NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Dabrafenib/DRB436

Trial Indication(s)

Healthy subjects with normal hepatic function and subjects with impaired hepatic function

Protocol Number

CDRB436A2107

Protocol Title

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

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase I

Study Start/End Dates

Study Start Date: 20 December 2016 (Actual)
Primary Completion Date: 12 October 2018 (Actual)
Study Completion Date: 8 April 2019 (Actual)

Reason for Termination (If applicable)

Study was terminated due to continued enrolment difficulties.

Study Design/Methodology

This was a phase I, open label, multicenter, parallel group study to evaluate the PK and safety of a single oral dose of dabrafenib (100 mg) in subjects with moderate and severe hepatic impairment compared to healthy subjects with normal hepatic function.

Centers

United States(4)

Objectives:

Primary Objective:

To evaluate the PK of dabrafenib and metabolites after a single oral dose of dabrafenib in subjects with hepatic impairment as compared to healthy subjects with normal hepatic function (Child-Pugh classification).

Secondary Objective:

To assess the safety of a single oral dose of dabrafenib in subjects with normal and impaired hepatic functions.

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 for the primary endpoint as the main purpose of the statistical analysis was to estimate the effects of hepatic impairment on the PK of dabrafenib and metabolites. Due to limited data,

primary PK data was only summarized for dabrafenib and metabolites and no formal comparisons were possible between the normal and impaired function groups.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria
(for all subjects)
- Male and/or female subjects 18-75 years of age
- Females must be of non-childbearing potential . All non-postmenopausal females must have a confirmed negative serum pregnancy
- Subjects in good health condition as determined by no clinically significant findings from medical history and physical examination.
- Body mass index (BMI) between ≥18.0 and ≤38.0 kg/m2, with body weight ≥ 50 kg and no more than 140 kg
- Laboratory values must be within normal limits (correction allowed) or considered clinically insignificant
- Do not participate in any other clinical trials with a BRAF or other RAF inhibitors

Additional inclusion criteria for patients with normal hepatic function (Control group):
- Absence of clinically significant deviation from normal in medical history, physical examination, vital signs, electrocardiograms and clinical laboratory determinations.
- Must match to at least one hepatic impairment subject by age, gender and bodyweight

Additional inclusion criteria for hepatic impaired subjects:
- Confirmed hepatic disease
- Stable Child-Pugh status within 28 days prior to dosing.

Exclusion criteria for all subjects

- Participation in any clinical investigation within 4 weeks prior to dosing
- Significant acute illness within the two weeks prior to dosing
- History of immunodeficiency diseases, including a positive HIV
- History of malignancy of any organ system, treated or untreated, within 5 years
- Any prior history of keratoacanthoma and/or cutaneous squamous cell carcinoma
- A known diagnosis of any of the RASopathies, such as NF-1, Noonan syndrome, or related conditions.
- History of drug or alcohol abuse within the 6 months prior to dosing
- Smoking: urine cotinine levels above 500 ng/mL on Day -1.

- Use of drugs known to affect CYP3A4 and/or CYP2C8 including both (strong or moderate) inhibitors and inducers, within 7 days prior to dosing
- Administration of medications that prolong the QT interval within 4 weeks prior to dosing and until EOT.
- History or current diagnosis of cardiac disease indicating significant risk of safety
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs.

Additional exclusion criteria for healthy subjects (control group):
- Clinical evidence of liver disease or liver injury
- History or presence of renal impairment as indicated by abnormal creatinine or BUN values
- A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C antibody

Additional exclusion criteria for subjects with hepatic impairment:
- Alcohol or drug abuse within one month prior to dosing or evidence of such
- History of liver transplantation at any time in the past and is on immunosuppressant therapy.
- Encephalopathy Grade 3 or worse within 28 days of dosing.
- History of surgical portosystemic shunt.
- Life expectancy ≤3 months

Participant Flow Table

Overall Study

	Group 1 - Control group	Group 2- Moderate hepatic impairment	Total
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.	
Started	1	4	5
Completed	1	4	5

Not Completed	0	0	0

Baseline Characteristics

	Group 1 - Control group	Group 2- Moderate hepatic impairment	Total
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.	
Number of Participants [units: participants]	1	4	5
Age Continuous (units: Years) Mean ± Standard Deviation			
	52.0±0.0	57.0±10.30	56.0±9.19
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			
Female	1	3	4
Male	0	1	1
Race/Ethnicity, Customized (units: Participants)			
White	1	4	5

Summary of Pharmacokinetics

Primary Outcome Result(s)

Pharmacokinetics (PK) parameter: AUCinf (dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
Pharmacokinetics (PK) parameter: AUCinf (dabrafenib) (units: (ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
	2,870 (NA%)[1]	12.300 (47.7%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter: AUClast (dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: AUClast (dabrafenib) (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
	2,860 (NA%)[1]	12,200 (47.7%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter: Cmax (dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with

		Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: Cmax (dabrafenib) (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
	506 (NA%)[1]	2,450 (31.5%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter: CL/F (dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	**Group 2- Moderate hepatic impairment**
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: CL/F (dabrafenib) (units: Litres/hour (L/hr)) Geometric Mean (Geometric Coefficient of Variation)		

	34.8 (NA%)[1]	8.15 (47.7%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter: Tmax (dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: Tmax (dabrafenib) (units: hour (hr)) Median (Full Range)		
	2.00 (2.00 to 2.00)	2.00 (1.00 to 2.00)

PK parameter: Lambda_z (dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of	This group comprised of

	subjects with normal hepatic function.	subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: Lambda_z (dabrafenib) (units: 1/hour (1/hr)) Geometric Mean (Geometric Coefficient of Variation)		
	0.143 (NA%)[1]	0.175 (19.4%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter: T1/2 (dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	**Group 2- Moderate hepatic impairment**
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: T1/2 (dabrafenib)		

(units: hour (hr)) Median (Full Range)		
	4.83 (4.83 to 4.83)	4.21 (3.01 to 4.67)

PK parameter: Vz/F (dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: Vz/F (dabrafenib) (units: Litres (L)) Geometric Mean (Geometric Coefficient of Variation)		
	243 (NA%)[1]	46.7 (28.6%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter: AUCinf (hydroxy-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: AUCinf (hydroxy-dabrafenib) (units: (ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
	1,740 (NA%)[1]	9,570 (32.4%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter: AUClast (hydroxy-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with

		Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: AUClast (hydroxy-dabrafenib) (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
	1,730 (NA%)[1]	9,540 (32.6%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter: Cmax (hydroxy-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	**Group 2- Moderate hepatic impairment**
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: Cmax (hydroxy-dabrafenib) (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		

	161 (NA%)[1]	799 (40.4%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter (secondary): Tmax (hydroxy-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter (secondary): Tmax (hydroxy-dabrafenib) (units: hour (hr)) Median (Full Range)		
	5.00 (5.00 to 5.00)	4.50 (3.00 to 6.03)

PK parameter (secondary): Lambda_z (hydroxy-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment

Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter (secondary): Lambda_z (hydroxy-dabrafenib) (units: 1/hour (1/hr)) Geometric Mean (Geometric Coefficient of Variation)		
	0.104 (NA%)[1]	0.107 (58.6%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter (secondary): T1/2 (hydroxy-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.

Number of Participants Analyzed [units: participants]	1	4
PK parameter (secondary): T1/2 (hydroxy-dabrafenib) (units: hour (hr)) Median (Full Range)		
	6.66 (6.66 to 6.66)	5.41 (4.26 to 14.2)

PK parameter: AUCinf (carboxy-debrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	**Group 2- Moderate hepatic impairment**
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: AUCinf (carboxy-debrafenib) (units: (ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
	17,300 (NA%)[1]	177,000 (50.0%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter: AUClast (carboxy-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: AUClast (carboxy-dabrafenib) (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
	16,800 (NA%)[1]	165,000 (48.0%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter: Cmax (carboxy-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal	This group comprised of subjects with moderate hepatic function with

	hepatic function.	Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: Cmax (carboxy-dabrafenib) (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
	519 (NA%)[1]	3,820 (41.0%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter (secondary): Tmax (carboxy-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter (secondary): Tmax (carboxy-dabrafenib) (units: hour (hr)) Median (Full Range)		

12.0 (12.0 to 12.0)	12.0 (12.0 to 12.0)

PK parameter (secondary): Lambda_z (carboxy-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter (secondary): Lambda_z (carboxy-dabrafenib) (units: 1/hour (1/hr)) Geometric Mean (Geometric Coefficient of Variation)		
	0.0413 (NA%)[1]	0.0314 (14.7%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter (secondary): T1/2 (carboxy-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

Group 1 - Control group	Group 2- Moderate hepatic impairment

Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter (secondary): T1/2 (carboxy-dabrafenib) (units: hour (hr)) Median (Full Range)		
	16.8 (16.8 to 16.8)	23.5 (17.8 to 24.3)

PK parameter: AUCinf (desmethyl-debrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4

PK parameter: AUCinf (desmethyl-debrafenib) (units: (ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
	2,640 (NA%)[1]	5.500 (128.8%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter: AUClast (desmethyl-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: AUClast (desmethyl-dabrafenib) (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
	2,210 (NA%)[1]	4,770 (123.1%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter: Cmax (desmethyl-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter: Cmax (desmethyl-dabrafenib) (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
	40.4 (NA%)[1]	105 (106.2%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter (secondary): Tmax (desmethyl-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal	This group comprised of subjects with moderate hepatic

	hepatic function.	function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter (secondary): Tmax (desmethyl-dabrafenib) (units: hour (hr)) Median (Full Range)		
	36.0 (36.0 to 36.0)	30.00 (12.0 to 48.0)

PK parameter (secondary): Lambda_z (desmethyl-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	**Group 2- Moderate hepatic impairment**
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter (secondary): Lambda_z (desmethyl-dabrafenib) (units: 1/hour (1/hr)) Geometric Mean		

(Geometric Coefficient of Variation)		
	0.0254 (NA%)[1]	0.0281 (17.3%)

[1] NA = Could not calculate the Geometric Coefficient of Variation as only 1 patient

PK parameter (secondary): T1/2 (desmethyl-dabrafenib)

(Time Frame: Predose through 96 hours postdose)

	Group 1 - Control group	Group 2- Moderate hepatic impairment
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.
Number of Participants Analyzed [units: participants]	1	4
PK parameter (secondary): T1/2 (desmethyl-dabrafenib) (units: hour (hr)) Median (Full Range)		
	27.3 (27.3 to 27.3)	23.0 (22.1 to 31.8)

Secondary Outcome Result(s)

See Summary of Safety Section

Summary of Safety

Safety Results

All-Cause Mortality

	Gtroup 1 - Control group N = 1	Group 2- Moderate hepatic impairment N = 4	All subjects N = 5
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.	Participants in both the Control & hepatic impairment groups
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

No Serious Adverse Events were reported during the trial

Other Adverse Events by System Organ Class

Time Frame	Adverse Event (AE) timeframe: Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of ???
Additional Description	Adverse Event (AE):An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after subject's signed informed consent has been obtained plus the 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Gtroup 1 - Control group N = 1	**Group 2- Moderate hepatic impairment N = 4**	**All subjects N = 5**
Arm/Group Description	This group comprised of subjects with normal hepatic function.	This group comprised of subjects with moderate hepatic function with Child-Pugh class B.	Participants in both the Control & hepatic impairment groups
Total participants affected	0 (0.00%)	2 (50.00%)	2 (40.00%)
General disorders and administration site conditions			
Pyrexia*	0 (0.00%)	1 (25.00%)	1 (20.00%)
Investigations			
Amylase increased*	0 (0.00%)	1 (25.00%)	1 (20.00%)

* Non-systematic Assessment

Conclusion:

Due to limited data (as the study was terminated early because of enrolment issues), the pharmacokinetics and safety of a single oral dose of dabrafenib in subjects with normal and impaired hepatic functions is not sufficient to inform a dabrafenib dose modification for hepatic impaired subjects.

Date of Clinical Trial Report

CSR Published: 6 Dec 2019

CSR Addendum Published: 24 Apr 2020