Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of CF102 in the Second-Line Treatment of Advanced Hepatocellular Carcinoma in Subjects with Child-Pugh Class B Cirrhosis

Summary

EudraCT number	2014-000489-23
Trial protocol	BG
Global end of trial date	17 March 2019

Results information

Result version number	v1 (current)
This version publication date	04 July 2021
First version publication date	04 July 2021

Trial information

Trial identification

Sponsor protocol code	CF102-201HCC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02128958
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Can-Fite BioPharma, Ltd
Sponsor organisation address	10 Bareket Street, Petach Tikva, Israel,
Public contact	Clinical Director, Can Fite BioPharma, Ltd, +972 528998672, sari@canfite.co.il
Scientific contact	Clinical Director, Can Fite BioPharma, Ltd, +972 528998672, sari@canfite.co.il

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	27 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 November 2017
Global end of trial reached?	Yes
Global end of trial date	17 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of orally administered CF102 25 mg twice daily (BID) as compared to placebo, as determined by Overall Survival (OS), when used as second-line therapy in subjects with advanced hepatocellular carcinoma (HCC) and Child-Pugh Class B (CPB) cirrhosis.

Protection of trial subjects:

This study was reviewed and approved by the IRB/EC representing each participating institution prior to enrolling subjects. It was conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and was consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements.

Background therapy:

None

Evidence for comparator:

Placebo as control

Actual start date of recruitment	07 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 41
Country: Number of subjects enrolled	Bulgaria: 11
Country: Number of subjects enrolled	Serbia: 15
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	78
EEA total number of subjects	52

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)	41
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 15 sites in 5 countries (3 sites in Bulgaria, 2 sites in Serbia, 1 site in Israel, 7 sites in Romania, 2 sites in the United States) . There were 78 subjects randomized to treatment between 07 Dec 2014 and 27 Nov 2017.

Pre-assignment

Screening details:

At a Screening Visit subjects who provided written informed consent had procedures performed including medical history, physical examination,eligibility criteria check, body weight, vital signs, laboratory tests, ECOG, ocncomitant medications, tumour imaging (double blind period only), and adverse events (open label period only).

Period 1

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

Blinding implementation details:

The trial was double-blind, meaning the subject and Investigator/staff did not have access to or knowledge of the subject's treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	CF102 25 mg

Arm description:

Medication (CF102 25 mg) was taken orally BID for consecutive 28-day cycles.

Arm type	Active comparator
Investigational medicinal product name	Methyl 1-[N6-(3-iodobenzyl)-adenin-9-yl]-β-D-ribofuronamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

25 mg capsule BID

Arm title	Placebo

Arm description:

Medication (placebo) was taken orally BID for consecutive 28 day cycles in a double-blinded fashion

Arm type	Placebo
Investigational medicinal product name	Placebo, matching for methyl 1-[N6-(3-iodobenzyl)-adenin-9-yl]-β-D-ribofuronamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Matching CF102 placebo capsule BID

Number of subjects in period 1	CF102 25 mg	Placebo
Started	50	28
Completed	29	18
Not completed	21	10
Adverse event, serious fatal	19	9
Consent withdrawn by subject	2	1

Baseline characteristics

Reporting groups	
Reporting group title	CF102 25 mg
Reporting group description:	
Medication (CF102 25 mg) was taken orally BID for consecutive 28-day cycles.	
Reporting group title	Placebo
Reporting group description:	
Medication (placebo) was taken orally BID for consecutive 28 day cycles in a double-blinded fashion	

Reporting group values	CF102 25 mg	Placebo	Total
Number of subjects	50	28	78
Age categorical			
Subjects with advanced hepatocellular carcinoma (HCC) and Child-Pugh Class B (CPB) cirrhosis			
Units: Subjects			
Adults (18-64 years)	28	13	41
From 65-84 years	22	15	37
Gender categorical Units: Subjects			
Female	25	14	39
Male	25	14	39

Subject analysis sets	
Subject analysis set title	Safety Analysis Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Population consisted of all subjects who received at least one dose of study medication. Analyses of safety assessments were performed using the Safety Population.	
Subject analysis set title	Intention-To-Treat Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent-To-Treat (ITT) Population was defined as all subjects in the Safety Population with any post-Baseline assessment recorded. Exclusion of subjects from the ITT Population was determined prior to unblinding. All efficacy analyses were performed using the ITT Population.	
Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol (PP) Population was defined as all subjects in the ITT Population with no major protocol deviations, including major violations of inclusion and exclusion criteria and violation of RECIST requirements regarding the number of target lesions at Screening. Exclusion of subjects from the PP Population was determined prior to unblinding. Tumor response was analyzed for the PP Population.	

Reporting group values	Safety Analysis Population	Intention-To-Treat Population	Per Protocol Population
Number of subjects	78	78	78
Age categorical			
Subjects with advanced hepatocellular carcinoma (HCC) and Child-Pugh Class B (CPB) cirrhosis			
Units: Subjects			
Adults (18-64 years)	41	41	41
From 65-84 years	37	37	37

Gender categorical Units: Subjects			
Female	39	0	0
Male	39	0	0

End points

End points reporting groups

Reporting group title	CF102 25 mg
Reporting group description:	
Medication (CF102 25 mg) was taken orally BID for consecutive 28-day cycles.	
Reporting group title	Placebo
Reporting group description:	
Medication (placebo) was taken orally BID for consecutive 28 day cycles in a double-blinded fashion	
Subject analysis set title	Safety Analysis Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Population consisted of all subjects who received at least one dose of study medication. Analyses of safety assessments were performed using the Safety Population.	
Subject analysis set title	Intention-To-Treat Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent-To-Treat (ITT) Population was defined as all subjects in the Safety Population with any post-Baseline assessment recorded. Exclusion of subjects from the ITT Population was determined prior to unblinding. All efficacy analyses were performed using the ITT Population.	
Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol (PP) Population was defined as all subjects in the ITT Population with no major protocol deviations, including major violations of inclusion and exclusion criteria and violation of RECIST requirements regarding the number of target lesions at Screening. Exclusion of subjects from the PP Population was determined prior to unblinding. Tumor response was analyzed for the PP Population.	

Primary: Overall survival - Primary

End point title	Overall survival - Primary
End point description:	
The time to event assessment for OS was the number of days from Day 1 of Cycle 1 to the day of death+1, where a death could have been due to any cause.	
End point type	Primary
End point timeframe:	
Baseline to time of death	

End point values	CF102 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	28		
Units: Months				
median (inter-quartile range (Q1-Q3))				
Overall survival	4.1 (2.2 to 14.8)	4.3 (2.0 to 8.9)		

Attachments (see zip file)	Product Limit Survival Estimates, OS (ITT Pop)/CF102-

Statistical analyses

Statistical analysis title	Time to Event - Overall Survival (months)

Statistical analysis description:

Time to event variables were summarized using the number observed, number censored, median, and 25th and 75th percentiles from Kaplan-Meier curves. Data were summarized using descriptive statistics (number of subjects (n), mean, median, standard deviation, minimum, and maximum) for continuous variables. Categorical variables were summarized using frequencies and percentages.

Comparison groups	CF102 25 mg v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.508 [2]
Method	Logrank

Notes:

[1] - Kaplan Meier log-rank test.

[2] - Calculated using logrank test

Statistical analysis title	Time to Event - Disease Progression (months)

Statistical analysis description:

Time to event variables were summarized using the number observed, number censored, median, and 25th and 75th percentiles from Kaplan-Meier curves. Data were summarized using descriptive statistics (number of subjects (n), mean, median, standard deviation, minimum, and maximum) for continuous variables. Categorical variables were summarized using frequencies and percentages.

Comparison groups	CF102 25 mg v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.371
Method	Logrank

Notes:

[3] - Kaplan Meier log-rank test.

Secondary: Disease Progression

End point title	Disease Progression

End point description:

Time to Progression (TTP) was the number of days from Day 1 of Cycle 1 to the day of PD+1.
Progression Free Survival was the number of days from Day 1 of Cycle 1 to the day of death or PD+1.

End point type	Secondary

End point timeframe:

Baseline to time to event

End point values	CF102 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	28		
Units: Months				
median (inter-quartile range (Q1-Q3))				
TTP	5.1 (1.9 to 11.2)	3.3 (1.9 to 33.2)		

Attachments (see zip file)	KM Curve for TTP (ITT)/CF102-201HCC_2014_000489_23

Statistical analyses

Statistical analysis title	TPP

Statistical analysis description:

Time to Progression (TTP) was the number of days from Day 1 of Cycle 1 to the day of PD+1.
Progression Free Survival was the number of days from Day 1 of Cycle 1 to the day of death or PD+1

Comparison groups	Placebo v CF102 25 mg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.371
Method	Logrank

Notes:

[4] - Kaplan Meier - Logrank

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression Free Survival was the number of days from Day 1 of Cycle 1 to the day of death or PD+1.

End point type	Secondary

End point timeframe:

Baseline to time of event

End point values	CF102 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	28		
Units: Months				
median (inter-quartile range (Q1-Q3))				
PFS	2.5 (1.8 to 6.1)	1.9 (1.8 to 3.8)		

Attachments (see zip file)	KM Curve for PFS (ITT)/CF102-201HCC_2014_000489_23

Statistical analyses

Statistical analysis title	Time to Event - Progression-free Survival (months)
Statistical analysis description: Progression Free Survival was the number of days from Day 1 of Cycle 1 to the day of death or PD+1.	
Comparison groups	CF102 25 mg v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.521
Method	Logrank

Notes:

[5] - Kaplan Meier - Logrank test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events that occurred during the study (Weeks 0 to 28 days)

Adverse event reporting additional description:

AEs coded by MedDRA v 21.0. No and % of subjects with AEs were tabulated by SOC and PT. Assessments included AE type, incidence, severity, seriousness, and treatment relationship. Dose interruptions/reductions, SAEs, AEs resulting in discontinuation, and deaths were collected. Severity grade were according to NCI-CTCAE criteria, v4.0.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	CF102

Reporting group description:

Analysed as the Safety Population during the treatment period (Baseline to Day 28).

Reporting group title	Placebo

Reporting group description:

Analysed as the Safety Population during the treatment period (Baseline to Day 28).

Serious adverse events	CF102	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 50 (74.00%)	20 / 28 (71.43%)	
number of deaths (all causes)	46	26	
number of deaths resulting from adverse events	23	10	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	5 / 50 (10.00%)	2 / 28 (7.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 5	0 / 2	
Metastases to lung			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 50 (2.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

Vascular disorders			
Vena cava thrombosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava occlusion			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Death			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Disease progression			
subjects affected / exposed	14 / 50 (28.00%)	5 / 28 (17.86%)	
occurrences causally related to treatment / all	0 / 14	0 / 5	
deaths causally related to treatment / all	0 / 14	0 / 5	
Chest pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 50 (2.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bilirubin conjugated increased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Myocardial infarction			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 50 (4.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Nervous system disorders			
Coma			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Encephalopathy			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	3 / 50 (6.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Subileus			

subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal adhesions			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	4 / 50 (8.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ascites			
subjects affected / exposed	2 / 50 (4.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritoneal haematoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	0 / 50 (0.00%)	2 / 28 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CF102	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 50 (92.00%)	26 / 28 (92.86%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Orthostatic hypotension			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Pallor			
subjects affected / exposed	1 / 50 (2.00%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	1 / 50 (2.00%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Haematoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	2 / 50 (4.00%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Oedema peripheral			
subjects affected / exposed	10 / 50 (20.00%)	5 / 28 (17.86%)	
occurrences (all)	13	6	
Chills			
subjects affected / exposed	2 / 50 (4.00%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	9 / 50 (18.00%)	3 / 28 (10.71%)	
occurrences (all)	11	4	
Pyrexia			
subjects affected / exposed	3 / 50 (6.00%)	2 / 28 (7.14%)	
occurrences (all)	4	2	
Chest pain			

subjects affected / exposed	2 / 50 (4.00%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Asthenia			
subjects affected / exposed	6 / 50 (12.00%)	6 / 28 (21.43%)	
occurrences (all)	6	9	
Peripheral swelling			
subjects affected / exposed	1 / 50 (2.00%)	1 / 28 (3.57%)	
occurrences (all)	1	2	
Facial pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Swelling			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 50 (10.00%)	3 / 28 (10.71%)	
occurrences (all)	5	3	
Dyspnoea			
subjects affected / exposed	3 / 50 (6.00%)	2 / 28 (7.14%)	
occurrences (all)	3	2	
Haemoptysis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	2 / 50 (4.00%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Respiratory failure			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Alveolitis			

subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 50 (2.00%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 50 (2.00%)	1 / 28 (3.57%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	2 / 50 (4.00%)	1 / 28 (3.57%)	
occurrences (all)	5	1	
Investigations			
Blood uric acid increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase decreased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 50 (2.00%)	3 / 28 (10.71%)	
occurrences (all)	1	4	
Weight decreased			
subjects affected / exposed	4 / 50 (8.00%)	4 / 28 (14.29%)	
occurrences (all)	7	5	
International normalised ratio abnormal			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	4	0	
Blood bilirubin increased			

subjects affected / exposed	0 / 50 (0.00%)	3 / 28 (10.71%)	
occurrences (all)	0	3	
Weight increased			
subjects affected / exposed	4 / 50 (8.00%)	3 / 28 (10.71%)	
occurrences (all)	5	4	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 50 (8.00%)	2 / 28 (7.14%)	
occurrences (all)	4	2	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 50 (4.00%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Blood creatine increased			
subjects affected / exposed	0 / 50 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	4	
Bilirubin conjugated increased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 50 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Tri-iodothyronine free decreased			
subjects affected / exposed	0 / 50 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Neutrophil count increased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
White blood cell count increased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Liver function test increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Traumatic haematoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	2	
Atrioventricular block first degree			
subjects affected / exposed	1 / 50 (2.00%)	1 / 28 (3.57%)	
occurrences (all)	1	5	
Bundle branch block left			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Atrial fibrillation			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Sinus tachycardia			
subjects affected / exposed	2 / 50 (4.00%)	1 / 28 (3.57%)	
occurrences (all)	3	1	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 50 (6.00%)	1 / 28 (3.57%)	
occurrences (all)	3	1	
Speech disorder			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Movement disorder			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Sciatica			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	3 / 50 (6.00%)	2 / 28 (7.14%)	
occurrences (all)	5	2	
Neuralgia			

subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 50 (14.00%)	6 / 28 (21.43%)	
occurrences (all)	8	11	
Thrombocytopenia			
subjects affected / exposed	2 / 50 (4.00%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Leukopenia			
subjects affected / exposed	2 / 50 (4.00%)	0 / 28 (0.00%)	
occurrences (all)	4	0	
Neutropenia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 50 (18.00%)	6 / 28 (21.43%)	
occurrences (all)	9	7	
Abdominal pain			

subjects affected / exposed	7 / 50 (14.00%)	3 / 28 (10.71%)	
occurrences (all)	7	5	
Vomiting			
subjects affected / exposed	3 / 50 (6.00%)	4 / 28 (14.29%)	
occurrences (all)	3	5	
Constipation			
subjects affected / exposed	0 / 50 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Ascites			
subjects affected / exposed	8 / 50 (16.00%)	3 / 28 (10.71%)	
occurrences (all)	19	3	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	2 / 50 (4.00%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Haematemesis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
subjects affected / exposed	2 / 50 (4.00%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			
subjects affected / exposed	1 / 50 (2.00%)	1 / 28 (3.57%)	
occurrences (all)	0	0	
Gingival bleeding			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			

subjects affected / exposed	2 / 50 (4.00%)	1 / 28 (3.57%)	
occurrences (all)	3	2	
Flatulence			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Hepatomegaly			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Hyperbilirubinaemia			
subjects affected / exposed	4 / 50 (8.00%)	0 / 28 (0.00%)	
occurrences (all)	4	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	2 / 50 (4.00%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Eczema			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Swelling face			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	3 / 50 (6.00%)	1 / 28 (3.57%)	
occurrences (all)	3	1	
Bone pain			
subjects affected / exposed	1 / 50 (2.00%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	1 / 50 (2.00%)	3 / 28 (10.71%)	
occurrences (all)	2	3	
Myalgia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Arthralgia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Infective glossitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Onychomycosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Cellulitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 50 (8.00%)	1 / 28 (3.57%)	
occurrences (all)	4	1	
Hypoalbuminaemia			

subjects affected / exposed	4 / 50 (8.00%)	2 / 28 (7.14%)	
occurrences (all)	5	2	
Hypokalaemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	2 / 50 (4.00%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Hyponatraemia			
subjects affected / exposed	2 / 50 (4.00%)	3 / 28 (10.71%)	
occurrences (all)	2	3	
Hyperkalaemia			
subjects affected / exposed	3 / 50 (6.00%)	2 / 28 (7.14%)	
occurrences (all)	4	2	
Hypoproteinaemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Hypocalcaemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 28 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2014	The original protocol CF102-201HCC was approved on 07 January 2014. Subsequently, the protocol was amended a first time on 16 June 2014: • Addressed comments and requests for information from FDA in correspondence dated 15 May 2014. • Clearly described rules for dose interruption due to toxicity and criteria for dose modification. • Revised eligibility to require prior treatment with sorafenib. • Required collection of data documenting the reasons for sorafenib intolerance and the duration of prior sorafenib treatment. • Added collection of sparse pharmacokinetic samples to allow for exploratory analyses of exposure-response relationships for CF102. • Added collection of additional ECGs at the anticipated maximal CF102 concentrations at steady state.
03 October 2014	The original protocol CF102-201HCC was approved on 07 January 2014. Subsequently, the protocol was amended a second time on 03 October 2014: • The Sponsor had recently completed the in-life portion of 90-day toxicology studies in monkeys and rats. In a 90-day monkey study (30, 100, 300 mg/kg/day), preliminary data indicated that there was a dose-related increase in incidence and severity of microscopic thyroid follicular atrophy/degeneration with or without a concurrent neutrophil infiltrate. Thyroid follicular change was noted as minimal in severity in 1 of 6 animals at the low dose, minimal-to-mild severity in 2 of 6 animals at the mid dose, and mild-to-moderate severity in 4 of 6 animals at the high dose. Recovery was not evaluated in this study. The highest non-severely toxic dose in this study was 30 mg/kg. This information was added to the protocol.
21 October 2015	The original protocol CF102-201HCC was approved on 07 January 2014. Subsequently, the protocol was amended a third time on 21 October 2015: • Changed the assay methodology for A3AR expression determination. • Revised information which was previously clarified, corrected or changed as per the following: o Global Note to File GLO_P_Am. 01_16Jun2014 dated 11 August 2014 o Global Note to File GLO_P_PBMC_08Oct2014 dated 01 April 2015 o Global Note to File GLO_P_WBC_08Oct2014 dated 02 June 2015 The protocol was modified to reflect the new procedure and correct already existing information.

21 September 2018	The original protocol CF102-201HCC was approved on 07 January 2014. Subsequently, the protocol was amended a fourth time on 21 September 2018: • Eliminated the requirement for 75 deaths prior to the end of the post-accrual period • Terminated the double-blind period of the study prior to the occurrence of 75 deaths • Deleted the MITT population • Added the PP population • Efficacy analyses were to be performed on the ITT population • Tumor response was to be analyzed using the PP population • Subjects who remained on blinded drug were offered the opportunity to continue dosing with open-label CF102 25 mg BID indefinitely, following the protocol-specified schedule of events.
06 November 2018	The original protocol CF102-201HCC was approved on 07 January 2014. Subsequently, the protocol was amended a fifth time on 06 November 2018: • Added Table 1-2: Schedule of Events for Open Label (OL) Treatment. • Amendment 5 implemented the transition to open-label (OL) dosing for patients who were surviving and remaining on drug at the time of analysis; and established the assessments and schedule of visits for the OL dosing aspect of the trial. This included defining the OL eligibility criteria; detailing the visit and assessment schedule; and specifying that the only patients still on treatment in this trial at the time of this amendment were in Romania. • Required a separate signed ICF prior to subject's continuation on OL treatment. • Provided for self-administration of CF102 or placebo BID in continuous 28-day cycles beginning on Day 1 of Cycle 1. • Provided for collection of information regarding the occurrence of adverse events during the OL period, up 28 days following the last dose of study drug (OL Follow-Up Visit). Any data for AEs related to study drug that were ongoing at the OL Follow-Up Visit would be collected until the AE resolved or stabilized. • Provided for PE, laboratory testing, ECG, liver chemistry, INR, and measuring of viral load during the OL period and OL Follow-Up.

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.

The primary endpoint was not met but the subgroup analysis showed a positive efficacy signal (OS) in subjects with CPB7.

Notes: