Sponsor

Novartis

Generic Drug Name

Dabrafenib

Trial Indication(s)

No specific product indication studied

Protocol Number

CDRB436A2106

Protocol Title

A phase I, open label, multicenter, single dose study to evaluate the pharmacokinetics of dabrafenib in healthy subjects with normal renal function and subjects with impaired renal function.

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase IV

Study Start/End Dates

19-Dec-2016/27-Sep-2019

Study Design/Methodology

This was a single-dose, open-label, parallel group single dose study to evaluate the pharmacokinetics (PK) and safety of a single oral dose of dabrafenib 100 mg in subjects with severe renal impairment (RI) or ESRD compared to matched healthy subjects with normal renal function (control group).

The study was planned to consist of up to approximately 32 eligible subjects (up to 16 in the control group and 8 in each of the renal function groups). Enrollment was closed with 8 subjects in the severe RI group, 3 subjects in the ESRD group and 11 matching normal control subject.

Centers

The study was conducted in 3 study centers in USA

Objectives:

Primary objective(s)

- To evaluate the pharmacokinetics of dabrafenib and metabolites after a single oral dose of dabrafenib in subjects with renal impairment as compared to healthy subjects with normal renal function

Secondary objective(s)

- To assess the safety of a single oral dose of dabrafenib in subjects with renal impairment.

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

All subjects received a single oral dose of 100 mg (2 capsules of 50 mg) dabrafenib.

Statistical Methods

No formal statistical hypothesis testing was performed as the main purpose of the statistical analysis was to estimate the effects of RI on the PK of dabrafenib and metabolites.

The primary PK data was summarized for dabrafenib and metabolites. Descriptive analyses were presented by renal function group (normal, severe RI and ESRD group) for all PK parameters, except Tmax, where only n, median, minimum and maximum is presented. AUC% extrapolated is listed.

The PAS was used for summaries and the Safety set was used for individual listings.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

All subjects:

- Females must be of non-childbearing potential and non-postmenopausal women must have negative pregnancy results at baseline
- Good health as determined by lack of clinically significant findings
- Subjects must have a BMI between 18.0 kg/m2 and 38.0 kg/m2, with a body weight of at least 50 kg and no more than 140 kg
- Vitals signs within normal range
- Laboratory values at screening within local normal ranges or considered non-clinically significant

Additional criteria for renal impairment subjects:

  - Stable renal disease without evidence of renal progression in the past 28 days prior to dosing
  - An absolute GFR ≥15 mL/min and ≤29 mL/min for severe renal impairment or an absolute GFR <15 mL/min for subjects with ESRD

Additional criteria for healthy matched subjects:

- Matched to at least 1 renal impairment subject by race, age (+/-10 years), gender and weight (+/-10%)
- An absolute GFR of at least 90 ml/min

Exclusion Criteria for all subjects:

- Significant acute illness within the two weeks prior to dosing
- History or current diagnosis of cardiac disease indicating significant risk such as uncontrolled or significant cardiac disease or clinically significant ECG abnormalities
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs.
- History of malignancy of any organ system, treated or untreated, within 5 years, regardless of where there is recurrence or metastases.
- Use of drugs known to prolong the QT interval within 4 weeks prior to dosing and for the duration of the study.
- Use of drugs known to affect CYP3A4 and/or CYP2C8 including both (strong or moderate) inhibitors and inducers, within 7 days prior to dosing or during the current study are prohibited

Participant Flow Table

Subject disposition (Full analysis set)

	Control N=11 n (%)	Severe RI* N=8 n (%)	ESRD N=3 n (%)	All subjects N=22 n (%)
Subjects treated				
Treated	11 (100.0)	8 (100.0)	3 (100.0)	22 (100.0)
Completed treatment	11 (100.0)	8 (100.0)	3 (100.0)	22 (100.0)

* Includes all subjects categorized as severe by Investigator at enrollment.
Control group consists of subjects with normal renal function.

Baseline Characteristics

Demographic and other baseline characteristics (FAS)

Demographic variable	Control N=11	Severe RI* N=8	ESRD N=3	All subjects N=22
Age (years)				
N	11	8	3	22
Mean (SD)	57.1 (5.80)	58.9 (8.43)	67.7 (3.21)	59.2 (7.30)
Median	58.0	57.5	69.0	60.0
Q1-Q3	53.0-61.0	52.5-66.5	64.0-70.0	54.0-64.0
Min-Max	47-67	48-70	64-70	47-70
Age category -n (%)				
18 - <65 years	10 (90.9)	6 (75.0)	1 (33.3)	17 (77.3)
65 - <85 years	1 (9.1)	2 (25.0)	2 (66.7)	5 (22.7)
Sex -n (%)				
Male	9 (81.8)	8 (100)	1 (33.3)	18 (81.8)
Female	2 (18.2)	0	2 (66.7)	4 (18.2)
Race -n (%)				
White	6 (54.5)	5 (62.5)	1 (33.3)	12 (54.5)
Black or African american	5 (45.5)	3 (37.5)	2 (66.7)	10 (45.5)
Ethnicity -n (%)				

Demographic variable	Control N=11	Severe RI* N=8	ESRD N=3	All subjects N=22
Not Hispanic Or Latino	10 (90.9)	2 (25.0)	2 (66.7)	14 (63.6)
Unknown	1 (9.1)	3 (37.5)	1 (33.3)	5 (22.7)
Hispanic/Latino	0	3 (37.5)	0	3 (13.6)
Body mass index (kg/m^2)				
N	11	8	3	22
Mean (SD)	30.07 (4.963)	30.94 (6.286)	30.49 (3.566)	30.44 (5.127)
Median	29.37	31.84	30.26	29.65
Q1-Q3	25.46-34.14	27.13-36.21	27.05-34.17	27.05-34.56
Min-Max	23.7-37.9	19.7-37.5	27.1-34.2	19.7-37.9

*Includes all subjects categorized as severe by Investigator at enrollment.
Control group consists of subjects with normal renal function.

Primary Outcome Result(s)

Primary PK parameters for dabrafenib (PAS)

Parameter	Statistics	Control N=11	Severe RI N=8	ESRD N=3
AUC_{inf} (ng*hr/mL)	n	11	7	3
	Mean (SD)	6710 (2300)	5920 (2670)	6960 (2830)
	CV%	34.3	45.2	40.6
	Geo-mean	6300	5390	6580
	Geo-CV%	41.2	50.7	43.5
	Median	6780	4790	6620
	Min-Max	2690-10200	2740-9260	4330-9950
AUC_{last} (ng*hr/mL)	n	11	8	3
	Mean (SD)	6700 (2300)	6100 (2560)	6930 (2830)
	CV%	34.4	41.9	40.9
	Geo-mean	6280	5590	6540
	Geo-CV%	41.2	48.9	44.0
	Median	6750	6160	6600
	Min-Max	2690-10200	2730-9250	4270-9910
C_{max} (ng/mL)	n	11	8	3
	Mean (SD)	1610 (568)	1520 (731)	1440 (739)
	CV%	35.2	48.1	51.3
	Geo-mean	1520	1360	1280
	Geo-CV%	39.2	54.1	69.4
	Median	1530	1420	1610
	Min-Max	763-2540	700-2520	632-2080

Primary PK parameters for dabrafenib (PAS)

Parameter	Statistics	Control N=11	Severe RI N=8	ESRD N=3
CL/F (L/hr)	n	11	7	3
	Mean (SD)	17.2 (7.94)	20.5 (9.68)	16.1 (6.58)
	CV%	46.3	47.3	40.9
	Geo-mean	15.9	18.6	15.2
	Geo-CV%	41.2	50.7	43.5
	Median	14.8	20.9	15.1
	Min-Max	9.79-37.1	10.8-36.5	10.1-23.1

n = number of subjects with corresponding evaluable PK parameters.
Control group consists of subjects with normal renal function.

Primary PK parameters for dabrafenib (Supportive PAS)

Parameter	Statistics	Control N=11	Severe RI N=4	ESRD N=3
AUC_{inf} (ng*hr/mL)	n	11	4	3
	Mean (SD)	6710 (2300)	5500 (2560)	6960 (2830)
	CV%	34.3	46.6	40.6
	Geo-mean	6300	5130	6580
	Geo-CV%	41.2	43.4	43.5
	Median	6780	4620	6620
	Min-Max	2690-10200	3510-9260	4330-9950
AUC_{last} (ng*hr/mL)	n	11	4	3
	Mean (SD)	6700 (2300)	5470 (2590)	6930 (2830)
	CV%	34.4	47.3	40.9
	Geo-mean	6280	5090	6540
	Geo-CV%	41.2	44.2	44.0
	Median	6750	4590	6600
	Min-Max	2690-10200	3440-9250	4270-9910
C_{max} (ng/mL)	n	11	4	3
	Mean (SD)	1610 (568)	1300 (839)	1440 (739)
	CV%	35.2	64.6	51.3
	Geo-mean	1520	1130	1280
	Geo-CV%	39.2	64.5	69.4
	Median	1530	997	1610
	Min-Max	763-2540	700-2500	632-2080

Primary PK parameters for dabrafenib (Supportive PAS)

Parameter	Statistics	Control N=11	Severe RI N=4	ESRD N=3
CL/F (L/hr)	n	11	4	3
	Mean (SD)	17.2 (7.94)	20.7 (7.36)	16.1 (6.58)
	CV%	46.3	35.6	40.9
	Geo-mean	15.9	19.5	15.2
	Geo-CV%	41.2	43.4	43.5
	Median	14.8	21.7	15.1
	Min-Max	9.79-37.1	10.8-28.5	10.1-23.1

n = number of subjects with corresponding evaluable PK parameters.
Control group consists of subjects with normal renal function.

Primary PK parameters for hydroxy-dabrafenib (PAS)

Parameter	Statistics	Control N=11	Severe RI N=8	ESRD N=3
AUC_{inf} (ng*hr/mL)	n	11	8	3
	Mean (SD)	5210 (1090)	5490 (2440)	5840 (2270)
	CV%	21.0	44.5	38.8
	Geo-mean	5100	5040	5500
	Geo-CV%	21.2	46.6	47.1
	Median	5030	5170	6560
	Min-Max	3870-6950	2860-9920	3300-7660
AUC_{last} (ng*hr/mL)	n	11	8	3
	Mean (SD)	5180 (1090)	5450 (2460)	5790 (2280)
	CV%	21.0	45.1	39.4
	Geo-mean	5080	4990	5430
	Geo-CV%	21.2	47.4	48.0
	Median	5000	5130	6500
	Min-Max	3860-6940	2850-9900	3240-7620
C_{max} (ng/mL)	n	11	8	3
	Mean (SD)	685 (156)	662 (329)	549 (197)
	CV%	22.7	49.7	35.9
	Geo-mean	668	601	522
	Geo-CV%	24.5	48.6	42.1
	Median	685	582	603
	Min-Max	452-888	311-1350	331-714

n = number of subjects with corresponding evaluable PK parameters.
Control group consists of subjects with normal renal function.

Table 11-12 Primary PK parameters for hydroxy-dabrafenib (Supportive PAS)

Parameter	Statistics	Control N=11	Severe RI N=4	ESRD N=3
AUC_{inf} (ng*hr/mL)	n	11	4	3
	Mean (SD)	5210 (1090)	4410 (1940)	5840 (2270)
	CV%	21.0	43.9	38.8
	Geo-mean	5100	4130	5500
	Geo-CV%	21.2	42.8	47.1
	Median	5030	3830	6560
	Min-Max	3870-6950	2860-7130	3300-7660
AUC_{last} (ng*hr/mL)	n	11	4	3

	Mean (SD)	5180 (1090)	4380 (1950)	5790 (2280)
	CV%	21.0	44.5	39.4
	Geo-mean	5080	4100	5430
	Geo-CV%	21.2	43.4	48.0
	Median	5000	3790	6500
	Min-Max	3860-6940	2850-7120	3240-7620
C_{max} (ng/mL)	n	11	4	3
	Mean (SD)	685 (156)	538 (178)	549 (197)
	CV%	22.7	33.1	35.9
	Geo-mean	668	513	522
	Geo-CV%	24.5	38.1	42.1
	Median	685	558	603
	Min-Max	452-888	311-724	331-714

n = number of subjects with corresponding evaluable PK parameters.
Control group consists of subjects with normal renal function.

Primary PK parameters for carboxy-dabrafenib (PAS)

Parameter	Statistics	Control N=11	Severe RI N=8	ESRD N=3
AUC_{inf} (ng*hr/mL)	n	11	7	3
	Mean (SD)	72000 (25100)	81600 (24400)	78200 (17300)
	CV%	34.8	29.9	22.1
	Geo-mean	68300	78300	77000
	Geo-CV%	34.9	33.2	21.6
	Median	63400	84900	72000
	Min-Max	42800-114000	44400-120000	64900-97800
AUC_{last} (ng*hr/mL)	n	11	8	3
	Mean (SD)	70200 (24200)	82400 (24500)	72600 (15600)
	CV%	34.4	29.7	21.5
	Geo-mean	66600	78900	71500
	Geo-CV%	34.4	33.6	20.7
	Median	60600	83100	64800
	Min-Max	42300-112000	43300-115000	62400-90500
C_{max} (ng/mL)	n	11	8	3
	Mean (SD)	2810 (897)	2540 (787)	1860 (308)
	CV%	31.9	31.0	16.5
	Geo-mean	2690	2420	1850
	Geo-CV%	31.9	36.4	16.2
	Median	2720	2640	1760
	Min-Max	1860-4510	1220-3620	1620-2210

n = number of subjects with corresponding evaluable PK parameters.
Control group consists of subjects with normal renal function.

Primary PK parameters for carboxy-dabrafenib (Supportive PAS)

Parameter	Statistics	Control N=11	Severe RI N=4	ESRD N=3
AUC_{inf} (ng*hr/mL)	n	11	3	3
	Mean (SD)	72000 (25100)	82900 (7950)	78200 (17300)
	CV%	34.8	9.6	22.1
	Geo-mean	68300	82600	77000
	Geo-CV%	34.9	9.8	21.6
	Median	63400	84900	72000
	Min-Max	42800-114000	74100-89600	64900-97800
AUC_{last} (ng*hr/mL)	n	11	4	3
	Mean (SD)	70200 (24200)	87000 (16400)	72600 (15600)
	CV%	34.4	18.9	21.5
	Geo-mean	66600	85900	71500
	Geo-CV%	34.4	18.3	20.7
	Median	60600	83100	64800
	Min-Max	42300-112000	71900-110000	62400-90500
C_{max} (ng/mL)	n	11	4	3
	Mean (SD)	2810 (897)	2580 (572)	1860 (308)
	CV%	31.9	22.2	16.5
	Geo-mean	2690	2520	1850
	Geo-CV%	31.9	23.6	16.2
	Median	2720	2640	1760

	Median	2720	2640	1760
	Min-Max	1860-4510	1870-3150	1620-2210

n = number of subjects with corresponding evaluable PK parameters.
Control group consists of subjects with normal renal function.

Primary PK parameters for desmethyl-dabrafenib (PAS)

Parameter	Statistics	Control N=11	Severe RI N=8	ESRD N=3
AUC_{inf} (ng*hr/mL)	n	9	3	0
	Mean (SD)	4690 (1960)	7170 (3100)	
	CV%	41.8	43.2	
	Geo-mean	4300	6770	
	Geo-CV%	48.4	41.6	
	Median	4140	5400	
	Min-Max	2030-7210	5360-10700	
AUC_{last} (ng*hr/mL)	n	11	8	3

Parameter	Statistics	Control N=11	Severe RI N=8	ESRD N=3
	Mean (SD)	4160 (1720)	5240 (3290)	4650 (2940)
	CV%	41.3	62.9	63.2
	Geo-mean	3850	4210	4110
	Geo-CV%	43.2	88.2	65.1
	Median	3510	5020	3380
	Min-Max	1960-7100	1320-10600	2560-8010
C_{max} (ng/mL)	n	11	8	3
	Mean (SD)	103 (49.8)	102 (68.3)	91.1 (52.6)
	CV%	48.4	67.2	57.8
	Geo-mean	93.9	77.2	81.3
	Geo-CV%	44.9	106.9	64.2
	Median	76.8	108	78.2
	Min-Max	60.3-203	20.8-203	46.1-149

n = number of subjects with corresponding evaluable PK parameters.
Control group consists of subjects with normal renal function.

Primary PK parameters for desmethyl-dabrafenib (Supportive PAS)

Parameter	Statistics	Control N=11	Severe RI N=4	ESRD N=3
AUC_{inf} (ng*hr/mL)	n	9	0	0
	Mean (SD)	4690 (1960)		
	CV%	41.8		
	Geo-mean	4300		
	Geo-CV%	48.4		
	Median	4140		
	Min-Max	2030-7210		
AUC_{last} (ng*hr/mL)	n	11	4	3
	Mean (SD)	4160 (1720)	5420 (3970)	4650 (2940)
	CV%	41.3	73.3	63.2
	Geo-mean	3850	4280	4110
	Geo-CV%	43.2	99.7	65.1
	Median	3510	4760	3380
	Min-Max	1960-7100	1560-10600	2560-8010
C_{max} (ng/mL)	n	11	4	3
	Mean (SD)	103 (49.8)	97.7 (79.3)	91.1 (52.6)
	CV%	48.4	81.2	57.8
	Geo-mean	93.9	72.8	81.3
	Geo-CV%	44.9	117.5	64.2
	Median	76.8	82.0	78.2
	Min-Max	60.3-203	23.8-203	46.1-149

Secondary PK parameters for dabrafenib (PAS)

Parameter	Statistics	Control N=11	Severe RI N=8	ESRD N=3
T_{max} (hr)	n	11	8	3
	Mean (SD)	NA	NA	NA
	CV%	NA	NA	NA
	Geo-mean	NA	NA	NA
	Geo-CV%	NA	NA	NA
	Median	1.98	1.00	2.00
	Min-Max	0.517-4.00	1.00-3.98	1.00-3.00
Lambda_z (1/hr)	n	11	7	3
	Mean (SD)	0.160 (0.0800)	0.128 (0.0750)	0.0753 (0.0218)
	CV%	49.9	58.5	29.0
	Geo-mean	0.139	0.0969	0.0729
	Geo-CV%	66.6	121.1	32.9
	Median	0.142	0.156	0.0830
	Min-Max	0.0365-0.286	0.0200-0.227	0.0506-0.0921
$T_{1/2}$ (hr)	n	11	7	3
	Mean (SD)	6.04 (4.72)	11.2 (12.4)	9.86 (3.35)
	CV%	78.2	111.4	34.0
	Geo-mean	4.98	7.15	9.51
	Geo-CV%	66.6	121.1	32.9

Parameter	Statistics	Control N=11	Severe RI N=8	ESRD N=3
	Median	4.89	4.45	8.35
	Min-Max	2.43-19.0	3.06-34.7	7.52-13.7
Vz/F (L)	n	11	7	3
	Mean (SD)	142 (108)	381 (512)	210 (35.9)
	CV%	76.0	134.3	17.1
	Geo-mean	114	192	208
	Geo-CV%	74.6	181.6	16.7
	Median	90.4	99.1	199
	Min-Max	49.7-404	69.1-1430	182-251
Aet (ng)	n	11	8	3
	Mean (SD)	562 (1080)	2430 (5160)	29400 (27800)
	CV%	192.0	212.3	94.7
	Geo-mean	1800	4190	20800
	Geo-CV%	78.9	156.2	142.8
	Median	0.00	0.00	20100
	Min-Max	0.00-2790	0.00-14900	7370-60700
CLr (L/hr)	n	11	7	3
	Mean (SD)	0.0000806 (0.000148)	0.000410 (0.000658)	0.00472 (0.00407)
	CV%	183.6	160.6	86.2
	Geo-mean	0.000276	0.000805	0.00311
	Geo-CV%	51.0	78.1	203.4
	Median	0.00	0.00	0.00453
	Min-Max	0.00-0.000377	0.00-0.00178	0.000747-0.00888

n = number of subjects with corresponding evaluable PK parameters.
Control group consists of subjects with normal renal function.

Secondary PK parameters for dabrafenib (Supportive PAS)

Parameter	Statistics	Control N=11	Severe RI N=4	ESRD N=3
T_{max} (hr)	n	11	4	3
	Mean (SD)	NA	NA	NA
	CV%	NA	NA	NA
	Geo-mean	NA	NA	NA
	Geo-CV%	NA	NA	NA
	Median	1.98	1.00	2.00
	Min-Max	0.517-4.00	1.00-3.98	1.00-3.00
Lambda_z (1/hr)	n	11	4	3
	Mean (SD)	0.160 (0.0800)	0.108 (0.100)	0.0753 (0.0218)
	CV%	49.9	92.4	29.0
	Geo-mean	0.139	0.0683	0.0729

Parameter	Statistics	Control N=11	Severe RI N=4	ESRD N=3
	Geo-CV%	66.6	177.7	32.9
	Median	0.142	0.0935	0.0830
	Min-Max	0.0365-0.286	0.0200-0.227	0.0506-0.0921
$T_{1/2}$ (hr)	n	11	4	3
	Mean (SD)	6.04 (4.72)	16.2 (15.2)	9.86 (3.35)
	CV%	78.2	94.0	34.0
	Geo-mean	4.98	10.2	9.51
	Geo-CV%	66.6	177.7	32.9
	Median	4.89	13.5	8.35
	Min-Max	2.43-19.0	3.06-34.7	7.52-13.7
Vz/F (L)	n	11	4	3
	Mean (SD)	142 (108)	569 (639)	210 (35.9)
	CV%	76.0	112.2	17.1
	Geo-mean	114	285	208
	Geo-CV%	74.6	276.8	16.7
	Median	90.4	389	199
	Min-Max	49.7-404	69.1-1430	182-251

Aet (ng)	n	11	4	3
	Mean (SD)	562 (1080)	1130 (1330)	29400 (27800)
	CV%	192.0	118.4	94.7
	Geo-mean	1800	2220	20800
	Geo-CV%	78.9	23.0	142.8
	Median	0.00	947	20100
	Min-Max	0.00-2790	0.00-2610	7370-60700
CLr (L/hr)	n	11	4	3
	Mean (SD)	0.0000806 (0.000148)	0.000271 (0.000313)	0.00472 (0.00407)
	CV%	183.6	115.7	86.2
	Geo-mean	0.000276	0.000541	0.00311
	Geo-CV%	51.0	6.6	203.4
	Median	0.00	0.000258	0.00453
	Min-Max	0.00-0.000377	0.00-0.000567	0.000747-0.00888

n = number of subjects with corresponding evaluable PK parameters.
Control group consists of subjects with normal renal function.