (dense) zone 3 perisinusoidal fibrosis;
· Stage 1c - Portal/periportal fibrosis only;
· Stage 2 - Zone 3 perisinusoidal fibrosis with portal/periportal fibrosis;
· Stage 3 - Bridging fibrosis;
· Stage 4 - Cirrhosis.

End point type	Secondary

End point timeframe:

at week 52

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	15	13	15
Units: Percentage of Participants				
number (confidence interval 95%)	15.4 (1.92 to 45.45)	0 (0 to 21.80)	7.7 (0.19 to 36.03)	6.7 (0.17 to 31.95)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with improvement in total NAS

End point title	Percentage of participants with improvement in total NAS

End point description:

Percentage of participants with an improvement of ≥ 2 points in the total NAS in more than one category of steatosis, lobular inflammation, and hepatocellular ballooning, and no worsening of liver fibrosis at Week 52. A participant with a change of ≤ -2 from baseline in total NAS, a change of ≤ -1 from baseline in more than one subscore, and a change of ≤ 0 from baseline in fibrosis stage is considered as a responder for this endpoint.

End point type	Secondary

End point timeframe:

at week 52

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	15	13	15
Units: Percentage of Participants				
number (confidence interval 95%)	7.7 (0.19 to 36.03)	6.7 (0.17 to 31.95)	15.4 (1.92 to 45.45)	13.3 (1.66 to 40.46)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with resolution of NASH

End point title	Percentage of participants with resolution of NASH

End point description:

Percentage of participants who demonstrate absence of ballooning, and lobular inflammation score of 0 or 1 at Week 52.
Absence of ballooning is defined as a score of 0 in hepatocellular ballooning. A participant with a score of 0 in ballooning, a score of 0 or 1 in lobular inflammation is considered as a responder for this endpoint.

End point type	Secondary

End point timeframe:

at week 52

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	15	13	15
Units: Percentage of Participants				
number (confidence interval 95%)	15.4 (1.92 to 45.45)	0 (0.00 to 21.80)	7.7 (0.19 to 36.03)	6.7 (0.17 to 31.95)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with resolution of NASH with no worsening of liver fibrosis

End point title	Percentage of participants with resolution of NASH with no worsening of liver fibrosis

End point description:

Percentage of participants who demonstrate absence of ballooning, and lobular inflammation score of 0 or 1 and no worsening of liver fibrosis at Week 52

Absence of ballooning is defined as a score of 0 in hepatocellular ballooning. Worsening of fibrosis stage was defined as progression of NASH CRN fibrosis stage. A participant with a score of 0 in ballooning, a score of 0 or 1 in lobular inflammation, and a change of ≤ 0 from baseline in fibrosis stage is considered as a responder for this endpoint.

End point type	Secondary

End point timeframe:

at week 52

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	15	13	15
Units: Percentage of Participants				
number (confidence interval 95%)	15.4 (1.92 to 45.45)	0 (0.00 to 21.80)	7.7 (0.19 to 36.03)	6.7 (0.17 to 31.95)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who progressed to cirrhosis

End point title	Percentage of participants who progressed to cirrhosis

End point description:

Percentage of participants who progress to cirrhosis

End point type	Secondary

End point timeframe:

at week 52

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	15	13	15
Units: Percentage of Participants				
number (confidence interval 95%)	0 (0 to 24.71)	0 (0.00 to 21.80)	7.7 (0.19 to 36.03)	6.7 (0.17 to 31.95)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Liver Biochemistry

End point title	Mean Change from Baseline in Liver Biochemistry

End point description:

Mean change from Baseline in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT)

End point type	Secondary

End point timeframe:

through week 52

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	0[2]	3	2
Units: U/L				
arithmetic mean (standard deviation)				
ALT (U/L)	26.0 (± 19.80)	()	-22.3 (± 14.19)	-6.5 (± 21.92)
AST (U/L)	9.5 (± 10.61)	()	-17.0 (± 10.15)	7.0 (± 4.24)
GGT (U/L)	13.0 (± 28.28)	()	-6.3 (± 5.86)	2.5 (± 58.69)

Notes:

[2] - No subjects in this arm were analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Metabolic Parameters

End point title	Mean Change from Baseline in Metabolic Parameters

End point description:

Mean change from baseline in total low density cholesterol (LDL) high density cholesterol (HDL), and triglycerides

End point type	Secondary

End point timeframe:
through week 52

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	0[3]	3	2
Units: mmol/L				
arithmetic mean (standard deviation)				
HDL (mmol/L)	0.005 (± 0.0354)	()	0.147 (± 0.2155)	0.120 (± 0.2687)
LDL (mmol/L)	0.970 (± 0.4525)	()	0.623 (± 0.3785)	-1.395 (± 1.3223)
Triglycerides (mmol/L)	-0.135 (± 0.0495)	()	0.027 (± 0.2650)	-0.805 (± 0.5445)

Notes:
[3] - No subjects in this arm

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax

End point title	Cmax

End point description:
Cmax is defined as maximum plasma concentration of the drug

End point type	Secondary

End point timeframe:
Day 1 and at Week 4

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	0[4]	2	0[5]
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1	501.0 (± 99999)	()	2938.8 (± 44.94)	()
Week 4	352.0 (± 99999)	()	2610.0 (± 99999)	()

Notes:
[4] - No subjects in this arm
[5] - No subjects in this arm

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax

End point title	Tmax

End point description:

Tmax is defined is the time to maximum plasma concentration

End point type	Secondary

End point timeframe:

Day 1 and at Week 4

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	0[6]	2	0[7]
Units: hours				
median (full range (min-max))				
Day 1	2.0 (2 to 2)	(to)	2.0 (2 to 2)	(to)
Week 4	2.0 (2 to 2)	(to)	4.0 (4 to 4)	(to)

Notes:

[6] - No subjects in this arm

[7] - No subjects in this arm

Statistical analyses

No statistical analyses for this end point

Secondary: AUC 0-t

End point title	AUC 0-t

End point description:

area under the plasma concentration time-curve. AUC from time 0 to the last time of quantifiable concentration

Here "99999" = NA

End point type	Secondary

End point timeframe:

Day 1 and at Week 4

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	0[8]	2	0[9]
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1	2322.7 (± 99999)	()	26803.9 (± 62.87)	()
Week 4	2530.5 (± 99999)	()	20918.8 (± 99999)	()

Notes:
[8] - No subjects in this arm
[9] - No subjects in this arm

Statistical analyses

No statistical analyses for this end point

Secondary: AUC t

End point title	AUC t

End point description:
area under the plasma concentration time-curve. AUC over the dosing interval

Here "99999" = NA

End point type	Secondary

End point timeframe:
Day 1 and at Week 4

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	0[10]	2	0[11]
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1	2322.7 (± 99999)	()	27173.7 (± 59.71)	()
Week 4	2530.5 (± 99999)	()	21182.1 (± 99999)	()

Notes:
[10] - No subjects in this arm
[11] - No subjects in this arm

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent total body clearance of the drug

End point title	Apparent total body clearance of the drug

End point description:
apparent total body clearance of the drug (CL/F)

Here "99999" = NA

End point type	Secondary

End point timeframe:
Day 1 and at Week 4

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	0[12]	2	0[13]
Units: L/h				
geometric mean (geometric coefficient of variation)				
Day 1	99999 (± 99999)	()	99999 (± 99999)	()
Week 4	39.5 (± 99999)	()	18.9 (± 99999)	()

Notes:

[12] - No subjects in this arm

[13] - No subjects in this arm

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with treatment related safety events

End point title	Number of participants with treatment related safety events

End point description:

Number of participants with treatment related safety events

Study Drug (SD)
Dose Interruption (DI)

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	15	13	15
Units: participants				
Participants with at least one TEAE	10	13	12	10
Subjects with ≥ 1TEAE related to study drug (SD)	4	5	10	3
Subjects with ≥ 1 serious TEAE	2	1	2	0
Subjects with ≥ 1 serious TEAE related to SD	0	1	0	0
Subjects with ≥ 1 grade 3/4 TEAE	2	1	2	1
Subjects with ≥ 1 grade 3/4 TEAE related to SD	0	1	0	0
Subjects with ≥ 1 TEAE leading to DI	2	1	2	0
Subjects with ≥ 1 TEAE leading to SD withdrawal	0	1	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline of ECG results - PR Intervals

End point title	Mean change from baseline of ECG results - PR Intervals

End point description:

Mean change from baseline in PR interval

PR Interval: Atrial depolarization and conduction through the AV node
Normal Range: 0.12 - 0.20 (120 to 200 msec)

End point type	Secondary

End point timeframe:

Up to week 52

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13[14]	15[15]	13[16]	15[17]
Units: msec				
arithmetic mean (standard deviation)				
Week 4	5.8 (± 10.42)	-5.5 (± 10.18)	3.6 (± 14.84)	5.0 (± 19.24)
Week 12	5.7 (± 10.32)	-2.3 (± 10.01)	2.3 (± 21.02)	15.2 (± 26.99)
Week 24	4.4 (± 7.46)	-2.8 (± 3.90)	-3.7 (± 8.99)	3.2 (± 12.75)
Week 52	-7.0 (± 9.90)	99999 (± 99999)	-7.7 (± 27.06)	13.5 (± 10.61)

Notes:

[14] - Number analyzed at given week
Week 4 - 11
Week 12- 9
Week 24 - 7
Week 52 - 2
[15] - Number analyzed at given week
Week 4 - 13
Week 12- 10
Week 24 - 5
Week 52 - 0
[16] - Number analyzed at given week
Week 4 - 10
Week 12- 10
Week 24 - 7
Week 52 -3
[17] - Number analyzed at given week
Week 4 - 12
Week 12- 9
Week 24 - 6
Week 52 -2

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline of ECG results - QRS Duration

End point title	Mean change from baseline of ECG results - QRS Duration

End point description:

Mean change from baseline in QRS duration

QRS Duration: Ventricular depolarization and atrial repolarization
Normal Range: 0.08 to 0.10 (80 to 100 msec)

End point type	Secondary

End point timeframe:

Up to week 52

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13[18]	15[19]	13[20]	15[21]
Units: msec				
arithmetic mean (standard deviation)				
Week 4	0.8 (± 2.93)	0.1 (± 5.79)	-0.1 (± 6.90)	-1.2 (± 3.59)
Week 12	4.0 (± 3.77)	0.7 (± 3.56)	-2.5 (± 5.38)	-2.8 (± 3.11)
Week 24	-8.7 (± 16.54)	0.6 (± 4.77)	-2.7 (± 3.77)	-1.0 (± 3.90)
Week 52	-5.5 (± 7.78)	99999 (± 99999)	-1.3 (± 4.16)	1.0 (± 7.07)

Notes:

[18] - Number analyzed at given week
Week 4 - 11
Week 12- 9
Week 24 - 7
Week 52 - 2

[19] - Number analyzed at given week
Week 4 - 13
Week 12- 10
Week 24 - 5
Week 52 - 0

[20] - Number analyzed at given week
Week 4 - 10
Week 12- 10
Week 24 - 7
Week 52 -3

[21] - Number analyzed at given week
Week 4 - 12
Week 12- 9
Week 24 - 6
Week 52 -2

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline of ECG results - QT Interval

End point title	Mean change from baseline of ECG results - QT Interval

End point description:

Mean change from baseline in QT interval

QT Interval: Ventricular depolarization plus ventricular repolarization
Normal Range: 400 to 460 msec

End point type	Secondary

End point timeframe:

Up to week 52

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13[22]	15[23]	13[24]	15[25]
Units: msec				
arithmetic mean (standard deviation)				
Week 4	0.4 (± 19.71)	-7.6 (± 12.52)	-0.5 (± 9.47)	1.0 (± 13.48)
Week 12	10.6 (± 24.57)	-9.8 (± 15.48)	-2.0 (± 27.22)	-3.3 (± 17.33)
Week 24	12.0 (± 11.55)	-11.2 (± 12.99)	0.6 (± 22.10)	13.5 (± 27.07)
Week 52	-6.0 (± 8.49)	99999 (± 99999)	-15.3 (± 21.73)	8.0 (± 25.46)

Notes:

[22] - Number analyzed at given week
Week 4 - 11
Week 12- 9
Week 24 - 7
Week 52 -2

[23] - Number analyzed at given week
Week 4 - 13
Week 12- 10
Week 24 - 5
Week 52 - 0

[24] - Number analyzed at given week
Week 4 - 10
Week 12- 10
Week 24 - 7
Week 52 -3

[25] - Number analyzed at given week
Week 4 - 12
Week 12- 9
Week 24 - 6
Week 52 -2

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline of ECG results - QTcB Interval

End point title	Mean change from baseline of ECG results - QTcB Interval

End point description:

Mean change from baseline in QTcB interval

QT Interval: Ventricular depolarization plus ventricular repolarization
Normal Range: 400 to 460 msec

QTc: QT interval corrected based on the patient's heart rate

QTcB: An electrocardiographic finding in which the QT interval corrected for heart rate using Bazzett's formula. $QTc = QT/\sqrt{(RR)}$ RR= Respiration Rate

End point type	Secondary

End point timeframe:

Up to week 52

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13[26]	15[27]	13[28]	15[29]
Units: msec				
arithmetic mean (standard deviation)				
Week 4	-0.8 (± 16.18)	-2.8 (± 17.51)	-4.0 (± 15.18)	-9.3 (± 10.81)
Week 12	-0.3 (± 19.75)	-1.5 (± 10.62)	-9.6 (± 22.59)	1.4 (± 9.25)
Week 24	7.9 (± 10.75)	1.2 (± 16.41)	0.7 (± 39.65)	-11.0 (± 10.55)
Week 52	-13.0 (± 1.41)	99999 (± 99999)	-35.0 (± 9.85)	4.5 (± 14.85)

Notes:

[26] - Number analyzed at given week
Week 4 - 9
Week 12- 9
Week 24 - 7
Week 52 -2

[27] - Number analyzed at given week
Week 4 - 12
Week 12- 10
Week 24 - 5
Week 52 -0

[28] - Number analyzed at given week
Week 4 - 9
Week 12- 9
Week 24 - 6
Week 52 -3

[29] - Number analyzed at given week
Week 4 - 12
Week 12- 9
Week 24 - 4
Week 52 -2

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline of ECG results - QTcF Interval

End point title	Mean change from baseline of ECG results - QTcF Interval

End point description:

Mean change from baseline in QTcF interval

QT Interval: Ventricular depolarization plus ventricular repolarization
Normal Range: 400 to 460 msec

QTc: QT interval corrected based on the patient's heart rate

QTcF: An electrocardiographic finding in which the QT interval corrected for heart rate using Fridericia's formula. QTc = QT/(RR) RR = Respiration rate

End point type	Secondary

End point timeframe:

Up to week 52

End point values	Treatment 1	Treatment 2	Treatment 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13[30]	15[31]	13[32]	15[33]
Units: msec				
arithmetic mean (standard deviation)				
Week 4	-3.9 (± 15.33)	-3.5 (± 14.45)	-1.4 (± 12.06)	-4.0 (± 10.53)
Week 12	1.0 (± 12.33)	-4.6 (± 6.43)	-6.3 (± 21.54)	-1.4 (± 11.24)
Week 24	9.4 (± 8.71)	-3.0 (± 10.49)	-0.9 (± 30.17)	2.2 (± 12.67)
Week 52	-11.5 (± 3.54)	99999 (± 99999)	-27.7 (± 7.77)	5.5 (± 0.71)

Notes:

[30] - Number analyzed at given week
Week 4 - 8
Week 12- 7
Week 24 - 5
Week 52 -2

[31] - Number analyzed at given week
Week 4 - 13
Week 12- 10
Week 24 - 5
Week 52 -0

[32] - Number analyzed at given week
Week 4 - 10
Week 12- 10
Week 24 - 7
Week 52 -3

[33] - Number analyzed at given week
Week 4 - 12
Week 12- 9
Week 24 - 6
Week 52 -2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events: up to 108 weeks
All-Cause Mortality: up to 108 weeks

Adverse event reporting additional description:

TEAE includes AEs that begin or worsen on or after the first dose of study drug following randomization at Week 0 through 31 days after the last dose of study drug or on the date of the actual last follow-up in the study, whichever is later.

All-cause mortality will be calculated from date of randomization to study completion.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Treatment 1

Reporting group description:

CC-90001 100 mg PO QD

Reporting group title	Treatment 2

Reporting group description:

CC-90001 200 mg PO QD

Reporting group title	400 mg QD

Reporting group description: -

Reporting group title	Placebo

Reporting group description:

Placebo in placebo controlled phase. CC-90001 100mg, 200mg or 400mg in active treatment extension phase

Serious adverse events	Treatment 1	Treatment 2	400 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 13 (15.38%)	1 / 15 (6.67%)	2 / 13 (15.38%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer metastatic			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ligament sprain			

subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spinal retrolisthesis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer metastatic			

subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Spinal retrolisthesis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Treatment 1	Treatment 2	400 mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 13 (76.92%)	13 / 15 (86.67%)	12 / 13 (92.31%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	1 / 13 (7.69%)	2 / 15 (13.33%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
Injection site pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Cough			

subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pleurisy			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Depression			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
Insomnia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Libido decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Liver function test increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Occult blood positive			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Urine cytology abnormal			

subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Joint injury			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Muscle strain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Tooth fracture			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Headache			

subjects affected / exposed	1 / 13 (7.69%)	2 / 15 (13.33%)	4 / 13 (30.77%)
occurrences (all)	2	3	6
Blood and lymphatic system disorders			
Allergic eosinophilia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Eosinophilia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Vertigo			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Abdominal distension			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Abdominal pain lower			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Chronic gastritis			

subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	2 / 13 (15.38%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	2	1	0
Diarrhoea			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	4	0	0
Dry mouth			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Epigastric discomfort			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Eructation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Frequent bowel movements			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Haematochezia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 13 (7.69%)	2 / 15 (13.33%)	0 / 13 (0.00%)
occurrences (all)	1	2	0
Hiatus hernia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Large intestine polyp			

subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	6 / 13 (46.15%)
occurrences (all)	1	1	8
Salivary hypersecretion			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Prurigo			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hand dermatitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Skin lesion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Skin mass			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Arthritis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Back pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Flank pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Joint stiffness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Muscle contracture			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Muscular weakness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Osteoarthritis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			

subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Pain in jaw			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Tendonitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
COVID-19			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	4 / 13 (30.77%)
occurrences (all)	0	0	4
Cystitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Hordeolum			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nail bed infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	2	0	0
Sinusitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1

Upper respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Diabetes mellitus			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 13 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 15 (73.33%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		

Non-cardiac chest pain			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Pleurisy			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Libido decreased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Investigations			

Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Liver function test increased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Occult blood positive			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Urine cytology abnormal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Joint injury			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Muscle strain			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Procedural pain			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Tooth fracture			

subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Allergic eosinophilia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Eosinophilia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Iron deficiency anaemia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Vertigo			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		

Abdominal distension				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Abdominal pain				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Abdominal pain upper				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Abdominal pain lower				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Chronic gastritis				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Constipation				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Diarrhoea				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Dry mouth				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Epigastric discomfort				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Eructation				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Frequent bowel movements				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			

Flatulence			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Haematochezia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Hiatus hernia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Large intestine polyp			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Salivary hypersecretion			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Prurigo			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Hand dermatitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Pruritus			

subjects affected / exposed occurrences (all) Skin lesion subjects affected / exposed occurrences (all) Skin mass subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 1 / 15 (6.67%) 1		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all)	 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Arthritis subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Flank pain subjects affected / exposed occurrences (all) Joint stiffness subjects affected / exposed occurrences (all) Muscle contracture	 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0		

subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Osteoarthritis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pain in jaw			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Tendonitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
COVID-19			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Gastroenteritis viral			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		

Hordeolum			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nail bed infection			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Diabetes mellitus			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2019	Changes in the following sections. Medical Monitor / Emergency Contact Information Celgene therapeutic area head signature page Introduction Exclusion Criteria for All Subjects Exclusion Criteria for All Subjects (Section 4.3.1) and Prohibited Concomitant Medications and Procedures Prohibited Concomitant Medications and Procedures Table of Events Sample Size and Power Considerations Discontinuations
26 September 2019	• Medical Monitor / Emergency Contact Information - Contact information was changed to replace medical monitor's phone numbers with hotline number • Protocol Summary and Overall Study Design (Section 3) - Screening period was extended to 10 weeks to allow enough time for completion of study procedures. • Study Population (Section 4) - Inclusion criterion #5 was updated to clarify that the historical liver biopsy in subjects who had been on therapy for treatment of NASH is not to be accepted. - Inclusion criteria #6 and #7 were updated to ensure stable doses of medications prior to and after historical liver biopsy is obtained, if the historical biopsy was going to be used for the inclusion criteria. - Exclusion criterion #3 was corrected. - Exclusion criterion #17 were updated to clarify that positive screening hepatitis B/C is also exclusionary for the study. - Exclusion criterion #31 was added to exclude subjects with history of Gilbert's syndrome since clinical manifestations of Gilbert's syndrome might confound the safety and efficacy assessments of CC-90001. • Table of Events (Section 5) and Procedures (Section 6) - Added screening α-fetoprotein test to Table of Events and Procedures sections. Protocol Section 4.3.2 Exclusion Criteria for the Subjects with Stage 3 Fibrosis excludes subjects with a screening α-fetoprotein ≥ 200 ng/mL and α-fetoprotein > 20 ng/mL should be discussed with Sponsor to review the evaluation of Hepatocellular Cancer (HCC). - Added ultrasound and α-fetoprotein test at Early Termination Visit to ensure HCC surveillance to be done for early terminated subjects with Stage 4 fibrosis. • Prohibited Concomitant Medications and Procedures (Section 8.2) - Acetaminophen dose was corrected. • Individual Subject Stopping Criteria (Section 11.1.1) - Clarification was made on FOBT stopping criterion.

11 November 2020	Protocol Summary, Rationale (Section 1.3), Study objectives and Endpoints (Section 2), Overall Study Design (Section 3), Study Population (Section 4), Method of Treatment Assignment (Section 7.3), Statistical Considerations (Section 9), Appendix B and Appendix C - Expanded study population to allow subjects with NASH and Stage 2 fibrosis in the study and evaluate efficacy and safety of CC-90001 in these subjects. - References to Appendix B and Appendix C were removed from Study population, Table of Events footnote and Procedures sections because they did not apply to Stage 2 fibrosis. Appendix B and Appendix C were removed as well. Study objectives and Endpoints (Section 2) - Added exploratory endpoint for Ishak score and Section 6.6 Efficacy Assessment was updated accordingly - Exploratory endpoints of 2-dimensional magnetic resonance elastography (MRE), 3-dimentional MRE and magnetic resonance imaging-proton density fat fraction (MRI-PDFF) were updated to add absolute change from baseline - Added N-terminal type III collagen propeptide (PRO-C3) to exploratory pharmacodynamic endpoint Added rationale on assessment of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) serologic status Added SARS-CoV-2 serology to the Table of Events and Section 6.8.1 Biomarkers/Pharmacodynamics - Added exploratory objective and endpoint on SARS-CoV-2 serology - Revised exclusion criterion #13 to clarify that subjects with SARS-CoV-2 infection within 4 weeks of Screening will be excluded and symptoms must have completely resolved - Added exclusion criterion #34 to exclude subjects who have received live attenuated or investigational SARS-CoV-2 vaccine within 3 months prior to the first dose of study treatment. - Changes were made to clarify that fasting is required for certain visits.
16 April 2021	100 mg dose treatment arm was removed - Data from non-clinical and clinical studies suggest that therapeutic doses in humans are likely to be 200 mg and 400 mg once daily (QD). 100 mg QD dose of CC-90001 is likely not as effective a dose in subjects with NASH and liver fibrosis. The subjects who are randomized to the 100 mg dose group prior to implementation of Protocol Amendment 4 will stay on 100 mg QD dose throughout the study. Stage 4 population was removed - The protocol was revised to focus on assessing the efficacy and safety of CC-90001 in subjects with NASH and Stage 2 or Stage 3 liver fibrosis in this study. Active Treatment/Extension Phase was removed - Active treatment/extension phase was removed to reduce burden for the subjects due to the Coronavirus Disease 2019 (COVID-19) pandemic and to shorten the duration of the study. Subjects who sign informed consent form (ICF) prior to the implementation of Protocol Amendment 4 will have an option to participate active treatment/extension phase. Exclusion criterion #21 “Subjects has 2 positive fecal occult blood test (FOBT) during Screening, collected at least 4 weeks apart” was removed - Gastrointestinal (GI) toxicity was noted in nonclinical studies. The clinical studies to date have not indicated an increased risk for GI bleeding. Positive FOBT may be caused by different cuases (such as rectal hemmorhage, ulcers, colitis, divertriculosis). The protocol has excluded the subjects with a history of inflammatory bowel disease and the subjects with a history of bleeding peptic ulcer or bleeding diverticular disease within 5 years. Furthermore, the protocol also implemented FOBT at Screening and approximately every 12 weeks during the study and discontinuation criteria for the subject with positive FOBT in the study. With all these in place the occurrence of GI bleeding in the study continues to be well monitored to ensure safety of subjects over the course of the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported