NOVARTIS

Sponsor

Novartis

Generic Drug Name

BZF961

Therapeutic Area of Trial

Translational Medicine, Infectious Diseases

Trial Indication

Investigational, safety and antiviral effect in hepatitis C virus infected patients

Protocol Number

CBZF961X2201

Protocol Title

A double-blind, randomized, placebo-controlled, multi-center trial to determine the safety and antiviral effect of 3 days of BZF961 with or without ritonavir boosting in hepatitis C virus (HCV) infected patients

Clinical Trial Phase

Phase Ib

Phase of Drug Development

Phase II

Study Start/End Dates

First patient first visit: 26-Mar-2013

Last patient last visit: 22-Dec-2014

Study Design/Methodology

This was a randomized, double-blinded placebo-controlled, multi-centered study in treatment-naïve patients with chronic HCV infection genotype-1. Patients were enrolled sequentially in two parts. All treatments were administered for 3 days.

Part I consisted of one cohort, comprised of 8 subjects (6:2; active:placebo). Part II consisted of four cohorts; one comprised of 20 subjects (18:2; active:placebo - in three dose groups) and the remaining three cohorts of 8 subjects (6:2; active:placebo) each. In the Part II cohorts,

BZF961 was co-administered with ritonavir 100 mg BID in order to boost the exposure of BZF961.

The study consisted of a 28-day screening period, one baseline visit, a 3-day treatment period, 1 day washout period, end of study assessments and a follow up period of one year.

Patients were given the option to receive the standard of care treatment at the end of study visit. For patients electing to receive standard of care treatment (once end of study evaluations were complete), an HCV therapy regimen was administered by the study investigator.

Centers

3 centers in the United States.

Publication

None

Objectives:

Primary objective

- To evaluate the antiviral activity of 3 days BZF961 compared to placebo in patients infected with HCV genotype-1.

Secondary objectives

- To determine the safety and tolerability of BZF961 given over 3 days to HCV infected patients.
- To evaluate the pharmacokinetics of BZF961 in HCV infected patients.

Test Product (s), Dose(s), and Mode(s) of Administration

BZF961 liquid in vial – 130 mg/g solution (Batch No. AEUS/2012-0164)
Vehicle for BZF961 powder (Batch No. AEUS/2011-0387)
Placebo (Batch No. AEUS/2011-0388) 0 mg/g oral solution
Ritonavir 100 mg doses were sourced locally by the study site

Part I: Monotherapy (active:placebo)

- Cohort I – 500 mg BID (6:2)

Part II: Dose finding (active:placebo)

- Cohort IIa – 6:6:6:2
  BZF961 10 mg QD and ritonavir 100 mg BID
  BZF961 20 mg QD and ritonavir 100 mg BID
  BZF961 50 mg QD and ritonavir 100 mg BID
- Cohort IIb – 6:2
  BZF961 10 mg BID and ritonavir 100 mg BID
- Cohort IIc – 6:2
  BZF961 20 mg BID and ritonavir 100 mg BID
- Cohort IId – 6:2

BZF961 50 mg BID and ritonavir 100 mg BID

BZF961, ritonavir or placebo were administered orally for 3 days.

Statistical Methods

HCV RNA improvement (decline) from baseline was compared to placebo at the completion of dosing. The primary analysis was a Bayesian analysis of the change in $\log_{10}$ HCV RNA from baseline at 72 hours after the first dose. A 90% two-sided Bayesian credible interval (CI) for the placebo-corrected change in $\log_{10}$ HCV RNA was formed. Furthermore, the posterior probabilities that this change (in terms of drop) exceeds 0, 1 and 2 were provided. The analysis included baseline viral load as a continuous covariate, and treatment group as a factor.

In Part II dose-response relationship was assessed using a normal dynamic linear model (NDLM).

Longitudinal plots of viral load were provided.

No inferential analysis was planned for safety data.

- Vital signs were examined for abnormal values for each subject and such occurrences were identified by subject and treatment in the data listing. Vital signs data are also summarized by treatment and visit/time.
- ECG abnormalities were identified by treatment group and subject in the data listing. ECG data were also summarized by treatment and visit/time.
- All clinical laboratory evaluations were listed by treatment, subject, and visit/time and abnormalities flagged. Summary statistics were provided by treatment and visit/time.
- All information obtained on AEs was displayed by subject and treatment in the data listing. The number and percentage of subjects having adverse events were tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system was only counted once towards the total of this body system.
- All concomitant therapies were listed by treatment group and subject.

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameters) were created.

BZF961 plasma concentration data were listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics were provided by treatment and visit/sampling time point and included mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this was Tmax, where median, minimum and maximum were presented.

Study Population: Key Inclusion/Exclusion

Inclusion criteria

1. Treatment naïve male and female subjects (18-60 years) with Hepatitis C genotype-1.
2. Screening HCV-RNA $\geq 10^5$
3. Written informed consent obtained before any assessment was performed and volunteers had to be able to communicate well with the investigator, to understand and comply with the requirements of the study

Exclusion criteria

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations.
2. Subjects that were previously treated for HCV infection.
3. Women of child bearing potential.

Participant Flow Table

Part I

	BZF961 500mg BID N=6 n (%)	Placebo N=2 n (%)	Total N=8 n (%)
Subjects			
Completed	5 (83.3)	2 (100)	7 (87.5)
Discontinued	1 (16.7)	0	1 (12.5)
Main cause of discontinuation			
Lost to follow-up	1 (16.7)	0	1 (12.5)

Part II

	Cohort IIa			Cohort IIb	Cohort IIc	Cohort IId		
	BZF961 10 mg QD + Ritonavir 100 mg BID N=6 n (%)	BZF961 20 mg QD + Ritonavir 100 mg BID N=6 n (%)	BZF961 50 mg QD + Ritonavir 100 mg BID N=6 n (%)	BZF961 10 mg BID + Ritonavir 100 mg BID N=6 n (%)	BZF961 20 mg BID + Ritonavir 100 mg BID N=6 n (%)	BZF961 50 mg BID + Ritonavir 100 mg BID N=7 n (%)	Pooled placebo N=8 n (%)	Total N=45 n (%)
Subjects								
Completed	6 (100)	5 (83.3)	6 (100)	5 (83.3)	6 (100)	6 (85.7)	8 (100)	42 (93.3)
Discontinued	0	1 (16.7)	0	1 (16.7)	0	1 (14.3)	0	3 (6.7)
Main cause of discontinuation								
Lost to follow-up	0	1 (16.7)	0	1 (16.7)	0	0	0	2 (4.4)
Administrative problems	0	0	0	0	0	1 (14.3)	0	1 (2.2)

Baseline Characteristics

Part I

		BZF961 500 mg BID N=6	Placebo N=2	Total N=8
Age (years)	Mean (SD)	46.0 (7.85)	44.0 (8.49)	45.5 (7.43)
	Median	46.5	44.0	46.5
	Range	36 - 57	38 - 50	36 - 57
Sex - n (%)	Male	6 (100 %)	1 (50 %)	7 (87.5 %)
	Female	0	1 (50 %)	1 (12.5 %)
Race - n (%)	Caucasian	4 (66.7 %)	2 (100 %)	6 (75 %)
	Black	2 (33.3 %)	0	2 (25 %)
Ethnicity - n (%)	Other	6 (100 %)	2 (100 %)	8 (100 %)
Weight (kg)	Mean (SD)	73.5 (7.37)	69.5 (12.16)	72.5 (7.95)
	Median	73.8	69.5	73.8
	Range	62.8 - 85.4	60.9 - 78.1	60.9 - 85.4
Height (cm)	Mean (SD)	174.9 (7.35)	168.5 (9.19)	173.3 (7.71)
	Median	178.0	168.5	176.5
	Range	163.0 - 182.5	162.0 - 175.0	162.0 - 182.5
BMI (kg/m^2)	Mean (SD)	24.07 (2.72)	24.36 (1.62)	24.14 (2.38)
	Median	22.79	24.36	23.35
	Range	21.95 - 28.23	23.21 - 25.50	21.95 - 28.23

Part II

		Cohort IIa			Cohort IIb	Cohort IIc	Cohort IId		
		BZF961 10 mg QD + Ritonavir 100 mg BID N=6	**BZF961 20 mg QD + Ritonavir 100 mg BID N=6**	**BZF961 50 mg QD + Ritonavir 100 mg BID N=6**	**BZF961 10 mg BID + Ritonavir 100 mg BID N=6**	**BZF961 20 mg BID + Ritonavir 100 mg BID N=6**	**BZF961 50 mg BID + Ritonavir 100 mg BID N=7**	**Pooled placebo N = 8**	**Total N = 45**
Age (years)	Mean (SD)	52.5 (5.32)	47.3 (7.53)	50.8 (11.32)	45.5 (6.89)	55.2 (3.76)	53.0 (6.68)	51.5 (6.76)	50.9 (7.34)
	Median	53.5	49.5	55.0	46.5	56.5	57.0	52.0	52.0
	Range	46 - 60	34 - 55	29 - 59	33 - 52	50 - 59	42 - 59	42 - 60	29 - 60
Sex - n (%)	Male	5 (83.3)	5 (83.3)	6 (100)	4 (66.7)	6 (100)	7 (100)	6 (75)	39 (86.7)
	Female	1 (16.7)	1 (16.7)	0	2 (33.3)	0	0	2 (25)	6 (13.3)
Race - n (%)	Caucasian	5 (83.3)	5 (83.3)	5 (83.3)	6 (100)	4 (66.7)	5 (71.4)	6 (75)	36 (80)
	Black	0	1 (16.7)	1 (16.7)	0	1 (16.7)	2 (28.6)	2 (25)	7 (15.6)
	Native American	1 (16.7)	0	0	0	1 (16.7)	0	0	2 (4.4)
Ethnicity - n (%)	Hispanic/Latino	4 (66.7)	1 (16.7)	2 (33.3)	4 (66.7)	2 (33.3)	0	1 (12.5)	14 (31.1)
	Other	2 (33.3)	5 (83.3)	4 (66.7)	2 (33.3)	4 (66.7)	7 (100)	7 (87.5)	31 (68.9)
Weight (kg)	Mean (SD)	84.4 (15.29)	83.9 (9.36)	87.8 (14.31)	81.1 (13.22)	82.4 (16.70)	85.9 (6.10)	77.7 (18.59)	83.1 (13.49)
	Median	82.6	86.9	83.5	81.9	80.0	87.0	72.1	83.0
	Range	60.2 - 103.8	71.4 - 94.5	72.1 - 108.8	59.8 - 99.9	61.2 - 110.1	77.1 - 93.8	57.0 - 104.0	57.0 - 110.1
Height (cm)	Mean (SD)	166.6 (7.30)	176.0 (6.57)	180.4 (10.51)	173.5 (10.08)	178.1 (5.95)	179.0 (6.28)	169.3 (4.71)	174.6 (8.46)
	Median	167.3	178.9	183.5	172.0	176.8	182.8	170.3	174.0
	Range	153.4 - 175.3	164.0 - 181.5	167.0 - 191.8	159.0 - 187.5	172.5 - 188.0	167.6 - 185.0	163.0 - 175.0	153.4 - 191.8
BMI (kg/m^2)	Mean (SD)	30.26 (4.33)	27.03 (1.91)	26.92 (3.11)	26.79 (2.55)	26.00 (5.27)	26.91 (3.16)	27.08 (6.34)	27.26 (4.10)
	Median	28.89	27.10	26.56	26.79	24.71	26.27	24.11	26.45
	Range	25.58 - 35.71	23.86 - 29.49	23.31 - 31.33	23.65 - 30.16	20.45 - 34.52	23.05 - 33.38	20.91 - 35.99	20.45 - 35.99

Summary of Efficacy

Primary Outcome Result(s)

Part I

Summary of statistical analysis of change in log HCVRNA from baseline at 72 hours – Part I

Formulations	N	Estimate (90% CI)	Difference between Estimate (90% CI) BZF961-Placebo	LOC<0	LOC<-1	LOC<-2
BZF961 500mg (T)	6	-3.26(-4.03,-2.47)	-3.21(-4.11,-2.29)	1.00	1.00	0.98
Placebo (C)	2	-0.06(-0.5,0.41)				

Level of confidence(LOC) for T-C<-x is the posterior probability that the drop induced by treatment exceeds x
Estimates of change from baseline are the posterior medians for the Bayesian model
CI= credible interval

Part II

Summary of statistical analysis of change in log HCVRNA from baseline at 72 hours – Part II

Dose	N	Estimate(90% CI)	Difference Between Estimate(90% CI) BZF961-Placebo	LOC T-C < 0	LOC T-C <-1	LOC T-C <-2
BZF961 10mg QD	6	-0.44(-0.87,0.03)	-0.56(-1.06,-0.01)	0.95	0.07	0.00
BZF961 20mg QD	6	-1.03(-1.48,-0.54)	-1.15(-1.71,-0.55)	1.00	0.66	0.01
BZF961 50mg QD	6	-2.12(-2.67,-1.57)	-2.24(-2.9,-1.59)	1.00	1.00	0.73
Placebo*	8	0.12(-0.22,0.45)				
BZF961 10mg BID**	6	-1.3(-1.77,-0.87)	-1.34(-1.9,-0.86)	1.00	0.87	0.03
BZF961 20mg BID**	6	-2.03(-2.48,-1.57)	-2.08(-2.63,-1.53)	1.00	1.00	0.60
BZF961 50mg BID**	6	-3.08(-3.65,-2.53)	-3.13(-3.78,-2.48)	1.00	1.00	1.00
Placebo#	8	0.05(-0.27,0.37)				

*Placebo Analyzed with QD #:Placebo Analyzed with BID
**BZF961 dose co-administered with ritonavir 100 mg BID
Level of confidence (LOC) for T(dose of BZF961)-C(placebo)<-x is the posterior probability that the treatment effect exceeds x
Estimates of the change from baseline are the posterior medians for the Bayesian model
CI = credible interval

Secondary Outcome Result(s)

Summary statistics of BZF961 plasma pharmacokinetic parameters by treatment

	Cohort I	Cohort IIa			Cohort IIb	Cohort IIc	Cohort IId
Pharmacokinetic Parameter Mean (SD) CV%	**BZF961 500 mg BID N = 6**	**BZF961 10 mg QD + Ritonavir 100 mg BID N=6**	**BZF961 20 mg QD + Ritonavir 100 mg BID N=6**	**BZF961 50 mg QD + Ritonavir 100 mg BID N=6**	**BZF961 10 mg BID + Ritonavir 100 mg BID N=6**	**BZF961 20 mg BID + Ritonavir 100 mg BID N=6**	**BZF961 50 mg BID + Ritonavir 100 mg BID N=7**
Cmax (ng/mL) Day 1	1620 (484) 29.9	45.3 (16.1) 35.5	78.5 (39.5) 50.4	311 (114) 36.6	63.4 (51.5) 81.1	74.4 (44.6) 59.9	363 (114) 31.5
Day 3	2200 (1350) 61.4	92.9 (24.7) 26.6	127 (49.8) 39.1	687 (166) 24.2	165 (107) 65.2	237 (83.9) 35.5	672 (261) 38.8 n=6
Tmax (h)# - Day 1	1.0 [0.500;1.00]	2.25 [1.00;4.00]	1.0 [1.00;8.00]	1.51 [1.00;4.00]	1.50 [1.00;2.00]	2.00 [1.00;6.00]	1.00 [1.00;2.00]
Day 3	1.0 [0.500;2.00]	1.5 [0.500;2.50]	2.50 [1.00;4.00]	1.51 [1.00;3.00]	1.00 [1.00;2.50]	1.50 [1.00;3.00]	1.0 [0.583;8.00] n=6
AUClast(h*ng/mL) Day 1	5240 (3610) 69.0	296 (81.2) 27.5	508 (202) 39.8	1860 (726) 39.1	370 (258) 69.6	485 (242) 49.8	2010 (504) 25.0
Day 3	9060 (9220) 101.7	626 (151) 24.1	932 (352) 37.8	4190 (1060) 25.4	1130 (739) 65.2	1610 (473) 29.3	4050 (1100) 27.2 n=6
AUCtau(h*ng/mL) Day 1	5240 (3600) 68.6	363 (89.6) 24.7	687 (272) 39.6 n=5	2300 (908) 39.4	370 (258) 69.6	486 (242) 49.9	2020 (504) 25.0
Day 3	9040 (9190) 101.6	825 (199) 24.1	1290 (510) 39.5	5550 (1630) 29.4	1130 (739) 65.1	1610 (473) 29.3	4310 (1030) 23.8 n=5
Racc	1.54 (0.455) 29.6	2.32 (0.544) 23.4	1.94 (0.229) 11.8 n=5	2.65 (0.888) 33.6	3.46 (1.62) 46.9	3.63 (0.960) 26.4	2.36 (0.413) 17.5 n=5
Cmin (ng/mL)*	352 (478) 135.6	18.3 (4.00) 21.8	32.9 (14.0) 42.6	129 (52.0) 40.3	67.6 (42.8) 63.3	76.7 (21.8) 28.5	233 (74.5) 32.0

Values for Tmax are Median [Min; Max]
*Concentration 72 hours post first dose

Safety Results

Incidence of AEs by primary system organ class - Part I

	BZF961 500mg BID N=6 n (%)	Placebo N=2 n (%)	Total N=8 n (%)
Subjects with AE(s)	1 (16.7)	1 (50.0)	2 (25.0)
System organ class			
Gastrointestinal disorders	1 (16.7)	1 (50.0)	2 (25.0)
Nervous system disorders	0	1 (50.0)	1 (12.5)

Arranged in descending order of frequency (in total group) and by system organ class

Incidence of AEs by preferred term – Part I

	BZF961 500mg BID N=6 n (%)	Placebo N=2 n (%)	Total N=8 n (%)
Subjects with AE(s)	1 (16.7)	1 (50.0)	2 (25.0)
Preferred term			
Toothache	1 (16.7)	0	1 (12.5)
Vomiting	0	1 (50.0)	1 (12.5)
Headache	0	1 (50.0)	1 (12.5)

Arranged in descending order of frequency (in total group) and by preferred term

Incidence of AEs by primary system organ class - Part II

	Cohort IIa			Cohort IIb	Cohort IIc	Cohort IId		
	BZF961 10 mg QD + Ritonavir 100 mg BID N=6 n (%)	BZF961 20 mg QD + Ritonavir 100 mg BID N=6 n (%)	BZF961 50 mg QD + Ritonavir 100 mg BID N=6 n (%)	BZF961 10 mg BID + Ritonavir 100 mg BID N=6 n (%)	BZF961 20 mg BID + Ritonavir 100 mg BID N=6 n (%)	BZF961 50 mg BID + Ritonavir 100 mg BID N=7 n (%)	Pooled placebo N=8 n (%)	Total N=45 n (%)
Subjects with AE(s)	2 (33.3)	0	1 (16.7)	2 (33.3)	3 (50.0)	2 (28.6)	1 (12.5)	11 (24.4)
System organ class								
Nervous system disorders	1 (16.7)	0	1 (16.7)	2 (33.3)	2 (33.3)	1 (14.3)	0	7 (15.6)
General disorders and administration site conditions	1 (16.7)	0	0	1 (16.7)	1 (16.7)	1 (14.3)	0	4 (8.9)
Gastrointestinal disorders	1 (16.7)	0	0	1 (16.7)	0	1 (14.3)	0	3 (6.7)
Skin and subcutaneous tissue disorders	2 (33.3)	0	0	0	0	0	1 (12.5)	3 (6.7)
Ear and labyrinth disorders	1 (16.7)	0	0	0	0	0	0	1 (2.2)
Infections and infestations	0	0	0	0	1 (16.7)	0	0	1 (2.2)
Musculoskeletal and connective tissue disorders	0	0	0	0	1 (16.7)	0	0	1 (2.2)

	Cohort IIa			Cohort IIb	Cohort IIc	Cohort IId		
	BZF961 10 mg QD + Ritonavir 100 mg BID N=6 n (%)	BZF961 20 mg QD + Ritonavir 100 mg BID N=6 n (%)	BZF961 50 mg QD + Ritonavir 100 mg BID N=6 n (%)	BZF961 10 mg BID + Ritonavir 100 mg BID N=6 n (%)	BZF961 20 mg BID + Ritonavir 100 mg BID N=6 n (%)	BZF961 50 mg BID + Ritonavir 100 mg BID N=7 n (%)	Pooled placebo N=8 n (%)	Total N=45 n (%)
Psychiatric disorders	0	0	1 (16.7)	0	0		0	1 (2.2)

Arranged in descending order of frequency (in total group) and by system organ class

Incidence of AEs by preferred term – Part II

	Cohort IIa			Cohort IIb	Cohort IIc	Cohort IId		
	BZF961 10 mg QD + Ritonavir 100 mg BID N=6 n (%)	BZF961 20 mg QD + Ritonavir 100 mg BID N=6 n (%)	BZF961 50 mg QD + Ritonavir 100 mg BID N=6 n (%)	BZF961 10 mg BID + Ritonavir 100 mg BID N=6 n (%)	BZF961 20 mg BID + Ritonavir 100 mg BID N=6 n (%)	BZF961 50 mg BID + Ritonavir 100 mg BID N=7 n (%)	Pooled placebo N=8 n (%)	Total N=45 n (%)
Subjects with AE(s)	2 (33.3)	0	1 (16.7)	2 (33.3)	3 (50.0)	2 (28.6)	1 (12.5)	11 (24.4)
Preferred term								
Headache	0	0	1 (16.7)	1 (16.7)	2 (33.3)	0	0	4 (8.9)
Fatigue	1 (16.7)	0	0	1 (16.7)	1 (16.7)	0	0	3 (6.7)
Paraesthesia	1 (16.7)	0	0	0	0	1 (14.3)	0	2 (4.4)
Rash	1 (16.7)	0	0	0	0	0	1 (12.5)	2 (4.4)
Abdominal pain	0	0	0	0	0	1 (14.3)	0	1 (2.2)
Abnormal dreams	0	0	1 (16.7)	0	0	0	0	1 (2.2)
Bronchitis	0	0	0	0	1 (16.7)	0	0	1 (2.2)
Dermatosis	1 (16.7)	0	0	0	0	0	0	1 (2.2)
Diarrhoea	1 (16.7)	0	0	0	0	0	0	1 (2.2)
Hypoaesthesia	0	0	0	1 (16.7)	0	0	0	1 (2.2)
Hypoaesthesia oral	1 (16.7)	0	0	0	0	0	0	1 (2.2)
Nausea	0	0	0	1 (16.7)	0	0	0	1 (2.2)
Neck mass	0	0	0	0	1 (16.7)	0	0	1 (2.2)
Nervousness	0	0	1 (16.7)	0	0	0	0	1 (2.2)
Oedema peripheral	0	0	0	0	0	1 (14.3)	0	1 (2.2)
Pain	0	0	0	1 (16.7)	0	0	0	1 (2.2)
Tinnitus	1 (16.7)	0	0	0	0	0	0	1 (2.2)
Vomiting	0	0	0	0	0	1 (14.3)	0	1 (2.2)

Arranged in descending order of frequency (in total group) and by preferred term

Overall, headache and fatigue were the most frequently reported AEs.

Other Relevant Findings

Conclusion:

Across all doses, administration of BZF961 was safe,well tolerated and resulted in a reduction in HCV RNA levels. There were no serious AEs. All AEs were Grade 1 or 2 (based on CTCAE v4 criteria) and did not result in the discontinuation of study drug for any patient. The most frequent adverse events occurring in BZF961 treated patients were headache,

fatigue, and paresthesia. There was no evidence of BZF961 induced hepatotoxicity in patients with chronic HCV infection.

Administration of BZF961 50 mg BID plus ritonavir 100 mg BID yielded Ctrough concentrations similar to that following the administration of BZF961 500 mg BID. Both dose levels provided trough concentrations approximately 10-fold higher than the predicted efficacious level (29 ng/mL); this increased exposure to BZF961 was associated with greater reductions of viral load.

There was a dose responsive effect of BZF961 exposure on HCV viral RNA reduction. The change from baseline in viral load showed a clinically meaningful anti-viral effect (> 3 Log_{10} IU/mL HCV RNA decline) in the patients receiving BZF961 500 mg BID and BZF961 50 mg BID plus ritonavir 100 mg BID compared to placebo.

Date of Clinical Trial Report 11-Sep-2015