A Study to Determine Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib In Children and Adolescent Subjects

This study is currently recruiting participants. (see Contacts and Locations)

Verified October 2016 by GlaxoSmithKline

Sponsor:
GlaxoSmithKline

Information provided by (Responsible Party):
GlaxoSmithKline

ClinicalTrials.gov Identifier:
NCT01677741

First received: August 30, 2012
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History of Changes

Purpose

This is a 2-part, study to determine the safety, tolerability and pharmacokinetics of oral dabrafenib in children and adolescent subjects with advanced BRAF V600 mutation-positive solid tumors. Part 1 (dose escalation study) will identify the recommended Part 2 (tumor-specific expansion study) dose and regimen using a dose-escalation procedure. Approximately 6 to 18 subjects will participate in Part 1 and will receive a starting dose of 3 mg/kg and dose will deescalate or escalate between 1.5 milligram (mg)/kilogram (kg) and 6 mg/kg. Up to 6 subjects will be enrolled at one dose level dependent upon the number of subjects at the current dose level, the number of subjects who have experienced a dose limiting toxicity (DLT) at the current dose level, and the number of subjects enrolled but with data pending at the current dose level. Escalation may proceed until either a maximum tolerated dose (MTD) is established, or until the dose in which the median pharmacokinetic parameters consistent with exposure in adults are achieved. Cohorts may be added in order to evaluate additional dose levels. Part 2 consists of four disease-specific cohorts of subjects with tumors known to have BRAF V600 activation (pediatric low-grade gliomas, pediatric high-grade gliomas, Langerhans cell histiocytosis [LCH], and other tumors such as melanoma and papillary thyroid carcinoma [PTC]). Each cohort will enroll at least 10 subjects with a pre-dose and at least 1 post-dose disease assessment. In both the parts of the study, on Day 1, a single first dose will be administered, and repeat dosing will begin on Day 2. PK sampling will be performed on Day 1 and Day 15 for subjects >=25 kg in weight. For subjects <25 kg and >=10 kg in weight, blood samples for PK analysis will be collected on Day 1 and Day 15. For subjects <10kg in weight, blood samples for PK analysis will be collected after repeated administration on Day 15 only. Safety and tolerability will be assessed throughout the study. Treatment with dabrafenib will be continued until disease progression or until no clinical benefit or development of an unacceptable toxicity, or until they withdraw consent or begin a new therapy. At the end of treatment, a final study visit will occur.

Condition	Intervention	Phase
Neoplasms, Brain	Drug: Dabrafenib	Phase 1

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Endpoint Classification: Safety Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Phase I/IIa, 2-Part, Multi-Center, Single-Arm, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Subjects With Advanced BRAF V600-Mutation Positive Solid Tumors

Resource links provided by NLM:

Drug Information available for: Dabrafenib

U.S. FDA Resources

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measures:

- Safety and tolerability of dabrafenib dose that achieves similar exposures to the dabrafenib adult dose as assessed by number of subjects with adverse events (AEs) [Time Frame: Up to 6 months] [Designated as safety issue: No]

  Safety and tolerability parameters will include recording of AEs, in Part 1 and Part 2 of the study.

- Safety and tolerability of dabrafenib dose that achieves similar exposures to the dabrafenib adult dose as assessed by change from Baseline in ECG readings [Time Frame: Up to 6 months] [Designated as safety issue: No]

  Safety and tolerability parameters will include the electrocardiogram (ECG) readings at Baseline and at end of Part 1 and Part 2 of the study.

- Safety and tolerability of dabrafenib dose that achieves similar exposures to the dabrafenib adult dose as assessed by change from Baseline in ECHO findings [Time Frame: Up to 6 months] [Designated as safety issue: No]

  Safety and tolerability parameters will include recording of echocardiogram (ECHO) at Baseline and at end of Part 1 and Part 2 of the study.

- Safety and tolerability of dabrafenib dose that achieves similar exposures to the dabrafenib adult dose as assessed by change from Baseline in laboratory values [Time Frame: Up to 6 months] [Designated as safety issue: No]

  Safety and tolerability parameters will include laboratory values at Baseline and at end of Part 1 and Part 2 of the study.

- Safety and tolerability of dabrafenib dose that achieves similar exposures to the dabrafenib adult dose as assessed by change from Baseline in vital signs [Time Frame: Up to 6 months] [Designated as safety issue: No]

  Safety and tolerability parameters will include vital signs at Baseline and at end of Part 1 and Part 2 of the study.

- Maximum concentration (Cmax) of dabrafenib dose(s) [Time Frame: Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.] [Designated as safety issue: No]

  To calculate the dabrafenib dose(s) for chronic dosing in pediatric subjects (infants, children, and adolescents), the Cmax of dabrafenib that achieves similar exposure to the dabrafenib adult dose will be evaluated.

- Area under the concentration-time curve over the dosing interval (AUC(0-τ)) and AUC from zero to infinity (AUC(0-inf)) of dabrafenib dose(s) [Time Frame: Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.] [Designated as safety issue: No]

  To calculate the dabrafenib dose(s) for chronic dosing in pediatric subjects (infants, children, and adolescents) the AUC(0-τ) and AUC(0-inf) of dabrafenib that achieves similar exposure to the dabrafenib adult dose will be evaluated.

Secondary Outcome Measures:

- Pre-dose (trough) concentration (C tau) of dabrafenib and its metabolites [Time Frame: Day 1-Predose, Day 15-Predose] [Designated as safety issue: No]

  Pharmacokinetic data will include C trough of dabrafenib and its metabolites (GSK2285403, GSK2167542 and GSK2298683).

- The AUC(0-t) and AUC(0-tau) of dabrafenib and its metabolites [Time Frame: Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.] [Designated as safety issue: No]

  Pharmacokinetic data will include area under the time-concentration curve from time zero (pre-dose) to last time of quantifiable concentration (AUC[0-t]), AUC(0-tau) of dabrafenib and its metabolites (GSK2285403, GSK2167542 and GSK2298683).

- Apparent clearance following oral dosing (CL/F) of dabrafenib [Time Frame: Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.] [Designated as safety issue: No]

  Pharmacokinetic data will include CL/F of dabrafenib.

- Cmax of dabrafenib, and its metabolites [Time Frame: Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.] [Designated as safety issue: No]

  Pharmacokinetic data will include Cmax of dabrafenib and its metabolites (GSK2285403, GSK2167542 and GSK2298683).

- Time from administration to Cmax (tmax) of dabrafenib and its metabolites [Time Frame: Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.] [Designated as safety issue: No]

  Pharmacokinetic data will include tmax of dabrafenib and its metabolites (GSK2285403, GSK2167542 and GSK2298683).

- Elimination half life (t½) of dabrafenib and its metabolites [Time Frame: Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.] [Designated as safety issue: No]

  Pharmacokinetic data will include t½ of dabrafenib and its metabolites (GSK2285403, GSK2167542 and GSK2298683).

- Longer term safety and tolerability of dabrafenib as assessed by number of subjects with AEs [Time Frame: Up to 6 months] [Designated as safety issue: No]

  Safety and tolerability parameters will include recording of AEs, in Part 1 and Part 2 of the study.

- Longer term safety and tolerability of dabrafenib as assessed by change from Baseline in ECG readings [Time Frame: Up to 6 months] [Designated as safety issue: No]

  Safety and tolerability parameters will include the electrocardiogram (ECG) readings at Baseline and at end of Part 1 and Part 2 of the study

- Longer term safety and tolerability of dabrafenib as assessed by change from Baseline in laboratory values [Time Frame: Up to 6 months] [Designated as safety issue: No]

  Safety and tolerability parameters will include laboratory values at Baseline and at end of Part 1 and Part 2 of the study.

- Longer term safety and tolerability of dabrafenib as assessed by change from Baseline in vital signs [Time Frame: Up to 6 months] [Designated as safety issue: No]

  Safety and tolerability parameters will include vital signs at Baseline and at end of Part 1 and Part 2 of the study.

- Overall tumor response of dabrafenib [Time Frame: Up to 6 months] [Designated as safety issue: No]

  Anti-tumor activity will be assessed based on clinical evidence and the response evaluation criteria in solid tumors (RECIST) version 1.1 criteria for solid tumors, response assessment in neuro-oncology (RANO) criteria (glioma subjects) and langerhans cell histiocytosis (LCH) scoring system.

- Effect of age and weight on CL/F of dabrafenib [Time Frame: Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.] [Designated as safety issue: No]

  The CL/F data with the effect of age and weight using a population pharmacokinetic approach will be evaluated.

- Effect of age and weight on volume of distribution (V/F) of dabrafenib [Time Frame: Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.] [Designated as safety issue: No]

  The V/F data with the effect of age and weight using a population pharmacokinetic approach will be evaluated.

- Effect of age and weight on absorption rate (ka) of dabrafenib [Time Frame: Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.] [Designated as safety issue: No]

  The ka data with the effect of age and weight using a population pharmacokinetic approach will be evaluated.

- Effect of age and weight on coefficients for significant covariates of dabrafenib [Time Frame: Day 1-Predose, 0.5, 2 and 4 hours post dose; Day 15-Predose, 0, 0.5, 1, 2, 3, 4, 6 and 8 hours post dose.] [Designated as safety issue: No]

  The coefficients for significant covariates data with the effect of age and weight using a population pharmacokinetic approach will be evaluated.

Estimated Enrollment:	86
Study Start Date:	February 2013
Estimated Study Completion Date:	February 2018
Estimated Primary Completion Date:	October 2016 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Part 1: Dabrafenib treatment Three subjects will receive a single dose of 3 mg/kg dabrafenib on Day 1 and repeat dose will begin from Day 2, evenly divided in two daily doses. Once all 3 subjects have been fully evaluated for the first 28 days (including Day 15 PK) and no DLTs are observed, a next subject will be enrolled at the next higher dose levels (i.e., dose escalation to 3.75 mg/kg [+1] and may be further to 4.5 mg/kg [+2] and so on). If all 3 subjects have not been fully evaluated for the first 28 days or 1 DLT occurred, the fourth subject will be enrolled at the same dose level. If 2 or more DLTs are observed, the next subject will be enrolled at the next lower dose level (i.e., de-escalated to 2.25 mg/kg [-1] and may be further to 1.5 mg/kg [-2]). Similarly, the process is repeated for the fifth and sixth subjects in a cohort. All subjects will receive treatment till end of study.	Drug: Dabrafenib Dabrafenib is available as 10 mg, 25 mg, 50 mg or 75 mg capsules and as oral suspension (10 mg/mL for subjects unable to swallow capsules). Dabrafenib (either formulation) will be administered orally as a single dose on Day 1 and twice daily from Day 2, based on weight at the appropriate study dose level.
Experimental: Part 2: Cohort 1 Low-Grade Gliomas with BRAF V600 mutations Subjects with low-grade gliomas with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.	Drug: Dabrafenib Dabrafenib is available as 10 mg, 25 mg, 50 mg or 75 mg capsules and as oral suspension (10 mg/mL for subjects unable to swallow capsules). Dabrafenib (either formulation) will be administered orally as a single dose on Day 1 and twice daily from Day 2, based on weight at the appropriate study dose level.
Experimental: Part 2: Cohort 2 High-Grade Gliomas with BRAF V600 mutations Subjects with high-grade gliomas with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.	Drug: Dabrafenib Dabrafenib is available as 10 mg, 25 mg, 50 mg or 75 mg capsules and as oral suspension (10 mg/mL for subjects unable

	to swallow capsules). Dabrafenib (either formulation) will be administered orally as a single dose on Day 1 and twice daily from Day 2, based on weight at the appropriate study dose level.
Experimental: Part 2: Cohort 3 LCH with BRAF V600 mutations Subjects with LCH with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.	Drug: Dabrafenib Dabrafenib is available as 10 mg, 25 mg, 50 mg or 75 mg capsules and as oral suspension (10 mg/mL for subjects unable to swallow capsules). Dabrafenib (either formulation) will be administered orally as a single dose on Day 1 and twice daily from Day 2, based on weight at the appropriate study dose level.
Experimental: Part 2: Cohort 4 Melanoma and PTC with BRAF V600 mutations Subjects with other tumors with BRAF V600 mutations will receive the single selected final dose (based on MTD and the age of the subjects) from Part 1 on Day 1. Repeat dosing will begin from Day 2, twice daily till end of study.	Drug: Dabrafenib Dabrafenib is available as 10 mg, 25 mg, 50 mg or 75 mg capsules and as oral suspension (10 mg/mL for subjects unable to swallow capsules). Dabrafenib (either formulation) will be administered orally as a single dose on Day 1 and twice daily from Day 2, based on weight at the appropriate study dose level.

Eligibility

Ages Eligible for Study: 12 Months to 17 Years (Child)
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Written informed consent - a signed informed consent and/or assent (as age appropriate) will be obtained according to institutional guidelines.
- Male or female >=12 months and <18 years of age at the time of signing the informed consent form.
- Recurrent disease, refractory disease, or progressive disease after having received at least one standard therapy for their disease. Note: Subjects with metastatic (and surgically unresectable) melanoma can be enrolled for first-line treatment; Melanoma subjects with CNS involvement may be enrolled.
- At least one evaluable lesion.
- BRAF V600 mutation-positive tumor as confirmed in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory or equivalent (the local BRAF testing may be subject to subsequent verification by centralized testing; centralized testing can confirm V600E and V600K mutations only).
- Performance score of >=50% according to the Karnofsky/Lansky performance status scale (subjects with a performance status of <=50% can be enrolled if the subject's confinement to bed and inability to carry out activities is due solely to cancer-related pain, as assessed by the investigator).
- Females of child-bearing potential (with negative serum pregnancy test within 7 days prior to the first dose of study medication) must be willing to practice acceptable methods of birth control .
- Must have adequate organ function as defined by the following values: Adequate bone marrow function defined as-absolute neutrophil count (ANC) >=1000/ microliter (µL), hemoglobin >=8.0 grams (g)/ deciliter (dL) (may receive red blood cell transfusions), platelets >=75,000/µL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment).
- Adequate renal and metabolic function defined as: calculated glomerular filtration rate (eGFR) (Schwartz formula), or radioisotope GFR >=90 milliliters/minutes (mL/min)/1.73 meter square (m^2); or a serum creatinine within the institutional reference range upper limit of normal (for age/gender, if available).
- Adequate liver function defined as: bilirubin (sum of conjugated + unconjugated) <=1.5 x upper limit of normal (ULN) for age, aspartate aminotransaminase (AST) and alanine transaminase (ALT) <=2.5 x ULN; AST/ALT may be <5 x ULN at baseline if disease under treatment involves the liver (requires radiographic confirmation of liver involvement).
- Adequate cardiac function defined as: left ventricular ejection fraction (LVEF) of either >=50% by ECHO or greater than institutional lower limit of normal (LLN) by echocardiogram (ECHO) (while not receiving medications for cardiac function), corrected QT using Bazett's (QTcB) interval <450 milliseconds (msecs).

Exclusion Criteria:

- Part 2 ONLY: Previous treatment with dabrafenib, another RAF inhibitor, or a mitogen-activated protein kinase (MEK) inhibitor (exception: prior treatment with sorafenib is permitted).
- Malignancy OTHER than the BRAF mutant malignancy under study.

- Had chemotherapy or radiotherapy within 3 weeks (or 6 weeks for nitrosoureas or mitomycin C) prior to administration of the first dose of study treatment.
- The subject has received an investigational product within the following time period prior to the first dosing day in the current study: 28 days or 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is warranted by the data).
- History of another malignancy. Exception: (a) Subjects who have been successfully treated and are disease-free for 3 years, (b) a history of completely resected non-melanoma skin cancer, (c) successfully treated in situ carcinoma, (d) CLL in stable remission are eligible.
- Current use of a prohibited medication or herbal preparation or requires any of these medications during the study.
- Unresolved toxicity greater than National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 Grade 2 or higher from previous anti-cancer therapy, including major surgery except those that in the opinion of the investigator are not clinically relevant given the known safety/toxicity profile of dabrafenib (e.g., alopecia and/or peripheral neuropathy related to platinum or vinca alkaloid based chemotherapy).
- Has leukaemia.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to dabrafenib and its excipients.
- Autologous or allogeneic stem cell transplant within 3 months prior to enrolment [NOTE: subjects with evidence of active graph versus host disease are excluded].
- History of myocardial infarction, severe or unstable angina, peripheral vascular disease or familial QTc prolongation.
- Subjects with abnormal cardiac valve morphology (>=grade 2) documented by echocardiogram (NOTE: subjects with grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study).
- Subjects with moderate valvular thickening.
- Known, uncontrolled cardiac arrhythmias (except sinus arrhythmia) within the past 24 weeks
- Uncontrolled medical conditions (e.g., diabetes mellitus, hypertension, liver disease or uncontrolled infection), psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol; or unwillingness or inability to follow the procedures required in the protocol.
- Presence of active GI disease or other condition (e.g., small bowel or large bowel resection) that will interfere significantly with the absorption of drugs.
- Hepatitis B Virus, or Hepatitis C Virus infection (subjects with laboratory evidence of Hepatitis B Virus clearance may be enrolled).
- Pregnant females as determined by positive human chorionic gonadotropin (hCG) test at screening or prior to dosing.
- Lactating females who are actively breast feeding.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT01677741

Contacts

Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com

Show 25 Study Locations

Sponsors and Collaborators

GlaxoSmithKline

Investigators

Study Director: GSK Clinical Trials GlaxoSmithKline

More Information

Responsible Party:	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01677741 History of Changes
Other Study ID Numbers:	116013
Study First Received:	August 30, 2012
Last Updated:	October 24, 2016
Health Authority:	United States: Food and Drug Administration

Keywords provided by GlaxoSmithKline:

Children and Adolescents
BRAF
dabrafenib
dose escalation
BRF116013
V600-mutation positive
BRF

Additional relevant MeSH terms:

Brain Neoplasms
Central Nervous System Neoplasms
Nervous System Neoplasms
Neoplasms by Site
Neoplasms
Brain Diseases
Central Nervous System Diseases
Nervous System Diseases
Dabrafenib
Antineoplastic Agents
Protein Kinase Inhibitors
Enzyme Inhibitors
Molecular Mechanisms of Pharmacological Action

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