Official Title: An Open-Label, Extension (Rollover) Study of Vemurafenib in Patients With $BRAF^{V600}$ Mutation-Positive Malignancies Previously Enrolled in an Antecedent Vemurafenib Protocol

NCT Number: NCT01739764

Document Date: Protocol Version 5: 20-August-2018

PROTOCOL

TITLE:	**AN OPEN-LABEL, EXTENSION (ROLLOVER) STUDY OF VEMURAFENIB IN PATIENTS WITH BRAF^{V600} MUTATION–POSITIVE MALIGNANCIES PREVIOUSLY ENROLLED IN AN ANTECEDENT VEMURAFENIB PROTOCOL**
PROTOCOL NUMBER:	GO28399
VERSION NUMBER:	5
EUDRACT NUMBER:	2012-003144-80
IND NUMBER:	73,620
TEST PRODUCT:	Vemurafenib (Zelboraf®, formerly known as RO5185426)
MEDICAL MONITOR:	[redacted], *M.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 7 September 2012
DATES AMENDED:	Version 2: 25 September 2013 Version 3: 21 March 2014 Version 4: *13 March 2015* *Version 5:* See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	20-Aug-2018 22:13:50

PROTOCOL AMENDMENT, VERSION 5: RATIONALE

Protocol GO28399 has been amended to remove the Roche-designated central pathology laboratory because cuSCC is an identified risk that no longer requires further evaluation by an independent central pathology review. Changes to the protocol are summarized below:

- Safety follow-up visits at 3 and 6 months have been removed because secondary malignancies are no longer characterized as an important safety concern (Sections 1.3, 3.1.1, 4.4.2, 4.5.1, 4.5.2, 4.5.3, 5.1.1, and 5.1.2.3).
- End of study safety follow up and dermatological evaluations have been updated to assessment until 28 days after the last dose of study drug (Sections 3.3, 4.5.1.9, and 5.1.2.3).
- Follow-up for new primary malignancies has been updated to per investigator's discretion (Section 4.4.2).

Additional changes to the protocol, along with a rationale for each change, are summarized below:

- Additional new safety information, including acute kidney injury and Dupuytren's contracture, has also been added per the current Vemurafenib Investigator's Brochure (Section 1.2.1.5).
- Study drug storage details have been referred to the study drug label (Section 4.3.1.1).
- Adverse events of special interest and the reporting language have been clarified (Sections 5.2.3 and 5.4.2).
- Section 5.2.4 (Selected Adverse Events) has been deleted and information from that section is consolidated in Section 5.3.5.9 (Worsening of Malignancy).
- Adverse event reporting has been clarified (Section 5.3.1).
- Persistent adverse event reporting has been clarified (Section 5.3.5.3).
- The reporting of the term "sudden death" has been updated to also require the presumed cause of death (Section 5.3.5.7).
- Event reporting for hospitalization has been clarified (Section 5.3.5.10).
- Language has been revised to account for the fact that some sites may not allow follow-up on partner pregnancies (Section 5.4.3.2).
- Reporting of pregnancy in a partner of a male patient has been clarified to when permitted by site (Section 5.4.3.2).
- Follow up of patients after an adverse event and reporting of adverse events after the reporting period have been clarified (Sections 5.5 and 5.6).
- Manual signature page has been removed because it is no longer needed given the use of an electronic signature stamp on the cover page.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, EXTENSION (ROLLOVER) STUDY OF VEMURAFENIB IN PATIENTS WITH BRAF^{V600} MUTATION–POSITIVE MALIGNANCIES PREVIOUSLY ENROLLED IN AN ANTECEDENT VEMURAFENIB PROTOCOL**
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MEDICAL MONITOR:	[redacted], *M.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return a copy of the form as instructed by your local study monitor. Please retain the original for your study files.

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL, EXTENSION (ROLLOVER) STUDY OF VEMURAFENIB IN PATIENTS WITH BRAF^{V600} MUTATION–POSITIVE MALIGNANCIES PREVIOUSLY ENROLLED IN AN ANTECEDENT VEMURAFENIB PROTOCOL**
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VERSION NUMBER:	5
EUDRACT NUMBER:	2012-003144-80
IND NUMBER:	73,620
TEST PRODUCT:	Vemurafenib (Zelboraf®, formerly known as RO5185426)
PHASE:	Open-label extension study
INDICATION:	*BRAF*^{V600} mutation–positive patients previously enrolled in an antecedent vemurafenib protocol
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Primary Objective

The primary objective of this study is to provide continued access to vemurafenib for eligible patients with *BRAF*^{V600} mutation–positive malignancy who were previously treated in an antecedent vemurafenib protocol and did not meet the protocol's criteria for disease progression or are being treated beyond progression and still deriving clinical benefit, as assessed by investigator, and may potentially benefit from continued treatment with vemurafenib.

Secondary Objective

The secondary objective is to collect and describe safety and tolerability data for patients who continue vemurafenib treatment in this extension (rollover) study.

Study Design

Description of Study

This is an open-label, multicenter, non-randomized study to provide continued access to vemurafenib for eligible patients with *BRAF*^{V600} mutation–positive malignancy who were previously enrolled and treated in an antecedent vemurafenib protocol and did not meet the protocol's criteria for disease progression or are being treated beyond progression and still deriving clinical benefit (as assessed by the investigator) and may therefore potentially benefit from continued treatment with vemurafenib. *The maximum number of days between the last dose of study drug in the antecedent protocol and first dose in this extension (rollover) study will be 15 days.* Results of the study completion visit or other visit in the antecedent protocol may be used as screening/baseline for this extension (rollover) study. Screening/baseline is combined into one visit if completed within time intervals, as specified in the protocol. The first vemurafenib treatment in the extension (rollover) study will be recorded as Cycle 1, Day 1. Patients will receive treatment with oral vemurafenib at 960 mg twice daily (BID), 720 mg BID, or 480 mg BID, depending on the last dose in the antecedent protocol. Treatment will continue until progression of disease or as long as the patient is deriving clinical benefit, as judged by the investigator (case-by-case decision with approval of the Medical Monitor), death, withdrawal of

consent, unacceptable toxicity, loss to follow-up, or decision of the Sponsor to terminate the study, whichever occurs first.

One cycle is defined as 28 days. Clinic visits will occur on Day 1 of Cycles 1–7 and on Day 1 of every other cycle through Cycle 15. Then, for patients still receiving treatment, clinic visits will occur on Day 1 of every third cycle (i.e., screening/*baseline* and Day 1 of every third cycle *from* Cycle 18+ for patients with ≥17 cycles of vemurafenib on an antecedent study) *until unacceptable toxicity or disease progression, as defined by the investigator*. In patients with measurable disease, tumor assessments will be conducted for purposes of evaluating whether treatment should be discontinued via routine tumor assessments (computed tomography [CT]/magnetic resonance imaging) consistent with institutional standards of care, as outlined in the Schedule of Assessments.

Tumor assessments as specified and conducted in the antecedent protocol, including any evaluable and measurable disease, will have been documented at screening in the antecedent protocol. In the extension (rollover) study, tumor assessments, including radiological tumor assessments of chest, abdomen, pelvis for measuring extent or progression of disease (CT scan is the preferred method) will be done at the discretion of the investigator according to local institutional standard of care for purposes of evaluating whether treatment should be discontinued.

Safety evaluations will also be conducted during the study. Safety evaluations will begin on Day 1 of the study and will continue throughout the study until 28 days after the last dose of study drug*, withdrawal of consent, initiation of non-protocol therapy, death, or loss to follow-up, whichever is earliest*. Adverse events related to the study medication will be monitored until resolution. The tolerability and toxicity (safety) profile of vemurafenib will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0.

Target Population

The target population includes patients with *BRAF*^{V600} mutation–positive malignancy (including metastatic melanoma or other cancer types) who were previously enrolled and treated in an antecedent vemurafenib protocol and did not meet the protocol's criteria for disease progression or are being treated beyond progression and still deriving clinical benefit, as assessed by investigator and may potentially benefit from receiving continued treatment with vemurafenib. Patients with malignant tumor types other than malignant melanoma harboring a V600-activating mutation of *BRAF* who have no acceptable standard treatment options will also be allowed to participate in the trial.

Inclusion Criteria

A patient may be included if he or she meets all of the following criteria:

Disease-Specific Inclusion Criteria:

1. *BRAF*^{V600} mutation-positive malignancy
2. Prior eligibility for and received study treatment on an antecedent vemurafenib protocol
3. Ability to begin treatment in the extension (rollover) protocol within 15 days following the last day of the study in the antecedent protocol

General Inclusion Criteria:

1. Signed Informed Consent Form(s)
2. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to always use two adequate methods of contraception including at least one method with a failure rate of <1% per year during the course of this study and for at least 6 months after completion of study treatment.
    - Females of childbearing potential are defined as sexually mature women without prior hysterectomy who have had any evidence of menses in the past 12 months. In order to be considered not of childbearing potential, amenorrhea for a period of 12 months or longer must have occurred in the absence of chemotherapy, anti-estrogen therapy, or ovarian suppression.

- Effective forms of contraception include surgical sterilization, a reliable barrier method with spermicide, birth control pills, contraceptive hormone implants, or vasectomized partner.

3. Negative serum pregnancy test within 7 days prior to commencement of dosing in women of childbearing potential; women of non-childbearing potential may be included if they are either surgically sterile or have been naturally menopausal for ≥ 1 year. Women of non-childbearing potential need not undergo the pregnancy test.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Adverse event requiring discontinuation of vemurafenib in the antecedent protocol
2. Progressive disease during the antecedent protocol. If approval to treat beyond progression was already given in the antecedent protocol, the patient may roll over into the current protocol without Sponsor's approval. Under special circumstances, when it is felt that the patient may clinically benefit from continued therapy with vemurafenib, enrollment into this protocol and dosing beyond progression may be considered if it is judged by the investigator, in consultation with the Sponsor, to be in the best interest of the patient. All such cases will require approval of the Sponsor before enrolling the patient into this protocol.
3. Meeting any of the following exclusion criterion of the antecedent study at the time the patient is considered for the extension (rollover) study:
   - Current, recent (within 28 days prior to Day 1), or planned use of any anti-tumor therapy outside of this study
   - Any other serious concomitant medical conditions that, in the opinion of the investigator, would compromise the safety of the patient or compromise the patient's ability to participate in the study
   - History of malabsorption or other clinically significant metabolic dysfunctions
   - History of clinically significant cardiac or pulmonary dysfunction as specified in antecedent study

Length of Study

Treatment will continue until disease progression (as defined by investigator) or as long as the patient is deriving clinical benefit, as assessed by investigator, if treated beyond progression (case-by-case decision discussed and approved by the Medical Monitor), death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the Sponsor to terminate the study, whichever occurs first.

End of Study

The study will end when all enrolled patients have discontinued study treatment and have been followed for safety *assessment until 28 days after the last dose of study drug*, death, withdrawal of consent, loss to follow-up, or if the Sponsor has decided to terminate the study, whichever occurs first.

Outcome Measures

Efficacy Outcome Measures

There are no protocol-specific efficacy outcome measures for this study.

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and intensity (severity) of adverse events and serious adverse events, graded according to the NCI CTCAE v4.0

Investigational Medicinal Products

Patients will receive treatment with oral vemurafenib at 960 mg BID, 720 mg BID, or 480 mg BID, depending on the last dose in the antecedent protocol. All doses will be administered as the 240-mg film-coated vemurafenib tablets.

Statistical Methods

Efficacy Analysis

No protocol-specific efficacy analysis will be performed for this study.

Safety Analysis

The safety analysis will include all patients who receive at least one dose of vemurafenib.

Incidence, nature, and intensity (severity) of adverse events and serious adverse events, graded according to NCI CTCAE v4.0 will be summarized.

Changes in vital signs (blood pressure, pulse, temperature), ECGs, and clinical laboratory results during the course of study will be summarized.

Determination of Sample Size

The number of patients will be determined by the number of patients who continue on vemurafenib treatment following enrollment in the antecedent protocol.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALP	alkaline phosphatase
AUC	area under the plasma concentration–time curve
BCC	basal cell carcinoma
BID	twice daily
BORR	best overall response rate
BRAF	proto-oncogene B-Raf
C/A/P	chest/abdomen/pelvis
CPK	creatine phosphokinase
CRO	contract research organization
CT	computed tomography
cuSCC	cutaneous squamous cell carcinoma
DRESS	drug reaction with eosinophilia and systemic symptoms
DTIC	dacarbazine [5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide]
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GCSF	granulocyte colony–stimulating factor
GGT	gamma glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act
HPV	human papilloma virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug Application
IRB	Institutional Review Board
KA	keratoacanthoma
MAPK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
ms	millisecond
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation	Definition
OS	overall survival
Pap	Papanicolaou
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
QTc	corrected QT
RECIST	Response Evaluation Criteria in Solid Tumors
SCC	squamous cell carcinoma
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON *BRAF*^{V600}-POSITIVE MALIGNANCY

BRAF is a human gene that makes a protein called B-Raf. The B-Raf protein is involved in sending signals inside cells, which are involved in directing cell growth.

Some mutations in the *BRAF* gene result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. In 2002, the *BRAF* gene was shown to be mutated in human cancers (Davies et al. 2002). Specifically, oncogenic mutations in *BRAF* kinase, predominantly V600E, have been observed in approximately 8% of all solid tumors, including 50% of metastatic melanomas, 30% to 70% of thyroid carcinomas, 30% of ovarian carcinomas, and 10% of colorectal carcinomas (Davies et al. 2002; Fransen et al. 2004; Garnett and Marais 2004; Libra et al. 2005).

Vemurafenib (Zelboraf®) (Zelboraf [vemurafenib] U.S. Package Insert), a low molecular weight, orally available inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF^{V600E}, was approved by the U.S. Food and Drug Administration (FDA) on 17 August 2011 for the treatment of patients with unresectable or metastatic melanoma with the BRAF^{V600E} mutation as detected by an FDA-approved test (Zelboraf [vemurafenib] U.S. Package Insert). Vemurafenib was approved in Europe on 17 February 2012 as monotherapy for the treatment of adult patients with *BRAF*^{V600} mutation–positive unresectable or metastatic melanoma. Vemurafenib is also approved or has been submitted for approval in other countries. Vemurafenib approval was based primarily on Study NO25026, an international, randomized, open-label trial in patients with previously untreated metastatic or unresectable melanoma with the *BRAF*^{V600E} mutation, as detected by the **cobas**® 4800 BRAFV600 Mutation Test (Roche Molecular Systems, Inc.).

1.2 ROLE OF BRAF KINASE IN MELANOMA

Recent advances in understanding of the biology of melanoma have identified the role of BRAF kinase. Mutated BRAF dimers constitutively activate the mitogen-activated protein kinase (MAPK) pathway leading to the generation of transcriptional signaling that promotes tumor growth. *BRAF* mutations have been identified in 50% to 68% of metastatic melanomas, specifically melanomas that arise from intermittent sun-exposed skin (e.g., superficial spreading and nodular melanomas [Maldonado et al. 2003; Beeram et al. 2005; Curtin et al. 2005; Lang and Mackie 2005]). *BRAF* mutations are uncommon in acral, mucosal, and uveal melanomas. In addition, *BRAF* mutations are common in benign nevi, suggesting that they are an early event in melanoma oncogenesis. About 90% of the *BRAF* mutations seen in metastatic melanoma occur in codon V600, and more than 90% of the V600 mutations involve the substitution of valine for glutamate at amino acid 600 of the BRAF kinase (i.e., V600E; 1799 T>A [Catalogue of Somatic Mutations in Cancer (COSMIC)]). Other uncommon variants such as V600K, V600R, and V600D (in order of decreasing frequency) have also been

identified, primarily in melanoma. Nonclinical data indicate that these variant mutations, like V600E, result in constitutive activation of the BRAF kinase. Most of the transforming activity of $BRAF^{V600}$ is thought to occur through the constitutive activation of the MAPK pathway (Gray-Schopfer et al. 2007). Depletion of messenger RNA that codes for mutated BRAF by small interfering RNA leads to growth inhibition of melanoma cell lines in vitro (Sumimoto et al. 2004). This has led to the development of agents that can inhibit mutated BRAF kinase as well as tests to identify V600 mutations (Flaherty 2006; Ascierto et al. 2010; Vultur et al. 2011).

1.2.1 Vemurafenib (RO5185426) BRAF Inhibitor

Vemurafenib is a low molecular weight, orally available inhibitor of some mutated forms of BRAF serine-threonine kinase, including $BRAF^{V600E}$. See the Vemurafenib Investigator's Brochure (IB) for additional details.

1.2.1.1 Nonclinical Pharmacology

Nonclinical pharmacology information about vemurafenib is summarized in the Vemurafenib IB.

1.2.1.2 Nonclinical Metabolism and Pharmacokinetics

Nonclinical metabolism and pharmacokinetic (PK) information is presented in the Zelboraf® [vemurafenib] U.S. Package Insert and the Vemurafenib IB.

1.2.1.3 Clinical Pharmacokinetics of Vemurafenib

The clinical pharmacokinetics of vemurafenib are based on data available from six studies in patients who received the commercial formulation: PLX06-02, the initial Phase I dose-escalation study to determine the maximum tolerated dose (MTD): Study NP22676, a cytochrome P450 metabolism study in patients with *BRAF*^{V600E} mutation–positive Stage IV melanoma; Study NP25158, a mass-balance study in patients with *BRAF*^{V600} mutation–positive Stage IV melanoma; Study NP25163, a dose-escalation study in patients with *BRAF*^{V600E} mutation–positive unresectable Stage IIIc or Stage IV melanoma; Study NP22657, a Phase II, open-label study in patients with *BRAF*^{V600E} mutation–positive Stage IV melanoma, in which the effects of vemurafenib on the QT interval were evaluated; and Study NO25026, a Phase III, randomized controlled study in patients with *BRAF*^{V600E} mutation–positive unresectable Stage IIIc or IV melanoma. Detailed descriptions of the design and PK results for each of these studies are provided in the Vemurafenib IB.

On the basis of dose-limiting toxicities reported at the 1120-mg twice daily (BID) dose level in Study PLX06-02, the 960-mg BID dose was considered the MTD and selected for use in all subsequent clinical trials, including the Phase I (Study PLX06-02; Vemurafenib IB; Flaherty et al. 2010) treatment-extension cohorts, as well as the aforementioned clinical pharmacology studies, and the Phase II (Study NP22657; Vemurafenib IB; Sosman et al. 2012) and Phase III (Study NO25026; Vemurafenib IB;

Chapman et al. 2011) studies in patients with unresectable Stage IIIc or metastatic melanoma.

Population PK analysis with the use of pooled data from 458 patients estimated the median of the steady-state maximum plasma concentration (C_{max}), the minimum plasma concentration (C_{min}), and area under the concentration-time curve from 0 to 12 hours ($AUC_{0\text{-}12hr}$) to be 62 μg/mL, 59 μg/mL, and 734 μg/mL•hour, respectively. The pharmacokinetics of vemurafenib have been shown to be dose proportional between 240 and 960 mg BID, and a population PK analysis also confirmed that the pharmacokinetics of vemurafenib are linear. The median of the individual elimination half-life estimate for vemurafenib is 57 hours (the 5th and 95th percentile range is 30–120 hours).

Vemurafenib at 960 mg BID as a 240-mg tablet is absorbed with a median time to maximum concentration (t_{max}) of approximately 4 hours. Vemurafenib exhibits marked accumulation after repeat dosing at 960 mg BID, with high inter-patient variability. On the basis of the population PK analysis, the median accumulation ratio estimate for the BID regimen is 7.36. In the Phase II study, mean plasma vemurafenib concentrations 4 hours postdose increased from 3.6 μg/mL on Day 1 to 49.0 μg/mL on Day 15 (range: 5.4–118 μg/mL).

At steady state, the mean vemurafenib exposure in plasma is stable (concentrations predose and 2–4 hours after the morning dose), as indicated by the mean ratio of 1.13. Relatively high marked inter-patient variability in plasma exposure (area under the plasma concentration-time curve [AUC]; range: 32–46%) was observed at the steady-state dose reduction.

Following oral dosing, the absorption rate constant for the population of metastatic melanoma patients was estimated to be 0.19 hr^{-1} (with 101% intra-patient variability).

The apparent volume of distribution for vemurafenib in patients with metastatic melanoma on the basis of population PK analysis is estimated to be 91 L (with 64.8% intra-patient variability). Vemurafenib is highly bound to human plasma proteins in vitro ($>$ 99%).

The relative proportions of vemurafenib and its metabolites were characterized in a human mass-balance study. On average, 95% of the dose was recovered within 18 days, the majority (94%) in feces, with $<$ 1% recovered in urine. The parent compound was the predominant component (95%) in plasma (refer to the Vemurafenib IB). CYP3A4 is identified as the primary enzyme responsible for vemurafenib metabolism.

The commercial dosage form of vemurafenib is a 240-mg film-coated tablet.

1.2.1.4 Efficacy of Vemurafenib in Patients with *BRAF*^{V600E} Mutation–Positive Metastatic Melanoma

Study NO25026 was a Phase III, open-label, multicenter, international study of vemurafenib in previously untreated patients with *BRAF*^{V600E} mutation–positive unresectable or metastatic melanoma. Patients were randomized to treatment with vemurafenib (960 mg BID) or dacarbazine (DTIC) (1000 mg/m^2 every 3 weeks).

A total of 675 patients were randomized to receive vemurafenib (n = 337) or DTIC (n = 338; Vemurafenib IB). Randomization was stratified according to disease stage, serum LDH level, Eastern Cooperative Oncology Group (ECOG) Performance Status, and geographic region. Baseline characteristics were well balanced between treatment groups. Of the patients randomized to receive vemurafenib, most patients were male (59%) and Caucasian (99%), the median age was 56 years (28% were ≥ 65 years old), all patients had ECOG Performance Status of 0 or 1, and the majority of patients (66%) had Stage M1c disease.

The co-primary efficacy endpoints of the study were overall survival (OS) and progression-free survival (PFS). Key secondary endpoints included confirmed best overall response rate (BORR) and response duration.

Statistically significant and clinically meaningful improvements were observed in OS ($p < 0.0001$) and PFS ($p < 0.0001$, by unstratified log-rank test). OS was longer with vemurafenib treatment compared with DTIC, with a hazard ratio of 0.37 (95% CI: 0.26, 0.55), which represents a 63% decrease in the hazard of death with vemurafenib compared with DTIC (Vemurafenib IB). Kaplan–Meier estimates of the 6-month survival rates were 84% (95% CI: 78%, 89%) for vemurafenib and 64% (95% CI: 56%, 73%) for DTIC. Consistent improvement in OS, PFS, and confirmed BORR in favor of vemurafenib treatment was generally observed across subgroups defined by age, sex, baseline serum LDH level, ECOG Performance Status, metastatic disease stage, and geographic region. Ninety-four patients (28%) treated with vemurafenib in the aforementioned Phase III study were ≥ 65 years old. The effects of vemurafenib on OS, PFS, and confirmed BORR were similar for patients < 65 and ≥ 65 years old.

1.2.1.5 Safety of Vemurafenib

The safety evaluation of vemurafenib is based on results in patients from three Genentech clinical pharmacology studies (Study NP22676, n = 25; Study NP25163, n = 52; and Study NP25158, n = 7), a Phase I study (Study PLX06-02, n = 108; Vemurafenib IB), a single-arm, Phase II study in previously treated patients with *BRAF*^{V600} mutation–positive Stage IV melanoma (Study NP22657, n = 132; Vemurafenib IB), and a Phase III, randomized, open-label, multicenter, global study in patients with unresectable Stage IIIC or Stage IV *BRAF*^{V600} mutation–positive melanoma (Study NO25026, n = 675; Vemurafenib IB). The type and incidence of adverse events observed across all studies in patients with *BRAF*^{V600} mutation–positive unresectable or metastatic melanoma were consistent.

In the clinical pharmacology Study NP25163, all 52 patients (100%) had at least one adverse event. Nearly all patients (96%) had at least one treatment-related adverse event. The majority of adverse events were of mild or moderate intensity. The most common adverse events (reported in ≥30% of patients) in the vemurafenib group were fatigue (58%), arthralgia (58%), nausea (50%), rash (38%), and diarrhea (33%). Fifty-four percent of patients had at least one Grade ≥3 adverse event; 40% of patients had at least one treatment-related adverse event. The most commonly reported treatment-related adverse events (incidence ≥5%) were squamous cell carcinoma (SSC) of skin (23%), increased gamma glutamyl transferase (GGT; 9%), basal cell carcinoma (BCC; 7%), rash (7%), maculopapular rash (6%), and arthralgia (6%). Twelve patients (23%) experienced at least one Grade 4 adverse event, including 2 patients who experienced two Grade 4 adverse events. Five of the 12 patients had Grade 4 adverse events that were assessed by the investigator as treatment related. The most frequent Grade 4 adverse event was increased GGT (n=5 patients, assessed as related to treatment in 4 patients). The other Grade 4 adverse events were hyperuricemia (assessed as related to treatment) and pneumonia, sepsis, convulsion, pseudomonas infection, staphylococcal infection, multi-organ failure, and pulmonary embolism (all of which were assessed as unrelated to study treatment).

Study PLX06-02 (Vemurafenib IB) assessed the safety of escalating doses of vemurafenib. At the highest dose administered (1120 mg BID), dose-limiting rash (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 3) and fatigue (Grade 3) were observed in multiple patients. Vemurafenib doses of up to 960 mg BID (the MTD) were generally well tolerated.

In the Phase II clinical trial (Study NP22657; Vemurafenib IB), all patients experienced at least one adverse event, the most common of which were arthralgia (68%), fatigue (57%), rash (54%), photosensitivity (52%), nausea (42%), alopecia (38%), pruritus (32%), diarrhea (32%), skin papilloma (31%), and hyperkeratosis (30%). Seventy-three percent of patients experienced at least one Grade ≥3 adverse event. Sixty-one percent of patients had at least one Grade ≥3 treatment-related adverse event. The most commonly reported, treatment-related adverse events (incidence ≥5%) were *squamous cell carcinoma (*SCC*)* of skin (23%), increased serum GGT (9%), BCC (7%), rash (7%), maculopapular rash (6%), and arthralgia (6%). The Vemurafenib IB summarizes the Grade 3 or 4 study drug–related adverse events observed in Study NP22657.

In the Phase III randomized study of vemurafenib versus DTIC (BRIM-3, Study NO25026, clinical cutoff: 1 March 2011; Vemurafenib IB), the safety results showed that vemurafenib was generally tolerable and toxicity was manageable with dose modifications. Ninety-nine percent and ninety-one percent of patients in the vemurafenib and DTIC treatment groups, respectively, experienced at least one adverse event. The majority of adverse events were of mild or moderate intensity. The most common adverse events (reported in ≥30% of patients) in the vemurafenib group were in the system organ class of skin and subcutaneous tissue disorders; the most common

of which were alopecia, rash, and photosensitivity. Other adverse events that occurred in ≥10% of vemurafenib-treated patients and at an incidence of more than twice that observed in the DTIC group included SCC of skin, skin papilloma, arthralgia, headache, dysgeusia, pyrexia, peripheral edema, pain in extremity, myalgia, decreased appetite, diarrhea, hyperkeratosis, seborrheic keratosis, and dry skin. Of the 37 patients who switched from DTIC to vemurafenib, 32 patients (86%) had at least one adverse event and 26 patients (70%) reported at least one treatment-related adverse event. The majority of adverse events were of mild or moderate intensity.

Fifty-nine percent of patients in the vemurafenib arm and thirty-three percent of patients in the DTIC arm experienced one or more adverse events of Grade ≥3 in intensity. Treatment-related adverse events of Grade ≥3 occurred in 49% of patients in the vemurafenib arm and 20% in the DTIC arm. Sixteen percent and nine percent of vemurafenib-treated patients had cutaneous squamous cell carcinoma (cuSCC) and keratoacanthoma (KA), respectively, compared with <1% and 0% for DTIC-treated patients. For reporting purposes, all cases of cuSCC and KA were considered to be treatment related, Grade 3, and serious. Other common Grade ≥3 adverse events in the vemurafenib group included photosensitivity reaction (9%), rash (8%), maculopapular rash (8%), and arthralgia (4%); the corresponding frequency of these adverse events in the DTIC group were 0%, 0%, 0%, and <1%. The most common Grade ≥3 adverse event in the DTIC group was neutropenia, occurring in 9% of patients; <1% of patients in the vemurafenib group experienced neutropenia. Of the 37 patients who crossed over from DTIC to vemurafenib, 11 (30%) experienced one or more Grade ≥3 adverse event after crossover. These events consisted of fatigue (2 patients), muscle weakness, pyrexia, anemia, hyperkeratosis, BCC, maculopapular rash, rash, cellulitis, palmar-plantar erythrodysesthesia syndrome, and decreased neutrophil counts (all 1 patient each). Of these, eight events were considered by the investigator to be treatment related.

The percentage of patients who experienced one or more Grade 4 adverse event was lower in the vemurafenib group (13 patients [4%]) than in the DTIC group (22 patients [8%]). Grade 4 adverse events in the vemurafenib group included pulmonary embolism (3 patients), increased GGT (2 patients), increased blood creatine phosphokinase (CPK), increased blood bilirubin, increased lipase, ageusia, intraventricular hemorrhage, pneumonia, pneumothorax, respiratory distress, and neutropenia (1 patient each). Five patients treated with vemurafenib had a total of six Grade 4 adverse events that were assessed as related to treatment (increased blood bilirubin, GGT increased [2 patients], ageusia, increased CPK, and neutropenia). One of the 37 patients who crossed over experienced a Grade 4 decreased neutrophil count after crossover. It was assessed as unrelated to treatment and non-serious.

Grade 5 adverse events were reported in 6 patients (2%) in the vemurafenib group. Only one adverse event (intracranial tumor hemorrhage) was assessed as treatment related. Each of the other 5 patients experienced the following Grade 5 adverse events

(all unrelated to study treatment): general physical health deterioration, cerebrovascular accident, pneumonia, aortic aneurysm rupture, and cardiac failure. Grade 5 adverse events were reported in 8 DTIC-treated patients (3%). Fatigue and mucosal inflammation, initially classified as Grade 5 adverse events in 1 patient, were subsequently considered to be symptoms of disease progression and downgraded to Grade 1, resulting in a total of 7 patients with Grade 5 adverse events. Only one adverse event (shock) was assessed as treatment related. Dyspnea, lung infection, cardiac arrest, and cardiac tamponade were reported in 1 patient each, and cardiopulmonary failure was reported in 2 patients. No Grade 5 adverse events were reported in the 37 patients who crossed over from DTIC to vemurafenib.

The incidence of cuSCC in vemurafenib-treated patients was approximately 20% across studies. The majority of the excised lesions reviewed by an independent central dermatopathology laboratory were classified as SCC–KA subtype or with mixed KA features (52%), both of which are less invasive types of cuSCC. Most lesions classified as “other” (43%) were benign skin lesions (e.g., verruca vulgaris, actinic keratosis, benign keratosis, cyst/benign cyst). cuSCC usually occurred early in the course of treatment, with a median time to the first appearance of 7–8 weeks. Of the patients who experienced cuSCC, approximately 33% experienced more than one occurrence, with a median time between occurrences of 6 weeks. Cases of cuSCC were typically managed with simple excision, and patients generally continued receiving treatment without dose modification. A risk mitigation plan, including regular dermatologic and head and neck examinations and chest computed tomography (CT) scans, has been established to monitor for and treat SCC (both cutaneous and non-cutaneous) in patients receiving vemurafenib in clinical trials (see Section 5.1.2.3).

Eight skin lesions in 7 of 337 vemurafenib-treated patients were reported as new primary malignant melanomas in Study NO25026 (Vemurafenib IB). No cases were reported in 338 patients treated with DTIC. Cases were managed with excision and without sequelae, and patients continued treatment without dose adjustment. Surveillance measures to monitor for the occurrence of new primary melanomas as well as cuSCC are outlined in Section 5.1.2.3.

Severe dermatologic reactions have been reported in patients receiving vemurafenib, including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. One notable treatment–related serious adverse event occurred in a vemurafenib-treated patient in the pivotal Phase III trial (Study NO25026) after the 1 March 2011 clinical cutoff date for safety. This patient developed toxic epidermal necrolysis. The event improved slightly after the patient was given treatment but was not resolved at last report. The patient was discharged from the hospital and permanently discontinued treatment with vemurafenib.

As of 31 March 2013, 12 cases of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been observed with vemurafenib treatment.

No fatal cases have been reported. The time to onset was 7 to 25 days. In the majority of patients (n = 7), vemurafenib was discontinued. Some patients (n = 5) were treated with systemic steroids with corresponding improvement or resolution of symptoms. In addition, 2 patients who were treated with vemurafenib after ipilimumab presented with Grade 3 rash and had biopsies that showed pathology consistent with drug hypersensitivity reaction (Harding et al. 2012). Full details are provided in the current Vemurafenib IB.

Two cases of SCC of the head and neck have been reported in 2 patients treated with vemurafenib in excess of 300 days while enrolled in a clinical trial. Pathology examination of both tumors (one a primary *tonsillar* tumor, the other a primary tongue tumor) revealed the presence of invasive SCC. Of note, the first patient's medical history was significant for risk factors for head and neck cancer and the tumor tissue tested positive for human papilloma virus (HPV). The second patient does not appear to possess any risk factors for head and neck cancer, and the preliminary examination of the tumor tissue did not reveal the presence of HPV genome. Full details are provided in the current Vemurafenib IB.

Five cases of adenomatous colonic polyps have been reported in patients who received vemurafenib for more than 2 years (Chapman et al. 2012). The first patient developed an upper gastrointestinal bleed, and, on work-up, was found to have duodenal ulceration (non-malignant), hyperplastic gastric polyps, and five colonic polyps (three of which were adenomatous). A previous colonoscopy in 2008, at the time of a jejunal resection for recurrent melanoma, documented no prior evidence of colonic polyps. All polyps were resected, and the patient subsequently resumed vemurafenib therapy. The second patient was found, on elective colonoscopy, to have seven colonic polyps (five of which were adenomatous), and all were detected and removed. This patient had not undergone a previous colonoscopy. The third patient had, on elective colonoscopy, 10 colonic polyps (7 of which were adenomatous). This patient had a previous colonoscopy 7 years prior to starting vemurafenib. The fourth patient had, on elective colonoscopy, one adenomatous colonic polyp. The fifth patient had, on elective colonoscopy, three adenomatous colonic polyps. The latter two patients had histories of no prior colonoscopy. In addition, a patient in the Expanded Access Program had one colonic adenoma discovered after treatment with vemurafenib for 0.57 years. This patient had a colonoscopy 1.3 years prior to starting vemurafenib, and a polyp was found and resected at that time.

One case of progression of *NRAS*-mutated chronic myelomonocytic leukemia occurred in a male patient with metastatic melanoma treated with vemurafenib for less than 2 weeks (Callahan et al. 2012). After the first dose of vemurafenib, laboratory results showed a marked leukocytosis and monocytosis, and vemurafenib treatment was subsequently held. There was a temporal relationship between vemurafenib treatment and increase in WBC and absolute monocyte counts through multiple cycles of dechallenge and rechallenge. In vitro studies demonstrated proliferation of the leukemic

cell population upon stimulation with a BRAF inhibitor, an effect that was reversed upon addition of MEK inhibitor. Further, the cells exhibited dose-dependent and reversible activation of extracellular-signal-regulated kinase (ERK) in the *NRAS*-mutated leukemic clone. A second case of progression of a preexisting RAS-mutated malignancy (pancreatic adenocarcinoma with KRAS mutation) was reported with vemurafenib in 2014. On the basis of its mechanism of action, vemurafenib may cause progression of cancers associated with *RAS* mutations. Vemurafenib should be used with caution in patients with a prior or concurrent cancer associated with *RAS* mutation. Full details are provided in the current Vemurafenib IB.

In a Phase I trial (Study CA 184161, sponsored by Bristol-Myers Squibb), asymptomatic Grade 3 increases in transaminases and bilirubin occurred with concurrent administration of ipilimumab (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID) (Ribas et al. 2012). All liver laboratory abnormalities were asymptomatic and reversible with permanent discontinuation of the study drugs or, in some cases, administration of corticosteroids. On the basis of these data, concurrent administration of ipilimumab and vemurafenib is not recommended outside of a clinical trial. Full details are provided in the current Vemurafenib IB.

An analysis of liver-related adverse events reported with vemurafenib use showed that 63 cases (out of an estimated exposure of approximately 20,000 patients) of medically confirmed serious adverse events were consistent with drug-induced liver injury on the basis of clinical chemistry criteria from the Drug-Induced Liver Injury Expert Working Group (Aithal et al. 2011). Of the 63 cases, two were assessed as severe; both were reported as hepatic failure, and the outcomes of both cases are considered resolved. There were no reported deaths among the 63 cases of liver injury. The median time to onset of the adverse events was 44 days after initial dose. The median ALT to alkaline phosphatase (ALP) ratio was calculated as 1.5, suggesting a trend toward cholestatic pattern of liver injury. The analysis did not reveal any risk factors or populations at risk.

A review of the Roche safety database found neutropenia to be an uncommon (6 cases per 1000 person-years, 0.6%) adverse drug reaction associated with the use of vemurafenib, typically occurring during the first 6–12 weeks of treatment. Neutropenia appeared to be reversible, usually within 2 weeks, with temporary interruption, dose reduction, or discontinuation of vemurafenib and, in some cases, was managed with granulocyte colony–stimulating factor (GCSF).

The effects of vemurafenib on the QT interval were investigated as part of the Phase II Study NP22657 (Vemurafenib IB). This was not a “thorough” QT study as defined by health authorities because vemurafenib cannot be administered to healthy volunteers and it was not feasible to administer a positive or negative control to patients with metastatic melanoma. However, the centrally read ECG data obtained in triplicate at serial, time-matched points before and after dosing met the regulatory expectations for robust assessment of oncology therapeutics on the QT interval. The maximum

absolute corrected QT (QTc) values at any point after dosing were as follows: >450 millisecond (ms), 49 patients (37.1%); >480 ms, 6 patients (4.5%); >500 ms (Grade 3), 2 patients (1.5%). One patient (0.8%) had a maximal QTc increment >60 ms (Grade 2) compared with baseline. The upper boundary of the one-sided 95% CI for mean QTc prolongation reached a maximum of 17.7 ms on Day 105 of study treatment, based on measurements in 90 patients. Mean QTc interval prolongation closely tracked with the mean vemurafenib steady-state concentration over time. None of the QT prolongation events were serious or led to premature withdrawal from treatment or dose modification/interruption; none were clearly associated with prolongation of cardiac repolarization, arrhythmia, or any other cardiac function disorder. Additional information on the relationship between vemurafenib exposure and QT interval prolongation may be found in the Vemurafenib IB.

As of Q2 2014, an adverse drug reaction of pancreatitis has been identified in patients treated with vemurafenib. Seventeen cases of pancreatitis with no strong risk factors or alternative explanations were reported. Eight of the seventeen cases were assessed as likely associated with vemurafenib use on the basis of event onset latency and rechallenge/dechallenge information. The clinical presentation including mild to moderate severity was consistent with the clinical picture of drug-induced pancreatitis (Lankisch et al. 1995).

As of Q4 2014, an adverse drug reaction of potentiation of radiation treatment toxicity has been identified in patients treated with radiation either prior, during, or subsequent to vemurafenib treatment. This is based on twenty cases of radiation injuries, adjudicated as radiation recall (n =8) and radiation sensitization (n =12). The nature and severity of the events in all 20 cases were evaluated as worse than expected for the normal tissue tolerance to therapeutic radiation with fatal outcome in 3 cases. The reaction was seen in the skin, esophagus, lung, liver, rectum, and urinary bladder. Vemurafenib should be used with caution when given concomitantly or sequentially with radiation treatment. Full details are provided in the current Vemurafenib IB.

Acute kidney injury, including interstitial nephritis, has been observed in patients treated with vemurafenib. The majority of these cases have been characterized by mild to moderate increases in serum creatinine (some observed in the setting of dehydration events), with recovery after dose modification. Serum creatinine will be monitored throughout the study. Vemurafenib acute kidney injury dose modification guidelines should be used when applicable, and it is recommended to routinely monitor serum creatinine levels in all patients undergoing vemurafenib therapy.

Dupuytren's contracture and plantar fascial fibromatosis have been reported with vemurafenib. The majority of cases were Grade 1 or 2, but severe, disabling cases of Dupuytren's contracture have also been reported.

For a review of serious adverse events and adverse events that led to discontinuation of study treatment, consult the Vemurafenib IB.

See the Vemurafenib IB and/or prescribing information for additional details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This is an open-label, multicenter, non-randomized study to provide continued access to vemurafenib for eligible patients with *BRAF*^{V600} mutation–positive malignancy (including metastatic melanoma and other cancer types) who were previously enrolled and treated in an antecedent vemurafenib study protocol without meeting the protocol's criteria for disease progression or are being treated beyond progression and still deriving clinical benefit, as assessed by investigator.

Safety evaluations will be conducted during the study. Safety evaluations will begin on Day 1 of the study, and safety will continue to be monitored throughout the study until 28 days after the last dose of study drug. Adverse events related to the study drug will be monitored until resolution.

In summary, these patients have limited alternative treatment options and may potentially benefit from continued treatment with vemurafenib. Therefore, the potential benefits of participating in this study outweigh the potential associated risks.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to provide continued access to vemurafenib for eligible patients with *BRAF*^{V600} mutation–positive malignancy who were previously treated in an antecedent vemurafenib protocol and did not meet the protocol's criteria for disease progression or are being treated beyond progression and still deriving clinical benefit, as assessed by investigator, and may potentially benefit from continued treatment with vemurafenib.

2.2 SECONDARY OBJECTIVE

The secondary objective is to collect and describe safety and tolerability data for patients who continue vemurafenib treatment in this extension (rollover) study.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview

This is an open-label, multicenter, non-randomized study to provide continued access to vemurafenib for eligible patients with *BRAF*^{V600} mutation–positive malignancy who were previously enrolled and treated in an antecedent vemurafenib protocol and did not meet

the protocol's criteria for disease progression or are being treated beyond progression and still deriving clinical benefit (as assessed by the investigator) and may therefore potentially benefit from continued treatment with vemurafenib. *The maximum number of days between the last dose of study drug in the antecedent protocol and first dose in this extension (rollover) study will be 15 days.* Results of the study completion visit or other visit in the antecedent protocol may be used as screening/baseline for this extension (rollover) study. Screening/baseline is combined into one visit if completed within time intervals, as specified in Section 4.5.2.1 and Appendix 1. The first vemurafenib treatment in the extension (rollover) study will be recorded as Cycle 1, Day 1. Patients will receive treatment with oral vemurafenib at 960 mg BID, 720 mg BID, or 480 mg BID, depending on the last dose in the antecedent protocol. Treatment will continue until progression of disease or as long as the patient is deriving clinical benefit, as judged by the investigator (case-by-case decision with approval of the Medical Monitor), death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the Sponsor to terminate the study, whichever occurs first.

One cycle is defined as 28 days. Clinic visits will occur on Day 1 of Cycles 1–7 and on Day 1 of every other cycle through Cycle 15. Then, for patients still receiving treatment, clinic visits will occur on Day 1 of every third cycle (i.e., screening*/baseline* and Day 1 of every third cycle *from* Cycle 18+ [*see* Appendix 1] for patients with ≥17 cycles of vemurafenib on an antecedent study) *until unacceptable toxicity or disease progression, as defined by the investigator*. In patients with measurable disease, tumor assessments will be conducted for purposes of evaluating whether treatment should be discontinued via routine tumor assessments (CT/magnetic resonance imaging [MRI]) consistent with institutional standards of care, as outlined in the Schedule of Assessments (see Appendix 1).

Tumor assessments as specified and conducted in the antecedent protocol, including any evaluable and measurable disease, will have been documented at screening in the antecedent protocol. In the extension (rollover) study, tumor assessments, including radiological tumor assessments of chest, abdomen, and pelvis (C/A/P) for measuring extent or progression of disease (CT scan is the preferred method) will be done at the discretion of the investigator according to local institutional standard of care for purposes of evaluating whether treatment should be discontinued.

Safety evaluations will also be conducted during the study. Safety evaluations will begin on Day 1 of the study and will continue throughout the study until 28 days after the last dose of study drug*, withdrawal of consent, initiation of non-protocol therapy, death, or loss to follow-up, whichever is earliest*. Adverse events related to the study medication will be monitored until resolution. The tolerability and toxicity (safety) profile of vemurafenib will be evaluated using the NCI CTCAE, Version 4.0.

The target population includes patients with *BRAF*^{V600} mutation–positive malignancy (including metastatic melanoma or other cancer types) who were previously enrolled and

treated in an antecedent vemurafenib protocol and did not meet the protocol's criteria for disease progression or are being treated beyond progression and still deriving clinical benefit, as assessed by investigator and may potentially benefit from receiving continued treatment with vemurafenib. Patients with malignant tumor types other than malignant melanoma harboring a V600-activating mutation of *BRAF* who have no acceptable standard treatment options will also be allowed to participate in the trial.

3.2 LENGTH OF STUDY

Treatment will continue until disease progression (as defined by investigator) or as long as the patient is deriving clinical benefit, as assessed by investigator, if treated beyond progression (case-by-case decision discussed and approved by the Medical Monitor), death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the Sponsor to terminate the study, whichever occurs first.

3.3 END OF STUDY

The study will end when all enrolled patients have discontinued study treatment and have been followed for safety *assessment until 28 days after the last dose of study drug*, death, withdrawal of consent, loss to follow-up, or if the Sponsor has decided to terminate the study, whichever occurs first.

3.4 RATIONALE FOR STUDY DESIGN

This is an open-label, multicenter, non-randomized study to provide continued access to vemurafenib for eligible patients with *BRAF*^{V600} mutation–positive malignancies who participated in an antecedent vemurafenib protocol and did not meet the protocol's criteria for disease progression or are being treated beyond progression and still deriving clinical benefit, as assessed by investigator, and may potentially benefit from continued treatment with vemurafenib. The purpose of the current protocol is to provide such patients with continued access to treatment with vemurafenib.

3.4.1 Rationale for Test Product Dosage

The dose of vemurafenib in this study will be 960 mg BID, which is the approved dose of vemurafenib for malignant melanoma or, if the dose was reduced in an antecedent protocol, the dose of the last visit of the antecedent study (minimum 480 mg orally BID) will be used.

3.4.2 Rationale for Patient Population and Analysis Groups

Vemurafenib is approved in the United States for the treatment of patients with unresectable or metastatic melanoma with *BRAF*^{V600E} mutation and in the European Union as monotherapy for the treatment of adult patients with *BRAF*^{V600} mutation-positive unresectable or metastatic melanoma. Vemurafenib is also approved or has been submitted for approval in other countries worldwide. Accordingly, patients enrolled in this study may have unresectable Stage IIIc or Stage IV metastatic melanoma positive for the *BRAF*^{V600} mutation. In addition, patients with other malignant

tumor types harboring a V600-activating mutation of *BRAF* who have no acceptable standard treatment options will also be allowed to participate in the trial.

3.5 OUTCOME MEASURES

3.5.1 Efficacy Outcome Measures

There are no protocol-specific efficacy outcome measures for this study.

3.5.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and intensity (severity) of adverse events and serious adverse events, graded according to the NCI CTCAE v4.0

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population will be patients with *BRAF*^{V600} mutation–positive melanoma or other malignancies who were previously enrolled in an antecedent vemurafenib protocol and may potentially still benefit from treatment with vemurafenib.

4.1.1 Inclusion Criteria

A patient may be included if he or she meets all of the following criteria:

Disease-Specific Inclusion Criteria

1. *BRAF*^{V600} mutation-positive malignancy
2. Prior eligibility for and received study treatment on an antecedent vemurafenib protocol
3. Ability to begin treatment in the extension (rollover) protocol within 15 days following the last day of the study in the antecedent protocol

General Inclusion Criteria

1. Signed Informed Consent Form(s)
2. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to always use two adequate methods of contraception including at least one method with a failure rate of $<1\%$ per year during the course of this study and for at least 6 months after completion of study treatment.
    - Females of childbearing potential are defined as sexually mature women without prior hysterectomy who have had any evidence of menses in the past 12 months. In order to be considered not of childbearing potential, amenorrhea for a period of 12 months or longer must have occurred in the absence of chemotherapy, anti-estrogen therapy, or ovarian suppression.
    - Effective forms of contraception include surgical sterilization, a reliable barrier method with spermicide, birth control pills, contraceptive hormone implants, or vasectomized partner.

3. Negative serum pregnancy test within 7 days prior to commencement of dosing in women of childbearing potential; women of non-childbearing potential may be included if they are either surgically sterile or have been naturally menopausal for $\geq$1 year. Women of non-childbearing potential need not undergo the pregnancy test.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Adverse event requiring discontinuation of vemurafenib in the antecedent protocol
2. Progressive disease during the antecedent protocol. If approval to treat beyond progression was already given in the antecedent protocol, the patient may roll over into the current protocol without Sponsor's approval. Under special circumstances, when it is felt that the patient may clinically benefit from continued therapy with vemurafenib, enrollment into this protocol and dosing beyond progression may be considered if it is judged by the investigator, in consultation with the Sponsor, to be in the best interest of the patient. All such cases will require approval of the Sponsor before enrolling the patient into this protocol.
3. Meeting any of the following exclusion criterion of the antecedent study at the time the patient is considered for the extension (rollover) study:
    - Current, recent (within 28 days prior to Day 1), or planned use of any anti-tumor therapy outside of this study
    - Any other serious concomitant medical conditions that, in the opinion of the investigator, would compromise the safety of the patient or compromise the patient's ability to participate in the study
    - History of malabsorption or other clinically significant metabolic dysfunctions
    - History of clinically significant cardiac or pulmonary dysfunction as specified in antecedent study

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

All patients will receive vemurafenib under this protocol.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

Study drug packaging will be overseen by the Roche clinical trial supplies department and will bear a label with the identification required by local law, protocol number, drug identification, and dosage.

The packaging and labeling of the study medication will be in accordance with Roche standards and local regulations.

Local packaging and labeling requirements in some countries may be different.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals, and temperature

conditions and report any deviations or product complaints to the study monitor upon discovery.

Vemurafenib will be stored at the clinical site under the recommended storage conditions as indicated on the study drug label. Patients will be requested to store study medication at the recommended storage conditions noted on the label, out of the reach of children or other co-inhabitants.

4.3.1.1 Vemurafenib

Vemurafenib is supplied in 240-mg film-coated tablets packed in bottles for oral administration. For additional batch-specific instructions and information for vemurafenib film-coated tablets, refer to the packaging.

The inactive ingredients in vemurafenib tablets are as follows: hypromellose acetate succinate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, hydroxypropyl cellulose (tablet core), polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, and iron oxide red (tablet coating).

Vemurafenib will be labeled in compliance with Good Manufacturing Practice.

For further details, refer to the local prescribing information for vemurafenib or the Vemurafenib IB.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Vemurafenib

Patients will receive treatment with oral vemurafenib at 960 mg BID, 720 mg BID, or 480 mg BID, depending on the last dose in the antecedent protocol. All doses will be administered as the 240-mg film-coated vemurafenib tablets.

The first dose is to be taken in the morning, and the second dose is to be taken approximately 12 hours later in the evening. The study-drug tablets are to be swallowed whole with water. The tablets should not be chewed or crushed. If a dose is missed, it can be taken 4 or more hours before the next dose to maintain the twice-daily regimen. Both doses should not be taken at the same time.

Patients will be asked to return all used and unused drug supply containers as a measure of compliance. All supplies including partially used or empty containers of study drug must be returned to the Roche study monitor at the end of the study, unless alternative destruction has been authorized by Roche or required by local or institutional regulations. Copies of all drug dispensing and inventory logs must be returned to the Roche study monitor at the end of the study.

Guidelines for interruption, dose modification, and permanent discontinuation of vemurafenib are provided in Section 5.1.

4.3.3 Investigational Medicinal Product Accountability

The investigational medicinal product (IMP) required for completion of this study (supplied as 240-mg film-coated tablets packed in bottles for oral administration) will be provided by Roche. The investigational site will acknowledge receipt of the IMP, through use of the interactive web (or voice) response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMP will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Roche with the appropriate documentation. The site's method of IMP destruction must be agreed upon by Roche. The site must obtain written authorization from Roche before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of the IMP received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to Vemurafenib

Roche does not intend to provide vemurafenib to patients after the conclusion of the study or any earlier withdrawal (see Section 3.3).

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient within 15 days before enrolling into this study through to the end of treatment visit. Patients who use oral contraceptives, hormone-replacement therapy, or maintenance therapy should continue their use as outlined in the eligibility criteria concerning adequate contraception during and for at least 6 months after the completion of study treatment (see Section 4.1.1). Patients who experience toxicities may be treated symptomatically as clinically indicated. All concomitant medications should be recorded on the appropriate electronic Case Report Form (eCRF).

At the discretion of the investigator, prophylactic anti-emetic and antidiarrheal medications may be used per standard clinical practice before doses of the study drug.

Hematopoietic growth factors (e.g., erythropoietin and GCSF) and pain medications administered as dictated by standard practice are acceptable while the patient is enrolled in the study. However, growth factors should not be administered prophylactically before initial treatment with the study drug.

Because of the underlying illness and the frequency of co-existent medical conditions in this patient population, all concomitant medication or treatment required by the patient will be administered at the discretion of the treating physician.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study (i.e., from 7 days before the initiation of vemurafenib treatment [on Study GO28399] until the end of treatment visit):

- St. John's wort or hyperforin
- Any concomitant therapy intended for the treatment of cancer (approved by health authorities or experimental), including chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy, investigational agents, or herbal therapy; certain forms of radiation therapy may be considered for pain palliation following consultation with the medical monitor. Study treatment should be suspended during radiation therapy. Undergoing radiation therapy ≤ 1 week prior to first administration of vemurafenib and stereotactic radiotherapy is prohibited.

Patients who require the use of any of these agents will be discontinued from study treatment and followed for safety outcomes for 28 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever comes first. Follow-up for new primary malignancies will continue *per investigator's discretion*.

4.4.3 Medication Precautions in Case of Drug-Drug Interactions

4.4.3.1 Vemurafenib

Results from a drug-drug interaction study in patients with metastatic melanoma demonstrated no interaction of vemurafenib with CYP2C19 and CYP2C9. However, drug interactions were observed with CYP1A2 and CYP3A4.

CYP1A2 inhibition was observed when a single dose of caffeine (a CYP1A2 substrate) was co-administered after repeat dosing with vemurafenib for 15 days, resulting in a 2.6–fold increase in the mean AUC of caffeine.

CYP3A4 induction was observed when a single dose of midazolam (a CYP3A4 substrate) was co-administered after repeat dosing with vemurafenib for 15 days, resulting in a 39% decrease in the mean AUC of midazolam.

An interaction between vemurafenib and dextromethorphan (a CYP2D6 substrate) was suggested by a mean increase in dextromethorphan $AUC_{0\text{-last}}$ of 47% based on the no effect 90% CI boundary. However, this interaction is not likely to be the result of the inhibition of CYP2D6 by vemurafenib, because the $AUC_{0\text{-last}}$ of the dextromethorphan metabolite dextrorphan also increased by 46%.

In nonclinical in vitro evaluation, the concentration for 50% inhibition of vemurafenib to CYP2C9 was 5.9 μM. When a single dose of warfarin (a CYP2C9 substrate) was co-administered after repeat dosing with vemurafenib for 15 days, some patients exhibited increased warfarin exposure (mean 18% for S-warfarin).

In summary, vemurafenib may increase the plasma exposure of drugs predominantly metabolized by CYP1A2 and decrease the plasma exposure of drugs predominantly

metabolized by CYP3A4. If CYP1A2 substrates must be co-administered with vemurafenib, investigators should assess the safety risk associated with a potential increase in plasma concentrations of CYP1A2-metabolized drugs. If CYP3A4 substrates must be co-administered with vemurafenib, investigators should monitor for signs of reduced benefit of CYP3A4-metabolized drugs because of a potential decrease in their plasma concentration. Dose adjustments for medications predominantly metabolized via CYP1A2 or CYP3A4 should be considered on the basis of their therapeutic windows before concomitantly treating with vemurafenib. Doses of concomitant CYP1A2 and CYP3A4 metabolized drugs, but not the dose of vemurafenib, may be adjusted as necessary to alleviate the impact of drug interaction.

Caution should be exercised when vemurafenib is co-administered with warfarin (CYP2C9) in patients with melanoma (see prohibited concomitant therapies in Section 4.4.2).

No dose adjustment is recommended for drugs metabolized by CYP2D6 or CYP2C19.

Less than 10% of metabolites of vemurafenib were detected in plasma in nonclinical studies and in clinical data from a mass-balance study with 14C-vemurafenib in patients with melanoma (Study NP25158). Nonclinical studies suggest that CYP3A4 metabolism and subsequent glucuronidation are responsible for the metabolism of vemurafenib. No clinical data are currently available evaluating the effects of CYP3A4 inducers or inhibitors on vemurafenib exposure.

In vitro studies have demonstrated that vemurafenib is both a substrate and an inhibitor of the efflux transporter P-glycoprotein (P-gp). In the clinical setting, the effects of vemurafenib on drugs that are substrates of P-gp and the effects of P-gp inducers and inhibitors on vemurafenib exposure are unknown.

Appendix 3 includes a non-exhaustive list of typical examples of CYP1A2, CYP3A4, and CYP2C9 substrates and CYP3A4 inducers and inhibitors. A more extensive list of medications can be found online at the following link: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. For additional information, see the Vemurafenib IB. If co-administration cannot be avoided, the physician should exercise caution and a dose reduction of the concomitant CYP1A2 or CYP2D6 substrate drug should be considered.

4.4.4 Medications Affecting QT Interval

Certain medications could affect the results of QT intervals on ECG measurements required for this study. Specifically, anti-emetics other than those belonging to the 5-HT_3 receptor antagonist class (i.e., granisetron, ondansetron, dolasetron, palanosetron) are preferred, because the latter has the potential to prolong the QTc interval (see Section 5.1.2.3). Patients should avoid taking medications or herbal and vitamin supplements that may increase QTc interval, and investigators should closely monitor

patients who require taking these types of medications. Alternative treatment options for medications known to affect the QT interval should be discussed with each patient prior to their inclusion into this study. A complete list of medications that may cause QT interval prolongation is provided in Appendix 4 . Refer to http://www.azcert.org/ for additional information and references.

4.5 STUDY ASSESSMENTS

4.5.1 Description of Study Assessments

4.5.1.1 Medical History and Demographic Data

Medical history and demographic data will have been collected as part of the antecedent protocol.

4.5.1.2 Vital Signs

Vital signs will include measurements of heart rate, systolic and diastolic blood pressures while the patient is in a seated position, and oral or tympanic temperature (°C).

4.5.1.3 Physical Examinations

A complete physical examination will include the measurement of patients' weight and height, as well as an evaluation of the head, eye, ear, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

At subsequent visits, limited, symptom-directed physical examinations and, at minimum, examination of the eyes and the cardiovascular and dermatological systems should be performed.

New or worsened abnormalities should be recorded as adverse events on the Adverse Event eCRF.

As part of tumor assessments, physical examinations will include an evaluation of the presence of enlarged lymph nodes, hepatomegaly, and splenomegaly. Some visits allow symptom-directed examinations (physical examinations relevant to the patient's symptoms). As part of each symptom-directed examination in this study, patients will be asked about skin and vision changes.

4.5.1.4 Tumor and Response Evaluations

Any evaluable and measurable disease will have been documented as specified for screening in the antecedent protocol and/or according to local institutional standards of care. On-study tumor assessments will be done at the discretion of the investigator according to local institutional standard of care for purposes of the evaluation and definition of disease progression.

4.5.1.5 Performance Status

Performance status will be measured using the ECOG Performance Status scale (see Appendix 2). It is recommended, where possible, that the same person assess a patient's performance status throughout the study. Refer to Appendix 1 for details on when ECOG Performance Status will be collected.

A window of ±7 days of a scheduled study visit is allowed for the assessment of the ECOG Performance Status.

4.5.1.6 Clinical Safety Assessments

NCI CTCAE v4.0 will be used to characterize the toxicity profile of the study treatment. All patients will be assessed for adverse events. After signing the Informed Consent Form, all adverse events and serious adverse events (including serious adverse events due to invasive procedures required for the study, such as biopsies) will be collected. Patients will be assessed for adverse events at each study visit. All adverse events will be recorded until 28 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first.

4.5.1.7 Laboratory Assessments

A series of laboratory assessments will be made throughout the course of this study. These assessments will be performed to monitor patient safety.

Normal ranges for the study laboratory parameters, where available, must be supplied to Roche/designee before the study starts.

The laboratory assessments listed will be performed at a local laboratory:

- Hematology: WBC count, hemoglobin, hematocrit, platelet count, WBC differential count (neutrophils, bands, lymphocytes, eosinophils, basophils, and monocytes)
- Serum chemistries: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, phosphate, magnesium, total and direct bilirubin, albumin, AST, ALT, LDH, ALP
- Serum pregnancy test (for women of childbearing potential including premenopausal women who have had a tubal ligation) within 7 days preceding planned first dose of vemurafenib

4.5.1.8 Electrocardiograms

ECG recordings according local institutional standards will be obtained at each specified timepoint (see Appendix 1). ECGs for each patient should be obtained from the same machine, whenever possible. To minimize variability, it is important that patients be in a resting position for ≥10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be

performed prior to any vital sign measurements and at least 15 minutes prior to blood draws scheduled to be performed on the same day.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. ECG characteristics, including heart rate, QRS duration, and RR, PR, and QT intervals, will be monitored by the investigator. If the patient experiences a Grade 3 or Grade 4 QT prolongation (according to NCI CTCAE v4.0), the event should be recorded on the eCRF and reported as an expedited non-serious adverse event of special interest, including the QTc value.

4.5.1.9 Dermatologic *and* Squamous Cell Carcinoma Evaluations

Regular dermatological evaluation to screen and monitor for cuSCC will be performed by a dermatologist or his/her designee with expertise in the diagnosis and management of cutaneous neoplasms. A dermatological evaluation will be conducted at baseline (the most current examination from the antecedent protocol may be utilized as the screening examination for the extension [rollover] protocol if it was conducted within 30 days prior to first dose of vemurafenib on Study GO28399), at Cycles 2 and 3, and then every other cycle through Cycle 15. Then, for patients still receiving study treatment, a dermatological evaluation will continue to be conducted every third cycle starting at Cycle 18 (i.e., screening and every three cycles per the Cycle 18+ period in the Schedule of Assessments [Appendix 1] for patients with $\geq$17 cycles of vemurafenib on an antecedent study), at the end of treatment visit, or until withdrawal of consent, death, or loss to follow-up (whichever occurs earliest). A window of $\pm$21 days from the scheduled study visit (with exception of the baseline evaluation) is allowed for completion of the dermatologic assessments cited above.

Patients should see their physicians as needed for any new skin lesions while on the study drug. An unscheduled dermatology examination may be done at any time during treatment, if clinically indicated.

Evaluations will include the following:

- A complete history of prior dermatologic medications and cuSCC risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, precursor lesions, and phototherapy for psoriasis) must be collected. (Available information of dermatological history from the antecedent study can be used.)
- A designated dermatologist or his/her designee will perform skin evaluations to monitor for SCC, primary melanoma, BCC, actinic keratosis, and KA.
- Any suspicious lesions identified from the screening period until *28 days* after the completion of study treatment must be biopsied and*/or* excised and sent for pathologic examination. Actinic keratosis, KA, or other skin conditions identified by the dermatologist should be treated per local standards of care.

- The occurrence of any skin changes, including rash and photosensitivity, should be reported to the study investigator for adequate adverse event reporting, and patients will be referred to the dermatologist as required.

4.5.1.10 Safety Surveillance for Squamous Cell Carcinoma

A thorough head and neck examination to monitor for non-cutaneous SCC, consisting of at least a visual inspection of the oral mucosa and lymph node palpation, must be performed by the treating physician or other qualified physician at screening for all patients enrolled. The most current examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted within 30 days prior to first dose of vemurafenib on Study GO28399. Thereafter, the head and neck examination will be repeated by the treating physician or other qualified physician every other treatment cycle ($\pm$21 days) after initiation of study treatment and every other cycle through Cycle 15. Then, for patients still receiving treatment, the head and neck examination will continue to be conducted every third cycle starting at Cycle 18, (i.e., screening and every three cycles per the Cycle 18+ period in the Schedule of Assessments [Appendix 1] for patients with $\geq$17 cycles of vemurafenib on an antecedent study), or until withdrawal of consent, death, or loss to follow-up (whichever occurs earliest).

Chest CT scans must be performed at baseline, within 30 days before the start of study treatment on Study GO28399, and then every 6 months (with a window of $\pm$21 days) after the initiation of treatment until death, withdrawal of consent, *or* loss to follow-up, whichever occurs first. Available routine chest CT scans from the antecedent study or those performed for tumor assessments during the study period (at the discretion of the investigator, per local institutional standard of care) that fit the required timeline specification can be used for this safety surveillance.

Additionally, all patients are required to undergo examination of the anus by the treating physician or his/her designee at baseline and at the end of treatment visit. The most current examination may be utilized as the baseline examination for the extension (rollover) protocol if it was conducted during the screening period or conduct of the antecedent protocol.

Female patients must have a pelvic examination (including evaluation of the uterine cervix and Papanicolaou [Pap] smear) at baseline and at the end of treatment visit performed by gynecologist or designee. The most current examination may be utilized as the screening examination for the extension (rollover) protocol if it was conducted during the screening period or the conduct of the antecedent protocol.

4.5.1.11 Exploratory Molecular Assessments

- Patient specimens for dynamic (non-inherited) biomarker discovery and validation should be collected from patients participating in this study if the sample is available by routine biopsy.

- Analyses will depend on the type of lesion and may include but are not limited to:

  BRAF and H/K/N-RAS mutation analysis

  HPV diagnosis (HPV genotype, p16 expression)

  Epidermal growth factor receptor (EGFR) expression/gene copy number

At least 6–10 formalin-fixed paraffin embedded tissue slides are required.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening/Baseline and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific baseline tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

The investigator must maintain a patient Enrollment and Identification Code List.

Results from the study completion visit or other prior visit assessment in the antecedent protocol may be used as screening/baseline for this extension (rollover) study, if within time intervals, as specified in this section and Appendix 1; screening/baseline is combined into one visit.

Under no circumstance will patients be permitted to re-enroll in the study if they have previously enrolled in this study and completed/discontinued treatment as specified.

All required screening/baseline procedures including data collection or transfer from the antecedent study must be performed after the patient has provided informed consent within a maximum window of 15 days from the last *dose of study drug in* the antecedent study *to* until the *first dose* of treatment in this extension (rollover) study, or as specified in Section 4.5.1 and Appendix 1 for specific assessments.

All patients will be closely monitored for safety and tolerability during all cycles of therapy and at the study completion visit. After signing the Informed Consent Form, all adverse events and serious adverse events (including serious adverse events due to invasive procedures required for the study such as biopsies) will be collected. Patients will be assessed for adverse events prior to each subsequent cycle and as necessary throughout the study. All adverse events will be recorded until 28 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first.

Visits are based on a 28-day cycle. If the timing of a protocol-mandated procedure coincides with a holiday or another scheduling conflict that precludes the visit, the visit should be scheduled within ±3 days of the date in question, which may be earlier or later.

Screening/Baseline Assessments:

Screening/baseline is combined into one visit.

All screening/baseline assessments are outlined in the Schedule of Assessments (Appendix 1). Note that *for all screening/baseline assessments,* results of study assessments in the antecedent protocol may be utilized as the baseline assessments for the current protocol at the permitted intervals as noted below.

- Review of eligibility criteria
- Significant medical history—from the antecedent study
- Vital signs (blood pressure, pulse, respiratory rate, temperature)
- Height and weight (part of the physical examination)
- ECOG Performance Status
- Physical examination: An examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted within 30 days prior to first dose of vemurafenib on Study GO28399.
- Anus, anal canal, and pelvic examination (if female): A prior examination may be utilized as the screening examination for the extension (rollover) protocol if it was conducted during the screening period or the conduct of the antecedent protocol.
- Hematology (WBC count, hemoglobin, hematocrit, platelet count, WBC differential count [neutrophils, bands, lymphocytes, eosinophils, basophils, and monocytes]). An examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted within 15 days prior to first dose of vemurafenib on Study GO28399.
- Serum chemistries (sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, phosphate, magnesium, total and direct bilirubin, albumin, AST, ALT, LDH, and ALP). An examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted within 15 days prior to first dose of vemurafenib on Study GO28399.
- Serum pregnancy test (for women of childbearing potential, including premenopausal women who have had a tubal ligation) within 7 days preceding the planned first dose of treatment on Study GO28399.
- 12-lead ECG recording, according local institutional standards. An examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted within 14 days prior to first dose of vemurafenib on Study GO28399.
- Adverse events (from last treatment on the antecedent protocol)
- Concomitant medications and treatments

The following procedures must be performed in the current protocol only after patient eligibility has been confirmed and informed consent has been obtained:

- Thorough head and neck evaluation (completed by treating physician). An examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted within 30 days prior to first dose of vemurafenib on Study GO28399.
- CT scan of chest (for SCC risk management; can use routinely scheduled radiologic assessment for tumor burden while patient is in the study). An examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted within 30 days prior to first dose of vemurafenib on Study GO28399.
- Dermatology evaluation (required for all patients prior to Cycle 1, Day 1 in the extension [rollover] protocol). An examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted within 30 days prior to first dose of vemurafenib on Study GO28399.
- Any evaluable and measurable disease will have been documented as specified for screening in the antecedent protocol and/or according to local institutional standards of care. Type and pathologic stage of current underlying cancer will be assessed according to the American Joint Committee on Cancer v7.0 classification (Edge SB et al. 2010). This assessment will be performed with the use of physical examination and imaging studies (such as contrast-enhanced CT or MRI of the C/A/P and contrast-enhanced MRI of the brain [or CT if MRI is not generally available]), according to local institutional standard of care. A prior examination may be utilized as the baseline/screening examination for the extension (rollover) protocol if it was conducted during the screening period or the conduct of the antecedent protocol.

See Appendix 1 for the Schedule of Assessments.

4.5.2.2 Assessments during Treatment

Except where specified, all assessments will be performed on the day of the specified visit ±3 days for assessments scheduled every 28 days, unless otherwise specified in the protocol and the Schedule of Assessments (see Appendix 1). Assessments scheduled on a day of study drug administration should be performed prior to study drug administration unless otherwise noted.

- Imaging for tumor assessments during the study period will be performed at the discretion of the investigator per local institutional standard of care for the purpose of defining progression of disease.

The following assessments may be performed ≤4 days prior to the scheduled clinic visit (as applicable) for Day 1 of each treatment cycle:

- *Hematology*

- *Serum chemistries*
- ECG

Results of the assessments must be reviewed by the investigator prior to any study drug administration on the first day of treatment of a given cycle.

See Appendix 1 for the Schedule of Assessments performed during the treatment period.

Additional physical examination, clinical, laboratory (e.g., hematology, chemistry, ECG, etc.) and other diagnostic studies may be conducted at scheduled and non-scheduled timepoints to evaluate safety and to assess tumor status, as may be clinically indicated, at the discretion of the investigator or per institutional guidelines.

Patients who have received a minimum of 17 cycles of vemurafenib treatment in the antecedent study will undergo a screening/baseline visit and then proceed to every third-cycle study visits commencing with the Cycle 18 visit.

4.5.2.3 Assessments at Unplanned Visits

Additional physical examination, clinical, laboratory (e.g., hematology, chemistry), and other diagnostic studies may be conducted at scheduled and non-scheduled timepoints to evaluate safety and to assess tumor status, as may be clinically indicated, at the discretion of the investigator or per institutional guidelines.

4.5.2.4 End of Treatment Visit

Patients who complete the study or discontinue from the study drug for any reason will be asked to return to the clinic within 28 days after their last dose of vemurafenib or before starting new non-protocol therapy (whichever is earliest) for an end of treatment visit. The visit at which a response assessment showed disease progression will be used as the end of treatment visit. The following assessments will be performed:

- Physical examination (including examination of the eyes, ears, nose, and cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems and the safety surveillance assessment for new primary malignancy including head and neck, anus, and pelvic [for female patients only] examinations)
- Vital signs
- 12-lead ECG (prior to blood samples)
- ECOG Performance Status
- Hematology
- Serum chemistries
- Concomitant medications
- Adverse events

Refer to Appendix 1 for assessments to be performed at the study completion or early termination visit.

4.5.2.5 Adverse Event Follow-Up

After the study completion visit, ongoing adverse events thought to be related to study treatment will be followed until the event has resolved to baseline grade, is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse events.

After the study completion visit, investigators should report only serious adverse events that are deemed related to study treatment.

After the study completion/early termination visit, adverse events should be followed as outlined in Sections 5.5 and 5.6.

See Appendix 1 for the schedule of follow-up assessments.

4.5.3 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient.
- Patient non-compliance, specifically defined as patient's refusal to take the required doses of study drugs, unless for a reason, as defined below

In cases where the patient decides to prematurely discontinue study treatment ("refuses treatment"), he or she should be asked if he or she can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the eCRF. If the patient is lost to follow-up, the investigator should contact the patient or a responsible relative by telephone followed by registered mail to establish the reason for the withdrawal as completely as possible. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

When applicable, patients should be informed of circumstances under which their participation may be terminated by the investigator without the patient's consent. The investigator may withdraw patients from the study in the event of intercurrent illness,

adverse events, treatment failure after a prescribed procedure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), cure, or any reason where it is believed by the investigator that it is in the best interest of the patient to be terminated from the study. Any administrative or other reasons for withdrawal must be documented and explained to the patient. Any patient who discontinues will be encouraged to return to the study center for a study completion visit.

4.5.3.1 Discontinuation from Study Drug

Patients may continue to receive treatment with vemurafenib until disease progression (as defined by the investigator, according local institutional standard of care), unacceptable toxicity, or any other discontinuation criterion is met, as follows, whichever occurs first.

- Disease progression as assessed per institutional standards of care

  Progressive disease during the antecedent protocol. If approval to treat beyond progression was already given in the antecedent protocol, the patient may roll over into the current protocol.

  Under special circumstances, when it is believed that the patient may clinically benefit from continued therapy with vemurafenib (e.g., in case of mixed progression or progression of single lesion or appearance of a new single lesion), enrollment into this protocol and dosing beyond progression may be considered if it is judged by the investigator, in consultation with the Sponsor, to be in the best interest of the patient. All such cases will require approval of the Sponsor before continuing study drug treatment within this protocol.
- Intolerance of vemurafenib
- If treatment is suspended more than 28 days, the patient should be withdrawn from the study
- Initiation of other cancer medication
- Pregnancy

Patients who discontinue study drug prematurely will be asked to return to the clinic for an end of treatment visit (see Section 4.5.2.4 and Appendix 1). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

All patients who discontinue vemurafenib treatment will be followed for safety surveillance per the investigator's discretion.

Note: New primary melanomas identified as part of the dermatologic risk management plan outlined in Section 4.5.1.9, which are completely excised and without need for additional therapy, do not require patient discontinuation from study treatment.

4.5.3.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.5.4 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- All enrolled patients have discontinued study treatment.

The Sponsor will notify the investigator if the study is placed on hold or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include but are not limited to the following:

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Measures will be taken to ensure the safety of patients participating in this trial; in particular, the use of inclusion and exclusion criteria and close monitoring of patients.

5.1.1 Risks Associated with Vemurafenib

The toxicity profile for vemurafenib has been documented from safety data derived from seven studies of more than 600 treated patients with locally advanced unresectable or metastatic melanoma. The most common toxicities observed were rash, fatigue, arthralgia, myalgia, headache, nausea, photosensitivity, alopecia, and pruritus. The most common laboratory abnormalities reported as adverse events included elevations of liver function tests (i.e., GGT, ALP, ALT, AST, and bilirubin). The majority of adverse events reported in conjunction with Phase I to III clinical trials were of mild or moderate severity. Approximately one-half of all patients treated with vemurafenib required interruption and/or reduction of dose on at least one occasion, although treatment discontinuation due to adverse events has been rare.

Approximately 20% of vemurafenib recipients developed one or more localized, cutaneous SCCs (mainly KA type). The majority of SCCs were observed within the first 16 weeks of vemurafenib exposure and were not treatment limiting.

Eight cases of skin lesions in 7 vemurafenib-treated patients were reported as new primary malignant melanomas in Study NO25026. No cases were reported in patients treated with dacarbazine. Cases were managed with excision, and patients continued treatment without dose adjustment. Surveillance measures to monitor for the occurrence of new primary melanomas, SCC (cutaneous and non-cutaneous), and any new primary malignancies are outlined in Section 4.5.1.9.

Two cases of SCC of the head and neck have been reported in 2 patients treated with vemurafenib in excess of 300 days while enrolled in a clinical trial. Pathology examination of both tumors (one a primary *tonsillar* tumor, the other a primary tongue tumor) revealed the presence of invasive SCC. Of note, the first patient's medical history was significant for risk factors for head and neck cancer and the tumor tissue tested positive for HPV. The second patient does not appear to possess any risk factors for head and neck cancer, and the preliminary examination of the tumor tissue did not reveal the presence of HPV genome. Full details are provided in the current Vemurafenib IB.

Five cases of adenomatous colonic polyps have been reported in patients who received vemurafenib for more than 2 years, and 1 patient in the Expanded Access Program had one colonic *adenoma* discovered after treatment with vemurafenib for 0.57 years (Chapman et al. 2012).

Analysis of ECG data from the Phase II Study NP22657 of vemurafenib in previously treated patients with metastatic melanoma revealed a risk of QT interval prolongation without associated clinical symptomatology.

See Section 1.2.1.5 and the Vemurafenib IB for more details.

5.1.2 General Plan to Manage Safety Concerns

5.1.2.1 Eligibility Criteria

Eligibility criteria exclude patients who previously discontinued vemurafenib for any reason in an antecedent protocol or who met an exclusion criterion, as specified in the antecedent study or the extension (rollover) protocol.

5.1.2.2 Monitoring

Safety will be evaluated in this study through the monitoring of all adverse events and targeted laboratory assessments according to NCI CTCAE v4.0. Patients will be monitored on Day 1 of every subsequent cycle and as needed until *28 days* after the last dose of study treatment or initiation of other anti-cancer therapy, whichever occurs first.

All treatment-emergent adverse events and serious adverse events, whether or not deemed treatment related, will be followed until they resolve or become stabilized, the patient is lost to follow-up or withdraws consent, or it has been determined that the study treatment or participation is not the cause of the adverse event or serious adverse event. General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies including serum chemistries, liver function tests, and blood counts.

All serious adverse events and protocol-defined adverse events of special interest (see Section 5.4.2) will be reported in an expedited fashion.

5.1.2.3 Monitoring and Management of Specific Toxicities and Conditions That May Arise with Treatment with Vemurafenib

Non-Squamous Cell Carcinoma Skin Toxicity

The non-SCC skin toxicities observed in patients treated with vemurafenib include rash, pruritus, palmar-plantar erythrodysesthesia, dry skin, and exfoliation. Of these, the most common has been rash (maculopapular or acneiform), which has generally been manageable with supportive care. Skin toxicities other than lesions suspected of being cuSCC will be managed with supportive care according to institutional guidelines as well as by dose interruption/modification, as specified in Section 5.1.2.3.

Mild to severe photosensitivity has been reported in patients who received vemurafenib in clinical studies. All patients should be advised to avoid sun exposure while taking the study drug. Patients should be advised to wear protective clothing and use a broad spectrum UVA/UVB sunscreen and lip balm (sun protection factor $\geq$30) when outdoors to help protect against sunburn. For photosensitivity Grade $\geq$2 (intolerable) adverse reactions, dose modifications will be required (see Section 5.1.2.3).

Management and Safety Surveillance for Cutaneous Squamous Cell Carcinoma and New Primary Melanoma

If a patient develops cuSCC during the study, this information must be collected and reported as a non-serious adverse event of special interest to the Sponsor, whether it is deemed related or unrelated to study drug.

If a patient develops a new primary melanoma during *the* study, this information must be collected and reported as a non-serious adverse event of special interest to the Sponsor, whether it is deemed related or unrelated to study drug. An unscheduled dermatologic examination may be performed during treatment for investigation of any new suspicious skin lesions.

Confirmed cuSCC and/or new primary melanoma should be completely resected and treated according local institutional standard of care. Vemurafenib treatment interruption and/or dose modifications are not recommended (see Section 5.1.2.3).

See Section 4.5.1.9 for more details.

Management and Safety Surveillance for Non-Cutaneous Squamous Cell Carcinoma:

- A thorough head and neck examination to monitor for non-cutaneous SCC, consisting of at least a visual inspection of the oral mucosa and lymph node palpation, must be performed by the treating physician or other qualified physician at screening for all patients enrolled. The most current examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted within 30 days prior to the first dose of vemurafenib. Subsequent head and neck examinations will be performed as outlined in Section 4.5.1.10.
- Chest CT scans must be performed at baseline, within 30 days before the start of study treatment and then every 6 months (with a window of $\pm$ 21 days) after initiation of treatment until death, withdrawal of consent, or loss to follow-up, whichever occurs first. Available routine chest CT scans from previous assessments may be used, as outlined in Section 4.5.1.10.
- Additionally, all patients are required to undergo examination (visual and digital) of the anus and anal canal by the treating physician or his/her designee at baseline and at the end of the study (end of treatment visit). The most current examination from the antecedent protocol may be used, as outlined in Section 4.5.1.10.
- Female patients must have a pelvic examination (including evaluation of the uterine cervix by Pap smear) at baseline and at the end of the study (end of treatment visit), performed by a gynecologist or designee. The most current examination from the antecedent protocol may be used, as outlined in Section 4.5.1.10.
- An unscheduled examination may be performed during treatment for the investigation of any new lesion or symptom suspected to be SCC (head and neck, anus, pelvic for female patients only, chest CT).

New Primary Invasive Malignancies

All new primary invasive malignancies will be reported until $28\ days$ after treatment completion, withdrawal of consent, loss to follow-up, or death, whichever occurs earliest.

If a patient develops a new primary invasive malignancy during or up to $28\ days$ after study treatment completion, this event must be reported to the Sponsor as a serious adverse event, whether it is deemed related or unrelated to study drug. Thereafter, only new primary malignancies thought to be related to study treatment will be reported as serious adverse events.

Any identified lesion suspected to be a new primary malignancy (including cuSCC, non-cutaneous SCC, and/or new primary melanoma) must be biopsied or excised and sent for pathological examination and should be treated according local institutional standard of care.

Hepatic Toxicity

Cases of liver injury, including severe cases of liver injury, have been reported with vemurafenib use. These have been generally managed with interruption of treatment and dose reduction. All patients will undergo liver function testing at periodic intervals while on study treatment (see Appendix 1). Guidelines for interruption or dose reduction of vemurafenib in the setting of liver function abnormality are provided in Section 5.1.3.

See also the Vemurafenib IB for updated safety information.

Hematologic Toxicity

Patients will have hematologic parameters monitored throughout the study. See the Vemurafenib IB for full details of potential hematologic adverse events reported in association with vemurafenib treatment.

Gastrointestinal Toxicity

Gastrointestinal toxicities will be managed according to institutional guidelines/standard of care. During the study, patients are to receive maximal supportive care as clinically indicated. Any modification of study treatment for diarrhea must strictly follow the instructions in Table 1.

Pancreatic Toxicity

The Sponsor recommends that workup of any suspected case of pancreatitis should include serum amylase and lipase testing, in addition to other appropriate testing (e.g., CT abdomen).

Ocular Toxicity

See the Vemurafenib IB for further details on the occurrence of anterior uveitis and a single case of retinal vein occlusion reported in association with vemurafenib treatment.

Examination of the eyes (inspection of conjunctivae and pupils) is part of the physical examination.

Cardiac Toxicity

Patients with a baseline QTc $>$ 450 ms or a history of congenital long QT syndrome should not receive treatment with vemurafenib. Refer to the Vemurafenib IB for additional details.

The following recommendations have been developed to minimize the risk of cardiac toxicity in patients with metastatic melanoma treated with vemurafenib in this study:

- Avoid combination with other medications with known potential to lead to prolongation of the QTc interval, if possible (see Appendix 4)
- ECG monitoring will occur at baseline and at specified intervals, as outlined in the Schedule of Assessments (see Appendix 1).

- If the QTc increases to $>$500 ms, or if a change from baseline of $\geq$60 ms is observed during the study, vemurafenib treatment should be temporarily interrupted. Electrolytes (K, Mg, albumin, and Ca) should be monitored, and any electrolyte abnormalities, especially hypokalemia, should be corrected prior to re-institution of therapy. ECG should be monitored weekly until the QTc normalizes before therapy is reinstituted at a reduced dose. Dose reduction should occur as described in Table 1. A second sustained occurrence of QTc interval prolongation to $>$500 ms, despite dose reduction, will require discontinuation of vemurafenib.
- Vemurafenib treatment should be permanently discontinued if the QTc increases to $>$500 ms and changes from baseline exceed 60 ms.

5.1.3 Dose Interruption/Modification for Adverse Events

If a dose is missed, it can be taken 4 or more hours before the next dose to maintain the twice-daily regimen. Both doses should not be taken at the same time.

Management of symptomatic adverse drug reactions (e.g., arthralgia, fatigue, rash) may require either temporary interruption or dose reduction of vemurafenib treatment or both. When dose reduction is needed, dose reduction in 240-mg BID increments is recommended depending on individual safety and tolerability. Dose escalation after dose reduction is generally not recommended unless under special circumstances (i.e., increased likelihood of clinical benefit for the dose increase and no safety concerns). This should be done after discussion with the Sponsor. Dose increases above 960 mg BID will not be allowed.

For Grade 1 and tolerable Grade 2 toxicities, patients may continue with the full dose. For intolerable Grade 2 toxicities or Grade 3 toxicities, dosing will be interrupted until resolution to Grade 1 or lower and dose reductions in 240-mg increments are required. On the third appearance of intolerable Grade 2 or Grade 3 toxicity, despite two dose reductions, it is recommended that patients discontinue vemurafenib.

For Grade 4 toxicities, patients should discontinue study treatment or, on the basis of investigator judgment, study treatment should be interrupted until resolution to Grade 1 or lower with dose reduction of 50% upon restarting study drug. It is recommended that patients permanently discontinue vemurafenib for a second occurrence of any Grade 4 toxicities.

If treatment interruption has occurred for $>$28 days for whatever reason, the patient will be considered to have permanently discontinued study treatment. Exceptions may be granted for reversible laboratory abnormalities with no clinical sequelae and/or clinical significance following consultation with the study's Medical Monitor. See Table 1 below.

Table 1 Dose Interruption/Modification Criteria for Vemurafenib; Regular Dose 960 mg BID

Grade [a]	Recommended Dose Modification
Grade 1 or Grade 2 (tolerable)	Maintain vemurafenib at a dose of 960 mg BID
Grade 2 (intolerable) or Grade 3	
First appearance	Interrupt treatment until Grade 0–1. Resume dosing at 720 mg BID
Second appearance	Interrupt treatment until Grade 0–1. Resume dosing at 480 mg BID
Third appearance	Discontinue permanently
Grade 4	
First appearance	Discontinue permanently or interrupt vemurafenib treatment until Grade 0–1. Resume dosing at 480 mg BID
Second appearance	Discontinue permanently

BID = twice daily; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] The intensity of clinical adverse events graded by the NCI CTCAE, Version 4.0.

Special consideration must be taken with any patient in the study who experiences an increase in QTc > 500 ms or change from baseline > 60 ms. If the QTc exceeds 500 ms or the change from baseline is > 60 ms on ECG, vemurafenib treatment should be temporarily interrupted. When the QTc decreases to < 500 ms, re-initiation of vemurafenib treatment may occur and the dose should be reduced by one dose level.

Permanent discontinuation of vemurafenib treatment is recommended if the QTc increase meets both criteria of > 500 ms and > 60 ms change from pretreatment.

Dose modifications or interruptions are not recommended for cuSCC or new primary melanoma adverse reactions (suspected lesion should be biopsied or resected and confirmed by pathology). Confirmed cuSCC or new primary melanoma should be completely resected and treated according local institutional standard of care.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest, measurement of protocol-specified clinical laboratory assessments, measurement of protocol-specified vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for GCP, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to Roche)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life-threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability or incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly or birth defect in a neonate or infant born to a mother exposed to the study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above)

A new primary invasive malignancy (other than cuSCC or new primary melanoma) or progression or recurrence of a prior invasive malignancy (other than the disease under study) will be characterized as a serious adverse event.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe or according to NCI CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to Roche)

*A*dverse events of special interest are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- *Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see* Section 5.3.5.6*)*
- Suspected transmission of an infectious agent by the study drug*, as defined below*

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Grade 3 or 4 QTc interval prolongation
- cuSCC
- New primary melanoma

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

Adverse events still ongoing or not resolved at the time of enrollment in the extension (rollover) study should be recorded on the Adverse Event eCRF, as specified in the protocol, with the original onset date from the antecedent study.

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies).

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 28 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever comes first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale for Adverse Events Not Listed in the NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the NCI CTCAE, Version 4.0, which can be found at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF. Colloquialisms and abbreviations should be avoided.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

For adverse events, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by a mild, non-serious infection, only neutropenia should be reported on the eCRF.
- If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. *The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.*

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event of special interest the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor within 24 hours after learning of the event, either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to recurrence of the underlying malignancy should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. *If the cause of death is unknown and cannot be ascertained at the time of reporting,* ***"unexplained death"*** *should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term* ***"sudden death"*** *should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

If the death is attributed to progression of the underlying malignancy, this should not be recorded on the Adverse Event eCRF but should be captured in the Death and Disease Progression/Final Treatment Visit eCRFs.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 (see Appendix 5).

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the baseline/screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF (see Appendix 1).

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., more frequent headaches").

5.3.5.9 Worsening of Malignancy

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. In most cases, the expected pattern of progression will be based on *Response Evaluation Criteria in Solid Tumors (RECIST)* criteria. In rare cases, the determination of clinical progression will

be based on symptomatic deterioration. However, every effort should be made to document progression with use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not suffered an adverse event.

  Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Elective hospitalizations or surgical procedures that are a result of a patient's preexisting condition(s) that have not worsened since receiving trial medication. Examples may include but are not limited to cholecystectomy for gallstones, joint replacement surgery, and diagnostic testing. Such events should still be recorded as medical procedures in the eCRF.

5.3.5.11 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

The investigator must report the following events to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor within 24 hours after becoming aware of the information. New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality on the basis of new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board (IRB)/Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

24 HOUR MEDICAL COVERAGE (Roche Emergency Medical Call Center Help Desk): Within the United States, on weekends, holidays, and after 5:00 pm, call: 1-866-286-9573 and ask for the physician on call. From Australia, call 1-800-031-902 and ask for the physician on call. (Note: the number for Australia cannot be dialed from a mobile phone.)

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of serious adverse events and non-serious adverse events of special interest, investigators should record all case details that can be gathered within 24 hours on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system.

A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Non-Serious Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the event with use of the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 months after the last doses of study drug. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue vemurafenib and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the pregnancy with use of the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of vemurafenib. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. *When permitted by the site,* pregnant partner *would* need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. *If* the authorization has been signed, the investigator *should* update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, reporting instructions provided in Section 5.4.3.1 should be followed.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (because the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4.3.4 Congenital Anomalies or Birth Defects

Any congenital anomaly or birth defect in a child born to a female patient (or female partner of a male patient exposed to vemurafenib) should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse event of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS *THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD*

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days [see Section 5.3.1] after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by

scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document(s):

- Vemurafenib IB
- Local prescribing information for Zelboraf® (vemurafenib)
- Vemurafenib (Zelboraf) Core Data Sheet

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

There is no formal hypothesis testing in this extension (rollover) study. Data will be collected and reported descriptively for all study endpoints.

The final analysis of this study will be performed when all patients have been followed up per protocol (see Section 3.2 and Section 3.3).

6.1 SUMMARIES OF CONDUCT OF STUDY

A clinical study report will be written and distributed to Health Authorities as required by applicable regulatory requirements. Enrollment, eligibility violations, and study treatment administration will be summarized. Patient disposition will be summarized and include whether treatment was completed or discontinued early and the reason for early treatment discontinuation.

6.2 EFFICACY ANALYSIS

No protocol-specific efficacy analysis will be performed for this study.

6.3 SAFETY ANALYSIS

The safety analysis will include all patients who receive at least one dose of vemurafenib.

Incidence, nature, and intensity (severity) of adverse events and serious adverse events, graded according to NCI CTCAE v4.0 will be summarized.

Changes in vital signs (blood pressure, pulse, temperature), ECGs, and clinical laboratory results during the course of study will be summarized.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

Roche will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC with use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, Roche will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

Roche will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to Roche, with use of Roche's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at Roche and records retention for the study data will be consistent with Roche's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to Roche and should be handled in accordance with instructions from Roche.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate

and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of Roche. Written notification should be provided to Roche prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting) (see Appendix 5). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union/European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

Roche's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Roche or its designee must review and approve any proposed deviations from Roche's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to Roche for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to Roche for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in

each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from Roche. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC and archived in the site's study file.

8.4 CONFIDENTIALITY

Roche maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Roche location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Roche monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 SITE INSPECTIONS

Site visits will be conducted by Roche or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Roche monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech and will be managed by Roche and a Contract Research Organization (CRO). The CRO will be responsible for medical monitoring, operations, site monitoring and management, and data management (with oversight of data management provided by Roche).

After written informed consent has been obtained and eligibility has been established, the study site will obtain the patient's unique identification number from an interactive voice response system.

Data will be recorded through Medidata EDC and eCRFs.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Roche prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

Roche will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Roche will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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Zelboraf® (vemurafenib) U.S. Package Insert. Genentech USA, Inc. A Member of the Roche Group.

Appendix 1 Schedule of Assessments

										Follow-Up after Study Treatment
Cycle	Screening/Baseline (15-Day Window from Last Dose in Antecedent Study until Day 1/Cycle 1)	2	3	4	5	6	7	Every Other Cycle (9, 11, 13, 15), Except as Noted	Every Third Cycle (18, 21, 24, etc.), Except as Noted	End of Treatment Visit within 28 Days Post-Last Dose
Informed consent	x									
Review of eligibility criteria	x									
Medical history	x [a]									
Vital signs	x [a]	x	x	x	x	x	x	x	x	x
Physical exam [b]	x [a]	x	x	x	x	x	x	x	x	x
Anus, anal canal, and pelvic exam (if female) [c]	x [a]									x
ECOG Performance Status	x [a]	x	x	x	x	x	x	x	x	x
Hematology [d]	x [a]	x	x	x	x	x	x	x	x	x
Serum chemistry [e]	x [a]	x	x	x	x	x	x	x	x	x
ECG [f]	x [a]	x	x		x		x	x	x	x
Head and neck exam [g,h]	x [a]		x		x		x	x	x	x
Dermatology evaluation [i,h]	x [a]	x	x		x		x	x	x	x
Chest CT/MRI for SCC evaluation [j,h]	x [a]					x		x (at C12 ± 28 days)	x (at C18 and every 6 mos)	
Tumor assessments (C/A/P) [k]	x [a]	At investigator discretion according local institutional standard of care to assess disease								

Appendix 1 Schedule of Assessments (cont.)

										Follow-Up after Study Treatment
Cycle	Screening/Baseline (15-Day Window from Last Dose in Antecedent Study until Day 1/Cycle 1)	2	3	4	5	6	7	Every Other Cycle (9, 11, 13, 15), Except as Noted	Every Third Cycle (18, 21, 24, etc.), Except as Noted	End of Treatment Visit within 28 Days Post-Last Dose
Exploratory molecular assessments/tumor biopsies [l]										x
Serum pregnancy test [m]	x									
Urine pregnancy test [n]	x	x	x	x	x	x	x	x (prior to every cycle)	x (prior to every cycle)	x
Concomitant medications and treatments	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x
Drug dispense/drug accountability	x	x	x	x	x	x	x	x	x	

ALP = alkaline phosphatase; C = cycle; C/A/P = chest, abdomen, pelvis; CT = computed tomography; cuSCC = cutaneous squamous cell carcinoma; ECOG = Eastern Cooperative Oncology Group; mos = months; MRI = magnetic resonance imaging; pts = patients; SCC = squamous cell carcinoma.

Notes:

Cycle length = 28 days; study visits will occur on Day 1 (±3 days, unless otherwise specified) of each cycle through Cycle 7, and then on every other cycle (Cycles 9, 11, 13, 15). Then, for patients still receiving treatment, clinic visits will occur on Day 1 of every third cycle (i.e., Cycles 18, 21, 24, etc.) until unacceptable toxicity or disease progression, as defined by the investigator. Patients who have received a minimum of 17 cycles of vemurafenib treatment in the antecedent study will undergo the screening/baseline visit and then move directly to every-third-cycle study visits commencing with the Cycle 18 visit. *Visits are to be scheduled from screening/baseline visit.*

On the day of scheduled assessments, assessments should be performed prior to study drug dosing, unless otherwise specified.

All required screening/baseline procedures including data collection/transfer from the antecedent study need to be performed after the patient provides inform consent within a maximum window of 15 days from the last day of the antecedent study until treatment start in the extension (rollover) study, except where otherwise indicated.

a. Results from the study completion visit or other prior visit assessment in the antecedent protocol may be used as screening/baseline for this extension (rollover) study, if within the time intervals, as specified below.

b. Complete physical examination will include the measurement of patients' weight and height, as well as an evaluation of the head, eye, ear, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems at baseline and end of treatment visit.
Results from antecedent study can be used for baseline/screening assessment if it was performed within 30 days before treatment on Study GO28399.

At subsequent visits, limited, symptom-directed physical examinations, and, minimally, examination of the eye and the cardiovascular and dermatological systems should be performed.

c. Visual and digital evaluation of the anus and anal canal will be performed at baseline (unless previously done in the antecedent protocol) and at the end of treatment visit. In addition, all female patients will undergo a pelvic examination including visual inspection of the uterine cervix and Papanicolaou smear at baseline (unless previously performed in the antecedent protocol) and at the end of treatment visit.
An examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted during the screening period or the conduct of the antecedent protocol.

d. Hematology (hemoglobin, hematocrit, WBC count with differential [neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes], and platelet count may be obtained up to 4 days prior to the scheduled clinic visit (as applicable) for Day 1 of each treatment cycle.
An examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted within 15 days prior to first dose of vemurafenib on Study GO28399.

e. Serum chemistry (sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, phosphate, magnesium, total and direct bilirubin, albumin, AST, ALT, LDH, and ALP) may be obtained up to 4 days prior to the scheduled clinic visit (as applicable) for Day 1 of each treatment cycle. An examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol, if it was conducted within 15 days prior to first dose of vemurafenib.

f. ECG assessments will be taken every cycle through Cycle 3, followed by every other cycle through Cycle 15 and every third cycle starting at Cycle 18 and at the end of treatment visit. All ECGs will be taken at least 15 minutes before any type of blood draw. ECG assessments may be obtained up to 4 days prior to the scheduled clinic visit (as applicable) for Day 1 of each treatment cycle. An examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted within 14 days prior to first dose of vemurafenib on Study GO28399.

g. A thorough head and neck examination to monitor for non-cutaneous SCC, consisting of at least a visual inspection of the oral mucosa and lymph node palpation, must be performed by the treating physician or other qualified physician at screening for all patients enrolled. The screening examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted within 30 days prior to first dose of vemurafenib on Study GO28399. Thereafter, the head and neck examination will be repeated by the treating physician or other qualified physician every other treatment cycle after initiation of study treatment and every other cycle through Cycle 15. Then, for patients still receiving treatment, the head and neck examination will continue to be conducted every third treatment cycle starting at Cycle 18 (i.e., screening and every three cycles per the Cycle 18+ period for patients with ≥ 17 cycles of vemurafenib on an antecedent study), and until withdrawal of consent, death, or loss to follow-up (whichever occurs earliest). A window of ± 21 days from the scheduled study visit (with exception of the baseline evaluation) is allowed for completion of the assessment.

h. Any identified lesion suspected to be a new primary malignancy (including cuSCC, non-cutaneous SCC, and/or new primary melanoma) must be biopsied or excised and sent for pathological examination and should be treated according local institutional standard of care.

i. A dermatological evaluation will be conducted at baseline, prior to treatment, at Cycles 2 and 3, then every other cycle through Cycle 15. Then, for patients still receiving treatment, a dermatological evaluation will continue to be conducted every third treatment cycle starting at Cycle 18 (i.e., screening and every three cycles per the Cycle 18+ period for patients with ≥ 17 cycles of vemurafenib on an antecedent study), and until withdrawal of consent, death, or loss to follow-up (whichever occurs earliest). A window of ± 21 days from the scheduled study visit (with exception of the baseline evaluation) is allowed for completion of the dermatologic assessments cited above. It is recommended that the examination to be performed by a dermatologist; however, it can also be performed by a qualified physician. All patients will be followed for cuSCC, as well as other new cutaneous neoplasms, until $28\ days$ after treatment completion, death, withdrawal of consent, or loss to follow-up, whichever occurs first. Patients should see their physicians as needed for any new skin lesions while on the study drug. An unscheduled dermatology examination may be performed at any time during treatment, if clinically indicated. An examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted within 30 days prior to first dose of vemurafenib on Study GO28399.

j. Chest CT scans must be performed at baseline, within 30 days before start of study treatment on Study GO28399, and every 6 months (within a window of ±21 days) after initiation of treatment until death, withdrawal of consent, loss to follow up or up to $28\ days$ after study drug discontinuation, whichever occurs first. Available routine chest CT scans (e.g., performed for tumor assessments during the antecedent study period) that fit the required timeline specification can be used for this safety surveillance.

k. Tumor assessments, including radiological tumor assessments of chest, abdomen, pelvis, and brain, for measuring extent of disease (CT scan is the preferred method) will be done at the discretion of the investigator or per institutional guidelines. An examination from the antecedent protocol may be utilized as the screening examination for the extension (rollover) protocol if it was conducted within 30 days prior to the first dose of vemurafenib.

l. Patient specimens for dynamic (non-inherited) biomarker discovery and validation may be collected from patients participating in this study if the sample is available by routine biopsy.

m. A serum pregnancy test for women of childbearing potential, including premenopausal women who have had a tubal ligation, must be collected at baseline within 7 days preceding the planned first dose of treatment on Study GO28399.

n. Urine pregnancy test prior to each treatment cycle for women of childbearing potential, including premenopausal women who have had a tubal ligation, may be obtained up to 4 days prior to the scheduled clinic visit (as applicable) for Day 1 of each treatment cycle. If positive, a serum pregnancy test should be performed.

Additional physical examination, clinical, laboratory (e.g., hematology, chemistry, ECG, etc.) and other diagnostic studies may be conducted at scheduled and non-scheduled timepoints to evaluate safety and to assess tumor status, as may be clinically indicated, at the discretion of the investigator or per institutional guidelines.

Appendix 2 ECOG Performance Status Scale

Patients will be graded according to the ECOG Performance Status scale and criteria as described below:

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.

Appendix 3 Impact of Vemurafenib on Concomitant Medications

Do not use prohibited medications as outlined in Section 4.4.2 that also occur on this list.

Impact of RO5185426 on Concomitant Medications		
Substrates		
CYP 1A2[1]	CYP 2C9[1]	CYP3A4[2]
amitriptyline	**NSAIDs:**	**Macrolide antibiotics:**
caffeine	diclofenac	clarithromycin
clomipramine	ibuprofen	erythromycin
clozapine	lornoxicam	telithromycin
cyclobenzaprine	meloxicam	Anti-arrhythmics:
estradiol	S-naproxen_Nor	quinidine_3OH
fluvoxamine	piroxicam	
haloperidol	suprofen	**Benzodiazepines:**
imipramine N-DeMe		alprazolam
mexilletine	**Oral Hypoglycemic:**	diazepam_3OH
naproxen	tolbutamide	midazolam
olanzapine	glipizide	triazolam
ondansetron	Angiotensin II	
phenacetin_	Blockers:	**Immune Modulators:**
acetaminophen	losartan	cyclosporine
propranolol	irbesartan	tacrolimus (FK506)
riluzole	Sulfonylureas:	HIV Antivirals:
ropivacaine	glyburide	indinavir
tacrine	glibenclamide	nelfinavir
theophylline	glipizide	ritonavir
tizanidine	glimepiride	saquinavir
verapamil	tolbutamide	Prokinetic:
(R)warfarin	amitriptyline	cisapride
zileuton	celecoxib	
zolmitriptan	fluoxetine	**Antihistamines:**
	fluvastatin	astemizole
	glyburide	chlorpheniramine
	nateglinide	terfenadine
	phenytoin-4-OH2	
	rosiglitazone	**Calcium Channel Blockers:**
	tamoxifen	amlodipine
	torsemide	diltiazem
	S-warfarin	felodipine
		lercanidipine
		nifedipine2
		nisoldipine
		nitrendipine
		verapamil

Appendix 3 Impact of Vemurafenib on Concomitant Medications (cont.)

CYP 1A2[1]	CYP 2C9[1]	CYP3A4[2]
		HMG CoA Reductase Inhibitors: atorvastatin cerivastatin lovastatin simvastatin Steroid 6beta-OH: estradiol hydrocortisone progesterone testosterone **Miscellaneous:** alfentanyl aprepitant aripiprazole buspirone cafergot caffeine cilostazol cocaine codeine-Ndemethylation dapsone dexamethasone dextromethorphan docetaxel domperidone eplerenone fentanyl finasteride gleevec haloperidol irinotecan lidocaine methadone nateglinide ondansetron pimozide propranolol quetiapine quinine risperidone salmeterol

Appendix 3 Impact of Vemurafenib on Concomitant Medications (cont.)

		sildenafil sirolimus tamoxifen taxol terfenadine trazodone vincristine zaleplon ziprasidone zolpidem

[1] Exposure of these drugs may be increased following vemurafenib treatment.
[2] Exposure of these drugs may be decreased following vemurafenib treatment.

Appendix 4 Medications Affecting the QT Interval

Do not use prohibited medications as outlined in Section 4.4.2 that also occur on this list; information is available at http://www.azcert.org.

Albuterol	Doxepin	Lithium	Quinidine
Alfuzosin	Droperidol	Mesoridazine	Ranolazine
Amantadine	Ephedrine	Metaproterenol	Risperidone
Amiodarone	Epinephrine	Methadone	Ritodrine
Amitriptyline	Erythromycin	Methylphenidate	Roxithromycin
Amphetamine	Felbamate	Mexiletine	Salmeterol
Arsenic trioxide	Fenfluramine	Midodrine	Sertindole
Astemizole	Flecainide	Moexipril	Sertraline
Atazanavir	Fluconazole	Moxifloxacin	Sibutramine
Atomoxetine	Fluoxetine	Nicardipine	Sibutramine
Azithromycin	Foscarnet	Nilotinib	Solifenacin
Bepridil	Fosphenytoin	Norepinephrine	Sotalol
Chloral hydrate	Galantamine	Nortriptyline	Sparfloxacin
Chloroquine	Gatifloxacin	Octreotide	Sunitinib
Chlorpromazine	Gemifloxacin	Ofloxacin	Tacrolimus
Ciprofloxacin	Granisetron	Ondansetron	Tamoxifen
Cisapride	Halofantrine	Oxytocin	Telithromycin
Citalopram	Haloperidol	Paliperidone	Terbutaline
Clarithromycin	Ibutilide	Paroxetine	Terfenadine
Clomipramine	Imipramine	Pentamidine	Thioridazine
Clozapine	Indapamide	Perflutren lipid microspheres	Tizanidine
Cocaine	Isoproterenol	Phentermine	Tolterodine
Desipramine	Isradipine	Phenylephrine	Trimethoprim-Sulfa
Dexmethylphenidate	Itraconazole	Phenylpropanolamine	Trimipramine
Disopyramide	Ketoconazole	Pimozide	Vardenafil
Dobutamine	Lapatinib	Probucol	Venlafaxine
Dofetilide	Levafloxacin	Procainamide	Voriconazole
Dolasetron	Levalbuterol	Protriptyline	Ziprasidone
Domperidone	Levomethadyl	Pseudoephedrine	
Dopamine	Lisdexamfetamine	Quetiapine	

Appendix 5 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any adverse event that at any dose fulfills at least one of the following criteria:

- Is fatal (results in death) (Note: Death is an outcome, not an event.)
- Is life threatening (Note: The term "life threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that could hypothetically have caused a death had it been more severe.)
- Required in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the Sponsor is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

An unexpected adverse event is an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

The investigator initially assesses causality. For serious adverse events, selecting one or more options indicates possible causes of the event. (Check all that apply.)

- Preexisting/underlying disease—specify
- Study treatment—specify the drug(s) related to the event
- Other treatment (concomitant or previous)—specify
- Protocol-related procedure
- Other (e.g., accident, new or intercurrent illness)—specify

The term severe is a measure of intensity; thus, a severe adverse event is not necessarily serious. For example, nausea of several hours of duration may be rated as severe but may not be clinically serious.

Appendix 5 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 (cont.)

A serious adverse event occurring during the study or that comes to the attention of the investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer—whether considered treatment-related or not—must be reported. In addition, a serious adverse event that occurs after this time, if considered related to test drug, should be reported.

Such preliminary reports will be followed by detailed descriptions later that will include copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the adverse events page of the electronic Case Report Form: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

ROCHE LOCAL COUNTRY CONTACT for Serious Adverse Events: Local Monitor

See attached Protocol Administrative and Contact Information & List of Investigators Form [gcp_for000227] for details of administrative and contact information.

ROCHE HEADQUARTERS CONTACT for Serious Adverse Events and other medical emergencies: Clinical Operations/Clinical Science

See attached Protocol Administrative and Contact Information & List of Investigators form [gcp_for000227] for details of administrative and contact information.

24 HOUR MEDICAL COVERAGE (Roche Emergency Medical Call Center Help Desk): Within the United States, on weekends, holidays, and after 5:00 pm, call: 1-866-286-9573 and ask for the physician on call. From Australia, call 1-800-031-902 and ask for the physician on call. (Note: the number for Australia cannot be dialed from a mobile phone.)