Clinical trial results:
A Phase 2, Randomized, Double-Masked, Placebo-Controlled, Parallel-Group Study of the Safety and Efficacy of Daily CF101 Administered Orally in Subjects with Elevated Intraocular Pressure

Summary

EudraCT number	2011-002777-27
Trial protocol	BG
Global end of trial date	10 February 2016

Results information

Result version number	v1 (current)
This version publication date	16 February 2020
First version publication date	16 February 2020

Trial information

Trial identification

Sponsor protocol code	CF101-231GL

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Can Fite Biopharma Ltd
Sponsor organisation address	10 Bareket St., Tikva, Israel,
Public contact	Medical Director, Can-Fite BioPharma Ltd., +972 39241114, info@canfite.co.il
Scientific contact	Medical Director, Can-Fite BioPharma Ltd., +972 39241114, info@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	10 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 February 2016
Global end of trial reached?	Yes
Global end of trial date	10 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the effects of oral CF101 in lowering intraocular pressure (IOP) when administered twice daily for 16 weeks in subjects with elevated IOP; and Determine the safety of oral CF101 in this subject population

Protection of trial subjects:

The study was conducted in compliance with applicable International Conference on Harmonisation (ICH) guidelines, the ICH E6 Good Clinical Practice (GCP) guideline,
and regulations, guidelines, and applicable laws and regulations of the locale and country where the study was conducted. The study was conducted with the approval of a duly constituted institutional review board (IRB) or ethics committee (EC) in accordance with the requirement of United States regulation Title 21 Code of Federal Regulations (CFR) Part 56 - Institutional Review Boards. The nature and risks of the study were fully explained to each subject and written consent obtained in accordance with the requirements of 21 CFR 50 - Protection of Human Subjects. Subjects were informed of their rights, including the right to withdraw from the study at any time.

Background therapy:

None

Evidence for comparator:

Placebo as control

Actual start date of recruitment	27 September 2012
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: 55
Country: Number of subjects enrolled	Bulgaria: 32
Country: Number of subjects enrolled	Israel: 2
Worldwide total number of subjects	89
EEA total number of subjects	87

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)	60
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

There were 89 subjects enrolled and randomised in 14 sites in 3 countries (Romania [7], Bulgaria [6], and Israel [1]) and included in the study between 02 Nov 2010 and 24 Sep 2015

Pre-assignment

Screening details:

At a Screening Visit subjects who provided written informed consent and fulfilled the inclusion criteria (notably: Ocular hypertension or open-angle glaucoma in at least 1 eye) underwent specified procedures.

Period 1

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

Blinding implementation details:

Treatment was allocated in a double-blinded (double-masked) fashion. The Investigator was supplied with sealed envelopes, each one containing the treatment allocation for the treatment assignment (randomization) number that appeared on the outside of the envelope.

Arms

Are arms mutually exclusive?	Yes
Arm title	CF101 1 mg

Arm description:

Medication was taken orally BID for 16 weeks in a double-blinded fashion

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	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 mg tablet BID

Arm title	CF101 2 mg

Arm description:

Medication was taken orally BID for 16 weeks in a double-blinded fashion

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	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg tablet BID

Arm title	Placebo

Arm description:

Medication was taken orally BID for 16 weeks 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	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching CF101 placebo tablet BID

Number of subjects in period 1	CF101 1 mg	CF101 2 mg	Placebo
Started	34	32	23
Completed	33	28	22
Not completed	1	4	1
Consent withdrawn by subject	1	1	-
Other	-	2	-
An unacceptable rise in IOP occurred, requiring a	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	CF101 1 mg
Reporting group description:	
Medication was taken orally BID for 16 weeks in a double-blinded fashion	
Reporting group title	CF101 2 mg
Reporting group description:	
Medication was taken orally BID for 16 weeks in a double-blinded fashion	
Reporting group title	Placebo
Reporting group description:	
Medication was taken orally BID for 16 weeks in a double-blinded fashion	

Reporting group values	CF101 1 mg	CF101 2 mg	Placebo
Number of subjects	34	32	23
Age categorical Units: Subjects			
Adults 18 years and over	34	32	23
Gender categorical Units: Subjects			
Female	25	28	20
Male	9	4	3
Diagnosis			
Glaucoma or ocular hypertension			
Units: Subjects			
Untreated ocular hypertension without glaucomatous	6	12	4
Glaucoma diagnosed within the past 2 months but un	7	7	4
Previously treated glaucoma, provided that previou	6	0	3
Currently treated glaucoma with inadequate IOP con	15	13	12
Family History Units: Subjects			
Yes	5	3	4
No	29	29	19
Time since diagnosis (Years) Units: Years			
geometric mean	3.27	1.69	5.84
standard deviation	± 4.831	± 2.778	± 9.441

Reporting group values	Total		
Number of subjects	89		
Age categorical Units: Subjects			
Adults 18 years and over	89		

Gender categorical Units: Subjects			
Female	73		
Male	16		
Diagnosis			
Glaucoma or ocular hypertension			
Units: Subjects			
Untreated ocular hypertension without glaucomatous	22		
Glaucoma diagnosed within the past 2 months but un	18		
Previously treated glaucoma, provided that previou	9		
Currently treated glaucoma with inadequate IOP con	40		
Family History Units: Subjects			
Yes	12		
No	77		
Time since diagnosis (Years) Units: Years			
geometric mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population consists of all subjects who received at least one dose of study medication and the opportunity for at least one safety assessment, ie, at least one post-Baseline visit. A listing of all subjects excluded from the Safety Population, including subjects who failed re-qualification at Baseline, will be provided.

Subject analysis set title	Intent-to-Treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population consists of all randomized subjects who received at least one dose of study medication with assessments sufficient to determine IOP for at least one post-baseline visit. Determination of the ITT population will be based on observed data, without imputation of missing data.

Reporting group values	Safety Population	Intent-to-Treat	
Number of subjects	89	89	
Age categorical Units: Subjects			
Adults 18 years and over	89	89	
Gender categorical Units: Subjects			
Female	73	73	
Male	16	16	
Diagnosis			
Glaucoma or ocular hypertension			
Units: Subjects			
Untreated ocular hypertension without glaucomatous	22	22	

Glaucoma diagnosed within the past 2 months but un	18	18	
Previously treated glaucoma, provided that previou	9	9	
Currently treated glaucoma with inadequate IOP con	40	40	
Family History			
Units: Subjects			
Yes	12	12	
No	77	77	
Time since diagnosis (Years)			
Units: Years			
geometric mean	3.37	3.37	
standard deviation	± 6.057	± 6.057	

End points

End points reporting groups

Reporting group title	CF101 1 mg
Reporting group description:	
Medication was taken orally BID for 16 weeks in a double-blinded fashion	
Reporting group title	CF101 2 mg
Reporting group description:	
Medication was taken orally BID for 16 weeks in a double-blinded fashion	
Reporting group title	Placebo
Reporting group description:	
Medication was taken orally BID for 16 weeks in a double-blinded fashion	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Population consists of all subjects who received at least one dose of study medication and the opportunity for at least one safety assessment, ie, at least one post-Baseline visit. A listing of all subjects excluded from the Safety Population, including subjects who failed re-qualification at Baseline, will be provided.	
Subject analysis set title	Intent-to-Treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intent-to-treat (ITT) population consists of all randomized subjects who received at least one dose of study medication with assessments sufficient to determine IOP for at least one post-baseline visit. Determination of the ITT population will be based on observed data, without imputation of missing data.	

Primary: Change from Baseline in IOP (Target Eye) at Week 16

End point title	Change from Baseline in IOP (Target Eye) at Week 16[1]
End point description:	
Change from Baseline in Intraocular Pressure (Target Eye) at Week 16	
End point type	Primary
End point timeframe:	
Baseline to Week 16	

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: The primary analysis for this study was limited to change from baseline in each arm as the planned comparisons to placebo did not show any significant difference. The p values were as follows: 0.628 for 1 mg v placebo and 0.428 for 2 mg v placebo.

End point values	CF101 1 mg	CF101 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	32	23	
Units: mmHg				
median (full range (min-max))	-3.67 (-10.5 to 2.5)	-3.75 (-11.0 to 10.5)	-5.00 (-10.5 to 7.5)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events that occurred during the study (Weeks 0 to 16).	
Adverse event reporting additional description:	
AEs were coded using MedDRA. All TEAEs were summarized by treatment group. Counts and percent were presented by treatment group for each observed SOC and preferred term as defined in MedDRA.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups	
Reporting group title	CF101 2 mg
Reporting group description:	
Analysed as the Safety Population during the treatment period (Weeks 0 to 16).	
Reporting group title	CF101 1 mg
Reporting group description:	
Analysed as the Safety Population during the treatment period (Weeks 0 to 16).	
Reporting group title	Placebo
Reporting group description:	
Analysed as the Safety Population during the treatment period (Weeks 0 to 16).	

Serious adverse events	CF101 2 mg	CF101 1 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 34 (0.00%)	1 / 32 (3.13%)	0 / 23 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Arterial hypertension			
subjects affected / exposed	0 / 34 (0.00%)	1 / 32 (3.13%)	0 / 23 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	CF101 2 mg	CF101 1 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 34 (17.65%)	6 / 32 (18.75%)	3 / 23 (13.04%)
Investigations			

Blood pressure increased			
subjects affected / exposed	0 / 34 (0.00%)	0 / 32 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 34 (0.00%)	1 / 32 (3.13%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 34 (0.00%)	1 / 32 (3.13%)	1 / 23 (4.35%)
occurrences (all)	0	1	2
General disorders and administration site conditions			
Feeling cold			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	0 / 34 (0.00%)	0 / 32 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	2
Ocular discomfort			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 34 (0.00%)	0 / 32 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Procedural nausea			
subjects affected / exposed	0 / 34 (0.00%)	0 / 32 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	0 / 34 (0.00%)	1 / 32 (3.13%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Skin disorder			

subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anger			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 34 (0.00%)	0 / 32 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	2
Spinal pain			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Conjunctivitis bilateral			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 32 (3.13%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0

Upper aerodigestive tract infection			
subjects affected / exposed	0 / 34 (0.00%)	0 / 32 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 34 (0.00%)	1 / 32 (3.13%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 32 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2010	• Amendment #1, Version 2.0, dated 21 April 2010: This amendment made 2 minor modifications in clinical procedures that enhanced feasibility and subject safety without affecting the efficacy objectives of the trial: o First, the type of tonometer was no longer limited to a single instrument, so that the protocol was more readily implemented at multiple sites. Since each subject served as his/her own control for tonometry measurements over the course of the trial, and since the same tonometer was always to be used within any given study site, intra-ocular pressure data analyses would not be affected. o Second, for purposes of safety monitoring, visual field (VF) testing was added at Week 8, and corneal pachymetry was added at Weeks 8 and 16. o This amendment also modified the inclusion criteria to further enhance subject safety by eliminating from consideration potential enrollees who would have had to discontinue previously efficacious ocular anti-hypertensive medication to qualify for the trial.
24 May 2010	• Amendment #2, Version 3.0, dated 24 May 2010: This amendment clarified the Exclusion Criteria by removing redundancy and introducing more precision about which patient population certain criteria applied to. o The Exclusion Criterion reading "Mean VF pattern standard deviation (PSD), on reliable testing, of ≥2.0 dB in either eye" was removed because it was applicable only to patients with ocular hypertension, who were already well defined in Inclusion Criterion #1.a and Exclusion Criterion #5 (in this amendment); and contradicted Inclusion Criterion #1.b, because most glaucoma patients have a mean VF PSD of >2.0 dB. It was therefore removed because it was redundant and potentially confusing. o The Exclusion Criterion relating to "advanced VF defect in either eye" (Exclusion Criterion #4 in this amendment) was modified to refer specifically to patients with glaucoma, because it was not relevant to patients with ocular hypertension. Likewise, the Exclusion Criterion relating to the "Ocular Hypertension Treatment Study Group and European Glaucoma Prevention Study Group Primary Open-Angle Glaucoma Risk Table" (Exclusion Criterion #5 in this amendment) was modified to refer specifically to patients with ocular hypertension, because it is used only in this population to stratify risk. o In sum, these changes were made to ensure consistency of patient population definitions and application of the entry criteria, and did not impact upon patient safety. o Additional editorial changes were made to clarify screening and inclusion procedures and details of selected ophthalmologic examinations. None altered the nature or the conduct of the protocol.
15 February 2011	• Amendment #3, Version 4.0, dated 15 February 2011 (Israel only): The purpose of this amendment was to specify the expected enrollment in the 2 countries involved in this trial for informational and regulatory purposes. There were no changes to any protocol procedures, and patient safety was not affected.

03 July 2012	• Amendment #4, Version 5.0, dated 03 July 2012: The purpose of this amendment was to specify the 3 countries involved in this trial for informational and regulatory purposes and allow the enrollment of a more representative patient population without compromising the trial's safety or efficacy objectives.
03 January 2013	• Amendment #5, Version 6.0, dated 03 January 2013: The purpose of this Amendment was to facilitate protocol enrollment and operations, without affecting subject risk. Since both ophthalmologists and patients were accustomed to treating elevated IOP and glaucoma with available therapies, it had been difficult to enroll untreated patients under the original protocol entry criteria, despite the rigorous safety incorporated into the trial. These original criteria excluded concomitant ocular hypotensive treatments, in an attempt to isolate the pharmacologic activity of CF101 monotherapy in this population. Amendment 5 allowed CF101 to be used in combination with standard topical regimens, and was therefore expected to facilitate enrollment without interfering with the efficacy objectives of the trial. In recognition of the fact that subjects would now enter the trial already receiving standard ocular hypotensive therapy, the minimum entry IOP was reduced from 24 to 22 mmHg. Since the sample size calculation was based not on absolute IOP values but on relative differences between active and placebo groups, no change in sample size was necessary. Amendment 5 also made several minor editorial and administrative modifications and clarifications, reconciled the use of "subject" and "patient", and removed the names of participating countries to allow for flexibility.
20 May 2013	• Amendment #6, Version 7.0, dated 20 May 2013: At the request of study sites, the sponsor clarified the examination procedures.
23 June 2014	• Amendment #7, Version 8.0, dated 23 June 2014: The initial rationale for this clinical trial is described in protocol Section 6.6. Since the launch of CF101-231GL, the Sponsor completed enrollment in protocol CF101-301KCS, a Phase 3 trial in 237 subjects with keratoconjunctivitis sicca. Analysis of IOP data from that trial indicated that the 1 mg BID dose of CF101 was less effective in reducing IOP than initially found in protocol CF101-201KCS (see protocol Section 6.6). It should be noted that in that trial, all enrolled subjects were ocularly normotensive, and that IOP was measured as a safety, not an efficacy, assessment. Thus, even though Segment 1 of the current trial had not completed or been reviewed by the planned Data Review Committee, there were data from an external source strongly suggesting that a higher dose range of CF101 needed to be explored in subjects with elevated IOP. Therefore, this Amendment did the following: o Eliminated the possibility of a CF101 0.1 mg dose group, based on data suggesting this dose will be too low to be effective; o Formalized the CF101 2.0 mg dose group, to explore a higher and perhaps more efficacious dose level and to better define the dose-range of CF101 in this patient population; and o Eliminated the requirement for the Data Review Committee, as no new dosing decisions would have to be made based on current knowledge. o Given existing and accumulating data from Phase 2 trials in other indications (see current Clinical Investigator Brochure), no new risks to subjects are anticipated from the dosing changes proposed in this Amendment.

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.

None

Notes: