Official Title: STEVIE—A SINGLE-ARM, OPEN-LABEL, PHASE II, MULTICENTER STUDY TO ASSESS THE SAFETY OF VISMODEGIB (GDC-0449) IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC BASAL CELL CARCINOMA

NCT Number: NCT01367665

Document Date(s): Protocol Version 7: 04-Apr-16

PROTOCOL

TITLE:	**STEVIE—A SINGLE-ARM, OPEN-LABEL, PHASE II, MULTICENTER STUDY TO ASSESS THE SAFETY OF VISMODEGIB (GDC-0449) IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC BASAL CELL CARCINOMA**
PROTOCOL NUMBER:	MO25616/ NCT01367665
VERSION NUMBER:	7
EUDRACT NUMBER:	2011-000195-34
IND NUMBER:	Not Applicable
TEST PRODUCT:	Vismodegib
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 11 February 2011
DATES AMENDED:	Version 2: 27 January 2012 Version 3: 08 November 2012 Version 4: 08 May 2013 Version 5: 03 October 2013 Version 6: 20 November 2013 Version 7: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	[redacted]	04-Apr-2016 16:12:47

PROTOCOL AMENDMENT, VERSION 7:
RATIONALE

In accordance with the revised Investigator's Brochure Version 10 (dated 29 January 2016), Protocol MO25616 has been amended to reflect new information on the elimination of vismodegib from the body after treatment discontinuation. Changes to the protocol, along with a rationale for each change, are summarized below.

1. **Revised the pregnancy prevention duration and the waiting time for blood donations after vismodegib discontinuation.**

   The population pharmacokinetic (popPK) model has been updated and finalized with additional pharmacokinetic data up to 12 months post-treatment obtained in this study. As a result of this popPK analysis, the recommended time period for females to avoid pregnancy and for males and females to avoid blood donations has been increased from 7 to 9 months after the last dose of vismodegib.

2. **Introduced additional wording to be in accordance with approved local labels.**

   Since vismodegib has been approved in many of the countries in which this study is being conducted, wording has been introduced in the protocol to emphasize that the contraception duration for male and female patients, accepted forms of contraception, blood and sperm donation waiting time, and timeframe to report pregnancies have to be in accordance with the approved local prescribing information (where applicable).

An addendum to the model Informed Consent Forms has been prepared (Model ICF Addendum 1 to ICF Version 7, dated 12 February 2016) reflecting the changes to the protocol.

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.

PROTOCOL AMENDMENT, VERSION 7:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.3: BENEFIT-RISK

Potential Risks of the Study

Finally, small-molecule inhibitors of the Hedgehog pathway are known teratogens that result in midline malformations and other severe developmental defects in mammalian model systems (see the Vismodegib Investigator Brochure). Consequently, to be eligible for this trial, female patients of childbearing potential must use two methods of acceptable contraception, including one highly effective means of contraception and one barrier method during treatment and for at least ~~7~~*9* months *or as per approved local prescribing information for vismodegib (where available), whichever is longer,* after completion of treatment. Fertile male patients must utilize a condom with spermicide~~,~~ *(where available),* even if he has had a vasectomy, during treatment. Additionally, female patients must exhibit negative serum pregnancy tests within 7 days prior to dosing and throughout the trial. After discontinuing treatment, female patients of childbearing potential must continue to use an effective method of contraception for at least ~~7~~*9* months *or as per approved local prescribing information for vismodegib (where available), whichever is longer.* Acceptable contraception and duration of contraceptive use should comply with locally approved vismodegib (Erivedge®, the trade name for vismodegib) Pregnancy Prevention Program or prescribing information where vismodegib is commercially available.

SECTION 3.1.5: Rationale for Pharmacokinetic Assessments at Designated Investigative Sites

Vismodegib is a teratogen and a threshold for plasma concentrations of vismodegib in patients has been established. Currently available post-treatment discontinuation PK data for vismodegib is limited to 56 days. Based on the elimination kinetics of vismodegib in plasma after treatment discontinuation, it is predicted that the vast majority of patients will have plasma concentrations below the threshold for teratogenicity after 7 months. Notably, there is some uncertainty in this extrapolation, and until additional post-treatment discontinuation PK data are available, the duration for pregnancy prevention measures in female patients taking vismodegib has been prolonged to 24 months in the EU. The PK data obtained from this study will be utilized to inform and possibly revise the current recommended duration for pregnancy prevention measures after discontinuation of vismodegib treatment.

Acceptable contraception and duration of contraceptive use and waiting time for blood donations should comply with locally approved vismodegib Pregnancy Prevention Program or prescribing information where vismodegib is commercially available.

SECTION 4.2: INCLUSION CRITERIA

10. Women of childbearing potential must use two methods of acceptable contraception including one highly effective method and a barrier method (see also Appendix 2), as directed by their physician during treatment and for at least ~~7~~*9* months *or as per approved local prescribing information for vismodegib (where available), whichever is longer,* after completion of study treatment. Highly-effective methods of contraception are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly (e.g., implants, injectables, or intra-uterine devices. At the discretion of the Investigator, acceptable methods of contraception may include total abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and postovulation methods) and withdrawal are not acceptable methods of contraception (see Appendix 2)

    NOTE: The pregnancy prevention duration for female patients was changed from 7 to 9 months or as per approved local prescribing information, whichever is longer, after all patients were enrolled in the study.

11. For male patients with female partners of childbearing potential, agreement to use a condom with spermicide *(where available)*, even after vasectomy, during sexual intercourse with female partners while being treated with vismodegib and for 2 months *or as per approved local prescribing information for vismodegib (where available), whichever is longer,* after completion of study treatment

    NOTE: The contraception duration for male patients was changed from 2 months to 2 months or as per approved local prescribing information, whichever is longer, after all patients were enrolled in the study.

12. Agreement not to donate blood or blood products during the study and for at least ~~7~~*9* months *or as per approved local prescribing information for vismodegib (where available), whichever is longer* after discontinuation of vismodegib. Because vismodegib has been detected in seminal fluid, in addition for men, agreement not donate sperm during the study or for at least 2 months *or as per approved local prescribing information for vismodegib (where available), whichever is longer* after discontinuation of therapy

    NOTE: The waiting time for blood donations was changed from 7 to 9 months or as per approved local prescribing information, whichever is longer, after all patients were enrolled in the study.

SECTION 5.3.5: <u>Post-Study Pregnancy Assessments</u>

Female patients of childbearing potential must continue to use an effective method of contraception for ~~7~~*9* months after the last dose of vismodegib. Acceptable contraception and duration of contraceptive use should comply with locally approved vismodegib (Erivedge®, the trade name for vismodegib) Pregnancy Prevention Program or prescribing information where vismodegib is commercially available. If a pregnancy occurs within ~~7~~*9* months *or within the designated window per approved local prescribing information for vismodegib (where available), whichever is longer,* of the last dose of vismodegib, the Investigator should report to the Sponsor (refer to Sections 7.1.1.4 and 7.1.2). The Investigator should counsel the patient, discussing the

risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

SECTION 7.1.2: Pregnancy and Lactation

Small-molecule inhibitors of the Hedgehog pathway are known teratogens that result in midline malformations, such as holoprosencephaly, cyclopia, and other severe developmental defects. The teratogenic potential of vismodegib has been confirmed in an embryo-fetal development study in rats (please see the updated Vismodegib Investigator Brochure). Women who plan to become pregnant (during a study or for ~~7~~*9* months after the last dose *or within the designated window per approved local prescribing information for vismodegib [where available], whichever is longer*) are excluded from all vismodegib clinical studies. Please refer to the Vismodegib Investigator Brochure for further information regarding the teratogenic potential of vismodegib.

- Pregnant women: Vismodegib is contraindicated in pregnant women or women planning to become pregnant during treatment and for ~~7~~*9* months *or within the designated window per approved local prescribing information for vismodegib (where available), whichever is longer,* after the last dose.

SECTION 7.1.2.1: Use in Women of Childbearing Potential

To prevent pregnancy and the risk of fetal exposure to vismodegib, female patients should not become pregnant or plan to become pregnant during treatment with vismodegib and for ~~7~~*9* months *or within the designated window per approved local prescribing information for vismodegib (where available), whichever is longer,* after the last dose.

Specific actions are required when treating female patients of childbearing potential. Patients should be thoroughly counseled and informed of the teratogenic potential of vismodegib. All pregnancy prevention measures for women of childbearing potential must be followed for the duration of the study and for ~~7~~*9* months *or within the designated window per approved local prescribing information for vismodegib (where available), whichever is longer,* after the last dose. Patients should be counseled on the use of contraception before beginning treatment with vismodegib. As appropriate, the treating physician should refer the subject to her gynecologist or other healthcare provider to ensure proper understanding of the use of her chosen contraceptive method. Acceptable contraception and duration of contraceptive use should comply with locally approved vismodegib (Erivedge®, the trade name for vismodegib) Pregnancy Prevention Program or prescribing information where vismodegib is commercially available.

SECTION 7.1.2.2: Male Patients

It is not known if vismodegib that may be present in seminal fluid would cause teratogenic effects in a fetus born to the female partner of a male subject. Therefore, sexually active male patients must utilize a barrier form of contraception, even if he has had a vasectomy, during vismodegib treatment and for 2 months *or as per approved*

local prescribing information for vismodegib (where available), whichever is longer, after the last dose.

SECTION 7.1.2.3: Pregnancy Reporting

If a female patient becomes pregnant while receiving investigational therapy with vismodegib or within ~~7~~*9* months *or within the designated window per approved local prescribing information for vismodegib (where available), whichever is longer,* after the last dose, the Investigator must report all pregnancies immediately i.e., no more than 24 hours after learning of the event to the Sponsor.

A female patient must be instructed to stop taking the test "drug" and immediately inform the Investigator if she becomes pregnant during the study. The Investigator should report all pregnancies immediately i.e., no more than 24 hours after learning of the event to the Sponsor, using the *Clinical Trial Pregnancy Reporting Form.* The Investigator should counsel the patient, discussing the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to ~~7~~*9* months *or within the designated window per approved local prescribing information for vismodegib (where available), whichever is longer,* after the completion of the study medication must also be reported to the Investigator.

If a female partner of a male patient becomes pregnant during vismodegib treatment or within 2 months *or within the designated window per approved local prescribing information for vismodegib (where available), whichever is longer,* after the last dose of vismodegib, the pregnancy must be reported to the Investigator and the Sponsor and alert the female partner to consult with her physician. The partner should be counseled and the risks of continuing the pregnancy discussed, as well as the possible effects on the fetus. Monitoring of the female partner should continue until conclusion of the pregnancy.

SECTION 7.1.4: Blood Donation

Patients must not donate blood or blood products while on study and for ~~7~~*9* months *or as per approved local prescribing information for vismodegib (where available), whichever is longer,* after discontinuation of vismodegib. Where vismodegib is commercially available, avoidance of blood donation should comply with locally approved prescribing information.

SECTION 7.2.1: Recording and Collection of Adverse Events

If a female patient becomes pregnant while receiving investigational therapy or within ~~7~~*9* months *or within the designated window per approved local prescribing information for vismodegib (where available), whichever is longer,* after the last dose of investigational product, the Investigator should report to the Sponsor immediately within one working day (24 hours) of learning of the pregnancy.

APPENDIX 2: Definition of Women of Childbearing Potential and Acceptable and Unacceptable Forms of Contraception

Appendix 2 has been revised to reflect the changes to the protocol.

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SYNOPSIS OF PROTOCOL MO25616

TITLE	STEVIE—A single-arm, open-label, phase II, multicenter study to assess the safety of vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma		
SPONSOR	F. Hoffmann-La Roche Ltd.	CLINICAL PHASE	Phase II
INDICATION	Locally advanced or metastatic basal cell carcinoma (BCC)		
OBJECTIVES	<u>Primary objective:</u> • To assess the safety of vismodegib (also known as GDC-0449) in patients with locally advanced or metastatic BCC <u>Secondary objectives:</u> • To assess the overall response rate (according to Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST, v1.1]) in those patients with measurable disease, as permitted by local regulatory requirements • To assess other efficacy parameters, such as time to response, duration of response, progression-free survival (PFS), and overall survival (OS) • To assess patient quality of life (QoL) (Skindex-16) • To assess the impact of vismodegib treatment on disease symptoms in patients with metastatic BCC who enrolled after approval of the Study Protocol, version 4.0, using the M.D. Anderson Symptom Inventory (MDASI) <u>Exploratory objectives</u> • To assess the status of the Hedgehog (Hh) pathway and/or other modifiers of vismodegib activity in tumor tissue obtained from patients with metastatic BCC who have disease progression on vismodegib therapy • To determine the post-treatment exposure of vismodegib in patients with adverse events that were reported to be related to vismodegib treatment and that are continuing at least 6 months after the last dose of vismodegib • To determine the post-treatment exposure of vismodegib in patients following daily oral dosing with 150 mg vismodegib for at least 2 weeks of consecutive dosing (steady-state exposure) and at 3, 6, 9, and 12 months after the last dose of vismodegib		

TRIAL DESIGN	This is an open-label, non-comparative, multicenter, phase II study of vismodegib in patients with locally advanced BCC or metastatic BCC who are otherwise without satisfactory treatment options.
NUMBER OF PATIENTS	Approximately 1200 patients. Once the enrollment of 1200 patients is completed, an assessment of how many patients with metastatic BCC were enrolled under Protocol Amendment Version 4 (dated 8 May 2013) will be made. At that time, enrollment may be extended for up to 15 additional metastatic BCC patients in order to ensure adequate collection of data regarding the effect of vismodegib in metastatic BCC patients, as per Protocol Amendment Version 4 (dated 8 May 2013).
TARGET POPULATION	The study population will consist of male or female patients at least 18 years of age with histologically confirmed diagnoses of locally advanced BCC or metastatic BCC. For patients with locally advanced BCC, the treating physician must consider the disease to be inoperable or there must be a clinical contraindication to surgery; furthermore, radiotherapy must have been previously administered (unless radiotherapy is contraindicated or inappropriate) and disease must have progressed after irradiation. For patients with suspected metastatic BCC, distant metastases must be histologically confirmed to be of basal cell origin. Patients are eligible for enrollment in this trial with measurable and/or non-measurable disease, as defined by RECIST, v1.1. Inclusion Criteria: 1. Written, signed informed consent 2. Age ≥18 years 3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1, or 2 4. For patients with metastatic BCC, histologic confirmation of distant BCC metastasis 5. For patients with locally advanced BCC, at least one histologically confirmed lesion 10 mm or more in diameter and written confirmation from a surgical specialist that the tumor is considered inoperable or that surgery is contraindicated. Examples of medical contraindications to surgery include but are not limited to: • BCC that has recurred in the same location after two or more surgical procedures and curative resection is deemed unlikely • Anticipated substantial morbidity and/or deformity from surgery (e.g., removal of all or part of a facial structure, such as nose, ear, eyelid, eye; or requirement for limb amputation)

6. For patients with locally advanced BCC, radiotherapy must have been previously administered for locally advanced BCC, unless radiotherapy is contraindicated or inappropriate (e.g., hypersensitivity to radiation due to genetic syndrome such as Gorlin syndrome, limitations because of location of tumor, or cumulative prior radiotherapy dose). For patients whose locally advanced BCC has been irradiated, disease must have progressed after radiation
7. Patients with Gorlin syndrome may enroll in this study but must meet the criteria for locally advanced or metastatic disease listed above
8. Patients with measurable and/or non-measurable disease (as defined by RECIST, v1.1) are allowed
9. Adequate organ function, as evidenced by the following laboratory results:
    - Hemoglobin >8.5 g/dL
    - Granulocyte count $\geq 1000/\mu L$
    - Platelet count $\geq 75{,}000/\mu L$
    - Aspartate aminotransferase (AST [SGOT]) and alanine aminotransferase (ALT [SGPT]) $\leq 3 \times$ upper limit of normal (ULN)
    - Total bilirubin $\leq 1.5 \times$ ULN or within $3 \times$ ULN for patients with documented Gilbert syndrome
10. Women of childbearing potential must use two methods of acceptable contraception including one highly effective method and a barrier method (see also Appendix 2), as directed by their physician during treatment and for at least *9* months *or as per approved local prescribing information for vismodegib (where available), whichever is longer,* after completion of study treatment. Highly-effective methods of contraception are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly (e.g., implants, injectables, or intra-uterine devices. At the discretion of the Investigator, acceptable methods of contraception may include total abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post ovulation methods) and withdrawal are not acceptable methods of contraception (see Appendix 2)

    NOTE: The pregnancy prevention duration for female patients was changed from 7 to 9 months, or as per approved local prescribing information, whichever is longer, after all patients were enrolled in the study.
11. For male patients with female partners of childbearing potential, agreement to use a condom with spermicide *(where available)*, even after vasectomy, during sexual intercourse with female partners while being treated with vismodegib and for 2 months *or as per approved local prescribing information for vismodegib (where available),*

whichever is longer, after completion of study treatment

NOTE: The contraception duration for male patients was changed from 2 months to 2 months or as per approved local prescribing information, whichever is longer, after all patients were enrolled in the study.

12. Agreement not to donate blood or blood products during the study and for at least *9* months *or as per approved local prescribing information for vismodegib (where available), whichever is longer,* after discontinuation of vismodegib. Because vismodegib has been detected in seminal fluid, in addition for men, agreement not donate sperm during the study or for at least 2 months *or as per approved local prescribing information for vismodegib (where available), whichever is longer,* after discontinuation of therapy

    NOTE: The waiting time for blood donations was changed from 7 to 9 months or as per approved local prescribing information, whichever is longer, after all patients were enrolled in the study.

13. Life expectancy $>$ 12 weeks
14. Negative serum pregnancy test within 7 days prior to commencement of dosing in premenopausal women. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for $\geq$ 1 year

Exclusion Criteria:

1. Inability or unwillingness to swallow capsules
2. Pregnancy or lactation
3. Concurrent non–protocol-specified anti-tumor therapy (e.g., chemotherapy, other targeted therapy, radiation therapy, or photodynamic therapy, including participation in an experimental drug study; note that treatment breaks up to 8 weeks for radiation therapy are allowed [see Section 6.1.1])
4. Completion of most recent anti-tumor therapy less than 21 days prior to initiation of treatment
5. Uncontrolled medical illnesses such as infection requiring treatment with intravenous antibiotics
6. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or that renders the patient at high risk from treatment complications
7. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol
8. Patients with one of the following rare hereditary

	conditions: galactose intolerance, primary hypolactasia, or glucose-galactose malabsorption
LENGTH OF STUDY	It is anticipated that approximately 1200 patients will be enrolled into this study over an approximately 3.5-year period. Enrollment will continue only until such time as vismodegib becomes commercially available for this patient population. Once the enrollment of 1200 patients is completed, an assessment of how many of patients with metastatic BCC were enrolled under Protocol Amendment Version 4 (dated 8 May 2013) will be made. At that time, enrollment may be extended for up to 15 additional metastatic BCC patients in order to ensure adequate collection of data regarding the effect of vismodegib in metastatic BCC patients, as per Protocol Amendment Version 4 (dated 8 May 2013). The trial will consist of a Screening Period (Day-28 to −1), a Treatment Phase, an End of Treatment Visit when the patient received the last dose of vismodegib and thereafter discontinues vismodegib (regardless of when it occurs), and five Safety Follow-Up Visits 1 month, 3 months, 6 months, 9 months, and 12 months after the last dose of vismodegib (± 5 days), as provided by this phase II safety study protocol. Day 1 of the study will be defined as the first day a patient receives vismodegib. Enrolled patients will receive study drug until Investigator-assessed disease progression, unacceptable toxicities most probably attributable to vismodegib, patient consent withdrawal, death, reasons deemed by the treating physician, or study termination by the Sponsor. Patients who discontinue study drug(s) for any reason other than disease progression or withdrawal of consent (e.g., an adverse event [AE]) will continue to be followed until the development of disease progression, consent withdrawal, loss to follow up, or beginning of another anti-cancer therapy.
END OF STUDY	Study enrollment is planned to end in the EU if vismodegib becomes commercially available after regulatory approval for the treatment of locally advanced or metastatic BCC. Study enrollment is planned to end successively in non-EU countries participating in this study if vismodegib becomes commercially available after regulatory approval for the treatment of locally advanced or metastatic BCC in the respective country. However, patients already enrolled in this study and who are still benefitting from vismodegib in the opinion of the Investigator will continue to receive vismodegib as a study medication until the development of progressive disease (as determined by the Investigator), unacceptable toxicity, consent withdrawal, death, reasons deemed by the treating physician, or study

	termination by the Sponsor. The study will end when the last patient on treatment develops progressive disease (as determined by the Investigator) or unacceptable toxicity, withdraws consent, or dies; the treating physician deems the patient is no longer benefitting from treatment and has completed the safety follow up visits, or the study is terminated by the Sponsor, or 12 months after the last dose of vismodegib in the last enrolled patient still on study, whichever occurs first. The Sponsor reserves the right to end study enrollment at any time. If study enrollment is stopped prior to commercial availability of vismodegib, patients already enrolled will be informed of the reason for discontinuation of study enrollment and, in the absence of a significant product safety concern or other circumstances, will be allowed to continue vismodegib until disease progression, unmanageable toxicity, withdrawal of consent, reasons deemed by the treating physician, or death of the patient, whichever occurs first.

INVESTIGATIONAL MEDICAL PRODUCT(S) DOSE/ ROUTE/ REGIMEN	Enrolled patients will receive continuous once-daily oral dosing of vismodegib at a dosage of 150 mg per administration. One cycle of therapy is defined as 28 days of treatment. Dosing of vismodegib will continue until one of the following occurs: • Investigator-assessed disease progression • Unacceptable toxicities most likely attributable to vismodegib • Patient consent withdrawal • Death • Reasons deemed by the treating physician • Study termination by the Sponsor No dose reductions will be allowed in this study. Treatment with vismodegib may be interrupted for up to: • Eight weeks if a patient becomes temporarily unable to swallow capsules • Eight weeks for an intolerable toxicity finding Patients with an asymptomatic or tolerable severe AE may continue to receive study drug provided the AE is manageable and the patient and the Investigator agree that continued study participation is acceptable. If a patient experiences two treatment interruptions, the Medical Monitor must be consulted before the patient can resume treatment.
CENTERS	This is an international multicenter study.
NON-INVESTIGATIONAL MEDICAL PRODUCTS	N.A.
COMPARATOR “DRUG” (or STANDARD OF CARE) DOSE/ ROUTE/ REGIMEN	No comparator
ASSESSMENTS OF: – SAFETY	Incidence, type, and severity of AEs Incidence and nature of serious adverse events (SAEs) Incidence of AEs leading to vismodegib discontinuation or interruption Cause of death on study (if not linked to disease progression)

– EFFICACY	For patients with measurable disease at baseline, tumor responses categorized according to Investigator assessment following RECIST, v1.1, as allowed by local regulatory guidelines. Information about other efficacy parameters, such as time to response, duration of response, progression-free survival, and overall survival, will be also collected.
– PHARMACOKINETICS/ PHARMACODYNAMICS	Adverse event-related pharmacokinetic testing will be performed on patients having any adverse events that were reported as being related to vismodegib treatment and that continued for at least 6 months after the last dose of vismodegib at selected sites. Post-treatment pharmacokinetic testing will be performed on 30 patients to further characterize the post-treatment elimination of vismodegib from steady-state exposure to 12 months after the last dose of vismodegib at selected sites.
– PHARMACOECONOMICS/ QUALITY OF LIFE (QoL)	The Skindex-16 questionnaire will be used in selected sites to measure patient QoL.
– DISEASE SYMPTOMS	The M.D. Anderson Symptom Inventory (MDASI) will be used to assess the impact of treatment on symptoms in metastatic BCC patients enrolled after approval of the Study Protocol, version 4.0.
– EXPLORATORY BIOMARKERS (non-inherited)	Archival tumor tissue from a metastatic BCC site will be collected in metastatic BCC patients who are on study after approval of the Study Protocol, version 4.0. Tumor biopsy samples will be collected from patients who have accessible progressing tumors (e.g., skin, superficial mass, or lymph node) while on vismodegib treatment.
– EXPLORATORY BIOMARKERS (inherited)	N.A.
– CLINICAL GENOTYPING (CG) SAMPLES	Whole-blood samples will be collected in metastatic BCC patients (in whom tumor biopsy samples are collected at progression) for the exclusive purpose of validating and confirming tumor specific genetic variants.

PROCEDURES (SUMMARY)

Informed consent must be obtained before any study related procedures are conducted.

The trial will consist of a Screening Period, a Treatment Phase, an End of Treatment Visit when the patient received the last dose of vismodegib and thereafter discontinues vismodegib (regardless of when it occurs), and five Safety Follow-Up Visits 1 month, 3 months, 6 months, 9 months, and 12 months after the last dose of vismodegib (± 5 days), as provided by this phase II safety study protocol.

Screening/Baseline Period Assessments:

Potential participants will undergo the following screening procedures no more than 28 days prior to Day 1, Cycle 1 (unless they have already been conducted during this time period as part of the patient's routine clinical care):

- Informed consent
- Archival tumor tissue from a metastatic BCC site in metastatic BCC patients who are on study after approval of the Study Protocol, version 4.0
- Complete medical history (including BCC history) and demographics
    - Collection of metastatic BCC history, such as evidence of progression prior to enrollment and reason(s) for discontinuation from prior treatment, will be collected in patients who are on study after approval of the Study Protocol, version 4.0
- Complete physical examination including weight and height at screening only.
- Vital signs (body temperature, blood pressure, and pulse)
- ECOG PS assessment
- Hematology (including hemoglobin, hematocrit, red blood cell count, full white blood cell count including differential, platelet count, and absolute neutrophil count [ANC])
- Biochemistry (including glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen [BUN], creatinine, creatine kinase [also known as creatine phosphokinase], total bilirubin, alkaline phosphatase, AST, and ALT)
- Serum pregnancy test (within 7 days prior to the commencement of vismodegib dosing) for women of child bearing potential (Main Protocol Appendix 2)
- For women of childbearing potential:
    - Record date of last menses
    - Ultrasound
    - Record any amenorrhea/irregular menses, relevant gynecologic medical history, and concurrent gynecologic conditions
    - Perform serum hormone evaluation, including follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and thyroid stimulating hormone (TSH)
- 12-lead electrocardiogram (ECG)
- AEs/SAEs. After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected. All AEs (either related to study specific procedures or otherwise) experienced after the patient has signed the Informed Consent Form, but before they have received study treatment, should be recorded as medical history
- Concomitant therapy
- Tumor assessment (the majority of patients in this study have locally advanced BCC and in this disease setting measurable tumors are accessible to evaluation by physical examination):
    - Measurable tumors accessible to evaluation by physical examination should be assessed within a maximum of 7 days prior to the first dose of study drug (baseline reading)
    - If assessment requires imaging, baseline computed tomography (CT) and/or magnetic resonance imaging (MRI) should be performed within a maximum of 28 days prior to the first dose of study drug
    - Non-measurable disease should be assessed within 28 days prior to study initiation
- In selected sites, patients will complete the Skindex-16 Quality of Life questionnaire (see Main Protocol Section 5.5 and Appendix 5)

- Patients with metastatic BCC (newly enrolled after approval of the Study Protocol, version 4.0) will complete the M.D. Anderson Symptom Inventory (see Main Protocol, Section 5.6 and Appendix 6) prior to having any study-related procedures performed at the visit

Treatment Phase Assessments:

Day 1 of the study will be defined as the first day a patient receives vismodegib. One cycle of therapy is defined as 28 days of treatment. During the Treatment Phase, all study assessments will be conducted on Day 1 (±3 days from Cycle 2 onwards) of each Cycle with the exception of tumor evaluation, for which a window of ±5 days will apply (see below). The assessments during the Treatment Phase are:

- Limited physical examination at every 28-Day visit
- Vital signs (body temperature, blood pressure, and pulse) and weight at every 28-Day visit
- ECOG PS assessment at every 28-Day visit
- Hematology (including hemoglobin, hematocrit, red blood cell count, full white blood cell count including differential, platelet count, and ANC) at every 28-Day visit
- Biochemistry (including glucose, sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatine kinase [also known as creatine phosphokinase], total bilirubin, alkaline phosphatase, AST, and ALT) at every 28-Day visit
- Urine pregnancy tests on Day 1 of each subsequent Cycle. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test
- 12-lead ECG (during the study if clinically indicated)
- Concomitant therapy and AEs (including SAEs) throughout the study
- For women of childbearing potential:
    - Record date of last menses
    - Ultrasound (as clinically indicated [see Schedule of Assessments])
    - Assess amenorrhea/irregular menses that develops while on study:
        1. At start of amenorrhea/irregular menses, perform serum hormone evaluation at study site, including FSH, LH, E2, and TSH, and refer to gynecologist or appropriate specialist for assessment of ovaries and uterus, including ultrasound
        2. At resolution of amenorrhea/irregular menses, perform serum hormone evaluation at site, including FSH, LH, E2, and TSH. Refer to gynecologist or appropriate specialist for follow-up ultrasound ONLY if there was abnormality identified during previous ultrasound
        3. If amenorrhea/irregular menses recurs, repeat evaluations at start of recurrence as detailed previously
- Vismodegib administration throughout the study
- Follow up for disease progression
- Tumor assessment (the majority of the patients in this study have locally advanced BCC and, in this disease setting, measurable tumors are accessible to evaluation by physical examination). Objective responses using RECIST, v1.1 should be confirmed by repeat assessments at least 4 weeks after initial documentation of response:
    - Measurable tumors accessible to evaluation by physical examination should be assessed every 4 to 8 weeks throughout the study from the time of the first dose, regardless of dosing delays

- If assessment requires imaging, baseline CT and/or MRI should be performed within a maximum of 28 days prior to the first dose of study drug and, if such scans demonstrate evidence of disease, follow-up imaging studies (CT and/or MRI) should be performed every 8 to 16 weeks from the time of the first dose, regardless of dosing delays, or per institutional standards. The same imaging technique (CT or MRI) should be used for each patient throughout the study
- In metastatic BCC patients (newly enrolled after approval of the Study Protocol, version 4.0), imaging at baseline (CT and/or MRI scan) should be performed within a maximum of 28 days before the first dose. Follow-up imaging studies (CT and/or MRI scan) should be performed every 8 weeks (±5 days) from the time of the first dose, regardless of dosing delays. The same imaging technique (CT or MRI) should be used for each patient throughout the study
- Other imaging techniques may be performed as clinically indicated, but should not be used for determining tumor response
- Patients with non-measurable disease at baseline should be assessed for disease progression when clinically indicated and in accordance with standard clinical practice. For metastatic patients, assessment of non-measurable disease should be according to RECIST version 1.1.

- In selected sites, patients will complete the Skindex-16 Quality of Life questionnaire after Cycle 1 and after Cycle 6 (i.e., after 6 months of treatment) for the patients still on study (see Main Protocol Section 5.5. and Appendix 5)
- Patients with metastatic BCC (newly enrolled after approval of the Study Protocol, version 4.0) will complete the M.D. Anderson Symptom Inventory (see Main Protocol Section 5.6 and Appendix 6) at every visit, prior to having any other assessments performed
- In selected sites, post-treatment pharmacokinetic (PK) testing will be performed on patients. This testing requires a single blood draw for PK testing at steady-state for comparison to the post-treatment samples collected. Steady-state is defined as any time point while a patient is taking vismodegib for at least 2 weeks continuously.

End of Treatment Visit Assessments:

The End of Treatment Visit will be performed when the patient discontinues vismodegib, regardless of when it occurs.

- Limited physical examination
- Vital signs (body temperature, blood pressure, and pulse) and weight
- ECOG PS assessment
- Hematology (including hemoglobin, hematocrit, red blood cell count, full white blood cell count including differential, platelet count, and ANC)
- Biochemistry (including glucose, sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatine kinase [also known as creatine phosphokinase], total bilirubin, alkaline phosphatase, AST, and ALT)
- Tumor assessment
- 12- lead ECG (if clinically indicated)
- Concomitant therapy and new anti-cancer therapy
- AEs (including SAEs)
- For women of childbearing potential:
  - Record date of last menses
  - Assess amenorrhea/irregular menses that develops while on study:
    1. At start of amenorrhea/irregular menses, perform serum hormone evaluation at study site, including FSH, LH, E2, and TSH, and refer to gynecologist or appropriate specialist for assessment of ovaries and uterus, including ultrasound

2. At resolution of amenorrhea/irregular menses, perform serum hormone evaluation at site, including FSH, LH, E2, and TSH. Refer to gynecologist or appropriate specialist for follow-up ultrasound ONLY if there was abnormality identified during previous ultrasound
3. If amenorrhea/irregular menses recurs, repeat evaluations at start of recurrence as detailed previously

- Follow up for disease progression
- Pregnancy test for women of childbearing potential
- In selected sites, patients will complete the Skindex-16 Quality of Life questionnaire (see Main Protocol Section 5.5 and Appendix 5).
- Patients with metastatic BCC (newly enrolled after approval of the Study Protocol, version 4.0) will complete the M.D. Anderson Symptom Inventory (see Main Protocol Section 5.6 and Appendix 6), prior to having any other assessments performed
- In metastatic BCC patients who develop tumor progression on vismodegib treatment, a biopsy will be performed if at least one of the progressing lesions is accessible, e.g., skin, superficial mass, or lymph node
- Collection of whole blood in metastatic BCC patients with tumor biopsy at progression

Safety Follow-Up Phase Assessments:

Patients who discontinue vismodegib treatment will be asked to return to the clinic for a safety follow-up assessment 1 month, 3 months, 6 months, 9 months, and 12 months after the last dose of vismodegib (±5 days), as provided by this phase II, safety study protocol.

- Hematology (including hemoglobin, hematocrit, red blood cell count, full white blood cell count including differential, platelet count, and ANC) as clinically indicated
- Biochemistry (including glucose, sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatine kinase [also known as creatine phosphokinase], total bilirubin, alkaline phosphatase, AST, and ALT) as clinically indicated
- Follow up for disease progression
- Concomitant therapy and new anti-cancer therapy
- AEs (including SAEs)
- For women of childbearing potential:
    - Record date of last menses
    - Assess amenorrhea/irregular menses that develops while on study:
        1. At start of amenorrhea/irregular menses, perform serum hormone evaluation at study site, including FSH, LH, E2, and TSH, and refer to gynecologist or appropriate specialist for assessment of ovaries and uterus, including ultrasound
        2. At resolution of amenorrhea/irregular menses, perform serum hormone evaluation at site, including FSH, LH, E2, and TSH. Refer to gynecologist or appropriate specialist for follow-up ultrasound ONLY if there was abnormality identified during previous ultrasound
        3. If amenorrhea/irregular menses recurs, repeat evaluations at start of recurrence as detailed previously
- Patients with metastatic BCC (newly enrolled after approval of the Study Protocol, version 4.0) will complete the M.D. Anderson Symptom Inventory (see Main Protocol Section 5.6 and Appendix 6), prior to having any other assessments performed at the visits

- In selected sites, patients will have blood draws for adverse event–related PK testing if any adverse events that were reported to be related to vismodegib treatment continue to be present at least 6 months after the last dose of vismodegib. Blood samples for the adverse event-related PK testing will be collected at the 6, 9, and 12 months Safety Follow-Up Visits. Blood samples for all time points will be collected even if the adverse event resolves after the 6 months Safety Follow-Up Visit.
- In selected sites, post-treatment PK testing will be performed on 30 patients. Patients, who previously provided a PK sample at steady-state, will have blood draws for post-treatment PK testing at the 3, 6, 9, and 12 months Safety Follow-up Visits.

STATISTICAL ANALYSES

The primary objective of this trial is to assess the safety of vismodegib in patients with locally advanced or metastatic BCC.

There are no formal statistical hypothesis tests to be performed. Continuous data will be summarized using mean, standard deviation, median, minimum, and maximum. Discrete data will be summarized using frequencies and percentages. No adjustments for multiplicity of endpoints or within-subgroup comparisons will be used in the analyses.

The final analysis for safety and efficacy will be performed when the last patient on treatment develops progressive disease (as determined by the Investigator) or unacceptable toxicity, withdraws consent, or dies; the treating physician deems the patient is no longer benefitting from treatment; or the study is terminated by the Sponsor, or 12 months after the last dose of vismodegib in the last enrolled patient still on study, whichever occurs first.

In addition to final analysis, there will be six interim analyses for publication of safety and efficacy results and DSMB reviews when the:

First 75 patients enrolled have been treated for at least 3 months,

First 150 patients enrolled have been treated for at least 3 months,

First 300 patients enrolled have been treated for at least 3 months,

First 550 patients enrolled have been treated for at least 3 months,

First 800 patients enrolled have been treated for at least 3 months, and

1200 patients enrolled have been treated for at least 3 months (see also Section 10).

- This last interim analysis will also include analysis of 500 enrolled patients who have been followed for at least 1 year

Safety Analyses:

All patients who receive at least one dose of vismodegib will be included in the safety analyses. Safety will be assessed through summaries of AEs, SAEs, AEs Grade 3 or 4, AEs that caused vismodegib discontinuation and interruption, and cause of death on study.

All AEs will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI-CTCAE, v 4.0) grading system. The analysis of AEs will focus on treatment-emergent AEs, i.e., AEs occurring on or after the first day of vismodegib administration. Non–treatment-emergent AEs (i.e., those occurring before commencement of study medication) will only be listed. The incidence, type, and severity of AEs will be summarized according to the primary system-organ class (SOC) and, within each SOC, by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. AEs of special interest, AEs leading to treatment interruption and discontinuation, and SAEs will be analyzed in a similar way to all AEs. Cause of death will also be summarized and listed.

Exposure to study medication will be summarized by means of descriptive statistics for the cumulative dose and frequency tables (percentages) by Cycles and/or Weeks of treatments.

The reason for the dose discontinuation, other than disease progression, will be also summarized.

Laboratory parameters, hematology, and serum biochemistry will be presented in shift tables of NCI-CTCAE, v4.0 grade at baseline versus worst grade during the treatment period. The laboratory parameters will be also summarized as continuous or discrete data when applicable.

Vital signs, ECOG PS, physical examination, and ECG (if available) will be summarized over time. Concomitant therapy will be summarized by frequency tables and percentages. New anti-cancer therapy will be analyzed in a similar way to concomitant therapy at the End of Treatment Visit. Protocol deviations will be listed.

Medical history including demographics, (age, gender, and race as applicable), clinically significant diseases, previous surgeries, prior skin cancer history, prior skin cancer therapies and procedures, response to prior therapies, and all medications used by the patient within 14 days preceding the screening visit) will be summarized at baseline.

In metastatic BCC patients (who are on study after approval of the Study Protocol, version 4.0), evidence of tumor progression prior to enrollment on study and reasons for treatment discontinuation of prior therapies will be summarized. Analysis of data regarding evidence of progression prior to enrollment and reasons for treatment discontinuation of prior therapies will be performed in metastatic BCC patients.

Efficacy Analyses:

ORR, assessed by the Investigator according to RECIST, v1.1, will be summarized. The summary will be performed on patients with measureable disease at baseline. The best overall response rates (complete and partial responders), together with the corresponding 95% Pearson-Clopper confidence intervals, will be presented.

Duration of response will be defined only for patients whose confirmed best response is complete response (CR) or partial response (PR) and will describe the time interval between the date of the earliest qualifying response and the date of progressive disease (PD) or death for any cause.

Time to response will be defined as the interval between the date of first treatment and the date of first documentation of confirmed CR or PR (whichever occur first).

PFS will be defined as the time interval between the date of the first therapy and the date of progression or death for any causes, whichever occurs first. Patients with non-measureable disease will be assessed for disease progression and included in this summary.

OS will be defined as the time from the date of first treatment to the date of death, regardless of the cause of death. Estimates for the survival function and corresponding 95% confidence interval for the time-to-event endpoints, PFS, OS, time to response, and duration of response using Kaplan-Meier estimates will be displayed by tables and graphs.

Quality of Life

The effects of skin disease on patient's quality of life will be accessed by the Skindex-16 questionnaire. Distribution of scores, mean scores, and changes from baseline for each domain, symptoms, emotions and function will be summarized over time by summary tables, line graphs with associated 95% confidence intervals, and box plots.

Disease Symptoms

The M.D. Anderson Symptom Inventory (MDASI) will be used to assess the impact of treatment on symptoms in metastatic BCC patients enrolled after approval of the Study Protocol, version 4.0. For these metastatic patients, incidence and type of disease symptoms will be summarized at baseline. In addition, the number of metastatic BCC patients with 30% reduction in disease-related symptoms with baseline score of 4 or more at any time during treatment will be summarized for each symptom.

Exploratory Pharmacokinetic Assessments

Individual and mean plasma vismodegib concentration versus time data will be tabulated and plotted. Plasma AAG concentration and unbound plasma concentration at selected time points will be estimated, tabulated and summarized (geometric mean, mean, standard deviation, coefficient of variation, median, minimum, and maximum). Additional PK analyses may be conducted as appropriate.

Determination of Sample Size

Approximately 1200 patients will be enrolled in this study.

Synopsis Table 1. Clopper-Pearson 95% Confidence Intervals for the observed AE incidence[1]

Number of AE events/ observed AE incidence	95% Clopper Pearson Confidence Interval
12 (1%)	0.5% – 2%
24 (2%)	1.3% – 3.0%
60 (5%)	3.8% – 6.4%
120 (10%)	8.4% – 11.8%
240 (20%)	17.8% – 22.4%
360 (30%)	27.4% – 32.7%

[1] Total number of patients is 1200

Therefore, for a sample size of 1200 patients, the true AE incidence rate can be estimated to within 1.6%–1.8% assuming an observed incidence of 10%, i.e., within 95% Clopper-Pearson confidence interval of 8.4%–11.8%.

Treatment scheme:

Screening	Study Treatment Phase	Safety Follow-Up
Day –28 to –1	Continuous once-daily oral dosing of vismodegib at a dosage of 150 mg per administration until one of the following occurs: disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator	Five Safety Follow-Up Visits 1 month, 3 months, 6 months, 9 months, and 12 months after the last dose of vismodegib (±5 days)

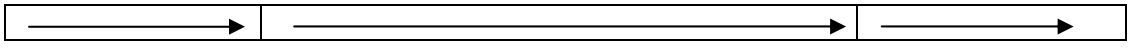

Table 1 Schedule of Assessments

	Screening / Baseline	Treatment Phase[1] (Allowed Visit Window +/- 3 days from Cycle 2 onwards)								End of Treatment Visit[2]	Safety Follow-Up Visits[3] (1 month, 3 months, 6 months, 9 months, 12 months after the last dose of vismodegib (GDC-0499)
Cycle		1	2	3	4	5	6	7	8 onwards		
Day	–28 to –1	1	29	57	85	113	141	169	Every 28 Days		
Informed Consent[4]	X										
Archival Tumor Tissue[5]	X										
Medical History and Demographics[6]	X										
Complete Physical Examination	X										
Limited Physical Examination[7]		X	X	X	X	X	X	X	X	X	
Height[8] and Weight	X	X	X	X	X	X	X	X	X	X	
Vital Signs[9]	X	X	X	X	X	X	X	X	X	X	
ECG	X	As clinically indicated								X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X[10]	X	X	X	X	X	X	X	X	X (if clinically indicated)
Biochemistry	X	X[10]	X	X	X	X	X	X	X	X	X (if clinically indicated)
Record Date of Last Menses[11]	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[12]	X	X	X	X	X	X	X	X	X	X	
Serum Hormone Evaluation[13]	X	As clinically indicated								As clinically indicated	As clinically indicated
Steady-state and post-treatment pharmacokinetic collection of blood (AT SELECTED SITES ONLY)[24]			One collection while taking vismodegib for at least 2 weeks continuously								At 3, 6, 9, and 12 Months ONLY
QoL Assessments using Skindex-16 (in selected sites)	X		X					X		X	

Table 1 Schedule of Assessments (cont.)

	Screening / Baseline	Treatment Phase[1] (Allowed Visit Window +/- 3 days from Cycle 2 onwards)								End of Treatment Visit[2]	Safety Follow-Up Visits[3] (1 month, 3 months, 6 months, 9 months, 12 months after the last dose of vismodegib (GDC-0499))
Cycle		1	2	3	4	5	6	7	8 onwards		
Day	–28 to –1	1	29	57	85	113	141	169	Every 28 Days		
Symptom Assessment using MDASI [14]	X	X	X	X	X	X	X	X	X	X	X
Tumor Assessments (physical examination)[15, 17]	X	Every 4 to 8 weeks from the time of the first dose (±5 days) regardless of dosing delays.								X	
Tumor Assessments (by imaging techniques, if required)16, 17	X	Every 8 to 16 weeks from the time of the first dose (±5 days) regardless of dosing delays or as per institutional standards In metastatic BCC patients (newly enrolled after approval of the Study Protocol, version 4.0), every 8 weeks from time of first dose (±5 days) regardless of dosing delay								X	
AEs / SAEs[18]	X	X								X	X
AE-related pharmacokinetic collection of blood (AT SELECTED SITES ONLY) [25]											At 6, 9, and 12 Months ONLY
Ultrasound[19]	X	As clinically indicated								As clinically indicated	As clinically indicated
Follow-up for disease progression		X								X	X
Tumor biopsy and collection of whole blood [20]										X	
Concomitant medication	X[21]	X								X	X
New anti-cancer therapy										X	X
Drug Dispensing		X (first day of each Cycle)									
Drug Accountability[22] Drug Dosing Exception Diary[23]			X	X	X	X	X	X	X	X	

Table 1 Schedule of Assessments (cont.)

Notes Results of screening tests or examination performed as standard of care before obtaining informed consent and within the specified interval may be used rather than repeating required evaluation. Day 1 = first dose of study drug vismodegib.

1. Visits during the treatment period are to be completed on Day 1 of every 28-Day Cycle.
2. End of Treatment Visit will be performed when the patient discontinues vismodegib regardless of when it occurs.
3. Safety Follow-Up Visit is to be performed approximately (+/- 5 days) 1 month, 3 months, 6 months, 9 months, and 12 months after the last dose of vismodegib.
4. Written, signed informed consent must be obtained prior to perform any study procedure including screening/baseline assessments.
5. Archival tumor tissue from a metastatic BCC site will be collected in metastatic BCC patients (who are on study after approval of the Study Protocol, version 4.0).
6. In women of childbearing potential, also record any amenorrhea/irregular menses, relevant gynecologic medical history, and concurrent gynecologic conditions. In metastatic BCC patients who are on study after approval of Study Protocol, version 4.0, record evidence of disease progression prior to enrollment on study and reasons for treatment discontinuation of any prior metastatic BCC therapy.
7. A limited physical examination should focus on organ systems that are related to a potential AE as suggested by a patient's interim medical history and/or existing clinical and preclinical data for vismodegib.
8. Height is only measured at screening.
9. Includes body temperature, blood pressure, and pulse.
10. Hematology and biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days of first vismodegib administration. NB: if it is necessary to repeat these blood tests, the results must be known before the patient receives first dose of vismodegib (to ensure inclusion/exclusion criteria related to these tests are met).
11. In women of childbearing potential ONLY.
12. For women of childbearing potential, including those who have had a tubal ligation. A serum pregnancy test is required within 7 days prior to first dose of vismodegib and urine pregnancy tests should be performed on Day 1 of each subsequent Cycle. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
13. For women of childbearing potential ONLY. To be performed at local laboratory. Includes FSH, TSH, LH and E2. Perform at Screening and at start of amenorrhea/irregular menses and at resolution of amenorrhea/irregular menses. If amenorrhea/irregular menses recurs, repeat evaluations at start of recurrence as detailed previously.
14. M.D. Anderson Symptom Inventory (MDASI) will be completed by metastatic BCC patients (newly enrolled after approval of Study Protocol, version 4.0), prior to having any assessments performed at each visit.
15. Tumor assessments for patients with measurable disease (the majority of the patients in this study have locally advanced BCC and in this disease setting measurable tumors are accessible to evaluation by physical examination) should be performed at screening within a maximum of 7 days prior to the first dose of study drug (baseline reading), and then every 4-8 weeks from the time of the first dose (±5 days) regardless of dosing delays until the end of treatment. In case of clinically measurable superficial (such as skin) lesions, repeated photographs should be used to document tumor response, these photos must include a ruler for documentation purposes. Objective responses using RECIST should be confirmed by repeat assessments at least 4 weeks after initial documentation of response.
16. Tumor assessments for patients with measurable disease (requiring imaging method) should be performed at screening; baseline CT/MRI scans should be performed within a maximum of 28 days prior to the first dose of study drug (Cycle 1, Day 1), and then every 8 to 16 weeks from the time of the first dose (±5 days) regardless of dosing delays as per institution standard of care thereafter but at a minimum every 16 weeks and at the end of the study. The same imaging method(s) must be used for a patient throughout the study. The same radiographic procedure used to define measurable disease sites at baseline must be used throughout the study (e.g. the same contrast protocol for CT scans). Objective responses using RECIST should be confirmed by repeat assessments at least 4 weeks after initial documentation of response. In metastatic BCC patients (enrolled after approval of the Study Protocol, version 4.0), tumor assessments should be performed at screening; baseline CT/MRI scans should be performed within a maximum of 28 days prior to the first dose of study drug (Cycle 1, Day 1), and then every 8 weeks from time of first dose (±5 days) regardless of dosing delay.

Table 1 Schedule of Assessments (cont.)

17. Non- measurable disease should be assessed within 28 days prior to study initiation, and thereafter as clinically indicated and in accordance with standard clinical practice. For metastatic patients assessment of non-measurable disease should be according to RECIST version 1.1.
18. AEs will be collected on Day 1 of each Cycle and at the follow-up or early termination visit. After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected. All AEs (either related to study specific procedures or otherwise) experienced after the patient has signed the Informed Consent form but before they have received study treatment, should be recorded as medical history. All AEs experienced after the patient has started study treatment must be recorded on the AE form of the eCRF, as well as all new AEs experienced during the study and up to 1 month, 3 months, 6 months, 9 months, 12 months after the last dose of study treatment (± 5 days). Additionally, non-serious, new AEs considered related to study drug which occur approximately (+/- 5 days) 1 month, 3 months, 6 months, 9 months, 12 months after the last dose of study drug should also be reported. SAEs considered related to study drug should be reported indefinitely.
19. In women of childbearing potential ONLY. At start of amenorrhea/irregular menses, refer to gynecologist or appropriate specialist for assessment of ovaries and uterus, including ultrasound. At resolution of amenorrhea/irregular menses, refer to gynecologist or appropriate specialist for follow-up ultrasound ONLY if there was abnormality identified during previous ultrasound. If amenorrhea/irregular menses recurs, repeat evaluations at start of recurrence as detailed previously. Obtain copy of results from ultrasound and enter any abnormal findings into the CRF.
20. In metastatic BCC patients who develop tumor progression on vismodegib treatment, a biopsy will be performed if at least one of the progressing lesions is accessible, e.g., skin, superficial mass, or lymph node and a whole blood sample will be collected.
21. All concomitant medications used within 14 days before study treatment and up to the end of treatment and approximately (± 5 days) 1 month, 3 months, 6 months, 9 months, and 12 months after the last dose of vismodegib at the Safety Follow-Up Visit must be recorded.
22. Study drug vismodegib accountability will be performed at every study visit from Cycle 2 onwards and at the End of Treatment Visit.
23. Patients will keep a diary to record ONLY those occasions when a vismodegib dose was missed. The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the Investigator.
24. A total of 30 patients will have blood collected for steady-state and post-treatment pharmacokinetic testing.
25. Collect blood if any adverse events that were reported to be related to vismodegib treatment continue to be present at least 6 months after the last dose of vismodegib. Blood samples for the adverse event-related PK testing will be collected at the 6, 9, and 12 months Safety Follow-Up Visits even if the adverse event resolves after the 6 months Safety Follow-Up Visit.

GLOSSARY OF ABBREVIATIONS

AAG	alpha 1 acid glycoprotein
AE	adverse event
ALT (SGPT)	alanine aminotransferase
AST (SGOT)	aspartate aminotransferase
AUC	area under the curve
BCC	basal cell carcinoma
BP	blood pressure
BORR	best overall response rate
ºC	degrees Celsius
CI	confidence interval
C_{max}	maximum concentration
CR	complete response
eCRF	electronic Case Report Form
CT	computer tomography
DDI	drug-drug interaction
DSMB	Data Safety Monitoring Board
E2	Estradiol
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	Electronic Data Capture
ESF	Eligibility Screening Form
EU	European Union
F	Fahrenheit
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
Hh	Hedgehog
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IRF	Independent Review Facility
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	intent to treat
KM	Kaplan-Meier
LH	Luteinizing hormone
MDASI	M.D. Anderson Symptom Inventory
MRI	magnetic resonance image
mm	millimeter

NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
P-gp	P-glycoprotein
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
QoL	Quality of Life
RECIST, v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SAE	serious adverse event
SD	stable disease
SMO	smoothened
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Events Reactions
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US FDA	United States Food and Drug Administration
USP/NF	United States Pharmacopeia/National Formulary

PART I: STUDY DESIGN AND CONDUCT

1. BACKGROUND, RATIONALE, AND BENEFIT-RISK

1.1 BACKGROUND

1.1.1 Advanced Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common malignancy; for example, of the more than 1 million cases of non-melanoma skin cancer reported in the United States in 2007, approximately 80% are BCC (1-3). Almost all of these cases are small BCCs that can be effectively treated by dermatologists using several surgical modalities. However, in a small subset of patients, invasion of the BCC into subcutaneous structures can occur. In some cases, this results from neglect of indolent BCCs, whereas in other cases patients may develop particularly aggressive BCCs that recur and progress despite standard surgical treatment. If further surgical resection is not possible, there is no approved therapy and no standard of care exists. Although palliative radiation therapy may be used, its use may be limited by the location of the tumor and the involved structures, as well as prior cumulative radiation dosage. Locally advanced BCC can be associated with significant morbidity as the result of chronic pain, risk of bacterial infection and sepsis, bleeding/oozing, and compromise of function, resulting from invasion of structures such as the ear, nose and eye. In some cases, invasion can progress to involve critical organs such as the meninges, brain, and spinal cord, resulting in death (4, 5).

Metastatic BCC is extremely rare, with a reported metastasis rate ranging from 0.0028% to 0.55%; most believe the true metastasis rate to be significantly less than 0.1% (6). A total of approximately 300 cases of metastatic BCC have been reported in the literature. The most common sites of metastasis are the lymph nodes, lung, bone, liver, other viscera, and soft tissue (7). Once metastasis is detected, survival can be short for some patients, with a range of 8 to 14 months reported by some Investigators. However, a 5-year survival rate of approximately 10% has also been reported, and individual patients have been reported to live for as many as 25 years with metastatic disease (8-10). No standard therapy for metastatic BCC exists, although there is anecdotal use of chemotherapeutic agents such as platinum compounds (11).

The Hedgehog (Hh) signaling pathway presents a novel and potentially beneficial target for cancer therapy. Hh signaling regulates epithelial and mesenchymal interactions in a variety of tissues during mammalian embryogenesis (12). The Hh ligand in the extracellular space binds to PATCHED (PTCH1), a 12-pass transmembrane receptor on the surface of cells. Hh binding relieves the inhibitory effect of PTCH1 on Smoothened (SMO), a 7 pass transmembrane domain protein and a member of the G-protein coupled receptor superfamily. Signal transduction by SMO then leads to the activation and nuclear localization of GLI transcription factors and induction of Hh target genes, many of which are involved in proliferation, survival, and differentiation.

A role for aberrant Hh signaling in cancer was initially discovered in patients with Gorlin syndrome, a rare genetic disorder associated with predisposition to BCC, medulloblastoma, and rhabdomyosarcoma. In these patients, mutations in the PTCH1 gene led to ligand-independent activation of SMO and constitutive activity of the Hh pathway (13). Recent molecular and genetic studies have demonstrated that the majority of sporadic human BCCs also have mutations in the Hh signaling pathway, resulting in aberrant activation of the pathway and uncontrolled proliferation of basal cells (14, 15). Two mutations commonly found in BCC result from either the inactivation of the PTCH1 receptor or the activation of SMO protein (16). Both have the same functional consequence, i.e., the uncontrolled activation of the Hh signaling pathway in the absence of the Hh protein. High expression levels of Hh target genes, such as GLI1 and PTCH1, are found in nearly all cases of human BCC examined (17, 18), suggesting that activation of this pathway is a causal event in the initiation of tumor formation. These data suggest that blocking the Hh signaling pathway at the level or downstream of SMO may provide a therapeutic benefit in the treatment of BCC (19).

The feasibility of blocking Hh signaling *in vivo* was first demonstrated as a result of teratogenic phenomena occurring in lambs with mothers that had ingested a particular forage plant, Veratrum californicum (20). Cyclopamine, a steroidal alkaloid isolated from this plant, was shown to induce midline deformities, including cyclopia, by blocking SMO signaling in the developing lamb fetuses (21). Cyclopamine has proven to be valuable as a tool compound to confirm the importance of Hh signaling in a subset of malignancies, such as slowing the growth of pancreatic cancer xenografts and blocking the metastatic potential of prostate cancer cells in mice (22, 23).

1.1.2 Vismodegib

Vismodegib (also known as GDC-0449) is a small molecule antagonist of the Hh signaling pathway with a molecular weight of 421.30 g/mol. The International Union of Pure and Applied Chemistry name for vismodegib is 2-chloro-*N*-(4-chloro-3-[pyridin-2-yl]-phenyl)-4-(methanesulfonyl)-benzamide.

Vismodegib binds to and inhibits SMO, thereby preventing the Hh signal. Vismodegib has proven to be efficacious in nonclinical tumor models of both mutated and ligand-overexpressing tumors.

1.1.2.1 Vismodegib Pharmacokinetics

The pharmacokinetics of vismodegib was evaluated in multiple clinical studies in patients with advanced solid tumors, advanced basal cell carcinoma (BCC), and in healthy volunteers.

1.1.2.1.1 Single and Multiple Dose Pharmacokinetics

After a single oral dose, vismodegib demonstrates a unique pharmacokinetic (PK) profile with high, sustained plasma levels and an estimated terminal half-life of 12 days. Parallel concentration−time profiles are observed in the terminal elimination phase

following oral and intravenous (IV) dosing, indicative of elimination rate-limited pharmacokinetics.

After continuous once-daily dosing, steady-state plasma concentrations in patients are typically achieved within approximately 7 days of continuous daily dosing. Increasing the daily dose from 150 mg to 270 or 540 mg does not result in higher steady-state plasma concentrations.

1.1.2.1.2 Absorption

Vismodegib is a highly permeable compound with low aqueous solubility (Biopharmaceutics Classification System Class 2). The single-dose absolute bioavailability of vismodegib is 31.8%. Under clinically relevant conditions (steady-state), the pharmacokinetics of vismodegib is not affected by food (see the Investigator's Brochure).

1.1.2.1.3 Distribution

The single-dose volume of distribution for vismodegib is 16.4 L and it increases (62% higher relative to single dose) with continuous daily dosing. In vitro binding of vismodegib to human plasma proteins is high (97%) and independent of vismodegib concentrations at clinically relevant levels. Vismodegib binds to both human serum albumin (HSA) and α-1-acid glycoprotein (AAG). In vitro binding to AAG is saturable at concentrations >25 µM. Ex vivo plasma protein binding in humans is $>99\%$. Vismodegib concentrations are strongly correlated with AAG levels, showing parallel fluctuations of AAG and total drug over time and consistently low unbound drug levels.

1.1.2.1.4 Metabolism

Metabolic pathways of vismodegib in humans include oxidation, glucuronidation, and uncommon pyridine ring cleavage. The major oxidative metabolite recovered in feces (M3) is produced by recombinant cytochrome P450 (CYP) 2C9 and to a lesser extent by CYP3A4/5, while another oxidative metabolite (M1) is formed primarily by recombinant CYP3A4/5. However, multiple isoforms are capable of forming both metabolites. These findings indicate that vismodegib and any associated metabolic products are eliminated primarily by the hepatic route. Vismodegib is predominantly found in plasma, with concentrations representing greater than 98% of the total circulating drug-related components.

1.1.2.1.5 Excretion

After oral administration of radiolabeled drug, vismodegib is absorbed and slowly eliminated by a combination of metabolism and excretion of parent drug, the majority of which is recovered in the feces (82% of the administered dose), with 4.4% of the administered dose recovered in urine.

1.1.2.1.6 Nonlinear Pharmacokinetics of Vismodegib

The pharmacokinetics of vismodegib are characterized by less than dose proportional increases in plasma concentration with increasing dose and lower than expected accumulation after continuous daily dosing; these observations are suggestive of nonlinear pharmacokinetics.

The nonlinear pharmacokinetics of vismodegib result from two separate, nonlinear processes: 1) saturable absorption; and 2) high-affinity, saturable protein binding. Nonlinear absorption is consistent with the poor solubility of vismodegib at physiologic pH and likely resulted in a lack of dose-proportional increase in exposure after a single dose of 270 and 540 mg vismodegib. The more clinically relevant nonlinear process for vismodegib is saturable binding to alpha-1-acid glycoprotein, which results in concentration-dependent changes in the pharmacokinetics of vismodegib.

Following intravenous (IV) administration at oral steady-state, mean vismodegib CL and volume of distribution increase $>50\%$, suggestive of concentration-dependent changes in pharmacokinetics. The fraction unbound of vismodegib increases approximately 3-fold after once-daily dosing relative to a single dose, which can account for the increase in vismodegib CL and volume of distribution after repeated dosing. With less frequent dosing of 150 mg vismodegib (three times a week [TIW] or once a week [QW]), total plasma vismodegib levels decrease in a less-than-dose-proportional fashion as compared with once-daily dosing, consistent with nonlinear pharmacokinetics. The decrease in unbound plasma vismodegib concentrations with less frequent dosing is more pronounced than for total drug and is proportional to the decrease in weekly dose amount.

1.1.2.1.7 Population Pharmacokinetics

The population PK analysis suggests that vismodegib pharmacokinetics at the clinical dose range can be adequately described by a one-compartment model with first-order absorption, first-order elimination (of unbound), and saturable binding to AAG with fast equilibrium. Overall, vismodegib pharmacokinetics are highly dependent on AAG concentration. None of the other covariates evaluated showed clinically relevant impact on steady-state vismodegib concentration. Sex, body mass index, baseline tumor burden, albumin, creatinine clearance, and hepatic function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total protein, and total bilirubin) did not appear to affect the pharmacokinetics of vismodegib. Age and body weight were identified as statistically significant covariates for the vismodegib disposition (unbound clearance and volume of distribution, respectively), but sensitivity analysis suggested that neither of these effects had a clinically significant impact on vismodegib concentration at steady-state. Patients with cancer showed slower drug absorption (lower ka) than healthy volunteers, but with no significant impact on vismodegib exposure at steady state.

No clinically relevant exposure-response relationship was observed for the most frequently reported adverse events of weight loss, alopecia, dysgeusia, fatigue, muscle spasms, or nausea. Furthermore, there was no evidence of an effect of vismodegib plasma concentration on QTc interval prolongation.

1.1.2.2 Clinical Development Program in BCC

1.1.2.2.1 Study SHH3925g

Study SHH3925g was an open-label, multicenter, two-stage phase I trial to evaluate the safety and tolerability of vismodegib in patients with a variety of solid tumors who were refractory to standard therapy (24). In total, 68 patients enrolled in the study at three centers, of whom 33 had advanced BCC. This study was closed in November 2009.

Enrollment in this study occurred in two stages. Stage 1 of the trial, the dose escalation portion of the study, was designed to estimate the safety, tolerability, pharmacokinetics, pharmacodynamics, and maximum tolerated dose of vismodegib. Patients received a single oral dose of vismodegib on Day 1, followed by a 7-day PK observation period, then daily administration at the same dose beginning on Day 8. Seven patients were assigned to receive 150 mg per day, nine patients 270 mg per day, and four patients 540 mg per day; each dose cohort included one patient with advanced BCC. No dose-limiting toxic effects were observed. On the basis of this study, the recommended phase II dose was set at 150 mg per day because PK analyses indicated that doses greater than this did not result in higher plasma concentrations of the drug.

Stage 2 of the study included an expansion cohort that received the recommended phase II dose, with the goal of obtaining additional information on PK and safety; 12 patients (none with advanced BCC) enrolled in this cohort, and all received 150 mg per day. The study was amended to include two further cohorts in Stage 2. The first of these cohorts was added because of evidence of clinical benefit in two patients with advanced BCC during Stage 1; this cohort consisted of 20 patients with advanced BCC, who were treated with 150 mg per day or 270 mg per day (with the dose chosen on the basis of drug availability) to evaluate the activity and safety of vismodegib in this population. The second additional cohort, which consisted of 16 patients with solid tumors (including 10 with advanced BCC), was added to investigate the PK properties of a new formulation of vismodegib at 150 mg per day. In Stage 2, all patients received continuous daily administration of the drug beginning on Day 1 and were treated until disease progression, the occurrence of intolerable toxic effects, or withdrawal from the study.

Between January 2007 and February 2010, 33 patients with locally advanced BCC or metastatic BCC enrolled in SHH3925g and received oral vismodegib: 17 patients received 150 mg per day, 15 patients received 270 mg per day, and one patient received 540 mg per day. Of these 33 patients, 19 had an objective response (OR) to vismodegib, according to assessment on imaging (seven patients), physical examination (ten patients), or both (one patient). Of the patients who had a response, two had a

complete response (CR) and 17 had a partial response (PR). The other 14 patients had either stable disease (SD; 10 patients) or progressive disease (PD; four patients). As of the data cutoff date (February 25th, 2010), the Kaplan–Meier estimate of the median time of participation in the study was 11.2 months and ongoing, and the median duration of response was 12.8 months and ongoing. At the time of study closure, 12 of 33 BCC patients had been on study for durations of 8.5 to 26.5 months. These 12 patients were enrolled onto the extension study SHH4437g to continue receiving vismodegib.

Of the 15 patients with locally advanced tumors, 13 were assessed on physical examination (clinical response), and two with measurable disease were assessed by imaging using the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST, v1.1). Of these 15 patients, two had a complete clinical response, and seven had a partial clinical response; four patients had SD as the best response, with a duration of participation in the study ranging from 2.1 to 19.0 months; two of the patients had PD. Overall, the response rate in patients with locally advanced tumors was 60% (95% confidence interval [CI], 33% to 83%).

Of the 18 patients with metastatic tumors, 15 had radiologically measurable disease, and seven of these patients had a PR, as assessed on imaging only (with six responses confirmed and one unconfirmed at the time of the data cutoff). Two other patients with metastatic tumors had PRs, one assessed on both imaging and physical examination and the other on physical examination only. Seven patients with metastatic tumors had SD (with six patients assessed with the use of RECIST, v1.1 and one on physical examination), and two had PD as the best response. The overall response rate (ORR) among the 18 patients with metastatic tumors was 50% (95% CI, 29–71%).

Eleven Grade 3 AEs that were deemed to be possibly related to the study drug were reported in six patients with advanced BCC, including five with fatigue, three with hyponatremia, one with muscle spasm, one with weight loss, and one with atrial fibrillation. In addition, one episode of Grade 4 paranoia and one case of Grade 4 pancreatic andenocarcinoma were considered to be related to vismodegib. One Grade 4 event, asymptomatic hyponatremia, was judged to be unrelated to vismodegib. One patient withdrew from the study because of AEs.

1.1.2.2.2 ERIVANCE BCC (SHH4476g)

ERIVANCE BCC (SHH4476g) was a pivotal, phase II, single-arm, multicenter, open-label trial evaluating the efficacy and safety of vismodegib in patients 18 years of age or older with advanced BCC (25). The trial included two cohorts: 1) patients with histologically-confirmed locally advanced BCC that was either unresectable or inappropriate for surgery; and 2) patients with metastatic BCC with histologically-confirmed and radiographically-measurable disease. Patients in the trial received 150 mg of oral vismodegib once-daily until evidence of progression, intolerable toxicities most probably attributable to vismodegib, or withdrawal from the study. One hundred and four patients enrolled at 34 study sites in the United States, England,

France, Germany, Belgium, and Australia. Ninety six were evaluable for efficacy, of whom 63 (65.6%) had locally advanced and 33 (34.4%) had metastatic disease.

In the cohort with locally advanced BCC, 27 patients responded for an ORR (primary efficacy variable) of 42.9% (95% CI, 30.5–56.0%; p<0.0001). Twenty-four patients (38.1%) exhibited stable disease and 8 patients (12.7%) exhibited disease progression. The clinical benefit rate was 75% (defined as the percentage of patients experiencing an objective response prior to or after onset of progressive disease plus the percentage of patients who experienced stable disease lasting ≥ 24 weeks). Median duration of response and PFS were 7.6 and 9.5 months, respectively. The median duration of therapy was 9.7 months (range, 1.1–18.7 months), with 45.1% of patients remaining on treatment as of the data cutoff date, which occurred 9 months after the last patient had enrolled.

In the cohort with metastatic BCC, 10 patients responded to therapy for an ORR of 30.3% (95% CI, 15.6–48.2%; p=0.0011). Twenty-one patients (63.6%) exhibited stable disease and 1 patient (3.0%) exhibited disease progression. The clinical benefit rate was 76%. Median duration of response and PFS were again 7.6 and 9.5 months. Finally, the median duration of therapy was 10.0 months (range, 0.7–16.4 months), with 57.6% of patients remaining on treatment as of the data cutoff date.

The most common AEs were muscle spasms (68%), alopecia (64%), dysgeusia (51%), weight loss (46%), fatigue (36%), nausea (29%), decreased appetite (23%), and diarrhea (22%); the large majority of these events were mild to moderate in intensity. Serious AEs were reported in 26 patients (25%), 4 (4%) of whom experienced SAEs possibly related to vismodegib administration (cholestasis [n=1], pulmonary embolism [n=1], syncope [n=1], and cardiac failure and pneumonia [n=1]). Fatal AEs were reported in 7 patients (7%; unknown cause [n=3], acute myocardial infarction [n=1], ischemic stroke [n=1], meningeal disorder [n=1], and hypovolemic shock [n=1]). In all patients who died on study, pre-existing risk factors and comorbid conditions had been present (30, 31).

1.2 RATIONALE FOR THE STUDY

Surgery cures most cases of BCC, but a few patients may exhibit progression to life-threatening, unresectable, locally advanced disease or metastatic tumors (5, 6, 11, 26). There is no standard therapy for locally advanced or metastatic BCC and, consequently, opportunities remain to improve outcomes for these patients.

In the Phase I study SHH3925g, a tumor response to vismodegib was observed in > 50% of patients with advanced BCC. Thus, of 33 patients with locally advanced or metastatic tumors, 18 had an OR to vismodegib. Of the remaining 15 patients, 11 had SD for up to 10.8 months and 4 had PD. There were no dose-limiting toxic effects or Grade 5 AEs, and only one Grade 4 AE occurred during continuous daily administration of vismodegib for up to 19 months.

The encouraging results from the Phase I study have generated significant interest and increased demand for access to vismodegib because of the unmet medical need in this patient population. However, since ERIVANCE BCC (SHH4476g) is now closed, no clinical studies of vismodegib are currently open to patients with advanced BCC. Therefore, because patients with advanced BCC do not have satisfactory therapeutic options, and because there is a need to establish a broader safety evidence for vismodegib when given to patients with locally advanced or metastatic BCC, this phase II study will enroll patients who qualify as having an unmet medical need. The study is expected to enroll approximately 1200 patients over an approximately 3.5-year period and will continue enrollment until such time as vismodegib becomes commercially available for this patient population.

1.3 BENEFIT-RISK

Potential Benefits of the Study

In general terms, the key benefit from this study will be an increase in our knowledge base for vismodegib. In particular, with its focus on safety (the primary objective), the trial should provide new data that can be used in future studies to optimize safe administration of vismodegib. Other analyses described in this protocol will serve to test the reproducibility of prior safety and efficacy results and to add new information on patient QoL.

Significant potential benefit is also expected to accrue to patients who enroll in the study. As described in earlier sections, locally advanced BCC can be associated with significant morbidity as a result of chronic pain, bacterial infection and sepsis, bleeding/oozing, and/or compromise of function; moreover, in some cases, death can result from local invasion of critical organs, such as the meninges, brain, and spinal cord (4, 5). Metastatic BCC also has a grim prognosis, with a median survival estimated by some investigators to be only 8 to 14 months (8). For patients lacking other therapeutic options, vismodegib may provide substantial utility as an anti-cancer agent of last resort, given its encouraging efficacy results in previous clinical trials.

Potential Risks of the Study

An important risk associated with this study, as with any clinical trial, is the potential enrollment of inappropriate patients. Minimization of this risk has been attempted via judicious choice of inclusion and exclusion criteria. Thus, for patients with locally advanced BCC, disease must be histologically confirmed and enrollees must have exhausted all other therapeutic options, i.e., only patients who are contraindicated for surgery and have undergone previous radiotherapy (or are inappropriate for radiotherapy) are eligible. Similarly, for those patients with metastatic disease, histological confirmation of distant metastasis is required.

As is true of any investigational agent, vismodegib may pose some safety risks for patients participating in the trial. These risks will be managed by careful monitoring of

AEs and laboratory tests throughout the study period. In addition, an independent Data Safety Monitoring Board (DSMB) will be established that will be responsible for monitoring patient safety data during the course of the study (see Section 10).

Finally, small-molecule inhibitors of the Hedgehog pathway are known teratogens that result in midline malformations and other severe developmental defects in mammalian model systems (see the Vismodegib Investigator Brochure). Consequently, to be eligible for this trial, female patients of childbearing potential must use two methods of acceptable contraception, including one highly effective means of contraception and one barrier method during treatment and for at least *9* months *or as per approved local prescribing information for vismodegib (where available), whichever is longer,* after completion of treatment. Fertile male patients must utilize a condom with spermicide *(where available)*, even if he has had a vasectomy, during treatment. Additionally, female patients must exhibit negative serum pregnancy tests within 7 days prior to dosing and throughout the trial. After discontinuing treatment, female patients of childbearing potential must continue to use an effective method of contraception for at least *9* months *or as per approved local prescribing information for vismodegib (where available), whichever is longer*. Acceptable contraception and duration of contraceptive use should comply with locally approved vismodegib (Erivedge®, the trade name for vismodegib) Pregnancy Prevention Program or prescribing information where vismodegib is commercially available.

With these risk mitigation safeguards in place, the potential benefits of the study (see previous section) encourage moving ahead with the trial.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

To assess the safety of vismodegib in patients with locally advanced or metastatic BCC

2.2 SECONDARY OBJECTIVES

- To assess the overall response rate (ORR; according to RECIST, v1.1) in those patients with measurable disease, as permitted by local regulatory requirement
- To assess other efficacy parameters, such as time to response, duration of response, progression-free survival (PFS), and overall survival (OS)
- To assess patient quality of life (QoL) (Skindex-16)
- To assess the impact of vismodegib treatment on disease symptoms in patients with metastatic BCC who enrolled after approval of the Study Protocol, version 4.0, using the M.D. Anderson Symptom Inventory (MDASI)

2.3 EXPLORATORY OBJECTIVES

- To assess the status of the Hh pathway and/or other modifiers of vismodegib activity in tumor tissue obtained from patients with metastatic BCC who have disease progression on vismodegib therapy

- To determine the post-treatment exposure of vismodegib in patients with adverse events that were reported to be related to vismodegib treatment and that are continuing at least 6 months after the last dose of vismodegib
- To determine the post-treatment exposure of vismodegib in patients following daily oral dosing with 150 mg vismodegib for at least 2 weeks of consecutive dosing (steady-state exposure) and at 3, 6, 9, and 12 months after the last dose of vismodegib

3. STUDY DESIGN

3.1 OVERVIEW OF STUDY DESIGN

This is an open-label, non-comparative, multicenter, phase II study of vismodegib in patients with locally advanced BCC or metastatic BCC who are otherwise without satisfactory treatment options.

The study population will consist of male or female patients at least 18 years of age with histologically confirmed diagnoses of locally advanced BCC or metastatic BCC. For patients with locally advanced BCC, the treating physician must consider the disease to be inoperable or there must be a clinical contraindication to surgery; furthermore, radiotherapy must have been previously administered (unless radiotherapy is contraindicated or inappropriate) and disease must have progressed after irradiation. For patients with suspected metastatic BCC, distant metastases must be histologically confirmed to be of basal cell origin. Patients are eligible for enrollment in this trial with measurable and/or non-measurable disease, as defined by RECIST, v1.1.

Enrolled patients will receive continuous once-daily oral dosing of vismodegib at a dosage of 150 mg per administration. One cycle of therapy will be defined as 28 days of treatment. All patients will receive study drug until the development of PD (as determined by the Investigator), unacceptable toxicity, consent withdrawal, death, reasons deemed by the treating physician, or study termination by the Sponsor. Dose reduction of vismodegib is not permitted, as there is only a 150-mg capsule strength available. Temporary discontinuation of drug for up to 8 weeks is allowed. Temporary discontinuation longer than 8 weeks must be discussed with the Roche Medical Monitor or his/her designee.

The trial will consist of a Screening Period (Day –28 to –1), a Treatment Phase, an End of Treatment Visit when the patient received the last dose of vismodegib and thereafter discontinues vismodegib (regardless of when it occurs), and five Safety Follow-Up Visits 1 month, 3 months, 6 months, 9 months and 12 months after the last dose of vismodegib (± 5 days), as provided by this phase II safety study protocol. Day 1 of the study will be defined as the first day a patient receives vismodegib. During the Treatment Phase, all study assessments will be conducted on Day 1 (± 3 days, from Cycle 2 onwards) of each Cycle with the exception of computed tomography (CT) and/or magnetic resonance imaging (MRI) for tumor evaluation, which should occur every 8 to 16 weeks or as per

institutional standards (see below). For a list of study assessments, see the Study Flowchart (Table 1. Schedule of Assessments).

Assessment of safety, the primary objective of this trial, will occur by examining the incidence, type, and severity of AEs; the incidence and nature of serious AEs (SAEs); the incidence of AEs leading to vismodegib discontinuation or interruption; and the cause of death on study (if not linked to disease progression).

The pharmacokinetics of vismodegib will be assessed in an exploratory manner at selected sites. Adverse event-related PK testing will be performed on patients having any adverse events that were reported as being related to vismodegib treatment and that continued for at least 6 months after the last dose of vismodegib. This PK sample collection will occur at 6 months, 9 months, and 12 months after the last dose of vismodegib (±5 days). In addition, post-treatment PK testing will be performed on 30 patients to further characterize the post-treatment elimination of vismodegib from steady-state exposure to 12 months after the last dose of vismodegib, with PK sample collection occurring at 3 months, 6 months, 9 months, and 12 months after the last dose of vismodegib (±5 days).

Efficacy will be assessed according to RECIST, v1.1. Measurable tumors accessible to evaluation by physical examination should be assessed within a maximum of 7 days prior to the first dose of study drug (baseline reading) and every 4 to 8 weeks thereafter. If assessment requires imaging, baseline CT and/or MRI should be performed within a maximum of 28 days prior to the first dose of study drug and, if such scans demonstrate evidence of disease, follow-up imaging studies (CT and/or MRI) should be performed every 8 to 16 weeks or as per institutional standards from the time of the first dose, regardless of dosing delays. Other imaging techniques may be performed as clinically indicated, but should not be used for determining tumor response. Objective responses using RECIST, v1.1 should be confirmed by repeat assessments at least 4 weeks after initial documentation of response.

In metastatic BCC patients (newly enrolled after approval of the Study Protocol, version 4.0), imaging at baseline (CT and/or MRI scan) should be performed within a maximum of 28 days before the first dose. Follow-up imaging studies (CT and/or MRI scan) should be performed every 8 weeks (±5 days) from the time of the first dose, regardless of dosing delays. The same imaging technique (CT or MRI) should be used for each patient throughout the study.

Non-measurable disease should be assessed within 28 days prior to study initiation. Patients with non-measurable disease at baseline should be assessed for disease progression when clinically indicated and in accordance with standard clinical practice. For metastatic patients, assessment of non-measurable disease should be according to RECIST version 1.1.

In addition to safety and efficacy assessments, skin-related quality of life will be assessed at selected sites using the Skindex-16 questionnaire, a validated QoL instrument (27) that has been shown to be useful in patients with non-melanoma skin cancers, including BCC, although data in patients with higher-burden tumors are limited (28, 29). In patients with metastatic BCC who have enrolled after approval of the Study Protocol, version 4, symptoms will also be assessed using the M.D. Anderson Symptom Inventory.

Study enrollment will end in the European Union (EU) if vismodegib becomes commercially available after regulatory approval for the treatment of locally advanced or metastatic BCC. Study enrollment will end successively in non-EU countries participating in this study if vismodegib becomes commercially available after regulatory approval for the treatment of locally advanced or metastatic BCC in the respective country. However, patients already enrolled in this study and who are still benefitting from vismodegib, in the opinion of the Investigator, will continue to receive vismodegib as a study medication until the development of PD (as determined by the Investigator), unacceptable toxicity, consent withdrawal, death, reasons deemed by the treating physician or study termination by the Sponsor.

It is anticipated that approximately 1200 patients will be enrolled over approximately 3.5 years. The study will end when the last patient enrolled in this study develops Progressive Disease (PD) (as determined by the Investigator), unacceptable toxicity, withdraws consent, dies, or the treating physician deems that patient is no longer benefitting from treatment or the study is terminated by the Sponsor, or 12 months after the last dose of vismodegib in the last enrolled patient still on study, whichever occurs first.

The Sponsor reserves the right to end enrollment at any time. If study enrollment is discontinued prior to commercial availability of vismodegib, patients already enrolled will be informed of the reason for discontinuation of study enrollment and, in the absence of a significant product safety concern or other circumstances, will be allowed to continue vismodegib until disease progression, unmanageable toxicity, withdrawal of consent, reasons deemed by the treating physician or death of the patient, whichever occurs first.

Treatment scheme:

Screening	Study Treatment Phase	Safety Follow-Up
Day –28 to –1	Continuous once-daily oral dosing of vismodegib at a dosage of 150 mg per administration once-daily until one of the following occurs: disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by Investigator	Five Safety Follow-Up Visits 1 month, 3 months, 6 months, 9 months, and 12 months after the last dose of vismodegib (±5 days)
→	→	→

3.1.1 Rationale for Study Design

The primary objective of this phase II study is to assess the safety of vismodegib in patients with locally advanced BCC or metastatic BCC. The potential utility of vismodegib for treatment of advanced BCC was established in the phase I Study SHH3925g and phase II Study ERIVANCE BCC (SHH4476g), both of which demonstrated significant antitumor activity for vismodegib in this patient population (24, 25).

Based on these results and still limited information about the safety profile of vismodegib in locally advanced or metastatic BCC (vismodegib has not been approved for use in this patient population), safety will be carefully assessed within a phase II study setting. For patients with measurable disease and at least two tumor assessments during the study period, objective tumor response (according to RECIST, v1.1) will also be assessed, as permitted by local regulatory requirements.

3.1.2 Rationale for Dose Selection

The recommended dose for vismodegib is 150 mg given orally on a continuous daily schedule. It was chosen based on the SHH3925g study, which was an open-label, multicenter, two-stage phase I trial that evaluated the safety and tolerability of vismodegib in patients with a variety of solid tumors refractory to standard therapy (24). This dosing regimen was also used in ERIVANCE BCC (SHH4476g).

3.1.3 Rationale for Disease Symptom Assessment

Disease-related symptoms associated with metastatic BCC and the impact of vismodegib treatment on disease-related symptoms are not well described. To collect data addressing these questions, the M.D. Anderson Symptom Inventory will be used in metastatic BCC patients who were newly enrolled after approval of the Study Protocol, version 4.

3.1.4 Rationale for Biomarker Assessments

Despite the clinical benefit observed with vismodegib, a subset of advanced BCC patients who initially responded to vismodegib discontinue therapy due to disease progression, indicating potential resistance to vismodegib. Acquired resistance to vismodegib has also been observed in a metastatic medulloblastoma patient who exhibited an initial response to therapy in a phase I study (35). Efforts to understand the mechanism(s) underlying acquired resistance in preclinical models of Hh-driven medulloblastoma have led to the identification of mutations in *SMO* that impact vismodegib binding, as well as gene amplifications in downstream signaling components that bypass the effects of SMO inhibition with vismodegib (36). However, no such molecular events have been observed to date in tissue obtained at progression from a limited number of advanced BCC patients treated with vismodegib. Genotyping of tissue samples from patients with metastatic BCC, as they are most likely to progress while on treatment, could identify novel mechanisms that lead to vismodegib resistance and hence impact future approaches to overcome the development of resistance in BCC patients.

3.1.5 Rationale for Pharmacokinetic Assessments at Designated Investigative Sites

Vismodegib is a teratogen and a threshold for plasma concentrations of vismodegib in patients has been established. Currently available post-treatment discontinuation PK data for vismodegib is limited to 56 days. Based on the elimination kinetics of vismodegib in plasma after treatment discontinuation, it is predicted that the vast majority of patients will have plasma concentrations below the threshold for teratogenicity after 7 months. Notably, there is some uncertainty in this extrapolation, and until additional post-treatment discontinuation PK data are available, the duration for pregnancy prevention measures in female patients taking vismodegib has been prolonged to 24 months in the EU. The PK data obtained from this study will be utilized to inform and possibly revise the current recommended duration for pregnancy prevention measures after discontinuation of vismodegib treatment.

Acceptable contraception and duration of contraceptive use and waiting time for blood donations should comply with locally approved vismodegib Pregnancy Prevention Program or prescribing information where vismodegib is commercially available.

3.1.6 End of Study

Study enrollment will end in the EU if vismodegib becomes commercially available after regulatory approval for the treatment of locally advanced or metastatic BCC. Study enrollment will end successively in non-EU countries participating in this study if vismodegib becomes commercially available after regulatory approval for the treatment of locally advanced or metastatic BCC in the respective country. However, patients already enrolled in this study and who are still benefitting from vismodegib in the opinion of the Investigator will continue to receive vismodegib until the development of progressive disease (as determined by the Investigator), unacceptable toxicity, consent withdrawal, death, reasons deemed by the treating physician, or study termination by the Sponsor.

It is anticipated that approximately 1200 patients will be enrolled over approximately 3.5 years. Once the enrollment of 1200 patients is completed, an assessment of how many patients with metastatic BCC were enrolled under Protocol Amendment Version 4 (dated 8 May 2013) will be made. At that time, enrollment may be extended for up to 15 additional metastatic BCC patients in order to ensure adequate collection of data regarding the effect of vismodegib in metastatic BCC patients, as per Protocol Amendment Version 4 (dated 8 May 2013). The study will end when the last patient on treatment develops progressive disease (as determined by the Investigator), unacceptable toxicity, withdraws consent, or dies; the treating physician deems that the patient is no longer benefitting from treatment; or the study is terminated by the Sponsor, or 12 months after the last dose of vismodegib in the last enrolled patient still on study, whichever occurs first.

The Sponsor reserves the right to end study enrollment at any time. If study enrollment is stopped prior to commercial availability of vismodegib, patients already enrolled will be informed of the reason for discontinuation of study enrollment and, in the absence of a significant product safety concern, will be allowed to continue on vismodegib until disease progression, unmanageable toxicity, withdrawal of consent, reasons deemed by the treating physician, or death of the patient, whichever occurs first.

3.2 NUMBER OF PATIENTS

It is anticipated that approximately 1200 patients will be enrolled over approximately 3.5 years. Once the enrollment of 1200 patients is completed, an assessment of how many patients with metastatic BCC were enrolled under Protocol Amendment Version 4 (dated 8 May 2013) will be made. At that time, enrollment may be extended for up to 15 additional metastatic BCC patients in order to ensure adequate collection of data

regarding the effect of vismodegib in metastatic BCC patients, as per Protocol Amendment Version 4 (dated 8 May 2013).

3.3 CENTERS

This is an international multicenter study.

4. STUDY POPULATION

4.1 OVERVIEW

The study population will consist of male or female patients at least 18 years of age with histologically confirmed diagnoses of locally advanced BCC or metastatic BCC. For patients with locally advanced BCC, the treating physician must consider the disease to be inoperable or there must be a clinical contraindication to surgery; furthermore, radiotherapy must have been previously administered (unless radiotherapy is contraindicated or inappropriate) and disease must have progressed after irradiation. For patients with suspected metastatic BCC, distant metastases must be histologically confirmed to be of basal cell origin. Patients are eligible for enrollment in this trial with measurable and/or non-measurable disease, as defined by RECIST, v1.1.

Under no circumstances are patients who enroll in this study permitted to re-enroll into this study for a second course of treatment.

4.2 INCLUSION CRITERIA

A patient may be included if the answer to all of the following statements is "yes."

1. Written informed consent
2. Age $\geq$ 18 years
3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1, or 2
4. For patients with metastatic BCC, histologic confirmation of distant BCC metastasis
5. For patients with locally advanced BCC, at least one histologically confirmed lesion 10 mm or more in diameter and written confirmation from a surgical specialist that the tumor is considered inoperable or that surgery is contraindicated. Examples of medical contraindications to surgery include but are not limited to:
    - BCC that has recurred in the same location after two or more surgical procedures and curative resection is deemed unlikely
    - Anticipated substantial morbidity and/or deformity from surgery (e.g., removal of all or part of a facial structure, such as nose, ear, eyelid, eye; or requirement for limb amputation)
6. For patients with locally advanced BCC, radiotherapy must have been previously administered for locally advanced BCC, unless radiotherapy is contraindicated or inappropriate (e.g., hypersensitivity to radiation due to genetic syndrome such as Gorlin syndrome, limitations because of location of tumor, or cumulative prior

radiotherapy dose). For patients whose locally advanced BCC has been irradiated, disease must have progressed after radiation

7. Patients with Gorlin syndrome may enroll in this study but must meet the criteria for locally advanced or metastatic disease listed above
8. Patients with measurable and/or non-measurable disease (as defined by RECIST, v1.1) are allowed.
9. Adequate organ function, as evidenced by the following laboratory results:
   - Hemoglobin >8.5 g/dL
   - Granulocyte count $\geq 1000/\mu L$
   - Platelet count $\geq 75{,}000/\mu L$
   - Aspartate transaminase (AST [SGOT]) and alanine transaminase (ALT [SGPT]) $\leq 3 \times$ upper limit of normal (ULN)
   - Total bilirubin $\leq 1.5 \times$ ULN or within $3 \times$ ULN for patients with documented Gilbert syndrome
10. Women of childbearing potential must use two methods of acceptable contraception including one highly effective method and a barrier method (see also Appendix 2), as directed by their physician during treatment and for at least *9* months *or as per approved local prescribing information for vismodegib (where available), whichever is longer,* after completion of study treatment. Highly-effective methods of contraception are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly (e.g., implants, injectables, or intra-uterine devices. At the discretion of the Investigator, acceptable methods of contraception may include total abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and postovulation methods) and withdrawal are not acceptable methods of contraception (see Appendix 2)

    NOTE: The pregnancy prevention duration for female patients was changed from 7 to 9 months or as per approved local prescribing information, whichever is longer, after all patients were enrolled in the study.
11. For male patients with female partners of childbearing potential, agreement to use a condom with spermicide *(where available)*, even after vasectomy, during sexual intercourse with female partners while being treated with vismodegib and for 2 months *or as per approved local prescribing information for vismodegib (where available), whichever is longer,* after completion of study treatment

    NOTE: The contraception duration for male patients was changed from 2 months to 2 months or as per approved local prescribing information, whichever is longer, after all patients were enrolled in the study.
12. Agreement not to donate blood or blood products during the study and for at least *9* months *or as per approved local prescribing information for vismodegib (where available), whichever is longer* after discontinuation of vismodegib. Because vismodegib has been detected in seminal fluid, in addition for men, agreement not donate sperm during the study or for at least 2 months *or as per approved local*

prescribing information for vismodegib (where available), whichever is longer after discontinuation of therapy

NOTE: The waiting time for blood donations was changed from 7 to 9 months or as per approved local prescribing information, whichever is longer, after all patients were enrolled in the study.

13. Life expectancy > 12 weeks.
14. Negative serum pregnancy test within 7 days prior to commencement of dosing in premenopausal women. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥ 1 year

4.3 EXCLUSION CRITERIA

A patient will be excluded if the answer to any of the following statements is "yes."

1. Inability or unwillingness to swallow capsules
2. Pregnancy or lactation
3. Concurrent non–protocol-specified anti-tumor therapy (e.g., chemotherapy, other targeted therapy, radiation therapy, or photodynamic therapy, including participation in an experimental drug study; note that treatment breaks up to 8 weeks for radiation therapy are allowed [see Section 6.1.1])
4. Completion of most recent anti-tumor therapy less than 21 days prior to initiation of treatment
5. Uncontrolled medical illnesses such as infection requiring treatment with intravenous antibiotics
6. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or that renders the patient at high risk from treatment complications
7. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol
8. Patients with one of the following rare hereditary conditions: galactose intolerance, primary hypolactasia, or glucose-galactose malabsorption

4.4 CONCOMITANT MEDICATION AND TREATMENT

4.4.1 Concomitant Therapy

Concomitant therapy includes any prescription medications or over the counter preparations used by a patient between the 14 days preceding the screening evaluation and the 12 months Safety Follow-up visit. All concomitant medications should be reported to the Investigator and recorded on the appropriate electronic case report form (eCRF).

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Results of a drug-drug interaction study conducted in cancer patients demonstrated that the systemic exposure of ethinyl estradiol and norethindrone is not altered when co-administered with vismodegib. However, the interaction study was of only 7 days duration, and it cannot be excluded that vismodegib upon longer treatment is a mild inducer of enzymes that metabolize ethinyl estradiol contraceptive steroids. This modest induction might lead to a decrease in systemic exposure of this contraceptive steroid, and thereby reduced contraceptive efficacy.

4.4.2 Excluded Therapy and Potential Interactions With Concomitant Drugs

Coadministration of St John's wort (Hypericum perforatum) and other concomitant anti-tumor therapies are prohibited during this study.

Medicinal products that alter the pH of the upper gastrointestinal tract (e.g., proton pump inhibitors, H2-receptor antagonists, and antacids) may alter the solubility of vismodegib and reduce its bioavailability. However, no formal clinical trial has been conducted to evaluate the effect of gastric pH altering agents on the systemic exposure of vismodegib. Increasing the dose of vismodegib when co-administered with such agents is not likely to compensate for the loss of exposure. Therefore, when vismodegib is co-administered with a proton pump inhibitor, H2-receptor antagonist, or antacid, systemic exposure of vismodegib may be decreased, and the effect on efficacy of vismodegib is unknown. Patients with achlorhydria would be subject to the same potential effect.

In vitro studies indicate that vismodegib is a substrate of the efflux transporter P-glycoprotein (P-gp) and the drug metabolizing enzymes CYP2C9 and CYP3A4. When vismodegib is co-administered with medicinal products that inhibit P-gp (e.g., clarithromycin, erythromycin, azithromycin, verapamil, cyclosporine), CYP2C9 (e.g., amiodarone, fluconazole, miconazole), or CYP3A4 (e.g., boceprevir, clarithromycin, coniraptan, indinavir, traconazole, ketoconazole, lopinavir/ritonavir, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole), systemic exposure of vismodegib and incidence of adverse events of vismodegib may be increased. When vismodegib is administered with CYP inducers (e.g., rifampin, carbemazepine, phenytoin, St. John’s wort) exposure to vismodegib may be decreased.

Results of a drug-drug interaction study conducted in cancer patients demonstrated that the systemic exposure of ethinyl estradiol and norethindrone is not altered when co-administered with vismodegib. However, the interaction study was of only 7 days duration, and it cannot be excluded that vismodegib upon longer treatment is a mild inducer of enzymes that metabolize ethinyl estradiol contraceptive steroids. This modest induction might lead to a decrease in systemic exposure of this contraceptive steroid, and thereby reduced contraceptive efficacy.

In vitro studies indicate that vismodegib has the potential to act as an inhibitor of breast cancer resistance protein (BCRP). In vivo interaction data are not available. It may not be excluded that vismodegib may give rise to increased exposure of drugs transported by this protein, such as rosuvastatin, topotecan, and sulfasalazin. Concomitant administration should be performed with caution and a dose adjustment may be necessary.

In vitro, CYP2C8 was the most sensitive CYP isoform for vismodegib inhibition. However, results of a drug-drug interaction study conducted in cancer patients demonstrated that the systemic exposure of rosiglitazone (a CYP2C8 substrate) is not altered when either agent is co-administered with vismodegib. Thus, inhibition of CYP enzymes by vismodegib in vivo may be excluded (33).

4.5 CRITERIA FOR PREMATURE STUDY WITHDRAWAL

Patients have the right to withdraw from the study at any time for any reason.

In the case that the patient decides to prematurely discontinue study treatment ("refuses treatment"), he/she should be asked if he/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 lost to follow-up, the Investigator should contact the patient or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. 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, AEs, 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 felt 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.

If the reason for the removal of a patient from the study is an AE, then the principal specific event will be recorded on the eCRF. The patient should be followed until the AE has resolved, if possible.

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

All scheduled study assessments are outlined in Table 1 (Schedule of Assessments).

All Screening/Baseline assessments, as outlined in Table 1, must be performed within 28 days prior to the first administration of vismodegib on Day 1, Cycle 1. Results of tests or examinations performed as standard of care before obtaining informed consent and within the 28 days prior to commencing vismodegib may be used. Tumor assessment by physical examination should be performed within a maximum of 7 days prior to the first dose of study drug (baseline reading). If tumor assessment requires imaging, baseline CT/MRI scans should be performed within a maximum of 28 days prior to the first dose of study drug (on Cycle 1, Day 1). Non-measurable disease should be assessed within 28 days prior to study initiation.

All assessments during the Treatment Phase must be performed within a window ±3 days, from Cycle 2 onwards of the day indicated on the schedule of assessment, with the exception of tumor assessments. The majority of the patients in this study have locally advanced BCC and in this disease setting measurable tumors are accessible to evaluation by physical examination every 4 to 8 weeks (±5 days). If assessment requires imaging, CT and/or MRI scans should occur every 8 to 16 weeks (±5 days) or as per institutional standards.

Eligibility for the study will be determined by the Investigator from the mandatory Screening/Baseline assessments performed during screening and according to the study inclusion/exclusion criteria. First dosing of vismodegib will be determined by the patient's eligibility and the laboratory assessments on Day 1 prior to dosing.

The treatment period will begin on Day 1, and patients will be followed until Investigator-assessed disease progression, unacceptable toxicities most probably attributable to vismodegib, patient consent withdrawal, death, reasons deemed by the treating physician, or study termination by the Sponsor. In addition, five Safety Follow-Up Visits 1 month, 3 months, 6 months, 9 months, and 12 months will occur after the last dose of vismodegib (± 5 days), as provided by this phase II safety study protocol. The first anti-cancer therapy received by the patient after discontinuation of study drug will also be recorded.

5.1 SCREENING EXAMINATION AND ELIGIBILITY SCREENING FORM

All patients must provide written informed consent before any study-specific assessments or procedures are performed.

Screening /baseline evaluations must be performed between Day −28 and −1. Patients who fulfill all the inclusion and none of the exclusion criteria will be accepted into the study.

An Eligibility Screening Form (ESF) documenting the Investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator.

A log must be maintained by the Investigator of all patients who fail screening. For those patients from whom Informed Consent has been obtained but who do not meet the Inclusion and Exclusion criteria on Day 1, only the Screening Log pages, demographics, and reason for screening failure will be collected.

5.2 PROCEDURES FOR ENROLLMENT OF ELIGIBLE PATIENTS

A patient who has fulfilled the entry criteria will attend on the morning of Day 1, at which time a patient number will be allocated by the Interactive Web-Based/Voice Response System, which has been established for the purpose of this study.

Under no circumstances will patients who enroll in this study and have completed treatment as specified be permitted to re-enroll in the study.

A Patient Enrollment and Identification Code List must be maintained by the Investigator.

5.3 CLINICAL ASSESSMENTS AND PROCEDURES

The following clinical assessments and procedures must be completed for all patients enrolled in this study at screening/baseline and during study visits.

All assessments must be performed within a window of 3 days prior to and after the scheduled visit date from Cycle 2 onwards of the day indicated on the schedule of assessment, except for tumor evaluations (see Section 5.3.1), for which a window of ±5 days will apply. Please refer to Table 1 (Schedule of Assessments) for specific details and time points collected on clinical assessments and procedures outlined below:

5.3.1 Screening/Baseline Period Assessments

Potential participants will undergo the following screening procedures no more than 28 days prior to Day 1, Cycle 1 (unless they have already been conducted during this time period as part of the patient's routine clinical care):

- Informed consent
- Archival tumor tissue from a metastatic BCC site in metastatic BCC patients who are on study after approval of the Study Protocol, version 4.0
- Complete medical history (including BCC history) and demographics
    - Collection of metastatic BCC history, such as evidence of progression prior to enrollment and reason(s) for discontinuation from prior treatment, will be collected in patients who are on study after approval of the Study Protocol, version 4.0
- Complete physical examination including weight and height at screening only
- Vital signs (body temperature, blood pressure, and pulse)

- ECOG PS assessment
- Hematology (including hemoglobin, hematocrit, red blood cell count, full white blood cell count including differential, platelet count, and absolute neutrophil count [ANC])
- Biochemistry (including glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, creatine kinase [also known as creatine phosphokinase], total bilirubin, alkaline phosphatase, AST, and ALT)
- Serum pregnancy test (within 7 days prior to the commencement of dosing) for women of child bearing potential (see Appendix 2)
- For women of childbearing potential:
    - Record date of last menses
    - Ultrasound
    - Record any amenorrhea/irregular menses, relevant gynecologic medical history, and concurrent gynecologic conditions
    - Perform serum hormone evaluation, including follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and thyroid stimulating hormone (TSH)
- 12-lead electrocardiogram (ECG)
- AEs/SAEs. After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected. All AEs (either related to study-specific procedures or otherwise) experienced after the patient has signed the Informed Consent form, but before they have received study treatment, should be recorded as medical history
- Concomitant therapy
- Tumor assessment (the majority of patients in this study have locally advanced BCC and in this disease setting measurable tumors are accessible to evaluation by physical examination):
    - Measurable tumors accessible to evaluation by physical examination should be assessed within a maximum of 7 days prior to the first dose of study drug (baseline reading)
    - If assessment requires imaging, baseline CT and/or MRI should be performed within a maximum of 28 days prior to the first dose of study drug
    - Non-measurable disease should be assessed within 28 days prior to study initiation
- In selected sites, patients will complete the Skindex-16 Quality of Life questionnaire (see Section 5.5 and Appendix 5)
- Patients with metastatic BCC (newly enrolled after approval of the Study Protocol, version 4.0) will complete the M.D. Anderson Symptom Inventory (see Main Protocol, Section 5.6 and Appendix 6) prior to having any study-related procedures performed at the visit

5.3.2 Treatment Phase Assessments

Day 1 of the study will be defined as the first day a patient receives vismodegib. One cycle of therapy is defined as 28 days of treatment. During the Treatment Phase, all study assessments will be conducted on Day 1 (±3 days) of each Cycle, with the exception of tumor evaluation, for which a window of ±5 days will apply (see below). The assessments during the treatment period are:

- Limited physical examination at every 28-day visit
- Vital signs (body temperature, blood pressure, and pulse) and weight at every 28-day visit
- ECOG PS assessment at every 28-day visit
- Hematology (including hemoglobin, hematocrit, red blood cell count, full white blood cell count including differential, platelet count, and ANC) at every 28-day visit
- Biochemistry (including glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, creatine kinase [also known as creatine phosphokinase], total bilirubin, alkaline phosphatase, AST, and ALT) at every 28-day visit
- Urine pregnancy tests on Day 1 of each subsequent Cycle. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test
- 12-lead ECG (during the study if clinically indicated)
- Concomitant therapy and AEs (including SAEs) throughout the study
- For women of childbearing potential:
    - Record date of last menses
    - Ultrasound (as clinically indicated [see Schedule of Assessments])
    - Assess amenorrhea/irregular menses that develops while on study:
        1. At start of amenorrhea/irregular menses, perform serum hormone evaluation at study site, including FSH, LH, E2, and TSH, and refer to gynecologist or appropriate specialist for assessment of ovaries and uterus, including ultrasound
        2. At resolution of amenorrhea/irregular menses, perform serum hormone evaluation at site, including FSH, LH, E2, and TSH. Refer to gynecologist or appropriate specialist for follow-up ultrasound ONLY if there was abnormality identified during previous ultrasound
        3. If amenorrhea/irregular menses recurs, repeat evaluations at start of recurrence as detailed previously
- Vismodegib administration throughout the study
- Tumor assessment (the majority of the patients in this study have locally advanced BCC and in this disease setting measurable tumors are accessible to evaluation by physical examination). Objective responses using RECIST, v1.1 should be confirmed by repeat assessments at least 4 weeks after initial documentation of response:

- Measurable tumors accessible to evaluation by physical examination should be assessed every 4 to 8 weeks throughout the study from the time of the first dose, regardless of dosing delays
- If assessment requires imaging, baseline CT and/or MRI should be performed within a maximum of 28 days prior to the first dose of study drug and, if such scans demonstrate evidence of disease, follow-up imaging studies (CT and/or MRI) should be performed every 8 to 16 weeks from the time of the first dose, regardless of dosing delays, or per institutional standards. The same imaging technique (CT or MRI) should be used for each patient throughout the study
- In metastatic BCC patients (newly enrolled after approval of the Study Protocol, version 4.0), imaging at baseline (CT and/or MRI scan) should be performed within a maximum of 28 days before the first dose. Follow-up imaging studies (CT and/or MRI scan) should be performed every 8 weeks (±5 days) from the time of the first dose, regardless of dosing delays. The same imaging technique (CT or MRI) should be used for each patient throughout the study
- Other imaging techniques may be performed as clinically indicated, but should not be used for determining tumor response
- Patients with non-measurable disease at baseline should be assessed for disease progression when clinically indicated and in accordance with standard clinical practice. For metastatic patients, assessment of non-measurable disease should be according to RECIST, version 1.1.

- Follow up for disease progression
- In selected sites, patients will complete the Skindex-16 Quality of Life questionnaire after Cycle 1 and after Cycle 6 (at 6 months of treatment) for the patients still on study (see Section 5.5 and Appendix 5)
- Patients with metastatic BCC (newly enrolled after approval of the Study Protocol, version 4.0) will complete the M.D. Anderson Symptom Inventory (see Section 5.6 and Appendix 6) at every visit, prior to having any other assessments performed
- In selected sites, post-treatment PK testing will be performed on 30 patients. This testing requires a single blood draw for PK testing at steady-state for comparison to the post-treatment samples collected. Steady-state is defined as any time point while a patient is taking vismodegib for at least 2 weeks continuously.

5.3.3 End of Treatment Visit Assessments

The End of Treatment Visit will be performed when the patient discontinues vismodegib, regardless of when it occurs.

The following evaluations will be conducted at the End of Treatment Visit:

- Limited physical examination
- Vital signs (body temperature, blood pressure, and pulse) and weight
- ECOG PS assessment

- Hematology (including hemoglobin, hematocrit, red blood cell count, full white blood cell count including differential, platelet count, and ANC)
- Biochemistry (including glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, creatine kinase [also known as creatine phosphokinase], total bilirubin, alkaline phosphatase, AST, and ALT)
- Tumor assessment
- 12- lead ECG (if clinically indicated)
- Concomitant therapy and new anti-cancer therapy
- AEs (including SAEs)
- For women of childbearing potential:
    - Record date of last menses
    - Assess amenorrhea/irregular menses that develops while on study:
        1. At start of amenorrhea/irregular menses, perform serum hormone evaluation at study site, including FSH, LH, E2, and TSH, and refer to gynecologist or appropriate specialist for assessment of ovaries and uterus, including ultrasound
        2. At resolution of amenorrhea/irregular menses, perform serum hormone evaluation at site, including FSH, LH, E2, and TSH. Refer to gynecologist or appropriate specialist for follow-up ultrasound ONLY if there was abnormality identified during previous ultrasound
        3. If amenorrhea/irregular menses recurs, repeat evaluations at start of recurrence as detailed previously
- Follow up for disease progression
- Pregnancy test for women of childbearing potential
- In selected sites, patients will complete the Skindex-16 Quality of Life questionnaire (see Section 5.5 and Appendix 5).
- Patients with metastatic BCC (newly enrolled after approval of the Study Protocol, version 4.0) will complete the M.D. Anderson Symptom Inventory (see Section 5.6 and Appendix 6), prior to having any other assessments performed
- In metastatic BCC patients who develop tumor progression on vismodegib treatment, a biopsy will be performed if at least one of the progressing lesions is accessible, e.g., skin, superficial mass, or lymph node
- Collection of whole blood in metastatic BCC patients with tumor biopsy at progression

5.3.4 Safety Follow-Up Phase Assessments

Patients who discontinue from the study will be asked to return to the clinic for a safety follow-up assessment 1 month, 3 months, 6 months, 9 months, and 12 months after the last dose of vismodegib (+/- 5 days), as provided by this phase II, safety study protocol,

or upon initiation of new non-permitted anti-cancer therapy. The assessments will include:

- Hematology (including hemoglobin, hematocrit, red blood cell count, full white blood cell count including differential, platelet count, and ANC) as clinically indicated
- Biochemistry (including glucose, sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatine kinase [also known as creatine phosphokinase], total bilirubin, alkaline phosphatase, AST, and ALT) as clinically indicated
- Follow up for disease progression
- Concomitant therapy and new anti-cancer therapy
- AEs (including SAEs)
- For women of childbearing potential:
    - Record date of last menses
    - Assess amenorrhea/irregular menses that develops while on study:
        1. At start of amenorrhea/irregular menses, perform serum hormone evaluation at study site, including FSH, LH, E2, and TSH, and refer to gynecologist or appropriate specialist for assessment of ovaries and uterus, including ultrasound
        2. At resolution of amenorrhea/irregular menses, perform serum hormone evaluation at site, including FSH, LH, E2, and TSH. Refer to gynecologist or appropriate specialist for follow-up ultrasound ONLY if there was abnormality identified during previous ultrasound
        3. If amenorrhea/irregular menses recurs, repeat evaluations at start of recurrence as detailed previously
- Patients with metastatic BCC (newly enrolled after approval of the Study Protocol, version 4.0) will complete the M.D. Anderson Symptom Inventory (see Section 5.6 and Appendix 6), prior to having any other assessments performed at the visits
- In selected sites, patients will have blood draws for adverse event–related PK testing if any adverse events that were reported to be related to vismodegib treatment continue to be present at least 6 months after the last dose of vismodegib. Blood samples for the adverse event-related PK testing will be collected at the 6, 9, and 12 months Safety Follow-Up Visits. Blood samples for all time points will be collected even if the adverse event resolves after the 6 months Safety Follow-Up Visit.
- In selected sites, post-treatment PK testing will be performed on 30 patients. Patients, who previously provided a PK sample at steady-state, will have blood draws for post-treatment PK testing at the 3, 6, 9, and 12 months Safety Follow-up Visits.

5.3.5 Post-Study Pregnancy Assessments

Female patients of childbearing potential must continue to use an effective method of contraception for *9* months after the last dose of vismodegib. Acceptable contraception and duration of contraceptive use should comply with locally approved vismodegib (Erivedge®, the trade name for vismodegib) Pregnancy Prevention Program or prescribing information where vismodegib is commercially available. If a pregnancy occurs within *9* months *or within the designated window per approved local prescribing information for vismodegib (where available), whichever is longer,* of the last dose of vismodegib, the Investigator should report to the Sponsor (refer to Sections 7.1.1.4 and 7.1.2). The Investigator should counsel the patient, discussing the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

5.3.6 Tumor Response Criteria

Tumor response will be evaluated according to the RECIST, v1.1 criteria (Appendix 1). The majority of patients in this study have locally advanced BCC and in this disease setting measurable tumors are accessible to evaluation by physical examination. This study allows for more than two target skin lesions, which takes into account patient with multiple BCC.

In this study, tumor response will be measured for patients with measurable disease by physical examination and/or imaging (CT and/or MRI scans), at the Investigator's discretion. Other imaging techniques may be performed as clinically indicated, but should not be used for determining tumor response. For each patient, the same method of assessment and the same technique **must** be used to evaluate each lesion throughout the entire study. If more than one method is used, the most accurate method according to RECIST should be selected when recording data.

Patients with non-measurable disease should be assessed for disease progression when clinically indicated and in accordance with standard clinical practice. For metastatic patients, assessment of non-measurable disease should be carried out according to RECIST, version 1.1.

For both metastatic and locally advanced BCC cohorts, a new cutaneous BCC will be considered as PD if the lesion is >5 mm and can be clearly documented as not being previously present, unless it is confirmed on biopsy not to be consistent with BCC.

Consistency of consecutive CT-scans, X-rays, or MRIs should be ensured during all assessments for each patient, with the same technique being used for evaluating lesions throughout the treatment period. (Use of spiral CT or MRI is required for baseline lesions <20 mm and must be documented in medical records and used consistently throughout the study.) The use of oral and IV contrast, etc., should be kept consistent as long as it is clinically possible. Tumor measurements should be made by the same Investigator/radiologist for each patient during the study to the extent that this is feasible.

In case of clinically measurable superficial lesions (such as skin), repeated photographs should be used to document tumor response. These photos must include a ruler for documentation purposes.

Tumor response will be confirmed a minimum of 4 weeks after the initial response was noted, or at the next scheduled tumor assessment if it is to occur more than 4 weeks after the initial response.

Scheduling of Tumor Assessments

The majority of patients in this study have locally advanced BCC, and in this disease setting measurable tumors are accessible to evaluation by physical examination.

Tumor assessment by physical examination should be performed within a maximum of 7 days prior to the first dose of study drug (baseline reading). If tumor assessment requires imaging, baseline CT/MRI scans should be performed within a maximum of 28 days prior to the first dose of study drug (on Cycle 1, Day 1). Non-measurable disease should be assessed within 28 days prior to study initiation.

Post-baseline measurable tumors accessible to evaluation by physical examination are to be performed every 4 to 8 weeks (±5 days). For tumor assessment requiring imaging and if the baseline scans demonstrate evidence of disease, CT and/or MRI scans should occur every 8 to 16 weeks (±5 days) or as per institutional standards. The same imaging technique must be used for a patient throughout the study.

In metastatic BCC patients who are newly enrolled after approval of the Study Protocol, version 4.0, imaging at baseline (CT and/or MRI scan) should be performed within a maximum of 28 days before first dose. Follow-up imaging studies (CT and/or MRI scan) should be performed every 8 weeks (±5 days) from the time of the first dose, regardless of dosing delays. The same imaging technique (CT or MRI) should be used for each patient throughout the study.

If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed.

All tumor assessments after baseline will be done within ±5 days of the scheduled visit. If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessment, unless signs of clinical progression are present.

5.3.7 Clinical Safety Assessments

The National Cancer Institute Common Terminology for Adverse Events, Version 4.0 (NCI-CTCAE, v4.0) will be used to evaluate the clinical safety of the treatment in this study (available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html). All patients who

receive at least one dose of vismodegib will be included in the safety analyses. Safety will be assessed through summaries of AEs, SAEs, AEs grade 3 or 4, AEs that caused vismodegib discontinuation and interruption, and cause of death on study.

All AEs will be assessed according to the NCI-CTCAE, v4.0 grading system. The analysis of AEs will focus on treatment-emergent AEs, i.e., AEs occurring on or after the first day of vismodegib administration. Non–treatment-emergent AEs (i.e., those occurring before commencement of study medication) will only be listed. The incidence, type, and severity of AEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. AEs of special interest, AEs leading to treatment interruption and discontinuation, and SAEs will be analyzed in a similar way to all AEs. Cause of death will also be summarized and listed.

Exposure to study medication will be summarized by means of descriptive statistics for the cumulative dose and frequency tables (percentages) by Cycles and/or Week of treatments. The reason for the dose discontinuation, other than disease progression, will also be summarized.

Laboratory parameters, hematology, and serum biochemistry will be presented in shift tables of NCI-CTCAE, v4.0 grade at baseline versus worst grade during treatment period. The laboratory parameters will be also summarized as continuous or discrete data when applicable.

Vital signs, ECOG PS, physical examination, and ECG (if available) will be summarized over time. Concomitant therapy will be summarized by frequency tables and percentages. New anti-cancer therapy will be analyzed in a similar way to concomitant therapy at the End of Treatment Visit. Protocol deviations will be listed.

5.3.8 Medical History and Demographics

Medical history includes all clinically significant diseases, previous surgeries, prior skin cancer history (especially BCC), prior skin cancer therapies, procedures, and responses to prior therapies (especially BCC). It will also include all medications used by the patient within 14 days preceding the screening visit. In women of childbearing potential, medical history will also include a record of any amenorrhea/irregular menses, relevant gynecologic medical history, and concurrent gynecologic conditions, as well as the date of last menses prior to study drug administration. In metastatic BCC patients who enrolled after approval of the Study Protocol, version 4.0, medical history will also include evidence of progression prior to enrollment on study and the reason for discontinuation from prior treatments (if applicable).

Demographic information will include age, gender, and race as applicable.

5.3.9 Performance Status

Performance status will be measured using the ECOG PS scale (see Appendix 3).

It is recommended, where possible, that a patient's performance status will be assessed by the same person throughout the study.

Performance status will be assessed at each visit, except in the Safety Follow-Up Visit.

5.3.10 Physical Examination

The initial complete physical examination should include the evaluation of the head, eyes, ears, nose and throat; and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Height and weight will also be recorded. Subsequent limited physical examinations for assessment of toxicity may be restricted to evaluation of specific systems or areas of interest, including those with previously abnormal findings or associated with symptomatic or laboratory evidence of toxicity. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs if appropriate.

In women of childbearing potential, the date of last menses should be recorded at each visit.

5.3.11 Vital Signs

Vital signs will be recorded for all patients and will include blood pressure (BP), temperature (°C), and pulse. Vital signs will be obtained at baseline (Day 1 pre-dose), at each monthly visit, and at the End of Treatment Visit.

5.3.12 Electrocardiographic Assessment

Electrical activity of the heart will be assessed by standard twelve-lead electrocardiograms (ECGs). ECGs will be performed at screening and thereafter throughout the study and at the End of Treatment Visit, as clinically indicated.

5.3.13 Ultrasound

If women of childbearing potential develop amenorrhea/irregular menses while on study, they will be referred to a gynecologist or appropriate specialist at the start of amenorrhea/irregular menses for assessment of their ovaries and uterus by ultrasound. At resolution of amenorrhea/irregular menses, they will be referred to a gynecologist or appropriate specialist for a follow-up ultrasound ONLY if there was abnormality identified during the prior ultrasound. Ultrasound analyses will be repeated if the amenorrhea/irregular menses recurs. The ultrasound report/results must be forwarded to the study site and any abnormal findings recorded in the CRF.

5.4 LABORATORY ASSESSMENTS

Samples for hematology, serum chemistry, and pregnancy will be analyzed at the study site's local laboratory. Normal ranges for the study laboratory parameters must be supplied to Roche before the study starts. Changes to the normal ranges during the course of the study should be notified to Roche as soon as possible.

Laboratory assessments will be performed at screening/baseline, at each 28-Day visit, at the End of Treatment Visit, and at five Safety Follow-Up Visits 1 month, 3 months, 6 months, 9 months, and 12 months after the last dose of vismodegib (±5 days), as provided by this phase II safety study protocol for hematology and biochemistry, if clinically indicated.

The total volume of blood loss for laboratory assessments will be approximately **220** mL throughout the duration of the study (slightly higher for women of childbearing potential).

5.4.1 Safety Laboratory Assessments

Samples for hematology, biochemistry, pregnancy, and serum hormone evaluation (in women of childbearing potential) will be analyzed at the study site's local laboratory.

- Hematology (hemoglobin, hematocrit, platelet count, white blood cell count, and percent or absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells])
- Biochemistry (including glucose, BUN, creatinine, creatine kinase [also known as creatine phosphokinase], sodium, potassium, chloride, bicarbonate (if routinely performed on venous blood samples), total bilirubin, alkaline phosphatase, AST, and ALT)
- Pregnancy test for all women of childbearing potential (including those who have had a tubal ligation). Women will have a serum pregnancy test within 7 days prior to the first dose of vismodegib, followed by urine pregnancy tests on Day 1 and every 4 weeks. A positive urine pregnancy test must be confirmed with a serum pregnancy test. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 year
- Serum hormone evaluation, including FSH, LH, E2, and TSH, for all women of childbearing potential at Screening. The serum hormone evaluation will be repeated at the start of amenorrhea/irregular menses and at the resolution of amenorrhea/irregular menses

5.4.2 Tumor Tissue Assessment

In metastatic BCC patients who are on study after approval of Study Protocol, version 4.0, archival tissue from a metastatic BCC site will be collected. In metastatic BCC patients who develop tumor progression on vismodegib treatment, a biopsy will be performed if at least one of the progressing lesions is accessible (e.g., skin, superficial mass, or lymph node). One or more biopsies of ONE representative progressing lesion is required per patient.

The archival and progression tumor-tissue samples will be reviewed for tumor histology. In addition, genome-wide technologies to identify somatic gene mutations (e.g., SMO mutations), copy number changes, or gene expression patterns will be carried out on DNA/RNA extracted from these tissues. DNA collected from whole blood will serve as a control for addressing tumor-specific genetic variants.

For sampling procedures and shipping instructions, see the laboratory manual. Assessments will be performed by the Sponsor or a Sponsor-selected vendor.

5.5 QUALITY OF LIFE ASSESSMENTS

In selected sites, QoL assessments using the Skindex-16 tool (Appendix 5) will be performed up to 4 times. Eligible patients will be asked to complete the questionnaire at baseline, i.e., before the start of treatment with vismodegib, after completion of Cycle 1, after completion of Cycle 6, and at the End of Treatment Visit.

Patients should complete the questionnaire at the beginning of each visit, before any extensive contact and consultation with the clinician/study Investigator, as the consultation may bias the patient's perceptions about his or her skin condition-related QoL.

Skindex-16 measures the effect of skin disease on patients' QoL through three major domains: skin symptom, effect on emotions, and effect on physical and social functioning. It has been shown to be useful in patients with non-melanoma skin cancers, including BCC (27, 29), but there are limited data in patients with higher burden tumors. Clinicians can use this tool to complement their own assessment of the severity of disease and response to therapy.

5.6 DISEASE SYMPTOM ASSESSMENT

The M.D. Anderson Symptom Inventory (MDASI, See Appendix 6) will be used to assess the impact of treatment on symptoms in patients with metastatic BCC who enrolled after approval of the Study Protocol, version 4.0. Eligible patients will be asked to complete the questionnaire at baseline, i.e., before the start of treatment with vismodegib, at every clinic visit while receiving vismodegib, at the End of Treatment Visit, and at every Safety Follow-Up Visit.

Patients should complete the questionnaire at the beginning of each visit, before any extensive contact and consultation with the clinician/study investigator, as the consultation may bias the patient's perceptions about his or her disease symptom(s).

The MDASI core instrument is a 19-item, valid, and reliable self-report questionnaire (34) that consists of two scales that assess symptom severity and symptom interference with different aspects of a patient's life. For 13 items (pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering things, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness or tingling), patients are asked to rate how

severe the symptoms were when “at their worst” in the last 24 hours. For an additional six items, patients are asked to rate how much the symptoms have interfered with six areas of functioning (i.e., general activity, walking, work, mood, relations with other people, and enjoyment of life) in the last 24 hours. In addition to the core set of items in the MDASI, one additional symptom related to metastatic BCC will be included (coughing from the Lung Cancer module). The MDASI items are rated from 0 to 10, with 0 indicating that the symptom is either not present or does not interfere with the patient’s activities and 10 indicating that the symptom is “as bad as you can imagine” or “interfered completely” with the patient’s life.

In metastatic patients (enrolled before approval of the Study Protocol, version 4.0), disease symptoms will be assessed based on a retrospective review. A comparison of concurrent conditions and sites of metastatic disease at baseline will be used to determine disease symptoms related to metastatic disease.

5.7 PHARMACOKINETIC ASSESSMENTS AT DESIGNATED INVESTIGATIVE SITES

At selected sites that have the capability for pharmacokinetic sample collection and processing, samples for pharmacokinetic testing, will be analyzed at a central laboratory. Samples will be collected and shipped to a central laboratory or to Genentech for measuring the concentrations of the following:

- Total vismodegib
- Unbound vismodegib
- AAG

Instruction manuals and supply kits will be provided for all pharmacokinetic assessments.

5.7.1 Adverse Event-Related Pharmacokinetic Assessments

Patients will have blood draws for adverse event–related PK testing if any adverse events that were reported to be related to vismodegib treatment continue to be present at least 6 months after the last dose of vismodegib. Site personnel must ensure that a thorough review of all ongoing adverse events that have been recorded in the medical chart and eCRF is performed with the patients at the 6 months Safety Follow-up Visit to ensure that all required PK samples are collected. Blood samples (5 mL each) for the adverse event-related PK testing will be collected at the 6, 9, and 12 months Safety Follow-Up Visits.

The total volume of blood loss for adverse event-related PK assessments will be approximately **15** mL throughout the duration of the study.

5.7.2 Post-Treatment Pharmacokinetic Assessments

Post-treatment PK testing will be performed on 30 patients to further characterize the post-treatment elimination of vismodegib from steady-state exposure to 12 months post-treatment discontinuation. Patients will have a single blood draw (5 mL) for PK testing at steady-state, defined as any time point while taking vismodegib for at least 2 weeks continuously, followed by blood draws (5 mL each) for post-treatment PK testing at the 3, 6, 9, and 12 months Safety Follow-up Visits.

The total volume of blood loss for post-treatment PK assessments will be approximately **25** mL throughout the duration of the study.

6. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

6.1 DOSE AND SCHEDULE

Enrolled patients will receive continuous once-daily oral dosing of vismodegib at a dosage of 150 mg per administration. One cycle of therapy is defined as 28 days of treatment. Dose reduction of vismodegib is not permitted, as there is only a 150-mg capsule strength available.

Dosing of vismodegib will continue until one of the following occurs:

- Investigator-assessed disease progression
- Unacceptable toxicities most likely attributable to vismodegib
- Patient consent withdrawal
- Death
- Reasons deemed by the treating physician
- Study termination by the Sponsor

If there is objective evidence of progressive disease, but the Investigator believes the patient is still deriving benefit from treatment, treatment with vismodegib may be continued after consultation with the medical monitor. However, if there is evidence of further disease progression at the next tumor assessment, vismodegib should be discontinued.

At each study visit, patients will be given enough capsules for dosing until the next study visit. The Investigator is required to confirm that any female patient of childbearing potential has a negative pregnancy test, understands the teratogenic potential of vismodegib, and is using an effective method of contraception prior to dispensing vismodegib. Patients will be instructed to take one 150 mg capsule per day.

Vismodegib should be taken at approximately the same time each day, with or without food. Capsules must be swallowed whole and must not be opened under any circumstances. If a patient misses a dose (e.g., due to emesis), he or she should be instructed not to take or make up that dose and to resume dosing with the next

scheduled dose. Missed doses will not be made up. Patients will be instructed to bring all unused capsules to each study visit for assessment of compliance.

If a patient is suspected to be pregnant, vismodegib must be immediately discontinued. If it is subsequently confirmed that the patient is not pregnant, dosing may be resumed.

The terminal half-life of vismodegib has been determined to be 10–14 days in humans, based on preliminary findings in healthy patients. If plasma concentrations of vismodegib need to be lowered emergently, animal studies suggest that oral administration of activated charcoal may lower plasma drug levels more quickly than dose cessation alone.

6.1.1 Dose Modifications, Interruptions, and Delays

No dose reductions will be allowed in this study.

Treatment with vismodegib may be interrupted for up to:

- Eight weeks if a patient becomes temporarily unable to swallow capsules
- Eight weeks for an intolerable toxicity finding

Any other proposed reasons for interruption of treatment should be discussed in advance with the Medical Monitor. The Medical Monitor must be consulted in all cases where study drug will be interrupted.

Intolerable toxicities are defined as new (not present at baseline) Grade 3 or 4 AEs considered related to vismodegib that are likely to be life-threatening or irreversible and, in the opinion of the Investigator, the risk outweighs the benefit of continued treatment with vismodegib. The following AEs are not considered intolerable:

- Grade 3 or 4 events that in the opinion of the Investigator are more likely related to ongoing or recent procedures or concomitant medications other than vismodegib
- Hematologic or metabolic/chemistry laboratory abnormalities that are found on routine testing and are not considered clinically significant
- Musculoskeletal abnormalities, skin ulceration, fracture, debridement or wound care, and dental or periodontal disease related to underlying medical conditions (e.g., basal cell carcinoma and nevoid basal cell carcinoma [Gorlin] syndrome)
- Nausea, vomiting, or diarrhea that are adequately controlled after optimization of medical management
- Grade 3 infection that is transient and treatable or manageable
- Grade 3 sterility
- Asymptomatic thromboembolism found incidentally on imaging and managed with anti-coagulation therapy

Patients with an asymptomatic or tolerable severe AE may continue to receive study drug provided the AE is manageable and the patient and the Investigator agree that continued study participation is acceptable.

If a patient experiences two treatment interruptions, the Medical Monitor must be consulted before the patient can resume treatment.

6.2 PREPARATION, STORAGE, AND HANDLING OF IMP

Vismodegib will be supplied as capsules to the study sites.

Vismodegib capsules will be stored in a secured location at the clinical site at room temperature conditions (between 59°F and 86°F [15°C and 30°C]). Patients will be requested to store vismodegib at the recommended storage conditions noted on the label, out of reach of children.

In case of accidental capsule breakage, these instructions should be followed by sites and/or patients:

- Keep your face away from the open container
- Close the container and return the medication to the pharmacists for proper handling
- In case of eye or skin contact or accidental inhalation follow first aid measures (see below)
- If the contents of the capsule have spilled outside the container, wear protective gloves and protective mask, remove the spilled material with a wet towel, wash the area with soap and water, and dispose any material that had contact with the substance in a closed container
- Observe local/national regulations regarding waste disposal
- Do not allow drug to enter drains or waterways

First-aid measures

- Eye contact: Rinse immediately with tap water for 10 minutes; open eyelids forcibly
- Skin contact: Remove immediately contaminated clothes, wash affected skin with water and soap. Do not use any solvents
- Inhalation: Take fresh air and keep calm. In the event of symptoms, seek medical treatment.

Note to physician: Treat symptomatically after accidental exposure. Women of childbearing potential who are not taking vismodegib actively or pregnant women should get medical advice from a physician. For women of childbearing potential who are not taking vismodegib actively or pregnant women, preserve blood and urine samples and notify Roche Drug Safety immediately.

6.3 FORMULATION, PACKAGING, AND LABELING

The formulated drug product vismodegib is provided in hard gelatin capsules of 150 mg. The 150-mg capsules are Size 1 with a grey-colored cap and a pink-colored body. Two black stripes may be printed on the capsule shell using a commercial, compendial grade black ink. Excipients included in the capsule formulations are microcrystalline cellulose, United States Pharmacopeia/National Formulary (USP/NF); lactose monohydrate, USP/NF; sodium lauryl sulfate, USP/NF; Povidone, USP/NF; Talc, USP; sodium glycolate, USP/NF; and magnesium stearate, USP/NF. Capsules are packaged in 75-mL round, white, high-density polyethylene (High-density polyethylene [HDPE]) bottles with two-piece HDPE child-resistant caps. The bottles are induction sealed and labeled for clinical trial use only. Each bottle contains 32 capsules. For additional batch specific instructions and information for vismodegib capsules, see the packaging.

For further details, see the Vismodegib Investigator Brochure.

The packaging and labeling of the study medication will be in accordance with Roche standards and local regulations. Vismodegib will be labeled in compliance with Good Manufacturing Practice (GMP).

Study drug packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, batch number, storage conditions, drug identification and dosage, and the statement, “For Clinical Trial Use Only.”

The study drug must be stored according to the details on the product label. The drug label indicates the storage temperature.

Local packaging 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 monitor upon discovery.

6.4 DISPOSAL CONSIDERATIONS

Observe local/national regulations regarding waste disposal. Incinerate in a qualified installation with flue gas scrubbing.

6.5 BLINDING AND UNBLINDING

Not applicable. This is an open-label non-comparative study.

6.6 ACCOUNTABILITY OF IMP AND ASSESSMENT OF COMPLIANCE

6.6.1 Accountability of IMP

The Investigator is responsible for the control of drugs under investigation. Adequate records for the receipts (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing Log) of the study drug must be maintained. Accountability and patient compliance will be assessed by maintaining adequate "drug dispensing" and return records.

Accurate records must be kept for each study drug provided by the Sponsor. These records must contain the following information:

- Documentation of drug shipments received from the Sponsor (date received, quantity, and batch number)
- Disposition of unused study drug not dispensed to patient

A Drug Dispensing Log must be kept current and should contain the following information:

- The identification of the patient to whom the study medication was dispensed
- The date(s), quantity and batch number of the study medication dispensed *to* the patient
- The date(s), quantity and batch number of the study medication returned *by* the patient

All records and drug supplies must be available for inspection by the Monitor at every monitoring visit.

Patients will be asked to return all used and unused drug supply containers at the end of the treatment as a measure of compliance.

This inventory must be available for inspection by the Monitor. All supplies, including partially used or empty containers and copies of the dispensing and inventory logs, must be returned to the Monitor at the end of the study, unless alternate destruction has been authorized by Roche or required by local or institutional regulations (Section 6.6).

6.6.2 Assessment of Compliance

Patient compliance will be assessed by maintaining adequate study drug dispensing records. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the Investigator.

6.7 DESTRUCTION OF THE IMP

Local or institutional regulations may require immediate destruction of used IMP for safety reasons, e.g., cytotoxicity. In these cases, it may be acceptable for investigational

site staff to destroy dispensed IMP before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, and destroyed. Written authorization must be obtained from the Sponsor at study start up before destruction.

Written documentation of destruction must contain the following:

- Identity (batch numbers and patient numbers) of investigational product(s) destroyed
- Quantity of investigational product(s) destroyed
- Date of destruction (date discarded in designated hazardous container for destruction)
- Method of destruction (the site must provide the Sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)
- Name and signature of responsible person who discarded the investigational product in a hazardous container for destruction

7. SAFETY INSTRUCTIONS AND GUIDANCE

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified hematology and clinical chemistry variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

7.1 ADVERSE EVENTS AND LABORATORY ABNORMALITIES

7.1.1 Clinical Adverse Events (AEs)

According to the International Conference of Harmonization (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject (patient) administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions which worsen during a study are to be reported as AEs.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with locally advanced or metastatic BCC that were not present prior to the AE reporting period (see Section 7.2.1)
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)

- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies, medication washout, or no treatment run-in)
- Pre-existing medical conditions that are judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

7.1.1.1 Intensity

Intensity of all AEs will be graded according to the NCI-CTCAE, v4.0 on a five-point scale (Grade 1 to 5) and reported in detail on the eCRF.

AEs not listed on the CTCAE should be graded as follows:

Table 2 Adverse Event Grading (Severity) Scale

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the subject
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the subject at direct risk.
Grade 4	Life threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death

AE = adverse event; CTC = common terminology criteria.

7.1.1.2 Drug–Adverse Event Relationship

The causality relationship of study drug to the AE will be assessed by the Investigator as either:

Yes or No

If there is a reasonable suspected causal relationship to the study medication, i.e., there are facts (evidence) or arguments to suggest a causal relationship, drug–event relationship should be assessed as **Yes**.

The following criteria should be considered in order to assess the relationship as **Yes:**

- Reasonable temporal association with drug administration

- It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- Known response pattern to suspected drug
- Disappears or decreases on cessation or reduction in dose
- Reappears on rechallenge

The following criteria should be considered in order to assess the relationship as **No**:

- It does *not* follow a reasonable temporal sequence from administration of the drug
- It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- It does not follow a known pattern of response to the suspected drug
- It does not reappear or worsen when the drug is re-administered

7.1.1.3 Serious Adverse Events [Immediately Reportable to Roche]

A serious AE (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution. These must be reported to Roche within 24 hours of the Investigator becoming aware of the event through the eSAE page in the eCRF. An SAE 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 which 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.

**The term sudden death should be used only when the cause of a cardiac origin as per standard definition. The term death and sudden death are clearly distinct and must not be used interchangeably.

Deaths that occur during the protocol-specified AE reporting period (see Section 7.2.1) that are attributed by the Investigator solely to progression of advanced BCC will be recorded only on the Study Discontinuation eCRF. All other on-study deaths, regardless of attribution except PD, will be recorded as an SAE on the AE eCRF and expeditiously reported to the Sponsor.

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 (Appendix 4).

After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

7.1.1.4 Other Safety Findings Requiring Expedited Reporting

Other safety findings may require expedited reporting depending on local legislation.

The following events are events of special interest and will need to be reported to the Sponsor expeditiously (see Section 7.1.2 for reporting instructions), irrespective of regulatory seriousness criteria:

7.1.2 Pregnancy and Lactation

Small-molecule inhibitors of the Hedgehog pathway are known teratogens that result in midline malformations, such as holoprosencephaly, cyclopia, and other severe developmental defects. The teratogenic potential of vismodegib has been confirmed in an embryo-fetal development study in rats (please see the updated Vismodegib Investigator Brochure). Women who plan to become pregnant (during a study or for *9* months after the last dose *or within the designated window per approved local prescribing information for vismodegib [where available], whichever is longer*) are excluded from all vismodegib clinical studies. Please refer to the Vismodegib Investigator Brochure for further information regarding the teratogenic potential of vismodegib.

- Pregnant women: Vismodegib is contraindicated in pregnant women or women planning to become pregnant during treatment and for *9* months *or within the designated window per approved local prescribing information for vismodegib (where available), whichever is longer,* after the last dose.
- Nursing mothers: Vismodegib is contraindicated in nursing mothers. The extent to which vismodegib or any of its metabolites are excreted in breast milk is not known.

7.1.2.1 Use in Women of Childbearing Potential

As of the data cutoff date of 15 December 2011, there have been no reports of pregnancy in female patients treated with vismodegib.

To prevent pregnancy and the risk of fetal exposure to vismodegib, female patients should not become pregnant or plan to become pregnant during treatment with vismodegib and for *9* months *or within the designated window per approved local prescribing information for vismodegib (where available), whichever is longer,* after the last dose.

Specific actions are required when treating female patients of childbearing potential. Patients should be thoroughly counseled and informed of the teratogenic potential of vismodegib. All pregnancy prevention measures for women of childbearing potential must be followed for the duration of the study and for *9* months *or within the designated window per approved local prescribing information for vismodegib (where available),*

whichever is longer, after the last dose. Patients should be counseled on the use of contraception before beginning treatment with vismodegib. As appropriate, the treating physician should refer the subject to her gynecologist or other healthcare provider to ensure proper understanding of the use of her chosen contraceptive method. Acceptable contraception and duration of contraceptive use should comply with locally approved vismodegib (Erivedge®, the trade name for vismodegib) Pregnancy Prevention Program or prescribing information where vismodegib is commercially available.

Please refer to Appendix 2 for a definition of women of childbearing potential and a list of acceptable and unacceptable forms of contraception.

Women of childbearing potential are required to have a negative medically-supervised serum or urine pregnancy test (sensitivity of at least 50 mIU/mL) within 7 days prior to the first dose of vismodegib. Every 4 weeks thereafter, medically supervised serum or urine pregnancy tests are required for women of childbearing potential, and the test must be negative within 7 days prior to receiving her supply of vismodegib capsules.

Treating physicians must confirm (with documentation in the medical record) a negative pregnancy test and non-childbearing status (both outlined above), that the patient is using two acceptable forms of contraception, that the patient understands the risk of teratogenicity with vismodegib, and that the patient has signed the informed consent understanding the pregnancy prevention program.

Patients must notify the treating physician if they have changed their forms of contraception from the previous month.

If a woman of childbearing potential believes that her contraceptive method has failed, she must immediately stop taking vismodegib, notify her treating physician immediately, and discuss available management options. For female patients outside of the United States, the patient should immediately consult with her physician or obstetrician/gynecologist (OB/GYN) regarding options for pregnancy testing, management, and treatment.

7.1.2.2 Male Patients

It is not known if vismodegib that may be present in seminal fluid would cause teratogenic effects in a fetus born to the female partner of a male subject. Therefore, sexually active male patients must utilize a barrier form of contraception, even if he has had a vasectomy, during vismodegib treatment and for 2 months *or as per approved local prescribing information for vismodegib (where available), whichever is longer,* after the last dose.

7.1.2.3 Pregnancy Reporting

If a female patient becomes pregnant while receiving investigational therapy with vismodegib or within *9* months *or within the designated window per approved local*

prescribing information for vismodegib (where available), whichever is longer, after the last dose, the Investigator must report all pregnancies immediately i.e., no more than 24 hours after learning of the event to the Sponsor.

A female patient must be instructed to stop taking the test "drug" and immediately inform the Investigator if she becomes pregnant during the study. The Investigator should report all pregnancies immediately i.e., no more than 24 hours after learning of the event to the Sponsor, using the *Clinical Trial Pregnancy Reporting Form.* The Investigator should counsel the patient, discussing the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to *9* months *or within the designated window per approved local prescribing information for vismodegib (where available), whichever is longer,* after the completion of the study medication must also be reported to the Investigator.

If a female partner of a male patient becomes pregnant during vismodegib treatment or within 2 months *or within the designated window per approved local prescribing information for vismodegib (where available), whichever is longer,* after the last dose of vismodegib, the pregnancy must be reported to the Investigator and the Sponsor and alert the female partner to consult with her physician. The partner should be counseled and the risks of continuing the pregnancy discussed, as well as the possible effects on the fetus. Monitoring of the female partner should continue until conclusion of the pregnancy.

NOTE: The Investigator should fill out a *Pregnancy Reporting Form* only if the pregnant partner has signed a *Pregnant Partner Data Release Form.*

7.1.3 Abortion, Congenital Anomaly and Birth Defects

Abortions, congenital anomalies and birth defects are events of special interest and will need to be reported to the Sponsor immediately i.e., no more than 24 hours after learning of the event (see Section 7.1.2 for reporting instructions).

Abortion, whether therapeutic or spontaneous, should always be classified as serious (as the Sponsor considers these medically significant), recorded on an SAE eCRF page, and reported to the Sponsor immediately i.e., no more than 24 hours after learning of the event.

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to the investigational product should be recorded and reported as an SAE to the Sponsor immediately i.e., no more than 24 hours after learning of the event.

7.1.4 Blood Donation

Patients must not donate blood or blood products while on study and for *9* months *or as per approved local prescribing information for vismodegib (where available), whichever is longer,* after discontinuation of vismodegib. Where vismodegib is commercially available, avoidance of blood donation should comply with locally approved prescribing information.

7.1.5 Progression of Underlying Malignancy

Progression of underlying malignancy is not reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer, as defined by RECIST criteria or other criteria as determined by protocol. Hospitalization due *solely* to the progression of underlying malignancy should *not* be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined to be exclusively due to the progression of the underlying malignancy, or do not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the Investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception, as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

7.1.6 Treatment and Follow-Up of Adverse Events (AEs)

After the five Safety Follow-Up Visits 1 month, 3 months, 6 months, 9 months, and 12 months from the last dose of study drug continue to follow up AEs as follows:

Related SAEs are to be reported indefinitely.

Related AEs. Follow until one of the following occurs:

- Resolved or improved to baseline
- Relationship is reassessed as unrelated
- Death
- Start of new anti-cancer regimen
- Investigator confirms that no further improvement can be expected
- Clinical or safety data will no longer be collected, or final database closure

Unrelated severe or life threatening AEs. Follow until one of the following occurs:

- Resolved or improved to baseline

- Severity improved to Grade 2
- Death
- Start of new anti-cancer regimen
- Investigator confirms that no further improvement can be expected
- Clinical or safety data will no longer be collected, or final database closure

Unrelated Grade 1 or Grade 2 AEs. Follow until 30 days from the last dose of study drug.

The final outcome of each AE must be recorded on the eCRF.

7.1.7 Laboratory Test Abnormalities

Local laboratories will be used for all laboratory tests. Laboratory test abnormalities will be recorded on the AEs pages of the eCRF.

Any laboratory result abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE page in the eCRF:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g., dose modification, interruption, or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy, or treatment)

7.1.8 Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

7.2 HANDLING OF SAFETY PARAMETERS

7.2.1 Recording and Collection of Adverse Events

Information about all AEs, whether volunteered by the patient, discovered by Investigator questioning, or detected through physical examination, laboratory test, or other means, will be collected on the Adverse Event eCRF page, documented in the patient's medical records, and followed as appropriate.

All AEs and SAEs, regardless of the relationship to the trial drug, will be recorded in the eCRF.

All AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to trial drug, action taken with the trial drug, outcome, and whether the AE is classified as serious.

All AEs experienced after the patient has started study treatment must be recorded on the AE form of the eCRF, as well as all new AEs experienced during the study and during further five Safety Follow-Up Visits 1 month, 3 months, 6 months, 9 months, and 12 months after the last dose of study treatment (±5 days). SAEs considered related to study drug are to be reported indefinitely.

A pre-existing medical condition that is present at the start of the study should be recorded on the Medical History eCRF.

Worsening and/or progression of advanced BCC should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only.

If a female patient becomes pregnant while receiving investigational therapy or within 9 months *or within the designated window per approved local prescribing information for vismodegib (where available), whichever is longer,* after the last dose of investigational product, the Investigator should report to the Sponsor immediately within one working day (24 hours) of learning of the pregnancy.

Abortion, whether therapeutic or spontaneous, should always be classified as serious (as the Sponsor considers these medically significant), recorded on the eCRF, and expeditiously reported to the Sponsor.

7.2.2 Reporting of Serious Adverse Events (Immediately Reportable)

Any clinical AE or abnormal laboratory test value that is *serious* and which occurs during the course of the study (as defined in Section 7.1.1.3 above), must be reported to Roche **within 24 hours** of the Investigator becoming aware of the event (expedited reporting).

The following proviso applies:

- **During the Screening Period, after written informed consent has been signed only SAEs related to protocol procedures will be reported.**
- **From the first administration of vismodegib, all SAEs must be reported.**

Related SAEs ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to Investigators at each site and associated Institutional Review Board/Independent Ethics Committee (IRB/IEC) when the following conditions occur:

- The event must be a SAE
- There must be a certain degree of probability that the event is an adverse reaction from the administered drug
- The adverse reaction must be unexpected, that is to say, not foreseen in the Investigator's Brochure (for an unauthorized medicinal product)

When all patients at a particular site are off treatment as defined by the protocol:

- Only individual SUSAR reports originating in that particular trial will be forwarded to the site and associated IRB/IEC on an expedited basis
- Individual SUSARs considered to be a significant safety issue and/or which result in Roche recommending a change to the ICF, will be reported in an expedited manner to all Investigators and IRBs/IECs
- SUSAR reports originating from other trials using the same IMP will be provided as 6-monthly SUSAR Reports to Investigators and IRBs/IECs where long-term follow-up studies are carried out, unless they are considered significant

Unrelated SAEs must be collected and reported during the study and for up to 12 months after the last dose of study medication.

This study adheres to the definition and reporting requirements of **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.** Complete information can be found in Appendix 4.

7.2.3 Reporting of Non-Serious Events of Special Interest

Not applicable.

7.2.4 PRO Data and Adverse Event Reporting

Adverse event reports will not be derived from PRO data. However, if any patient responses suggestive of a possible adverse event are identified during site review of the PRO questionnaires, site staff will alert the investigator, who will determine if the criteria for an adverse event have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an adverse event, it will be reported on the Adverse Event eCRF.

7.3 WARNINGS AND PRECAUTIONS

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the Investigators' Brochure.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 PRIMARY AND SECONDARY VARIABLES

The final analysis for safety and efficacy will be performed when the last patient on treatment develops progressive disease (as determined by the Investigator) or unacceptable toxicity, withdraws consent, or dies; the treating physician deems the patient is no longer benefitting from treatment; or the study is terminated by the Sponsor, or 12 months after the last dose of vismodegib in the last enrolled patient still on study, whichever occurs first.

Additional interim analyses will be performed as described in Section 8.2.1.2.

8.1.1 Primary Variables

The primary objective of this trial is to assess the safety of vismodegib in patients with locally advanced or metastatic BCC.

Consequently, the following safety variables are primary variables: all AEs, AEs Grade 3 or 4, AEs leading to drug interruptions or discontinuations, SAEs, cause of death on study, premature discontinuation from study and treatment, laboratory parameters (hematology and serum chemistry), and exposure to study medication.

Continuous data will be summarized using mean, standard deviation, median, minimum, and maximum. Discrete data will be summarized using frequencies and percentages. No adjustments for multiplicity of endpoints or within-subgroup comparisons will be used in the analyses.

8.1.2 Secondary Variables

Other safety secondary variables are: physical examinations, vital signs (body temperature, blood pressure, pulse and respiratory rate), electrocardiogram, ECOG PS, and concomitant therapies.

The following efficacy variables will also be secondary variables: ORR, duration of response, time to response, PFS, OS, QoL, and disease symptom.

8.2 HYPOTHESIS TESTING

No formal hypothesis testing is planned.

8.2.1 Types of Analyses

8.2.1.1 Efficacy Analysis

The efficacy summaries will be presented for the ITT population, which will include all patients enrolled in the study.

The efficacy variable of primary interest for this study is the overall response rate (ORR), as assessed by the Investigator according to RECIST, v1.1. The summary will be

performed on patients with measureable disease at baseline. The best overall response rate (BORR) will be reported. BORR is defined as the number of patients whose best objective response is CR or PR divided by the total number of treated patients in the group for which the BORR is estimated.

Duration of response is the key secondary efficacy variable. It is defined only for the patients whose confirmed best response is CR or PR as the time interval between the date of the earliest qualifying response and the date of PD or death for any cause. For patients who are alive without progression following the qualifying response, duration of response will be censored on the date of last evaluable tumor assessment or last follow-up for progression of disease. This will be done based on Investigator's assessments.

Time to response is defined as the interval between the date of first treatment and the date of first documentation of confirmed CR or PR (whichever occur first). This will be done based on Investigator's assessments.

Progression Free Survival (PFS) is defined as the time interval between the date of the first therapy and the date of progression or death for any causes, whichever occurs first. A patient who died without a reported progression will be considered as an event on the date of death. Patients who have neither progressed nor died will be censored on the date of last evaluable tumor assessment. This will be done based on Investigator's assessments. Patients with non-measureable disease will be assessed for disease progression and included in this summary.

Overall survival (OS) is defined as the time from the date of first treatment to the date of death, regardless of the cause of death. For patients who are alive at the time of analysis, OS time will be censored at the last date the patient was known to be alive. Patients with no post baseline information will be censored at the time of first treatment with vismodegib.

The best ORRs (confirmed complete and confirmed partial responders) together with the corresponding 95% Pearson-Clopper confidence intervals will be presented. A listing of tumor assessments and best overall response will also be presented.

Estimates for the survivor function for the time-to-event endpoints, including PFS, OS, time to response, and duration of response, will be displayed graphically using Kaplan-Meier (KM) curves. Estimates for the median time to event and the corresponding two-sided 95% confidence interval will be presented with the estimates for the other quartiles and the associated ranges (minimum, maximum). The estimates and KM curves will be presented for the ITT population.

8.2.1.2 Interim Analysis

In addition to final analysis, there will be six interim analyses for publication of safety and efficacy results and DSMB reviews when the:

- First 75 patients enrolled have been treated for at least 3 months,
- First 150 patients enrolled have been treated for at least 3 months,
- First 300 patients enrolled have been treated for at least 3 months,
- First 550 patients enrolled have been treated for at least 3 months,
- First 800 patients enrolled have been treated for at least 3 months, and
- 1200 patients enrolled have been treated for at least 3 months (see also Section 10).
    - This last interim analysis will also include analysis of 500 enrolled patients who have been followed for at least 1 year.

Relevant details will be described in the DSMB charter and Statistical Analysis Plan.

8.2.2 Safety Analysis

The safety variables will be summarized for the safety population, where the safety population will include all patients who received at least one dose of study medication.

If the safety population differs by less than 5 patients from the ITT population, then all summaries will be presented only for the safety population.

AEs, AE Grade 3 or 4, AEs leading to drug interruptions or discontinuation and SAEs

All AEs will be assessed according to the NCI-CTCAE, v4.0 grading system.

The analysis of AEs will focus on treatment-emergent AEs, i.e., AEs occurring on or after the first day of vismodegib administration. Non–treatment-emergent AEs (i.e., those occurring before commencement of study medication) will only be listed.

The incidence, type, and severity of AEs will be summarized according to the primary system organ class (SOC) and within each SOC by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Summary tables might be presented for time to first onset of the AE of special interest.

SAEs and AEs leading to drug interruptions or discontinuation will be analyzed similarly. Cause of death will also be summarized and listed.

Premature withdrawal from study and treatment

The number of patients who prematurely discontinued treatment, along with the corresponding reason(s) for discontinuation, will be summarized and listed. The discontinuation from study will be also summarized and listed.

Exposure to Study Medication

The exposure of vismodegib will be summarized by means of descriptive statistics for the cumulative dose and frequency tables (percentages) by Cycles and/or Weeks of treatment. The reason for the dose discontinuation other than disease progression will be also summarized.

Laboratory parameters

Laboratory parameters, hematology, and serum chemistry will be presented in shift tables of NCI-CTCAE grade at baseline versus worst grade during the treatment period. Summary of laboratory parameters will be presented by means, standard deviation, minimum, and maximum. Graphical presentations of the mean value of selected laboratory parameters might be also displayed.

Physical Examination

Physical examination variables will be summarized over time by visit and reported in patient listings.

Vital Signs and ECG

Vital signs and ECG will be summarized over time by means of mean, median, and range (mean and maximum), and will be presented graphically over time.

ECOG PS

The ECOG PS will be summarized by frequency tables over time, and the percentage of patients in different categories will be presented by bar charts at different time points.

Concomitant therapy and new anticancer-therapy

Concomitant therapy recorded during the study and new anticancer therapy at the End of Treatment Visit will be summarized for the safety population and presented by frequency tables and percentages.

8.2.3 Other Analyses

Medical history, including demographics, (age, sex, and race as applicable), clinically significant diseases, previous surgeries, prior skin cancer history, prior skin cancer therapies and procedures, response to prior therapies, and all medications used by the patient within 14 days preceding the screening visit will be summarized at baseline for the ITT and safety populations.

In metastatic BCC patients (who are on study after approval of the Study Protocol, version 4.0), evidence of tumor progression prior to enrollment on study and reasons for

treatment discontinuation of prior therapies will be summarized. Analysis of data regarding evidence of progression prior to enrollment and reasons for treatment discontinuation of prior therapies will be performed in metastatic BCC patients.

The following exploratory analyses will be performed:

- In metastatic BCC patients, measures of pathway signaling may include, but will not be limited to, one or more of the following: 1) quantitative RT PCR profiling of Hh ligands, the target of vismodegib (SMO), and transcriptional target genes; and 2) any other assessments related to the understanding of vismodegib resistance mechanism. Analyses of mutational status of relevant pathway may be performed to determine their possible role in the development of acquired resistance in metastatic BCC patients treated with vismodegib.
- In patients with any adverse events that were reported to be related to vismodegib treatment and that are continuing at least 6 months after the last dose of vismodegib, PK analyses will be performed to determine if vismodegib is still present and may correlate with the continuing adverse event at 6, 9, and 12 months after the last dose of vismodegib.
- In 30 patients, post-treatment PK analyses will be performed to characterize the elimination of vismodegib from steady-state to 3, 6, 9, and 12 months after the last dose of vismodegib.

Protocol deviations will be listed.

8.2.3.1 Subgroup Analyses

Exploratory subgroup analyses might be performed, e.g., younger versus elderly, ECOG performance status (PS 0–1 vs. PS >1), etc.

8.2.3.2 Quality of Life Analyses and Disease Symptoms Assessment

Skindex-16

The effects of skin disease on patient's quality of life (QoL) will be accessed by the Skindex-16 questionnaire. The Skindex-16 includes three domains: symptoms, emotions and function. For ease of interpretation of scores, responses will be transformed to a linear scale of 100 varying from 0 (never bothered, i.e., best) to 100 (always bothers, i.e., worst). Distribution of scores for each domain over time will be presented by box plots and summary tables for continuous variables by means of mean, standard deviation, median, minimum, maximum, and 25^{th} and 75^{th} percentile. The mean scores will be presented by line graphs and corresponding 95% confidence intervals over time. Changes from baseline will be summarized by descriptive statistics and displayed together with associated 95% confidence intervals. Individual items of interest for each domain might also be summarized by frequency tables and presented by bar charts.

M.D. Anderson Symptom Inventory

The MDASI instrument will be used to determine the rate and the number of patients who have a 30% reduction in disease-related symptoms in metastatic BCC patients (e.g. pain, fatigue, shortness of breath, lack of appetite, dry mouth and coughing) following treatment with vismodegib in patients who have at least a score of 4 points at baseline.

QoL will be analyzed for the ITT population. If the safety population differs by more than 5 patients from the ITT population, then some QoL summaries might be presented for the safety population, as well.

More details will be presented in the statistical analysis plan.

8.2.3.3 Exploratory Pharmacokinetic Analyses

Individual and mean plasma vismodegib concentration versus time data will be tabulated and plotted. Plasma AAG concentration and unbound plasma concentration at selected time points will be estimated, tabulated and summarized (geometric mean, mean, standard deviation, coefficient of variation, median, minimum, and maximum).

Additional PK analyses may be conducted as appropriate.

8.3 SAMPLE SIZE

Approximately 1200 patients will be enrolled in this study.

Table 3 Clopper-Pearson 95% Confidence Intervals for the Observed AE Incidence[1]

Number of AE events/ observed AE incidence	95% Clopper Pearson Confidence Interval
12 (1%)	0.5%-2%
24 (2%)	1.3%-3.0%
60 (5%)	3.8%-6.4%
120 (10%)	8.4%-11.8%
240 (20%)	17.8%-22.4%
360 (30%)	27.4%-32.7%

[1] Total number of patients is 1200

Therefore, for a sample size of 1200 patients, the true AE incidence rate can be estimated to within 1.6%–1.8% assuming an observed incidence of 10%, i.e., within 95% Clopper-Pearson confidence interval of 8.4%–11.8%.

9. DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the Roche Standard Operational Procedures.

Data for this study will be recorded via an Electronic Data Capture (EDC) system using electronic CRF**.** It will be transcribed by the site from the paper source documents onto the CRF. **In no case is the eCRF to be considered as source data for this trial.**

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the study monitor (source document verification), and the maintenance of a drug-dispensing log by the Investigator.

A comprehensive validation check program utilizing front-end checks in the eCRF and back-end checks in the Roche database will verify the data and discrepancies will be generated accordingly. These are transferred electronically to the eCRF at the site for resolution by the Investigator.

The result of the analysis must not be released with individual identification of the patient until the database is closed.

Assignment of Preferred Terms and Original Terminology

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the CRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology for AEs and diseases and the International Non-proprietary Name Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures Study Committees.

10. STUDY COMMITTEES

A Data Safety Monitoring Board (DSMB) will be established for this study. The DSMB will be responsible for monitoring patient efficacy and safety data during the course of the study. The DSMB will meet to review safety data after:

- First 75 patients enrolled have been treated for at least 3 months,
- First 150 patients enrolled have been treated for at least 3 months,
- First 300 patients enrolled have been treated for at least 3 months,
- First 550 patients enrolled have been treated for at least 3 months,
- First 800 patients enrolled have been treated for at least 3 months, and
- 1200 patients enrolled have been treated for at least 3 months and as per DSMB's recommendation.

The DSMB will be responsible for independently evaluating the safety and efficacy of the patients participating in the trial and will be led by a medically qualified Chairperson. Following each meeting, the DSMB will recommend to the Sponsor that the study continues according to the protocol or suggest changes to the protocol based on the outcome of the data review.

Further details of the DSMB responsibilities and logistics will be documented in the DSMB Charter.

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Part II: Ethics and General Study Administration

12. ETHICAL ASPECTS

12.1 LOCAL REGULATIONS/DECLARATION OF HELSINKI

The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline [January 1997] or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the Investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC].

In other countries where the "Guideline for Good Clinical Practice" exists Roche and the Investigators will strictly ensure adherence to the stated provisions.

12.2 INFORMED CONSENT

12.2.1 Main Study Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain signed informed consent from each patient prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.

The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The Case Report Forms for this study contain a section for documenting patient informed consent, and this must be completed appropriately. If new safety information results in significant changes in the **benefit-risk** assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

For the patient not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood.

12.3 INDEPENDENT ETHICS COMMITTEES (IEC)/INSTITUTIONAL REVIEW BOARD (IRB)

Independent Ethics Committees [non-US]: This protocol and any accompanying material provided to the patient [such as patient information sheets or descriptions of the study used to obtain informed consent] will be submitted by the Investigator to an Independent Ethics Committee. An approval letter or certificate (specifying the protocol number and title) from the IEC/IRB must be obtained before starting the study, and should be documented in a letter to the Investigator specifying the date on which the committee met and granted the approval. This applies whenever subsequent amendments/modifications are made to the protocol.

Any modifications made to the protocol, informed consent or material provided to the patient after receipt of the IEC/IRB approval must also be submitted by the Investigator to the Committee in accordance with local procedures and regulatory requirements.

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).

When no local review board exists, the Investigator is expected to submit the protocol to a regional committee. If no regional committee exists, Roche will assist the Investigator in submitting the protocol to the European Ethics Review Committee.

Roche shall also submit an Annual Safety Report once a year to the IEC and Competent Authorities (CAs) according to local regulatory requirements and timelines of each country participating in the study.

12.4 FINANCIAL DISCLOSURE

The Investigator(s) will provide the Sponsor with sufficient accurate financial information (PD35) to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The Investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last patient, last visit).

13. CONDITIONS FOR MODIFYING THE PROTOCOL

Requests from Investigators to modify the protocol to ongoing studies will be considered only by consultation between an appropriate representative of the Sponsor and the Investigator (Investigator representative[s] in the case of a multicenter trial). Protocol modifications must be prepared by a representative of the Sponsor and initially reviewed and approved by the International Medical Leader and Biostatistician.

All protocol modifications must be submitted to the appropriate IEC or IRB for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial patients, or when the change(s) involves only logistical or administrative aspects of the trial, e.g., change in monitor[s], change of telephone number[s].

14. CONDITIONS FOR TERMINATING THE STUDY

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Roche and the Investigator will assure that adequate consideration is given to the protection of the patient's interests. The appropriate IRB/IEC and Regulatory Agencies should be informed accordingly.

15. STUDY DOCUMENTATION, CRFS AND RECORD KEEPING

15.1 INVESTIGATOR'S FILES/RETENTION OF DOCUMENTS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: 1) Investigator's Study File, and 2) patient clinical source documents.

The Investigator's Study File will contain the protocol/amendments, Case Report and Query Forms and schedule of assessments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff *curriculum vitae* and authorization forms and other appropriate documents/correspondence, etc. 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, query resolution correspondence and reasons for changes, in human readable format on compact disc, which also has to be kept with the Investigator's Study File.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original

laboratory reports, ECG, EEG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and patient screening and enrollment logs. The Investigator must keep the two categories of documents as described above (including the archival CD) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, patient to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, Roche must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and Roche to store these in a sealed container(s) outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside of the site.

ICH GCP guidelines require that Investigators maintain information in the study patient's records which corroborate data collected on the CRF(s). Completed CRFs will be forwarded to Roche.

15.2 SOURCE DOCUMENTS AND BACKGROUND DATA

The Investigator shall supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

15.3 AUDITS AND INSPECTIONS

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Roche Quality Assurance or its designees, or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

15.4 CASE REPORT FORMS OR ELECTRONIC CASE REPORT FORMS

Data for this study will be captured via an Electronic Data Capture (EDC) system by using an online eCRFs. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change.

For each patient enrolled, an eCRF must be completed and electronically signed by the principal Investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the

study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

16. MONITORING THE STUDY

It is understood that the responsible Monitor will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the trial (eCRFs, source notes and other pertinent data) provided that patient confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the eCRF. The Investigator (or his/her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

17. CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The Investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by an identification code. The Investigator should keep a patient enrolment log showing codes, names and addresses.

18. CLINICAL STUDY REPORT

A clinical study report will be written and distributed to Health Authorities as required by applicable regulatory requirements.

19. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Roche will comply with the requirements for publication of study results.

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.

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 (ICMJE) authorship requirements. Any formal publication of the study in which input of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Roche personnel.

Appendix 1 New Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication with Supplementary Explanations (1)

1. MEASURABILITY OF TUMOR AT BASELINE

1.1 DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable Tumor lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm);
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable);
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also section 2.2 below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2 Non-measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter $<$10 mm or pathological lymph nodes with $\geq$10 to $<$15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inf ammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, or abdominal masses/abdominal organomegaly identif ed by physical exam that is not measurable by reproducible imaging techniques.

1.1.3 Special considerations regarding lesion measurability

Bone and cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, positron emission tomography (PET) scan or plain f lms are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to conf rm the presence or disappearance of bone lesions.

Appendix 1 New Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication with Supplementary Explanations (1) (cont.)

- Lytic bone lesions or mixed lytic-blastic lesions, *with identif able soft tissue components*, that can be evaluated by cross-sectional imaging techniques such as CT or MRI, can be considered as measurable lesions if the soft tissue component meets the def nition of measurability described above
- Blastic bone lesions are non-measurable

Cystic lesions:

- Lesions that meet the criteria for radiographically def ned simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by def nition, simple cysts
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the def nition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions

Lesions with prior local treatment:

Tumor lesions situated in a previously irradiated area, or in an area patiented to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

1.2.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identif ed and reported lesion at baseline and during study. Imaging based evaluation should always be the preferred option.

Clinical lesions: Clinical lesions will only be considered measurable when they are superf cial and $\geq$ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new

Appendix 1 New Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication with Supplementary Explanations (1) (cont.)

lesions. However, lesions on chest X-ray may be considered measurable if they are clearly def ned and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has def ned measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during study, should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward.</u>

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor markers, Cytology, Histology: The utilization of these techniques for objective tumor evaluation cannot generally be advised but will be dependent on the study design.

<u>2. TUMOR RESPONSE EVALUATION</u>

2.1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is def ned by the presence of at least one measurable lesion.

Appendix 1 New Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication with Supplementary Explanations (1) (cont.)

2.2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of f ve lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identif ed as target lesions and will be recorded and measured at baseline.

This means in instances where patients have only one or two organ sites involved, a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in that organ will be recorded as non-measurable lesions (even if size is greater than 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be *reproducible in repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted in Section 1.1.1, pathological nodes which are def ned as measurable and may be identif ed as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualif es as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Appendix 1 New Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication with Supplementary Explanations (1) (cont.)

All other lesions (or sites of disease) including pathological lymph nodes should be identif ed as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'.

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3 RESPONSE CRITERIA

This section provides the def nitions of the criteria used to determine objective tumor response for target lesions.

2.3.1 Evaluation of target lesions

- *Complete Response:* Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
- *Partial Response:* At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- *Progressive Disease:* At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including baseline (nadir). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)
- *Stable Disease:* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

2.3.2 Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identif ed as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is def ned as having a short axis of < 10 mm.

Target lesions that become *'too small to measure'*: while on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure

and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and 'below measurable limit' (BML) should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a def nable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked)

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked (BML is equivalent to a less than sign '<').

Lesions that split or coalesce on treatment: when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3 Evaluation of non-target lesions

This section provides the def nitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specif ed in the protocol.

Complete Response: Disappearance of all non-target lesions (and, if applicable, normalization of tumor marker level). All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression (see section 2.3.4) of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

Appendix 1 New Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication with Supplementary Explanations (1) (cont.)

2.3.4 Special notes on assessment of progression of non-target disease

When the patient also has measurable disease: **in this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.** A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for **unequivocal progression** status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: this circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantif ed (by def nition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as **'sufficient to require a change in therapy'**. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be **substantial**.

2.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specif c criteria for the identif cation of new radiographic lesions; however, the f nding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique and change in imaging modality or f ndings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or f are of pre-existing lesions). This is particularly important when the patient's baseline lesions show PR or

Appendix 1 New Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication with Supplementary Explanations (1) (cont.)

CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identif ed during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans conf rm there is def nitely a new lesion, then progression should be declared using the date of the initial scan.

2.4 EVALUATION OF RESPONSE

2.4.1 Time Point Response (Overall response)

It is assumed that at each protocol specif ed time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Time Point Response – Target (w/wo Non-Target) Lesions

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Appendix 1 New Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication with Supplementary Explanations (1) (cont.)

Table 2 Time Point Response – Non-Target Lesions Only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.4.2 Missing assessments and non-evaluable designation

When no imaging/measurement is conducted all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are indicated as 'not assessed', the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Appendix 1 New Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication with Supplementary Explanations (1) (cont.)

Best response determination in trials where conf rmation of complete or PR IS NOT required:

Best response is def ned as the best response across all time points (for example, a patient who has SD at f rst assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specif ed minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at f rst assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the f rst SD assessment would be considered not evaluable.

Best response determination in trials where conf rmation of complete or partial response is required:

Complete or PRs may be claimed only if the criteria for each are met at a subsequent time point as specif ed in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Table 3 Best Overall Response When Confirmation is Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.4.3 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order, not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the CRF.

Appendix 1 New Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication with Supplementary Explanations (1) (cont.)

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1 –Table 3.

For equivocal f ndings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is conf rmed, the date of progression should be the earlier date when progression was suspected.

In studies where patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should be also captured under target or non-target lesions as appropriate. This is to avoid wrong assessments of complete OR by statistical programs while the primary tumor is still present but not evaluable.

Frequency of tumor re-evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specif c and adapted to the type and schedule of treatment. However, in the context of phase II studies where the benef cial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a Cycle) or as per institutional standards is reasonable. Smaller or greater time intervals than these could be justif ed in specif c regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identif ed in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g., time to progression, disease-free survival, PFS) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specif ed sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identif ed on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and

Appendix 1 New Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication with Supplementary Explanations (1) (cont.)

should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

Conf rmatory measurement/duration of response

Conf rmation

In non-randomized trials where response is the primary endpoint, conf rmation of PR and CR is required to ensure responses identif ed are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required conf rmation in such trials. However, in all other circumstances, i.e., in randomized trials (phase II or III) or studies where SD or progression are the primary endpoints, conf rmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response conf rmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks, or as per institutional standards) that is def ned in the study protocol.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are f rst met for CR/PR (whichever is f rst recorded) until the f rst date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are f rst met for CR until the f rst date that recurrent disease is objectively documented.

Duration of SD

SD is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

References

1. Eisenhauer, *EA*, *et al.* New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-47.

Appendix 1 New Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication with Supplementary Explanations (1) (cont.)

2. Bogaerts J, Ford R, Sargent D, Schwartz LH, Rubinstein L, Lacombe D, et al. Individual patient data analysis to assess modifications to the RECIST criteria. Eur J Cancer. 2009 Jan;45(2):248-60.

Appendix 2 Definition of Women of Childbearing Potential and Acceptable and Unacceptable Forms of Contraception

Definition of childbearing potential

Female patients who meet at least one of the following criteria are defined as women of non-childbearing potential:

- ≥50 years old and naturally amenorrheic for ≥1 year
- Permanent premature ovarian failure confirmed by specialist gynecologist
- Previous bilateral salpingo-oophorectomy or hysterectomy
- XY karyotype, Turner's syndrome, or uterine agenesis

Female patients who do not meet at least one of the above criteria are defined as women of childbearing potential.

Additionally, the parent or guardian of young female patients who have not yet started menstruation should verify that menstruation has not begun. If a young female patient reaches menarche during the study, she is to be treated as a woman of childbearing potential from that time forward.

Acceptable contraception

Women of childbearing potential are required to use two forms of acceptable contraception (including one barrier method) during participation in the study and for *9* months *or as per approved local prescribing information for vismodegib (where available), whichever is longer,* following discontinuation of vismodegib. Acceptable contraception and duration of contraceptive use should comply with locally approved vismodegib (Erivedge®, the trade name for vismodegib) Pregnancy Prevention Program or prescribing information where vismodegib is commercially available.

Acceptable forms of barrier contraception include the following:

- Latex, non-latex, or any other male condom (always used with spermicide *[where available]*)
- Diaphragm (always used with spermicide *[where available]*)

Acceptable forms of secondary contraception, when used with a barrier method, include the following:

- Combination hormonal contraceptives, hormonal patch, subcutaneous hormonal implant, or hormonal intramuscular contraceptives (medroxyprogesterone acetate depot)

  Combination hormonal contraceptives, hormonal patch, and subcutaneous hormonal implant are not considered acceptable in the EU and some countries that follow the EU prescribing information for vismodegib.

Appendix 2 Definition of Women of Childbearing Potential and Acceptable and Unacceptable Forms of Contraception (cont.)

- Tubal sterilization

Other acceptable forms include the following:

- 100% commitment to abstinence from sexual intercourse (for medical or personal reasons)

Unacceptable contraception

The following are unacceptable forms of contraception:

- IUD progesterone T
- Progestin-only contraceptives
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield
- Vaginal contraceptive ring
- *Combination hormonal contraceptives, hormonal patch, and subcutaneous hormonal implant (for countries in the EU and some countries that follow the EU prescribing information for vismodegib)*

NOTE: Patients should be counseled on the use of contraception before beginning treatment with vismodegib. As appropriate, the treating physician should refer the subject to her gynecologist or other healthcare provider to ensure proper understanding of the use of her chosen contraceptive method.

Appendix 3 Eastern Cooperative Oncology Group Performance Status

Patients will be graded according to the Eastern Cooperative Oncology Group 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

As published in: Oken, MM, *et al.* Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-655.

Appendix 4 International Conference on Harmonization (ICH) Guidelines for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2

A serious adverse event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE 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 which 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 AE is one, the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the Investigator. For SAEs, possible causes of the event **are** indicated by selecting one or more options. (Check all that apply)

- Pre-existing/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

Appendix 4 International Conference on Harmonization (ICH) Guidelines for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2 (cont.)

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

Such preliminary reports will be followed by detailed descriptions later which 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 AEs page of the CRF: 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 SAEs: Local Monitor. The local Monitor will be the initial point of contact for all study related issues. The local monitor is responsible to provide administrative details and contact information of the Roche study team as required.

ROCHE HEADQUARTERS CONTACT for SAEs and other medical emergencies:

The local Monitor will be the initial point of contact for all study related issues. The local monitor is responsible to provide administrative details and contact information of the Roche study team as required.

See the attached *Protocol Administrative and Contact Information & List of Investigators form [gcp_for000227]*, for details of administrative, contact information, and Emergency Medical Call Center Help Desk toll-free numbers.

24 HOUR MEDICAL COVERAGE

Please refer to the Emergency Medical Call Center Help Desk toll-free numbers provided by your local Monitor.

Appendix 5 Skindex-16 Quality of Life Questionnaire

These questions concerns the skin condition which has bothered you the most during the past week.

During the past week, how often have you been bothered by:	Never Bothered ↓			•			Always Bothered ↓
1. Your skin condition itching	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Your skin condition burning or stinging .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Your skin condition hurting	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Your skin condition being irritated . . .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. The persistence / reoccurrence of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. Worry about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. The appearance of your skin condition .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. Frustration about your skin condition .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. Embarrassment about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. Being annoyed about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. Feeling depressed about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. The effects of your skin condition on your interactions with others (For example: interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. The effects of your skin condition on your desire to be with people	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Your skin condition making it hard to show affection.	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. The effects of your skin condition on your daily activities	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16. Your skin condition making it hard to work or do what you enjoy	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Have you answered every item? Yes ☐ No ☐

Appendix 6 M.D. Anderson Symptom Inventory (MDASI)

Date:_____ **Institution:**_____

Participant Initials:_____ **Hospital Chart # :** _____

Participant Number:_____

M. D. Anderson Symptom Inventory- (MDASI) Core Items

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering** things at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Date:_____ **Institution:**_____

Participant Initials:_____ **Hospital Chart # :** _____

Participant Number:_____

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
14. Your **coughing** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***:

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
15. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
16. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
17. **Work** (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
18. **Relations** with other people?	○	○	○	○	○	○	○	○	○	○	○
19. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
20. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○