PROTOCOL

STUDY TITLE:	A phase 2, single-center, single-arm, open-label trial of vismodegib in patients with keratocystic odontogenic tumors
STUDY DRUG:	ERIVEDGE® (vismodegib)
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1. INTRODUCTION

1.1 Disease Background

The keratocystic odontogenic tumor (KCOT) is a benign odontogenic neoplasm that has destructive and infiltrative behavior [1]. KCOT can occur as part of nevoid basal cell carcinoma syndrome (NBCCS) or as a sporadic case. KCOTs are the most prominent feature of NBCCS and they are present in 65-100% of cases [2]. Four to five percent of KCOT patients have NBCCS [3]. Although KCOTs are benign, they tend to be aggressive, with local invasion of bony structures, extensive growth, and potential for substantial disfigurement [4]. This condition has a high recurrence rate and it is estimated that after initial treatment with various procedures recurrence ranges from 2.5% to 62.5%[5];[6]. The only therapeutic option for patients affected by KCOT is surgery which can involve significant destruction of tissue; often multiple surgeries are required. Thus, the management of patients with KCOT has challenged and frustrated both patients and providers[6].

Research findings suggest that mutations in *PTCH1* are frequent in both sporadic KCOT (29%) and NBCCS-associated KCOT (approximately 88%). Thus *PTCH1* gene mutations may play a significant role in the pathogenesis of NBCCS and the related sporadic tumors [7]. In this study, we plan to test GDC-0449 (Vismodegib) as novel treatment in two groups of patients: NBCCS-associated KCOT and sporadic KCOT cohort. The inclusion of this two-group cohort is based on the evidence that mutations of the hedgehog (Hh) pathway are present in both groups and consequently all patients affected by KCOT may benefit from a systemic Hh pathway antagonist.

We hypothesize that an inhibitor of the sonic Hh can be an important therapeutic advancement in the treatment of KCOT. This study proposes to test GDC-0449 (Vismodegib) for treating patients with KCOT. This drug has the potential to reverse KCOT proliferation. GDC-0449 may be useful as a neo-adjuvant prior to surgery in patients with KCOT or may be a surgery substitute in some cases. The use of GDC-0449 prior to surgery may lead to tumor shrinkage and reduce the extent of required surgery or eliminate the need for surgery completely.

1.2 Rationale for the Selection of Vismodegib

GDC-0449 is a synthetic, small molecule inhibitor of the sonic Hh pathway, which is involved in tumorigenesis, thus providing a strong rationale for its use in the treatment of a variety of cancers. Phase I clinical trials in patients with advanced basal cell carcinoma (BCC) and medulloblastoma (MB) highlighted an objective response to GDC-0449. Reported side effects were minor, with only one grade 4 adverse event.

Phase II trials on GDC-0449 for the treatment of advanced BCC, metastatic colorectal cancer, ovarian cancer, MB and other solid tumors have recently been completed[8]. Because of its low toxicity and specificity for the Hh pathway, this drug has potential

advantages compared with conventional chemotherapy, and may also be used in combination treatments.

On 30 January 2012, the U.S. Food and Drug Administration (FDA) approved ERIVEDGE® (vismodegib) capsules for the treatment of adults with metastatic basal cell carcinoma (mBCC), or with locally advanced basal cell carcinoma (laBCC) that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation. On 12 July 2013, vismodegib was approved for the treatment of adult patients with symptomatic metastatic basal cell carcinoma and locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy based on a conditional marketing authorization from the European Medicines Agency (EMA).

Recently it was reported that GDC-0449 was effective in treating recurrent KCOTs in a single patient [9]. The patient was a 55-year-old man with NBCCS. In addition to having multiple BCCs over a 25 year period the patient had three mandibular KCOTs that had been unsuccessfully treated with surgery, chemotherapy and radiation. The patient was started on daily oral GDC-0449 for control of his BCCs. In addition to having resolution of his BCCs at 12-week follow-up he had complete resolution of the three mandibular KCOTs, as documented by dental radiographs, after 2 years of GDC-0449 therapy.

The dose of Vismodegib chosen in this study is the same as the FDA-approved dosing for the treatment of adults with metastatic basal cell carcinoma since the expected activity of that drug dose and regimen against keratocystic odontogenic tumor is expected to be similar to basal cell carcinoma, and is consistent with doses under study in the above noted phase I and II studies of other types of cancers.

There is no prior clinical research experience using Vismodegib for the indication of KCOT. Therefore, Vismodegib will be used according to the FDA approved dose of 150 mg orally once daily.

1.3 Clinical Experience, Vismodegib Safety and Efficacy

Background on Vismodegib

Vismodegib is a small molecule inhibitor of SMO developed by Genentech, Inc. for the treatment of tumors in which the Hh signaling pathway appears to contribute to the development and maintenance of tumorigenesis. Vismodegib, a systemic Hh pathway antagonist, has been shown to have oral bioavailability and potent anti-tumor activity in a variety of primary human tumor xenografts and tumor cell line xenograft models (see the Vismodegib Investigator's Brochure and the U.S. package insert for further details).

1.3.1 Malignancies with Mutation Driven Hh Pathway Signaling

1.3.1.1 Basal Cell Carcinoma

Phase I Study SHH3925g - Safety and Pharmacokinetics Assessment

A Phase I, company-sponsored clinical trial (SHH3925g) assessed the safety and pharmacokinetics (PK) of vismodegib and responses of metastatic BCC (mBCC) or locally advanced BCC (aBCC) to the drug [10]. Thirty-three patients with mBCC or locally aBCC received oral vismodegib at one of three doses: 17 patients received 150 mg per day, 15 patients received 270 mg per day, and 1 patient received 540 mg per day (median duration of treatment was 9.8 months). Of the 33 patients, 18 had an objective response to vismodegib, according to assessment on imaging (7 patients), physical examination (10 patients), or both (1 patient). Of the patients who had a response (see Table 1), 2 had complete responses (CRs) and 16 had partial responses (PRs). The other 15 patients had either stable disease (11 patients) or progressive disease (4 patients). Eight Grade 3 adverse events (AEs) that were deemed to be possibly related to the study drug were reported in 6 patients (see Table 2), including fatigue (4 AEs), hyponatremia (2 AEs), muscle spasm (1 AE), and atrial fibrillation (1 AE). One patient withdrew from the study because of AEs.

Table 1 SHH3925g Phase I Efficacy Results

	aBCC (n=33)
Objective response, n (%)	18 (54.5%)
Complete response, n (%)	2 (6.1%)
Partial response, n (%)	16 (48.5%)
Stable disease, n (%)	11 (33.3%)
Progressive disease, n (%)	4 (12.1%)

aBCC = advanced basal cell carcinoma.

Table 2 SHH3925g Phase I Adverse Events in Patients with aBCC (n=33)

Clinical Event	Grade 2	Grade 3	Grade 4
	Number of Patients With Event		
Fatigue	0	4	0
Hyponatremia	0	2	1
Muscle spasm	3	1	0
Atrial fibrillation	0	1	0
Dysgeusia	2	NA	NA
Anorexia	2	0	0
Weight loss	2	2	0
Dyspepsia	1	0	0
Dyspnea	0	2	0
Aspiration	0	1	0
Back pain	0	1	0
Corneal abrasion	0	1	0
Dehydration	0	1	0
Keratitis	0	1	0
Lymphopenia	0	1	0
Pneumonia	0	1	0
Urinary tract infection	0	1	0
Electrocardiographic event (prolonged QT interval)	0	1	0

aBCC=advanced basal cell carcinoma; NA=not applicable.

Phase II Study ERIVANCE (SHH4476g) in Metastatic and Locally Advanced Basal Cell Carcinoma

A multicenter, international, two-cohort, nonrandomized, pivotal, Phase II, company-sponsored study (SHH4476g) enrolled patients with mBCC and those with locally aBCC who had inoperable disease or for whom surgery was inappropriate (because of multiple recurrences and a low likelihood of surgical cure, or substantial anticipated disfigurement) [11]. In 33 patients with metastatic BCC (see Table 3), the independently assessed response rate was 30% (95% confidence interval [CI], 16 to 48; p=0.001). In 63 patients with locally aBCC (see Table 4), the independently assessed response rate was 43% (95% CI, 31 to 56; p<0.001), with complete responses in 13 patients (21%). The median duration of response was 7.6 months in both cohorts at the time of data cutoff. Muscle spasms, alopecia, dysgeusia, weight loss, and fatigue occurred in more than 30% of patients, whereas serious adverse events (SAEs) were reported in 25% of patients. Seven deaths due to AEs were reported and none of the deaths were related to vismodegib.

Based on the results of this pivotal trial, vismodegib was approved on 30 January, 2012 by the US Food and Drug Administration (FDA) for the treatment of adults with mBCC, or with locally aBCC that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation. [12].

Table 3: Efficacy Results from Primary Analysis

	Metastatic BCC (n=33)		**Locally Advanced BCC** (n=63)	
	IRF (1°)	**INV (2°)**	**IRF (1°)**	**INV (2°)**
Response ORR	10 (30%)	15 (45%)	27 (43%)	38 (60%)
95% CI	(16%, 48%)	(28%, 62%)	(30%, 56%)	(47%, 72%)
P value	0.001		<0.001	
Stable Disease	21 (64%)	15 (45%)	24 (38%)	15 (24%)
Progressive Disease	1 (3%)	2 (6%)	8 (13%)	6 (10%)
Unevaluable/ missing	1 (3%)	1 (3%)	4 (6%)	4 (6%)
Median DOR, mos	7.6	12.9	7.6	7.6

BCC = basal cell carcinoma; CI = confidence interval; DOR = duration of response; IRF = independent review facility; INV = investigator assessed; mos = months; ORR = overall response rate.

Table 4: ERIVANCE® Investigator Assessed Efficacy at the18-Month Update

Investigator Assessed	**mBCC** (n = 33)	**locally aBCC** (n = 63)	**Total** (n = 96)
ORR, n (%) [95% CI]	16 (48.5) [30.8-66.2]	38 (60.3) [47.2-71.7]	54 (56.3) [45.7-66.4]
Complete response	0	20	20
Partial response	16	18	34
Stable disease	14	15	29
Progressive disease	2	6	8
Median DOR, n (%) months(95% CI)	(n=16) 14.7 (5.6-17.0)	(n=38) 20.3 (9.0-NE)	(n=54) 16.8 (9.5-NE)
Median PFS, months, (95% CI)	9.3 (7.4-16.6)	12.9 (10.2-31.4)	12.8 (9.5-18.0)
Median OS, months, (95% CI)	30.9 (18.1-NE)	NE (NE-NE)	NE (NE-NE)
1-Year survival rate, % (95% CI)	78.7 (64.7-92.7)	93.1 (86.6-99.6)	NA

BCC=basal cell carcinoma; CI=confidence interval; DOR=duration of response; laBCC=locally advanced BCC; mBCC=metastatic BCC; NA=not applicable; NE=not estimable; ORR=overall response rate; OS=overall survival; PFS=progression-free survival.

Table 5: ERIVANCE® Safety Results at the 18-Month Update

Number (%) of Patients with Adverse Events	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 71)
All Patients with AEs	33 (100%)	71 (100%)
Grade 3-5 Adverse Event	14 (42.4%)	40 (56.4%)
Grade 5 Adverse Event§	1 (3%)	6 (8.5%)
Serious Adverse Events	8 (24.2%)	28 (39.4%)
Adverse Events Leading to Treatment Discontinuation	5 (15.2%)	16 (22.5%)

§ No new deaths on study since the primary data analysis. Fatal events included: Death of unknown cause (n=3), acute myocardial infarction (n=1), ischemic stroke (n=1), meningeal disorder (n=1), and hypovolemic shock (n=1). In all cases, clinically significant risk factors or comorbid conditions were present at baseline. Relationship between study drug and event is unknown.

BCC - basal cell carcinoma

Table 6: Most Frequent Treatment Emergent Adverse Events (>10% of patients) at the 18-Month Update

Number (%) of Patients with Adverse Event	NCI CTCAE Grade, (N = 104)					
	Total	**1**	**2**	**3**	**4**	**5**
Any adverse events	104 (100.0)	11 (10.6)	38 (36.5)	34 (32.7)	13 (12.5)	7 (6.7)
Muscle spasms	74 (71.2)	49 (47.1)	19 (18.3)	6 (5.8)	0	0
Alopecia	68 (65.4)	48 (46.2)	20 (19.2)	n/a	n/a	n/a
Dysgeusia	57 (54.8)	31 (29.8)	26 (25.0)	n/a	n/a	n/a
Weight decreased	53 (51.0)	29 (27.9)	17 (16.3)	7 (6.7)	n/a	n/a
Fatigue	44 (42.3)	32 (30.8)	7 (6.7)	4 (3.8)	1 (1.0)	0
Nausea	34 (32.7)	25 (24.0)	9 (8.7)	0	0	0
Decreased appetite	28 (26.9)	18 (17.3)	7 (6.7)	3 (2.9)	0	0
Diarrhea	28 (26.9)	20 (19.2)	5 (4.8)	3 (2.9)	0	0
Constipation	20 (19.2)	14 (13.5)	6 (5.8)	0	0	0

Number (%) of Patients with Adverse Event	NCI CTCAE Grade, (N = 104)					
	Total	1	2	3	4	5
Cough	20 (19.2)	16 (15.4)	4 (3.8)	0	0	0
Vomiting	18 (17.3)	15 (14.4)	3 (2.9)	0	0	0
Arthralgia	17 (16.3)	12 (11.5)	4 (3.8)	1 (1.0)	0	0
Headache	15 (14.4)	12 (11.5)	3 (2.9)	0	0	0
Nasopharyngitis	13 (12.5)	11 (10.6)	2 (1.9)	0	0	0
Squamous cell carcinoma	12 (11.5)	3 (2.9)	5 (4.8)	3 (2.9)	0	0
Ageusia	12 (11.5)	8 (7.7)	4 (3.8)	n/a	n/a	n/a
Hypogeusia	11 (10.6)	10 (9.6)	1 (1.0)	n/a	n/a	n/a

NA = not applicable; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

Expanded Access Study (SHH4811g) in Advanced BCC

An open-label, single-arm, multicenter, expanded access study (SHH4811g) of an oral repeating dose of vismodegib was conducted in patients with locally aBCC or mBCC, who are otherwise without satisfactory treatment options. Safety of vismodegib and objective response in patients with measurable disease (RECIST v1.0) were assessed (Weiss G, et al. 2012). The study has been completed following FDA approval and commercial availability of vismodegib.

Among 95 efficacy evaluable patients (56 patients with locally aBCC and 39 patients with mBCC) at the time of final analysis data cutoff date of 23 April 2012 the observed objective response rates (see Table 7) were 46.4% (95% CI, 33.0%, 60.3%) for patients with locally aBCC (n = 56) and 30.8% (95% CI, 17.0%, 47.6%) for patients with mBCC (n = 39). CR, PR, and stable disease (SD) were observed in 10.7%, 35.7%, and 48.2%, respectively, of patients with locally aBCC; no patients in this cohort exhibited progressive disease (PD) as best response. For patients with mBCC, CR, PR, and SD rates observed were 5.1%, 25.6%, and 51.3%, respectively. In this cohort, 7.7% of patients exhibited PD as best response. Among patients with locally aBCC who responded the median and mean times to response were 2.6 months and 3.5 months, respectively; and among patients with mBCC who responded the median and mean times to response were 2.6 months and 3.8 months, respectively.

As of the final analysis data cutoff date of 23 April 2012, 116 of 119 safety evaluable patients (97.5%) experienced at least one adverse event (22 SAEs total, see Table 8).

Adverse events that had the highest reported occurrences (≥ 20%) in 119 safety evaluable patients were: muscle spasms (84 patients; 70.6%), dysgeusia (84 patients; 70.6%), alopecia (69 patients; 58.0%), and diarrhea (30 patients; 25.2%). Only one of 22 SAEs (4.5%) was assessed as being related to treatment with vismodegib: a Grade 3 muscle spasm, reported in 1 patient. There have been three deaths among 119 safety-evaluable patients (2.5%); 2 assessed as unrelated to study drug, and 1 patient with PD.

Table 7: EAP SHH4811g Overall Response (RECIST) at Study Termination

	locally aBCC (n=56)	**mBCC** (n=39)
Objective response, n (%)	26 (46.4)	12 (30.8)
(95% CI)	(32.4-59.3)	(17.0-47.6)
Complete response, n (%)	6 (10.7)	2 (5.1)
Partial response, n (%)	20 (35.7)	10 (25.6)
Stable disease, n (%)	27 (48.2)	20 (51.3)
Progressive disease, n (%)	0	3 (7.7)
Unevaluable/missing, n (%)	3 (5.4)	4 (10.3)
Median time to response (range), months[a]	2.6 (1.0-11.0)	2.6 (1.4-12.6)

aBCC = advanced basal cell carcinoma; CI = confidence interval; mBCC = metastatic basal cell carcinoma.

Table 3 SHH4811g Vismodegib Expanded Access Study Common Treatment-Emergent Adverse Events

TEAEs (n=120)	Median Time to AE Onset, Days (95% CI)[a]	All AEs, n (%)	NCI CTCAE Grade 1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)
Muscle spasms	37 (28-44)	84 (70.0)	63 (52.5)	19 (15.8)	2 (1.7)	–	–
Dysgeusia	41 (30-51)	84 (70.0)	68 (56.7)	16 (13.3)	NA	NA	NA
Alopecia	87 (74-104)	69 (57.5)	57 (47.5)	12 (10.0)	NA	NA	NA
Diarrhea	38 (22-116)	30 (25.0)	23 (19.2)	5 (4.2)	1 (0.8)	1 (0.8)	–
Nausea	30 (11-130)	23 (19.2)	19 (15.8)	4 (3.3)	–	–	–
Fatigue	42 (16-120)	23 (19.2)	14 (11.7)	8 (6.7)	1 (0.8)	–	–
Weight decreased	175 (114-293)	19 (15.8)	12 (10.0)	7 (5.8)	–	–	–

AE = adverse event; NA = not applicable; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE = treatment emergent adverse event.

[a] For those patients experiencing the TEAE

Phase II BCNS Study (SHH4685s)

The anti–BCC efficacy of vismodegib was tested in a randomized, double-blinded, placebo-controlled, Investigator-sponsored trial in Gorlin syndrome (BCNS) patients with surgically eligible BCCs [13-15]. Forty-one patients were randomized 2:1 to receive oral vismodegib (n=26) or placebo (n=15). After a mean follow up of 8 months (range, 1 to 15 months), the per-patient rate of new surgically eligible BCCs (SEBs) was lower with vismodegib than with placebo (2 vs. 29 cases per group per year, p<0.001), as was the size (percent change from baseline in the sum of the longest diameter) of existing clinically significant BCCs (–65% vs. –11%, p=0.003). In some patients, all BCCs clinically regressed. No tumors progressed during treatment with vismodegib. Patients receiving vismodegib routinely had Grade 1 or 2 AEs of loss of taste, muscle cramps, hair loss, and weight loss. Overall, 54% of patients (14 of 26) receiving vismodegib discontinued drug treatment due to AEs. At 1 month, vismodegib use had reduced the Hh pathway's target-gene expression in BCC cells by 90% (p<0.001) and diminished tumor-cell proliferation, but apoptosis was not affected. No residual BCC was detectable in 83% of biopsy samples taken from sites of clinically regressed BCCs. At the second pre-specified interim analysis, a data safety and monitoring board concluded that the pre-determined threshold for a significant difference between the two groups had been reached (p<0.0113), and the treatment with placebo in this arm was terminated. AEs reported in ≥10% of patients are summarized in Table 9 See the Vismodegib Investigator's Brochure and the U.S. package insert for additional details on nonclinical and clinical studies on vismodegib.

Table 9: Phase II BCNS Study (SHH4685s) Adverse Events Reported in ≥10% of Patients

Number (%) of Patients with Grade 1 or 2 AEs	Vismodegib (n=26)	Placebo (n=15)	*P* Value
Taste disturbance, n	22 (85)	1 (7)	<0.001
Muscle cramps	21 (81)	0 (0)	<0.001
Hair loss	16 (62)	1 (7)	0.004
>5% weight decrease	11 (42)	0 (0)	0.003
GI upset	5 (19)	1 (7)	0.14
Acne	3 (12)	1 (7)	0.60

AE = adverse event; GI = gastrointestinal.

Phase II STEVIE (MO25616) Safety Study

Study MO25616 is an ongoing Phase II open-label, single-arm, multicenter (ex-U.S.) study of vismodegib in patients with locally aBCC or mBCC who are otherwise without satisfactory treatment options. The primary objective is to assess the safety of vismodegib in patients with locally aBCC or mBCC. Secondary objectives are to assess the overall response (according to RECIST Version 1.1) in those patients with measurable disease as permitted by local regulatory requirement and to assess other efficacy parameters such as time to response, duration of response, PFS and overall survival (OS).

All patients receive 150 mg vismodegib orally (PO) daily (QD) until investigator-assessed PD, unmanageable toxicities, or withdrawal from study (investigator/patient request) or termination by the Sponsor).

As of 6 November 2013, a total of 1228 patients have been enrolled into the study. Results of an interim analysis, when a total of 501 patients could be followed for 1 year, are presented below.

As of the cutoff date of 6 November 2013, safety data were available for 500 patients (469 with locally aBCC and 31 with mBCC) with follow up information for at least 3 months after treatment. Overall, 492 of 500 safety-evaluable patients (98.4%) experienced at least one AE. The most frequently reported AEs, regardless of relationship to study drug, in descending order of frequency, were: muscle spasms (63.2%), alopecia (61.0%), dysgeusia (53.8%), weight decreased (32.4%), asthenia (28.2%), decreased appetite (25.4%), and ageusia (22.4%).

As of 6 November 2013, 210 of 500 safety-evaluable patients (42.0%) experienced Grade 3−5 treatment-emergent adverse events (TEAEs). Of 500 patients, 165 patients (33.0%) experienced a Grade 3 AE, 24 patients (4.8%) experienced a Grade 4 AE, and

21 patients (4.2%) experienced a Grade 5 AE. All of the Grade 5 AEs were considered by investigator to be unrelated to treatment with vismodegib except for cardio-respiratory arrest and myocardial infarction.

Of the 500 patients, 107 (21.4%) experienced SAEs. The most common events were in the following system organ classes: infections and infestations, 30 patients (6.0%); neoplasms (benign, malignant, and unspecified, including cysts and polyps), 16 patients (3.2%); general disorders and administration site conditions, 12 patients (2.4%); nervous system disorders, 12 patients (2.4%); cardiac disorders, 11 patients (2.2%); injury, poisoning and procedural complications, 10 patients (2.0%); and metabolism and nutrition disorders, 10 patients (2.0%).

As of 6 November 2013, there have been 29 deaths among 500 safety-evaluable patients. The causes of death were PD in 4 patients, AE in 20 patients, and 5 patients with “other” as cause of death. Most patient deaths were considered unrelated to treatment with vismodegib. Two deaths (cardiopulmonary arrest and cardiac infarction) were assessed by the investigator as related to vismodegib; however, both patients had significant risk factors and comorbidities. Both events were considered by the investigator to be related because of the temporal relationship between the onset of the event and administration of vismodegib; therefore, an association could not be excluded.

As of 6 November 2013, 400 of 500 patients (80%) treated during Study MO25616 had discontinued study drug. Reasons for discontinuation of study drug included: AE (178 patients, 35.6%); progression of disease (70 patients, 14.0%); patient request (62 patients, 12.4%); death (10 patients, 2.8%); investigator request (14 patients, 2.8%); lost to follow-up (4 patients, 0.8%); and other (62 patients, 12.4%).

The majority of patients (98.2%) in Study MO25616 (STEVIE) experienced TEAEs. The most common ($>20\%$) TEAEs included muscle spasm (63.2 %), alopecia (61.0%), dysgeusia (53.8%), weight decreased (32.4%), asthenia (28.2%), decreased appetite (25.4%), and ageusia (22.4%). Twenty-four (4.8%) Grade 4 events and 21 (4.2%) Grade 5 events were reported. Two of the deaths were considered related to vismodegib treatment (cardio-respiratory arrest and myocardial infarction). There were 107 (21.4%) patients who reported SAEs. Common SAEs that were reported in $\geq 1\%$ of patients were pneumonia (1.8%, $n=9$), general physical health deterioration (1.4%, $n=7$), and dehydration (1.0%, $n=5$).

Interim results of the STEVIE study demonstrate that vismodegib is generally well tolerated in a patient population that is representative of patients treated in routine clinical practice, with a safety profile consistent with that previously observed in other vismodegib studies. Investigator-assessed response rates are consistent with those reported in the ERIVANCE study and confirm high rates of tumor control.

As the trial is ongoing, efficacy analyses will be presented at final analysis.

Phase II Operable Basal Cell Carcinoma (SHH4812g) Study

The ability of vismodegib to induce complete histological clearance (CHC) of BCC tumors, an important step in assessing the role of the drug in the setting of smaller resectable lesions, was examined in a single-arm, 3-cohort, Phase II study (Sofen et al. 2015). Patients in the trial were required to have one clinically operable, nodular BCC lesion on the scalp (0.5 – 2.0 cm maximum diameter) or in the "cape" area (chest, shoulders, or upper back; 1.0 – 3.0 cm maximum diameter). The nodular BCC required a positive biopsy that was limited to ≤ 25% of the target lesion. After 12 weeks of oral vismodegib (150 mg QD), patients were assessed clinically and then underwent excision of the target tumor site for pathologic assessment of residual carcinoma, followed by re-excision of the tumor site for margin assessment using standard Mohs techniques.

Efficacy objectives for CHC were not met in this study. The CHC rates were 42% (10/24) in Cohort 1, 16% (4/25) in Cohort 2, and 44% (11/25) in Cohort 3; these clearance rates were not statistically significant (p-values of 0.8463, 0.9668, and 0.7878, respectively). The low response rate in Cohort 2 (4 [16%] of 25 patients) indicates a lack of durable response. Investigator-assessed clinical response (CR and PR) did not correlate with CHC. Time to complete clinical clearance in patients in Cohorts 1 (10 patients), 2 (9 patients), and 3 (18 patients) with investigator-assessed CR, the time to first CR was 59.5 days (95% CI: 28.0 – 80.0 days), 84.0 days (95% CI: 27.0 – 120.0 days), and 60.0 days (95% CI: 55.0 – 86.0 days), respectively.

No new safety signals were noted for patients in this study after dosing with vismodegib 150 mg QD PO. No deaths occurred during this study. The safety profile of vismodegib 150 mg QD was similar among the 3 cohorts. The data generally showed reversibility of muscle spasms, dysgeusia, and ageusia 6 to 12 weeks after drug discontinuation, and reversibility of delayed-onset alopecia in most patients during the 24-week follow-up period in Cohort 2.

Efficacy objectives for CHC were not met in this study.

1.3.1.2 Medulloblastoma

Data from a phase II clinical trial evaluated vismodegib treatment at 150 mg QD PO in adult patients with medulloblastoma that was recurrent after or progressive while receiving standard (n=40) [16, 17]. Patients were stratified by histologic subtypes based on immunohistochemical (IHC) analysis into three strata: non-SHH group, SHH group, and indeterminate group. The primary endpoint was objective response rate as assessed by RECIST using independent review. Responses must be sustained at least 8 weeks. The study met its primary endpoint of sustained objective response, with 3/20 patients in SHH group exhibiting sustained responses. Secondary efficacy endpoints were consistent with the primary endpoint. Grade 3-4 TEAEs reported were lymphocytopenia, thromboembolic event, syncope, back pain, myalgia, seizure, and hypophosphatemia.

1.3.2 Malignancies with Ligand Driven Hh Signaling

1.3.2.1 Colorectal Cancer

A randomized phase II clinical trial evaluated addition of vismodegib or placebo to standard chemotherapy (mFOLFOX-6 or FOLFIRI) plus bevacizumab in patients with untreated metastatic colorectal cancer (n=199)[18]. Choice of chemotherapy regimen was based on investigator decision. The primary endpoint was improvement in progression-free survival (PFS). The study failed to meet its primary endpoint of improved PFS vs. chemotherapy + placebo (hazard ratio = 1.25 [90%, CI 0.89 -1.76], p =0.28) Secondary efficacy endpoints were consistent with the primary endpoint. The TEAEs (all grades) that differed in frequency by 10% or more vs. placebo were vomiting, asthenia, weight loss, decreased appetite, dehydration, muscle spasms, and dysgeusia. Grade 3-5 TEAEs that differed in frequency by 5% or more vs. placebo were fatigue, nausea, asthenia, mucositis, peripheral sensory neuropathy, weight loss, decreased appetite, and dehydration.

1.3.2.2 Ovarian Cancer

A randomized phase II clinical trial evaluated the use vismodegib or placebo as maintenance treatment for patients with ovarian cancer in second or third complete remission (n=104)[19]. The primary endpoint was improvement of PFS. The study failed to meet its primary endpoint of improved PFS vs. placebo (hazard ratio=0.79 95%CI 0.46-1.35, p=0.39). TEAEs occurring in greater than 10% of vismodegib treated patients were dysgeusia/ageusia, muscle spasms, alopecia, nausea, fatigue, constipation, abdominal pain, decrease appetite, upper abdominal pain, arthralgia, vomiting and hypomagnesemia.

1.3.2.3 Pancreatic Cancer

A randomized phase II clinical trial evaluated addition of vismodegib or placebo to standard chemotherapy (gemcitabine) in patients with untreated metastatic pancreatic cancer (n=106)[20]. The primary endpoint was improvement in progression-free survival. The study failed to meet its primary endpoint of improved PFS vs. chemotherapy + placebo (HR = 0.81 95%CI 0.54 - 1.21, p=0.3) Secondary efficacy endpoints were consistent with the primary endpoint. The frequency of Grade ¾ TEAEs reported vs. placebo (V/P) were neutropenia (32%/28%), hyponatremia (4%/15%), fatigue (13%/8%), hyperglycemia (23%/19%), elevated alanine aminotransferase (ALT; 13%/9%). TEAEs that differed in frequency by 10% or more vs. placebo were vomiting, asthenia, weight loss, decreased appetite, and dehydration.

1.3.2.4 Glioblastoma Multiforme

A phase II clinical trial evaluated vismodegib treatment at 150 mg QD PO in patients with glioblastoma multiforme that was recurrent after or progressive while receiving standard treatment (n=40) [21]. The primary endpoint was improvement in PFS at 6 months. The study failed to meet its primary endpoint of improved PFS at 6 months (median PFS 1.8 months 95%CI 1.40 - 1.9 months) Secondary efficacy endpoints were

consistent with the primary endpoint. TEAE reported were abdominal infection, abdominal pain, atrial flutter, fatigue, hypophosphatemia, lymphocytopenia, and thrombocytopenia (1 patient each).

1.3.2.5 Gastric Cancer

A randomized phase II clinical trial evaluated addition of vismodegib or placebo to chemotherapy (mFOLFOX-6) in patients with untreated metastatic gastric cancer (n=124)[22]. The primary endpoint was improvement in PFS. The study failed to meet its primary endpoint of improved PFS vs. chemotherapy + placebo (hazard ratio = 1.03 95%CI 0.69 - 1.55, p=0.64) Secondary efficacy endpoints were consistent with the primary endpoint. No significant differences in the rates of common grade ¾ TEAEs (≥ 5% incidence) were observed between the vismodegib and placebo arms. The rates of grade ½ TEAEs were comparable with no significant differences except for a higher incidence of dysgeusia in the vismodegib arm (42%/16%, p=0.003).

1.3.2.6 Small Cell Lung Cancer

A randomized phase II clinical trial evaluated addition of vismodegib or cixutumumab (IMC-A12) to standard chemotherapy (cisplatin/etoposide) in patients with untreated extensive stage SCLC (n=155)[23]. The primary endpoint was improvement in PFS. The study failed to meet its primary endpoint of improved PFS vs. cisplatin/etoposide chemotherapy (hazard ratio = 1.32, p=0.21) Secondary efficacy endpoints were consistent with the primary endpoint. Grade ¾ TEAEs reported (chemotherapy alone vs. chemotherapy+vismodegib) included anemia (25%/ 9%), febrile neutropenia (15%/13%), neutropenia (48%/47%), thrombocytopenia (22%/6%), leukopenia (46%/41%), nausea (11%/11%), vomiting (9%/6%), hyperglycemia (2%/2%), muscle weakness (4%/0%), and renal dysfunction (6%/0%)

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of the study are:

a. To evaluate the efficacy of GDC-0449 in reducing KCOT size (shrinkage) in NBCCS-associated KCOT and sporadic KCOT patients following 6 to 12 months of ingestion of 150 mg/day, up to 1 year of treatment and up to 2 years of post-treatment follow-up.

b. To evaluate the safety of this dose of GDC-0449 in these patients.

Tumor response (reduction in tumor volume and shrinkage) will be measured by volumetric CT scan.

Time Frame: Efficacy will be assessed at 1 year and 2 years after the study medication is stopped. Patients will undergo evaluation for 3 years (up to 1 year of treatment and up to 2 years of post-treatment follow-up). All patients will participate in the assessment of the safety and tolerability of the study drug. Safety monitoring will capture risks related to study participation and adverse events related to the study drug.

2.2 Secondary Objectives

The secondary objectives of the study are:

a. To determine the time of response of a GDC-0449 anti-proliferative effect (i.e. tumor shrinkage) after administration of the drug up to one year or until treatment is stopped;

b. To assay germ line *PTCH1* mutations before treatment with GDC-0449 in patients with NBCCS-associated KCOT;

If tumor removal is required, to assess tumor *PTCH1* mutations before and after treatment with GDC-0449 in NBCCS-associated KCOT and sporadic KCOT in order to determine the correlation of tumor response and the presence of tumor *PTCH1* mutation.

3. STUDY DESIGN

3.1 Description of the Study

This is a single-center, interventional, single-arm, open-label, two-cohort clinical trial. A total of 40 patients will be screened in order for 20 patients to be enrolled (10 with NBCCS-associated KCOT and 10 with sporadic KCOT) over a period of 2 years. This is a 3 year study where each patient will undergo up to 1 year of treatment and up to 2 years of post-treatment follow-up. If a patient is experiencing an ongoing adverse event at the time of the study completion, he/she will be followed-up until resolution of the adverse event or until the condition has stabilized. The same applies to patients who are withdrawn from the study due to adverse events.
It is estimated that it will take approximately 2 years to recruit 20 patients for the study (10 with NBCCS-associated KCOT and 10 with sporadic KCOT).

All patients will be assessed for safety and efficacy of the study drug GDC-0449 (Vismodegib).

3.2 Study Phases

There are 3 Phases in this study:

Phase 1/Screening

Baseline Visit

Note: Study procedures and assessments during the baseline visit can be conducted over several visits until all inclusion/exclusion criteria are verified and patient is eligible to proceed with treatment (first study drug administration)

Phase 2/ Treatment (1 Year)

1 Month Visit (+/- 7 days from first study drug administration)

3 Month Visit (+/- 7 days)

6 Month Visit (+/- 7 days)

1 Year Visit - End of Treatment Phase (+/- 7 days)

Note: Visits for safety assessment will be conducted at 2, 4, 5, 7, 8, 9, 10 and 11 months.

Phase 3/Post-Treatment (2 Year Follow-Up)

1 Month Visit (+/- 7 days from the end of the treatment phase)

1 Year Visit (+/- 7 days)

2 Year Visit - End of Follow-Up Phase

Note: Visits for safety assessment will be conducted at 2 and 3 months

Study procedures and assessments for these visits are outlined in Section 4.5. A schedule of assessments is provided in Appendix A.

3.3 Safety Plan

Patients will be evaluated at each study visit for the duration of their participation in the study (see Section 4.5 and Appendix A).

Specific potential safety issues for this trial are outlined below.

Please refer to the Vismodegib Investigator's Brochure for a detailed description of the safety profile of vismodegib.

See Section 5.1 for complete details of the safety evaluation for this study.

3.4 Compliance with Laws and Regulations

This study will be conducted in accordance with current U.S. FDA Good Clinical Practices (GCPs), and local ethical and legal requirements.

4. MATERIALS AND METHODS

4.1 Subject Selection

4.1.1 Inclusion Criteria

Patients are eligible to participate in the study if they meet the following criteria:

- Males and females, 18 years of age and above at the time the informed consent form is signed;
- Able to understand and sign the Informed Consent Form and other necessary paperwork prior to initiation of study procedures;
- Able to communicate with the investigator/study site personnel, understand and comply with the study requirements, and willing to return for specified visits at the appointed time;
- Patients who have received prior treatment for their KCOT and with a diagnosis of recurrent (maxillary or mandibular) sporadic KCOT or NBCCS-associated KCOT (single or multiple);
- Diagnosis of KCOT will be done by past pathology report or by biopsy at the study site, if applicable;
- Willingness to consent to biopsy of the lesion, if needed;
- Willingness to delay excision of the target tumor site, unless evidence of disease progression or lack of drug tolerability;
- For female patients of childbearing potential, agreement to use two acceptable methods of birth control, including one barrier method during the study and 24 months after discontinuation of study drug;
- For males with female partners of childbearing potential, agreement to use a male condom (with spermicide) and to advise their female partners to use an acceptable method of birth control during the study and for 3 months after the discontinuation of the study drug;
- Agreement not to donate blood/blood products during the study and for 24 months after the discontinuation of the study drug;
- For males not to donate sperm products or semen during treatment and for 3 months after the discontinuation of the study drug;
- Able and willing to swallow pill;

- No malabsorption syndrome or other condition that would interfere with enteral absorption;

- At least 4 weeks since last chemotherapy, investigational therapy, radiotherapy or major surgical procedure and recovered from the first study drug administration;

- KCOT measures at least 1 cm in one dimension on pretreatment volumetric CT scan;

- No clinically significant abnormalities with clinical laboratory assessments;

4.1.2 Exclusion Criteria

Patients are excluded from participation if the following applies:

- Concurrent anti-tumor therapy;

- Completion of the most recent anti-tumor therapy (including Vismodegib) less than 4 weeks prior to the initiation of treatment (first study drug administration);

- Uncontrolled medical illness;

- Pregnancy or lactation; female patients who are planning to become pregnant for the duration of the study and 24 months post-treatment;

- Inability or unwillingness to swallow capsules;

- Any medical or psychological illness or condition preventing adequate consent;

- History of significant atherosclerotic disease, including the following:
  - Coronary artery disease (i.e., myocardial infarction within the past year or unstable angina);
  - Documented carotid atheroma;

- Known HIV infection;

- Current alcohol abuse;

- History of resistance to vismodegib (patients who previous received vismodegib for BCC and had no clinical response will be excluded).

4.1.3 Subject Recruitment and Screening

Clinicians and staff at the clinical study site will be made aware of the study and trained on the eligibility criteria, the enrollment procedures and study procedures. A study coordinator will be available at the site. All patients who arrive at the clinic should be considered potentially eligible. The study coordinator will review appointment schedules and information available at the time of the patient appointments to identify potential subjects and to rule out patients who do not fall into the defined study population. Either the clinician or the study coordinator will inform the potential subjects about the study and ask if they are interested in participating. Patients will be informed that their participation in the study, or not, will have no influence on their clinical management. If the patient expresses interest, then the clinician or study coordinator will assess the patient's eligibility (screening for eligibility does not require any testing) and answer any questions the patient might have about the study. A signed consent form documenting informed consent for eligible subjects will be obtained prior to the start of any study procedures. Advertisements such as flyer and web ad will be used in this study for recruitment of subjects. Web ad will be posted on NYU Bluestone website. All advertisements will be approved by an Institutional Review Board prior to posting or dissemination. A doctoral referral letter will be sent out via email and/or mail to oral and maxillofacial surgeons, asking for referral of eligible subjects who might be interested in the study. A publically available directory will be used to obtain the contact information of the oral and maxillofacial surgeons. A doctoral referral letter will be accompanied with the drug package insert, inclusion/exclusion criteria, and the study flyer.

4.2 Study Treatment

This is a single-center, interventional, single-arm, phase II, open-label, two-cohort clinical trial. A total of 40 patients will be screened in order for 20 patients to be enrolled (10 with NBCCS-associated KCOT and 10 with sporadic KCOT) over a period of 2 years. Only patients with a diagnosis of recurrent (maxillary or mandibular) sporadic KCOT or NBCCS-associated KCOT (single or multiple) will be recruited. All patients will receive 150 mg/day of GDC-0449 (Vismodegib) orally for 1 year. All patients will be assessed for safety and efficacy of the study drug GDC-0449 (Vismodegib).

This is a 3 year study where each patient will undergo up to 1 year of treatment and up to 2 years of post-treatment follow-up.

The Sponsor Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all Vismodegib in accordance with 21 Code of Federal Regulations (C.F.R.), Part 312.57 and 312.62 and Genentech requirements.

Vismodegib Dosage

The recommended dose of Vismodegib is 150 mg taken QD PO until disease progression or until unacceptable toxicity. Vismodegib may be taken with or without food. Swallow capsules whole.

Do not open or crush capsules

If a dose of vismodegib is missed, do not make up that dose; resume dosing with the next scheduled dose.

Vismodegib Dose and Schedule Modifications

Vismodegib dose modifications and schedule modifications during the study are not recommended due to the pharmacokinetic characteristics of the drug (see Vismodegib Investigator Brochure v10, Section 5.9.3). Briefly, vismodegib's pharmacokinetic profile is a result of high affinity, reversible binding to Alpha-1 acid Glycoprotein (AAG) and binding to albumin, in addition to solubility limited absorption and slow metabolic elimination properties[24]. Initiation of less frequent administration schedules than the approved dose and schedule of vismodegib of 150 mg orally once daily,(i.e. 150 mg three times weekly [TIW] or 150 mg once weekly dosing), was associated with marked decrease in the pharmacologically active unbound fraction. Unbound steady-state vismodegib concentrations were 60% and 85% lower for the TIW and QW dose groups, respectively, relative to the QD dose group [25, 26]. Such decreases may be associated with loss of vismodegib activity based on findings from nonclinical models. Integrated PK/pharmacodynamic modeling of vismodegib in xenograft models has revealed a steep relationship between pathway modulation (GLI1 inhibition) and anti-tumor effect, suggesting that even small reductions in exposure could lead to dramatic loss in vismodegib activity (see Vismodegib Investigator's Brochure v10, Section 4.1.2.8)

Dose reduction of vismodegib is not permitted as there is only a 150-mg capsule strength available. Capsules should not be opened or crushed. If a treatment interruption occurs, and it is determined that vismodegib will be re-started, the original dose will be maintained

Vismodegib Overdosage

There is no information on overdosage in humans. In clinical trials, ERIVEDGE capsule was administered at 540 mg QD PO; exposure did not increase between 150 mg and 540 mg daily.

Vismodegib Clinical Formulation and Storage

For the clinical studies, hard gelatin capsules containing 150 mg vismodegib are available.

The 150-mg vismodegib drug product is a hard gelatin capsule formulation for oral administration. The capsule fill consists of vismodegib and the following excipients:

microcrystalline cellulose PH101, lactose monohydrate, sodium lauryl sulfate, povidone K29/32, sodium starch glycolate, talc, magnesium stearate, and purified water. All of these excipients are compendial (USP/NF-EP) grade. The capsule shell consists of gelatin, red iron oxide, black iron oxide, and titanium dioxide. A compendial-grade black printing ink may be used.

Vismodegib capsules should be stored in the recommended storage conditions at15°C−30°C Information on the shelf life of the capsules is provided on the label.

Vismodegib Packaging and Labeling

Genentech, Inc., the manufacture of ERIVEDGE®, will label and package the study drug on behalf of the Sponsor Investigator for this clinical research study.

Please refer to the Master Label Certification from Genentech, Inc. for detailed information about labeling and packaging for the study drug.

Preparation and Administration of Study Drug

Study drug will be supplied by Genentech, Inc in labeled 75cc HDPE bottle. Each bottle will contain 32 hard capsules Vismodegib 150mg. The first dose of study drug will be given during a study visit and the subjects will be monitored for 6 hours after taking the drug for the first time. After the first administration, the study drug will be given to the study subjects to be taken at home.

Subject Compliance Monitoring

The study subjects will be given enough study drugs to last until the next visit. Dispensing records will document quantities received and quantities dispensed, lot number (if applicable), date dispensed, patient identifier number, and initials of the person dispensing the study drugs. Subjects will bring back the study drug bottle with any unused study drug at each study visits to monitor their compliance.

Drug Accountability

Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

Storage

The boxes containing the study drug will be stored at room temperature under secured conditions with limited access. The study drug will be stored in room #236 in Bluestone Center for Clinical Research. Room #236 is a limited card swipe access secure room with approximately 50 square feet of space and approximately 15 linear feet of countertop space for processing medication orders. Room #236 contains two security cameras which are under 24 hour surveillance by NYU College of Dentistry's security team.

Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

4.3 Concomitant and Excluded Therapy

Drugs that Inhibit or Induce Drug Metabolizing Enzymes

Vismodegib elimination involves multiple pathways. Vismodegib is predominantly excreted as an unchanged drug. Several minor metabolites are produced by multiple CYP enzymes. Although vismodegib is a substrate of CYP2C9 and CYP3A4 *in vitro*, CYP inhibition is not predicted to alter vismodegib systemic exposure since similar steady-state plasma vismodegib concentrations were observed in patients in clinical trials concomitantly treated with CYP3A4 inducers (i.e., carbamazepine, modafinil, and phenobarbital) and those concomitantly treated with CYP3A4 inhibitors (i.e., erythromycin, and fluconazole).

Drugs that Inhibit Drug Transport Systems

In vitro studies indicate that vismodegib is a substrate of the efflux transporter P-glycoprotein (P-gp). When ERIVEDGE is coadministered with drugs that inhibit P-gp (e.g. clarithromycin, erythromycin, azithromycin), systemic exposure of vismodegib and incidence ofAEs of ERIVEDGE may be increased.

Drugs that Affect Gastric pH

Drugs that alter the pH of the upper gastrointestinal (GI) tract (e.g. proton pump inhibitors, H2-receptor antagonists, antacids) may alter the solubility of vismodegib and reduce its bioavailability. However, no formal clinical study has been conducted to evaluate the effect of gastric pH altering agents on the systemic exposure of vismodegib. Increasing the dose of ERIVEDGE when coadministered with such agents

is not likely to compensate for the loss of exposure. When ERIVEDGE is coadministered with a proton pump inhibitor, H2-receptor antagonist or antacid, systemic exposure of vismodegib may be decreased and the effect on efficacy of ERIVEDGE is unknown.

Effects of Vismodegib on Other Drugs

Results of a drug-drug interaction study conducted in cancer patients demonstrated that the systemic exposure of rosiglitazone (a CYP2C8 substrate) or oral contraceptives (ethinyl estradiol and norethindrone) is not altered when either drug is co-administered with vismodegib.

In vitro studies indicate that vismodegib is an inhibitor of CYP2C8, CYP2C9, CYP2C19 and the transporter BCRP. Vismodegib does not induce CYP1A2, CYP2B6, or CYP3A4/5 in human hepatocytes.

4.4 Study Assessments

Study assessments and procedures for efficacy and safety are detailed in Appendix A. Patients' screening information will be recorded on the Screening and Enrollment Log.

Clinical Laboratories and Vital Signs

Safety evaluations include clinical laboratory assessments as set forth in the Schedule of Study Assessments and Procedures in Appendix A. Safety and tolerability will be measured by adverse events, physical examination, complete blood count, vital signs, and oral cavity assessments. Details of laboratory procedures are provided in the laboratory manual for the study.

Samples of blood will be taken on selected visits (see Appendix A). 20 mL (inclusive) of blood will be obtained by venipuncture on each required visit. Approximately 100 mL of blood will be drawn over the course of the study (Screening through the completion of the Treatment Phase) for clinical laboratory assessments. Patients consenting to have a blood sample drawn for future DNA analysis will have an additional 7-10 mL of blood drawn at the baseline visit. Analysis of all clinical blood samples will be made at a central clinical laboratory. The investigator and clinical monitor will be provided with a list of the normal ranges used by the testing laboratory for all variables assayed during the study and a statement of accreditation (or similar) for the laboratory.

Complete blood count, serum pregnancy test, serum chemistry, coagulation time, and liver function will be assessed and include the following measures: white blood count, hemoglobin, platelets, glucose, uric acid, calcium, phosphorus, sodium, potassium, chloride, alkaline phosphatase, albumin, alanine transaminase (ALT), aspartate transaminase (AST), BUN and creatinine.

Female patients of childbearing potential will have a urine pregnancy test. A pregnancy test will be performed by the study center by use of a dipstick. All laboratory results will be reviewed and the reports signed by an investigator.

Any results considered to be of clinical significance must be dealt with and followed up as clinically appropriate. All laboratory results considered to represent an adverse event (AE) must be documented in the case report form (CRF). Repeat samples will be taken if required for clinical follow up or because the sample is lost or damaged. Any abnormal end of treatment clinical laboratory result of clinical significance must be repeated at regular intervals until it returns to normal, or until an investigator is satisfied that the abnormality is not related to the drug and needs no further investigation.
Vital signs (blood pressure, heart rate and temperature) will be obtained for safety monitoring.

Optional Blood Sample for Future Genetic Testing

If a subject agrees to provide a blood sample for future genetic testing, an additional blood sample will be collected at Baseline and also at one year visit if subject has new tumor. Human DNA will be extracted from the blood and stored at the Bluestone Center for Clinical Research for up to 10 years to be used for DNA sequencing as part of a future study related to KCOT. PCR amplification of exons encoding the open reading frame of genes associated with KCOT will be carried out using nested primers prior to sequencing PCR products in both the sense and antisense directions. Identified mutations will be confirmed by an independent PCR and sequencing reaction. The genetic testing will not include tests that can identify patients' risks for other conditions. Only users authorized by the Bluestone Center for Clinical Research and Genentech would have access to the samples. The stored samples will be labeled with the subject code, diagnosis and/or location of the sample. The linking key between subject code and subject identity will be maintained by the PI. The subject may withdraw their samples from storage and future use by providing a written request to the PI.

Oral Cavity Assessment, Head & Neck, & Physical Exam

At the scheduled time points, according to the Schedule of Study Assessments and Procedures in Appendix A, study personnel will perform a comprehensive oral exam consisting of an evaluation of oral hard and soft tissue structures for each patient. Oral hard tissue assessments will be performed with a dental mirror on the teeth and bony structures. Oral soft tissues will be performed by examining each patient's mouth and pharynx, including lips, tongue, floor of the mouth, palate, gingiva, alveolar mucosa, buccal mucosa, oropharynx, tonsils, uvula, and salivary glands using palpation techniques and visualization.

A complete extraoral physical exam of the head and neck regions will also be noted by visualization and bi-manual palpation. This assessment will be performed during the baseline visit and the treatment and post-treatment phase of the study.

In addition to the oral hard tissue assessments, extraoral and head and neck examinations, a complete physical exam will be done during the baseline and treatment

phase of the study. This exam will include the examination of the cardiovascular, pulmonary, abdomen and nervous system.

Dermatologic Assessments

A thorough skin examination will be performed by a study investigator for NBCCS-associated KCOT patients at different time points (see Appendix A for more details). The purpose of this exam will be to identify any suspicious lesions. Patients with suspicious findings will be referred to a dermatologist as per standard of care. Photographs of the lesions will be taken and all findings will be recorded on the relevant CRF. Follow-up visits with a dermatologist will be conducted for patients with suspicious lesions as per standard of care. All findings by a dermatologist will be kept with the study records.

Any abnormal findings will be documented. Any abnormalities noted at the Baseline visit, may be reason to exclude a patient from the study. At the time of the first study drug administration or post-dose, should an adverse event be reported, the investigator will determine which safety assessments should be performed. All findings will be recorded on the respective CRF.

Any clinically significant signs or symptoms that are present at, or during the Baseline visit, and that worsen during or after study drug administration, will be recorded as adverse events on the adverse event CRF. Non-significant clinical abnormalities will also be recorded on the relevant CRF.

Photography

When applicable, any suspicious lesions which are discovered during the skin examination will be photographed and filed in the patient's study chart. Photographs will only contain images of the suspicious lesion. The patient's face will not be visible in the photograph.

Panoramic Radiograph and Volumetric CT Scan

Tumor volume will be measured at baseline, and tumor response (reduction in tumor volume and recurrence) will be measured during the treatment phase and post-treatment phase by Panoramic Radiograph and Volumetric CT scan. The use of Panoramic Radiograph and Volumetric CT scan to measure the tumor volume are obtained for clinical assessment purposes only. No additional scans will be performed for research purposes. Disease progression during the treatment phase will be classified by an increase of at least 20%, with an absolute change greater than 5 mm in tumor size after 3 months of treatment. KCOTs grow within the bone. CT scan and panoramic radiograph are superior, with regard to sensitivity and specificity, in terms of evaluating bone involvement.

Biopsy and Analysis of the Tumor

If the patient had a previous biopsy performed, a tissue slide will be obtained for study purposes and confirmation of KCOT diagnosis. If clinically indicated, an additional biopsy of the tumor will be done and if the patient agrees, the leftover tissue from the tumor biopsy will be stored for future genetic analysis related to KCOT. The storing of tumor for future genetic analysis is optional and will be stored for 10 years. These additional biopsies will be flash-frozen in liquid nitrogen (LN2) and stored in LN2 at the Bluestone Center for Clinical Research.

The future genetic testing will not include tests that can identify patients' risks for other conditions. Only users authorized by the Bluestone Center for Clinical Research and Genentech would have access to the samples. The stored samples will be labeled with the subject code, diagnosis and/or location of the sample. The linking key between subject code and subject identity will be maintained by the PI. The subject may withdraw their samples from storage and future use by providing a written request to the PI.

Assessment of Gene Mutations and Gene Expression in Tumor Specimens: The additional fresh-frozen tumor specimens will be subjected to gene mutation and gene expression analysis. If no additional fresh-frozen specimen is obtained, the initial biopsy samples, which are formalin-fixed, paraffin-embedded (FFPE), will be used instead.

FFPE tissue scraped from serially cut slides will be deparaffinized using Envirene reagent (Hardy Diagnostics, Santa Maria, CA, USA) before isolation of RNA using the Roche High Pure FFPE RNA Micro Kit (Roche Diagnostics, Indianapolis, IN). RNA will be extracted from fresh-frozen tissue using the High Pure RNA Tissue Kit (Roche Diagnostics, Indianapolis, IN). RNA will be reversed transcribed using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA) with random primers. PCR will be carried out using the Taqman Universal PCR Master Mix (Applied Biosystems), with the following cycling conditions: 50°C for 2 min; 95°C for 10 min; 40 cycles of 95°C for 15 s, 60°C for 1 min. qRT-PCR profiling of genes associated with KCOT will be performed For analyses, gene expression from the genes of interest will be normalized to the average cycling threshold (Ct) of three housekeeping genes (GUSB, SDHA, and UBC).

For gene mutation analysis, DNA will be extracted from the fresh-frozen or formalin-fixed paraffin-embedded (FFPE) tissue sections. PCR amplification of exons encoding the open reading frame of genes associated with KCOT will be carried out using nested primers prior to sequencing PCR products in both the sense and antisense directions. Identified mutations will be confirmed by an independent PCR and sequencing reaction.

Potential Risks to Participants
Information on potential risks to patients participating in this study is as follows:

- *Oral Examinations/Head and Neck Examination:*

The oral examination will involve procedures that are routinely performed in dental practice. A licensed dentist/hygienist will perform the procedures. The risks from the oral examination include minor discomfort or minor pain during the procedures.

- *Biological Sample Collection:*

Urine (if female of child bearing potential) will be collected. This collection processes minimal risk to the patient.

- *Blood Sampling Collection:*

Peripheral blood sampling will be performed by a trained phlebotomist, nurse, dentist or physician utilizing standard venipuncture techniques. Patients may have some discomfort and/or bruising at the site of needle entry. There is a very small risk of fainting. Infection in the area of the needle insertion is rare. Preventive measures will be used during sample collection to reduce the risk of these rare side effects.

- *GDC-0449 Administration:*

Vismodegib is a previously studied drug. Our knowledge of adverse events related to vismodegib results from clinical trials. Adverse reactions and the associated incidence related to vismodegib are documented. Participants will be closely monitored for previously-reported and unrecognized adverse events. Tumor growth in participants on the drug is possible; however, participants will be monitored with both clinical and radiographic examination to identify such growth. Participants on vismodegib might avoid surgery and the morbidity (*i.e.,* loss of bone and teeth) associated with surgery.

GDC-0449 (Vismodegib) capsule is a Hh pathway inhibitor indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for radiation.
The most common adverse reactions (incidence ≥ 10%) are muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting and ageusia. In clinical trials, a total of 3 of 10 pre-menopausal women developed amenorrhea while receiving GDC-0449. Treatment-emergent Grade 3 laboratory abnormalities observed in clinical trials were hyponatremia in 6 patients (4%), hypokalemia in 2 patients (1%), and azotemia in 3 patients (2%).

The safety and efficacy of vismodegib in pediatric patients has not been established. Studies in animals indicate that oral Hh pathway inhibitors pose a substantial risk of developmental defects during the post-natal period, which includes irreversible effects on growing teeth or bones and male reproductive organs. The occurrence of premature epiphyseal fusion has been identified on routine pharmacovigilance through literature review and from serious adverse events (SAEs) reported in an Investigator Sponsored Trial (IST) of pediatric patients receiving vismodegib therapy. In some cases, fusion progressed after drug discontinuation.

In this study, the safety and efficacy of oral GDC-0449 in the management of NBCCS-associated KCOT and sporadic KCOT will be examined. The recommended dose is 150mg taken orally once daily until disease progression or until unacceptable toxicity. The capsule has a pink opaque body and a grey opaque cap with “150 mg” printed on the capsule body and “Vismo” printed on the capsule cap in black ink. It can be taken

with or without food and capsules should not be opened or crushed. If patients miss a dose, they will be advised not to make up that dose but instead to resume dosing with the next scheduled dose.

Pregnancy status prior to the initiation of GDC-0449 will be verified with a serum pregnancy test. Male and female patients will be advised of the risks of embryo-fetal death and severe birth defects and the need for contraception during and after treatment.

In addition, patients must agree not to donate blood or blood products during the study and for 24 months after discontinuation of vismodegib.

If a patient experiences unacceptable drug toxicity, he/she will be allowed a treatment break lasting for at least one month, up to three months. If the patient is unable to resume treatment after an 3 month treatment break, he/she will be discontinued from the study.

A potential risk of treatment of KCOT with vismodegib is disease progression, *i.e.* tumor growth. Participants will be closely monitored with clinical and radiographic examination for evidence of disease progression. The natural history of KCOTs is that the tumors grow and expand slowly relative to the proposed examination schedule. Therefore, it is highly unlikely that unanticipated growth in participants on vismodegib would be encountered.

The potential benefit of treatment of KCOT with vismodegib is decreased tumor recurrence and reduced surgical morbidity. Currently the management of KCOT is surgical. The surgical options include: 1. resection, 2. enucleation with or without treatment of the bony cavity using tissue fixatives or liquid nitrogen, or 3. surgical decompression. The morbidity of surgical resection and enucleation involves the loss of bone and teeth. In some cases the sensory nerve in the proximity of the tumor is removed leaving the patient with paresthetia or anesthesia in the distribution of the face or tongue. Replacement of bone and teeth is extremely difficult and in many cases not possible. Decompression involves placement of a drain into the tumor cavity followed by irrigation of the bony cavity three times a day for 12 to 24 months. Often after this treatment eventual removal of the tumor is required. A potential benefit for participants treated with vismodegib is that they might avoid the morbidity associated with the above-described surgery.

4.4.1 Phase 1: Screening

Potential patients (10 with NBCCS-associated KCOT and 10 with sporadic KCOT, males and females, ≥18 years) will be recruited from the Department of Oral and Maxillofacial Surgery at NYU College of Dentistry, NYU Langone Medical Center and Bellevue Hospital, as all these institutions represent major referral sources for head and neck pathology. Patients will also be recruited from other private and academic oral and maxillofacial surgery practices both in the New York area and other parts of the country

by referral. Investigator will present this study during society meetings so that other surgeons can refer KCOT patients to this study.

Before a patient's participation in the study, the investigator will be responsible for obtaining written ICF from the patient, after adequate explanation of the aims, methods, anticipated benefits and potential risks of the study and before any protocol specific screening procedure is performed or the study drug is administered. The patient will be given ample time to consider the information provided and ask questions before giving written consent.

The acquisition of informed consent will be thoroughly documented in the patient's chart and the informed consent form with be personally signed and dated by both the patient and the person who conducted the informed consent discussion. A patient will be considered enrolled in the study, once the informed consent form is signed. The original informed consent will be retained and a copy will be provided to the patient. The same process will be followed for the consenting for optional future genetic testing on blood and on the tumor.

4.4.2 Baseline Visit

The following procedures will be performed at Baseline visit (study procedures and assessments during the baseline visit can be conducted over several visits until all inclusion/exclusion criteria are verified and patient is eligible to proceed with treatment (first study drug administration).

After obtaining written Informed Consent for a potential subject, a unique Screening number will be assigned and the following evaluations will be performed to screen for eligibility:

- Informed Consent and Screening
- Review of Inclusion/Exclusion Criteria
- Review of Medical Records, if applicable
- Medical/Dental History
- Concomitant Medications
    - All prescription, non-prescription medicines, vitamins and herbal supplements will be recorded at the baseline visit in the concomitant medication CRF. Throughout the study, any changes in concomitant medication must be recorded by the investigator.
- Demographics (including height and weight)
    - In addition to the height and weight, the following information will be collected: date of birth, gender and race.

- Serum Pregnancy Test (if female patient of child bearing potential):
    - Female patients of reproductive potential are required to use two forms of acceptable contraception during therapy and for 24 months after completing therapy. See appendix B for definition of reproductive potential and acceptable contraception. Male patients must use condoms at all times, even after a vasectomy, during sexual intercourse with female partners of reproductive potential during treatment with vismodegib and for 2 months after the last dose to avoid exposing a pregnant partner and unborn fetus to vismodegib.
    - If 7 days have passed between the patient's enrollment in the study (date the ICF was signed) and the first study drug administration, the serum pregnancy test will be repeated.

- Oral Cavity Assessment (soft & hard tissues, extraoral, head & neck)

- Physical Exam

- Clinical Laboratories
    - Complete blood count, serum pregnancy test, serum chemistry, coagulation time, and liver function will be assessed: white blood count, hemoglobin, platelets, glucose, uric acid, calcium, phosphorus, sodium, potassium, chloride, alkaline phosphatase, albumin, alanine transaminase (ALT), aspartate transaminase (AST), BUN and creatinine
    - All laboratory results will be reviewed and the reports will be signed by the investigator. Any results considered to be of clinical significance must be dealt with and followed up as clinically appropriate. All laboratory results considered to represent an AE must be documented in the CRF. Repeat samples will be taken if required for clinical follow up or because the sample is lost or damaged. Any abnormal end of treatment clinical laboratory result of clinical significance must be repeated at regular intervals until it returns to normal, or until the investigator is satisfied that the abnormality is not related to the study drug and needs no further investigation.

- Genetic Testing of blood for *PTCH1* mutation

- Genetic Testing of the tumor (if biopsy on excision is required for *PTCH1* mutation)

- Vital Signs (blood pressure, heart rate, temperature)

- Verification of KCOT Diagnosis
    - If a patient had an outside biopsy, then a copy of the pathology report and slides confirming the KCOT diagnosis will be obtained. For patients with multiple KCOTs associated with NBCCS, the pathology report and slides associated with each of the lesions will be obtained. If a patient has a lesion that is suspicious for KCOT, but no biopsy, then a biopsy will be performed as a standard of care. If a patient has multiple KCOTs associated with

NBCCS but there is no biopsy of any of the lesions, then a biopsy will be performed on selected lesions.
    - The investigator will review the patient's medical records to confirm that the patient was treated with the standard of care and that the KCOT is recurrent.

- Biopsy of the Tumor, if applicable

- Panoramic Radiograph

- Volumetric CT Scan
    - Once the diagnosis of recurrent KCOT is confirmed a baseline volumetric CT scan will be obtained. The baseline CT will include the jaws and the brain. Patients must have at least one lesion measuring at least 1 cm in dimension to be enrolled.

- Skin Examination (for NBCCS-associated KCOT patients)
    - The entire skin will be examined and basal cell carcinomas, if present, will be mapped by location and size

- Photographs of Skin Lesions, if applicable

- Study Drug Administration – First Dose
    - Once the baseline visit assessments are complete and eligibility is confirmed, all patients will receive the same treatment (150 mg/day of GDC-0449 orally for 1 year). After the first study drug administration, patients will be observed and monitored by the investigator for 6 hours. Patients will maintain the medication regimen until they are required to discontinue the study drug due to disease progression, or unacceptable toxicity, as assessed by the investigator.

- Study Drug Dispense until next visit

- Adverse Events

Upon discharge from the clinic, specific instructions will be given to patients regarding the use of the medication, as well as adequate study drug supplies until their next visit. Patients will be instructed the following:

- Not to donate blood or blood products while receiving GDC-0449 and for at least 24 months after the last dose of the study drug.
- Not to get pregnant during the study and for 24 months after the last dose of the drug (see more details in Appendix 2)
- To take 150 mg of GDC-0449 orally once daily with or without food and to swallow capsules whole. Capsules should not be opened or crushed.

- If a dose is missed, not to make up that dose but to resume dosing with the next scheduled dose.
- To notify the investigator immediately if they notice any changes with their health status or if they become pregnant.

4.4.3 Phase 2: Treatment (1 Year)

<u>1 Month, 3 Month, 6 Month and 1 Year Visit (+/- 7 Day Window)</u>

- Continuance Criteria: patients will be released from study participation for the following reasons:
  - non-compliance with study procedures
  - development of a medical condition or taking a medication which would affect the study outcome, as covered in the exclusion criteria
  - disease progression or unacceptable toxicity of study drug, as assessed by the investigator
  - pregnancy
  - withdrawal of patient consent
  - protocol violation
  - lost to follow-up

- Review of Medical Records, if applicable

- Medical/Dental History update

- Concomitant Medications update

- Urine Pregnancy Test (if female of child bearing potential)

- Oral Cavity Assessment (soft & hard tissues, extraoral, head & neck)

- Physical Exam

- Clinical Laboratories (at 3 month, 6 month and 1 year visit)

- Genetic Testing for Blood (at 1 year visit)

- Genetic Testing for the Tumor (at 1 year visit)

- Vital Signs (blood pressure, heart rate, temperature)

- Panoramic Radiograph

- Volumetric CT Scan (at 6 month and 1 year visit)

- Skin Examination for NBCCS-associated KCOT patients at 6 month and 1 year visit

- Photographs of Skin Lesions, if applicable

- Compliance with Study Drug

    - Compliance with study drug will be checked by counting the capsules that were returned to the site versus the capsules that were administered to patient at the end of the last visit. Any discrepancy will be documented in the patient's chart and in the drug accountability log. Study reminders regarding compliance will be reviewed with the patient in order to maximize the proper use of the study drug.

- Study Drug Dispense until next visit

- Adverse Events

Upon discharge from the clinic, specific instructions will be given to patients regarding the use of the medication, as well as adequate study drug supplies until their next visit. Patients will be instructed the following:

- Not to donate blood or blood products while receiving GDC-0449 and for at least 24 months after the last dose of the study drug.
- Not to get pregnant during the study and for 24 months after the last dose of the drug (see more details in Appendix B)
- To take 150 mg of GDC-0449 orally once daily with or without food and to swallow capsules whole. Capsules should not be opened or crushed.
- If a dose is missed, not to make up that dose but to resume dosing with the next scheduled dose.
- To notify the investigator immediately if they notice any changes with their health status or if they become pregnant.

<u>2 Month, 4 Month, 5 Month, 7 Month, 8 Month, 9 Month, 10 Month and 11 Month Visit (+/- 7 Day Window)</u>

- Continuance Criteria: patients will be released from study participation for the following reasons:
    - non-compliance with study procedures
    - development of a medical condition or taking a medication which would affect the study outcome, as covered in the exclusion criteria
    - disease progression or unacceptable toxicity of study drug, as assessed by the investigator
    - pregnancy
    - withdrawal of patient consent
    - protocol violation
    - lost to follow-up

- Review of Medical Records, if applicable

- Medical/Dental History update

- Concomitant Medications update

- Urine Pregnancy Test (if female of child bearing potential)
- Compliance with Study Drug

    - Compliance with study drug will be checked by counting the capsules that were returned to the site versus the capsules that were administered to patient at the end of the last visit. Any discrepancy will be documented in the patient's chart and in the drug accountability log. Study reminders regarding compliance will be reviewed with the patient in order to maximize the proper use of the study drug.

- Study Drug Dispense until next visit

- Adverse Events

Upon discharge from the clinic, specific instructions will be given to patients regarding the use of the medication, as well as adequate study drug supplies until their next visit. Patients will be instructed the following:

- Not to donate blood or blood products while receiving GDC-0449 and for at least 24 months after the last dose of the study drug.
- Not to get pregnant during the study and for 24 months after the last dose of the drug (see more details in Appendix B')
- To take 150 mg of GDC-0449 orally once daily with or without food and to swallow capsules whole. Capsules should not be opened or crushed.
- If a dose is missed, not to make up that dose but to resume dosing with the next scheduled dose.
- To notify the investigator immediately if they notice any changes with their health status or if they become pregnant.

4.4.4 Phase 3: Post-Treatment (2 Years Follow-up):

<u>7 Month, 1 Year and 2 Years Post-Treatment Visits (+/- 7 Day Window)</u>

- Continuance Criteria: patients will be released from study participation for the following reasons:
    - non-compliance with study procedures
    - development of a medical condition or taking a medication which would affect the study outcome, as covered in the exclusion criteria

    - disease progression or unacceptable toxicity of study drug, as assessed by the investigator
    - pregnancy
    - withdrawal of patient consent
    - protocol violation
    - lost to follow-up

- Review of Medical Records, if applicable
- Medical/Dental History update
- Concomitant Medications update
- Urine Pregnancy Test (if female patient of child bearing potential)
- Oral Cavity Assessment (soft & hard tissues, extraoral, head & neck)
- Vital Signs (blood pressure, heart rate, temperature)
- Panoramic Radiograph
- Volumetric CT Scan (at 1 year and 2 year post-treatment visit)
- Skin Examination for NBCCS-associated KCOT patients at 1 year post-treatment visit
- Photographs of Skin Lesions, if applicable
- Adverse Events
- Study Completion/Discharge (at 2 year post-treatment visit)

During the 2 year post treatment phase and visits, patients will be reminded of the following:

- Not to donate blood or blood products while receiving GDC-0449 and for at least 24 months after the last dose of the study drug.
- Not to get pregnant during the study and for 24 months after the last dose of the drug (see more details in Appendix B)
- To notify the investigator immediately if they notice any changes with their health status or if they become pregnant

Should a patient decide to withdraw from the study or is discontinued by the investigator (see continuance criteria in phase 1 and 2), all efforts will be made to complete the discontinuation visit procedures and assessments (see Appendix A).

1 Month, 2 Month and 3 Month Post-Treatment Visits (+/- 7 Day Window)

- Continuance Criteria: patients will be released from study participation for the following reasons:
  - non-compliance with study procedures
  - development of a medical condition or taking a medication which would affect the study outcome, as covered in the exclusion criteria
  - disease progression or unacceptable toxicity of study drug, as assessed by the investigator
  - pregnancy
  - withdrawal of patient consent
  - protocol violation
  - lost to follow-up

- Review of Medical Records, if applicable

- Medical/Dental History update

- Concomitant Medications update

- Urine Pregnancy Test (if female of child bearing potential)

- Adverse Events

4.5 Discontinuation of Protocol-Specified Therapy

No dose reductions will be allowed in this study. Treatment with vismodegib may only be interrupted for up to:

- Two consecutive weeks if a patient becomes temporarily unable to swallow capsules

- Two consecutive weeks in case of an intolerable toxicity finding

A total up to eight weeks of dose interruptions (e.g., 4 x 2-week interruptions, 8 x 1-week interruptions, etc.) is allowed during the Treatment Phase.

Protocol-specified therapy may be discontinued for any of the following reasons:

- Progressive disease (PD)
- Unacceptable toxicity
- Patient election to discontinue therapy (for any reason)
- Physician's judgment

4.6 Subject Discontinuation

Study subjects may be discontinued from the study for any of the following reasons:

- non-compliance with study procedures
- development of a medical condition or taking a medication which would affect the study outcome, as covered in the exclusion criteria
- disease progression or unacceptable toxicity of study drug, as assessed by the investigator
- pregnancy
- withdrawal of patient consent
- protocol violation
- lost to follow-up

Should a patient decide to withdraw from the study or is discontinued by the investigator, all efforts will be made to complete the discontinuation visit procedures and assessments (see Appendix A).

In the event that a subject becomes pregnant during the study, the subject will be withdrawn from the study immediately upon confirmation of pregnancy. These subjects will be required to return to the study site to undergo discontinuation visit assessments. In addition, any documented pregnancy will be tracked and followed through outcome.

4.7 Study Discontinuation

The Genentech Study Center and the Principal Investigator have the right to terminate this study at any time. Reasons for terminating the study may include the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording are inaccurate or incomplete
- Study protocol not followed

Both the investigator and Genentech, Inc. reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, both the investigator and Genentech, Inc. will assure that adequate consideration is given to the protection of the patients' interests. All patients will undergo an exit examination if the study is terminated prematurely.

Patient's medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Patients will receive written copies of all laboratory data, and radiographs to bring to their health care provider. All reports and communications relating to patients in this study will identify each patient only by their initials and number. Medical information resulting from a patient's participation in this study may be given to the patient's personal physician or to

the appropriate medical personnel responsible for the patient's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, Genentech's medical monitor (or designee), and the Institutional Review Board (IRB).

4.8 Statistical Methods

a. Analysis of the Conduct of the Study

Accrual rates and sampling bias will be determined by computing the recruitment rate from among those identified as eligible.

Retention and compliance will be evaluated as the proportion of completers at the four primary time points: after 6 and up to 12 months of treatment, and then 1 and 2 years after treatment. We will detail and tabulate reasons for loss to follow-up and relate retention to baseline age, KCOT severity and between NBCSS-associated and sporadic cohorts.

b. Efficacy Analysis

i. Primary Endpoint

The effect of GDC-0449 will be evaluated (at a significance level of 5% and controlling the false discovery rate) using Wilcoxon signed rank tests to compare the mean KCOT volume at baseline to those acquired at 6, 12, 24,36 and 48 months. These comparisons will also be accomplished using paired t-tests.

ii. Subject population for this analysis. As a primary intention to treat (ITT) analysis, we will analyze data from all randomized subjects who complete Phase 1. For these analyses, Phase 1 values will be substituted for missing observations. Should more than 20% of the data be missing at any observation interval, analysis of that interval will be abandoned. Deviations from this plan, for example, emergent interest in the analysis of the all-treated or protocol-compliant subjects, will be transparently pursued and reported.

iii. Treatment of missing data. Two secondary effectiveness analyses will either carry the last observation forward into missing cells, or use maximum likelihood estimates of those values. We expect the best estimate of efficacy is likely to lie within the limits set by these conservative (ITT) and liberal (LOCF, ML) treatments of missing data.

iv. Secondary Endpoints

Secondary analysis will quantify the proportion of patients achieving minimal clinically significant changes in their tumors and comparing that to a theoretical expectation of 5% improvement with a Fisher exact test, and the effect of the *PTCH1* mutation on tumor volume reduction will be assessed with an independent samples t-test. These analyses will use the same population as the primary endpoint.

All analyses will be done using IBM SPSS Version 21.

v. Sample size determination. Twenty subjects will be recruited. Analysis of the primary endpoint is capable of detecting changes in tumor volume in the Wilcoxon tests of approximately 1.0 and .68 SD, assuming a 2-tailed type 1 error of 5% and power of 80% and then assuming either n=10 (separate analysis of the NBCSS-associated and sporadic cohorts) or n=20 (combined analysis of both cohorts), respectively (G*Power, v3.1).

c. Safety Analysis

All safety-related interventions, events, and findings will be summarized by incidence and duration and event classification. An adverse event will be considered treatment emergent if the onset date and time occur on or after the recorded clock time of the administration of study drug. Adverse events will be coded to preferred terms and system organ classes according to the Medical Dictionary for Regulatory Activities (MedDRA®). The severity of each adverse event will be determined from the World Health Organization (WHO) Toxicity Criteria or by protocol specified criteria. In addition, all adverse events will be assessed as to whether the onset of the event was related to the study drug or not and they will be followed to final resolution. Other safety assessments include vital signs, oral cavity examinations, and complete blood count. In the unlikely event that treatment is associated with increasing tumor size, tumor area, determined from panoramic radiographs acquired at each visit, will be compared to baseline.

4.9 Data Quality Assurance

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures.

5. REPORTING OF ADVERSE EVENTS

5.1 Assessment of Safety

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with KCOT that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Data Safety Monitoring Plan

- The principal investigator will be responsible for data and safety monitoring of this single site study. Adverse events, serious adverse events, unanticipated problems, and subject status will be reviewed at least annually after enrollment begins. Both the investigator and Genentech, Inc. reserve the right to terminate the study, if the incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, both the investigator and Genentech, Inc. will assure that adequate consideration is given to the protection of the patients' interests. All patients will undergo an exit examination if the study is terminated prematurely. Data safety monitoring summary will be submitted to the IRB at the time of annual continuation review.

5.2 Methods and Timing for Assessing AND Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment. All AEs occurring from the start of study treatment through to study completion, whether or not they are related to the study, will be recorded in the subject chart.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of vismodegib, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to vismodegib; and/or the AE abates or resolves upon

discontinuation of vismodegib or dose reduction and, if applicable, reappears upon re-challenge

No
Evidence exists that the AE has an etiology other than vismodegib (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to vismodegib administration (e.g., cancer diagnosed 2 days after first dose of vismodegib).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator's Brochure.

Unexpected adverse events are those not listed in the Package Insert or current Investigator's Brochure or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the Package Insert or current Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected if the Package Insert or current Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

5.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation timepoints should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be

reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 24 months after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech. If a male subject receiving study drug (or within 3 month after the last dose of study drug) impregnates a female partner, then the female partner will be requested to provide informed consented to permit a report of the pregnancy to be completed and expeditiously submitted to Genentech.

Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to study drug should be reported as an SAE.

Additional information on any vismodegib-exposed pregnancy and infant will be requested by Roche Drug Safety at specific timepoints (i.e., after having received the initial report, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant’s life).

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior vismodegib exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

g. Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange quaterly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the "Activation Package."

h. AEs of Special Interest (AESIs)

There are no Adverse Events of Special Interest (AESIs)for vismodegib.

I. Instructions for Reporting Adverse Events

Serious Adverse Events Reporting

Investigators must report all SAEs and AESIs to Genentech within the timelines described below. The completed MedWatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225-4682 or
(650) 225-4630

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports that are related to vismodegib and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.

Non-Serious Adverse Events

Bluestone Center for Clinical Research will forward a copy of the Final Study Report to Roche upon completion of the Study.

Special Situations Reports

In addition to SAEs, pregnancy reports, and AESIs, the following Special Situations Reports should be collected and transmitted to Roche even in the absence of an Adverse Event within thirty (30) calendar days:

- Data related to product usage during pregnancy or breastfeeding

- Data related to overdose, abuse, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Lack of therapeutic efficacy
- Suspected Transmission of an Infectious Agent (STIAMP) by the study drug
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

MEDWATCH 3500a REPORTING GUIDELINES

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication.

Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at the following website:
http://www.fda.gov/medwatch/getforms.html

5.4 Safety Reporting Requirements for IND Exempt Studies

For Investigator-Sponsored IND-Exempt Studies, there are some reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 314.80.

Postmarketing 15-Day "Alert Report"

The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of vismodegib. An unexpected AE is one that is not already described in the Investigator's Brochure. Such reports are to be submitted to the FDA (2 copies) at the following address: Central Document Room, 12229 Wilkins Avenue, Rockville, MD 20852.

All Postmarketing 15-Day "Alert Reports" submitted to the FDA by the Sponsor-Investigator must also be faxed to:

Genentech Drug Safety

Fax: (650) 225-4682 or (650) 225-4630

Please use the safety reporting fax cover sheet in the appendices of this protocol for your fax transmission.

Questions Related to Safety Reporting

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

5.5 Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech.
Copies of study reports should be mailed to the assigned Clinical Operations contact for the study:

Vismodegib (GDC0449) Protocols:

Email: hedgehog-gsur@gene.com

Fax: 866-741-3639

6. RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, subject records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of vismodegib. All state and local laws for retention of records also apply.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the U.S. FDA IND regulations and the relevant national and local health authorities, whichever is longer.

7. RESPONSIBILITIES

7.1 Investigator Responsibilities

7.1.1 Compliance with Good Clinical Practice

The Sponsor-Investigator will ensure this study is conducted in accordance with the basic principles of "Good Clinical Practice," as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, part 54, and part 56, as well as applicable requirements of the International Conference on Harmonization (ICH) Guideline of Good Clinical Practice (ICH E6) and the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

7.1.2 Institutional Review Board (IRB)

This protocol, any protocol amendments and any study related materials (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted to the IRB. Approval from the IRB must be obtained before starting the study and documented in a letter to the investigator specifying the protocol number, if applicable, protocol version, documents reviewed, and date on which the IRB granted the approval.

All unexpected SAEs related to study participation will be reported to the IRB within 5 business days.

7.1.3 Informed Consent

Informed Consent for patients ≥ 18 years of age:

For inclusion of patients 18 years or older, the investigator will obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking

any study-related procedures. The investigator will utilize an IRB-approved consent form.

Each ICF will be signed and dated by the individual participating in the study and the person obtaining the consent. By signing the ICF, the patient agrees to complete all evaluations unless the patient withdraws consent or is terminated from the study for any reason.

As part of the informed consent, the investigator will obtain HIPAA compliant authorization from patients to use and disclose relevant protected health information (PHI) and permission for authorized representatives of Genentech Inc., or regulatory authorities including the FDA, to review in confidence any records identifying patients in the clinical study.

Recruitment efforts may precede obtaining informed consent; however, informed consent must be obtained prior to any protocol specific procedures being performed.

The investigator will communicate any new information on safety to patients who consent to participate in this study in accordance with IRB requirements. The ICF will be updated, if necessary.

7.1.4 Confidentiality

The investigator will assure that patients' anonymity will be strictly maintained and that their identities will be protected from unauthorized parties. Only patient initials and an identification code (i.e., not names) will be recorded on any form submitted to the sponsor or IRB.

The investigator agrees that all information received from Genentech, Inc., including but not limited to the Investigator's Brochure, the study drug, and any other study information, are the sole and exclusive property of Genentech Inc. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Genentech Inc.

The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

7.1.5 Study Files and Retention of Records

The investigator will maintain adequate and accurate records that fully document the conduct of the study and enable study data to be verified. These documents should be classified into separate categories: 1) investigator's study file (regulatory binder) and 2) patient clinical source documents.

- The investigator's study file (regulatory binder) includes the original protocol, protocol amendments, CRFs and query forms, IRB approval with correspondence,

approved informed consent forms, drug records, staff curriculum vitae (CV) and authorization forms, and other appropriate documents and correspondence.

- Patient clinical source documents include, but are not limited to, the patient's medical/dental records, laboratory reports, radiographs, pathology and special assessment reports, consultant letters, screening and enrollment log, as applicable.

The investigator will make the source documents for this study available for inspection to Genentech, Inc. or its representatives, or to regulatory or health authority inspectors. The investigator will retain all study documents for at least two years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region (i.e., United States, Europe, or Japan), and until there are no pending or contemplated marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the investigator will retain all study documents for at least two years after the investigation is discontinued and regulatory authorities have been notified.

If no application is filed or if the application is not approved for such indication, the investigator will retain all study documents for at least two years after the investigation is discontinued and regulatory authorities have been notified. The investigator may retain documents longer if required by applicable regulatory requirements or by agreement with Genentech, Inc.

7.1.6 Case Report Forms

The investigator is responsible for the completeness and accuracy of information collected on the CRFs for each individual enrolled. The investigator will review and approve all CRFs; document the reason that a patient withdraws from the study on the appropriate CRF and attempt to obtain termination assessments; and continue follow-up to document the outcome of any adverse event.

7.1.7 Drug Accountability

The investigator is responsible for ensuring adequate accountability of all used and unused study drug, including acknowledgment of receipt of each shipment of study products (quantity and condition) and patient dispensing records. Dispensing records will document quantities received and quantities dispensed, lot number (if applicable), date dispensed, patient identifier number, and initials of the person dispensing the study drugs.

Unused study drug must not be discarded or destroyed by the investigator until requested in writing by the sponsor. The sponsor may request in writing that study drug inventory be destroyed in compliance with their institutional requirements.

7.1.8 Inspections

The investigator will make the source documents for this study available to Genentech, Inc. or its authorized designee, or to the regulatory or health authority inspectors.

8. Conflict of Interest

The Sponsor-Investigator does not participate in any financial arrangement with the funding sponsor, Genentech other than for this study and its associated usual and customary fees; has no proprietary interest in this product or significant equity interest in Genentech; and was not and is not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f))

9. Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

1. **Bhargava, D., A. Deshpande, and M.A. Pogrel, *Keratocystic odontogenic tumour (KCOT)--a cyst to a tumour.* Oral Maxillofac Surg, 2012. 16(2): p. 163-70.**
2. **Gorlin, R.J., *Nevoid basal-cell carcinoma syndrome.* Medicine, 1987. 66(2): p. 98-113.**
3. **Gorlin, R.J. and R.W. Goltz, *Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib. A syndrome.* The New England Journal of Medicine, 1960. 262: p. 908-12.**
4. **Goldberg, L.H., et al., *Resolution of odontogenic keratocysts of the jaw in basal cell nevus syndrome with GDC-0449.* Arch Dermatol, 2011. 147(7): p. 839-41.**
5. **Bell, R.B. and E.J. Dierks, *Treatment options for the recurrent odontogenic keratocyst.* Oral Maxillofac Surg Clin North Am, 2003. 15(3): p. 429-46.**
6. **Kaczmarzyk, T., I. Mojsa, and J. Stypulkowska, *A systematic review of the recurrence rate for keratocystic odontogenic tumour in relation to treatment modalities.* Int J Oral Maxillofac Surg, 2012. 41(6): p. 756-67.**
7. **Sun, L.S., X.F. Li, and T.J. Li, *PTCH1 and SMO gene alterations in keratocystic odontogenic tumors.* J Dent Res, 2008. 87(6): p. 575-9.**
8. **De Smaele, E., E. Ferretti, and A. Gulino, *Vismodegib, a small-molecule inhibitor of the hedgehog pathway for the treatment of advanced cancers.* Curr Opin Investig Drugs, 2010. 11(6): p. 707-18.**
9. **Goldberg, L.H., et al., *Resolution of odontogenic keratocysts of the jaw in basal cell nevus syndrome with GDC-0449.* Archives of dermatology, 2011. 147(7): p. 839-41.**
10. **Von Hoff, D.D., et al., *Inhibition of the hedgehog pathway in advanced basal-cell carcinoma.* N Engl J Med, 2009. 361(12): p. 1164-72.**
11. **Sekulic, A., et al., *Efficacy and safety of vismodegib in advanced basal-cell carcinoma.* N Engl J Med, 2012. 366(23): p. 2171-9.**
12. ***Erivedge [package insert]*, 2015, Genentech, Inc.: South san Francisco, CA.**
13. **Gorlin, R.J., *Nevoid basal-cell carcinoma syndrome.* Medicine (Baltimore), 1987. 66(2): p. 98-113.**
14. **Gorlin, R.J. and R.W. Goltz, *Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib. A syndrome.* N Engl J Med, 1960. 262: p. 908-12.**
15. **Tang, J.Y., et al., *Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome.* N Engl J Med, 2012. 366(23): p. 2180-8.**
16. **Gajjar, A.J., S. Gururangan et al, *A prospective phase II study to determine the efficacy of GDC 0449 (vismodegib) in adults with recurrent medulloblastoma (MB): A Pediatric Brain Tumor Consortium study (PBTC 25B).* ASCO Poster Presentation, 2013.**
17. **Asklund, T., et al., *Early and persisting response to vismodegib in a patient with bone metastasizing medulloblastoma.* Acta Oncol, 2013. 52(4): p. 862-6.**
18. **Berlin, J., et al., *A randomized phase II trial of vismodegib versus placebo with FOLFOX or FOLFIRI and bevacizumab in patients with previously untreated metastatic colorectal cancer.* Clin Cancer Res, 2013. 19(1): p. 258-67.**
19. **Kaye, S.B., et al., *A phase II, randomized, placebo-controlled study of vismodegib as maintenance therapy in patients with ovarian cancer in second or third complete remission.* Clin Cancer Res, 2012. 18(23): p. 6509-18.**
20. **Catenacci, D.V.T., N. Bahary et al, *Final analysis of a phase Ib/Randomized phase II study of Gemcitabine plus Placebo or Vismodegib, a Hedgehog pathway inhibitor, in patients with metastatic pancreatic cancer: A University of Chicago Phase II Consortium Study 2013.* ASCO Poster Presentation, 2013.**
21. **Sloan, A.E., C.J. Nock et al, *Targeting glioma stem cells in GBM ABTC-0904: phase 0/II study of hedgehog pathway inhibitor GDC-0449.* SNO Poster Presentation, 2012.**
22. **Cohen, D.J., P. Christos et al, *A randomized phase II study of vismodegib, a hedgehog pathway inhibitor, combined with FOLFOX in patients with advanced gastric and gastroesophageal junction carcinoma: A New York Cancer Consortium led study.* ASCO Poster Presentation, 2013.**
23. **Belani, C.P., S.E. Dahlberg et a, *Three-arm Randomized phase II study of cisplatin and etoposide (CE) versus CE with either vismodegib (V) or cixutumumab (Cx) for patients with extensive stage-small cell lung cancer (ES-SCLC).* ASCO Poster Presentation, 2012.**
24. **Graham, R.A., et al., *Pharmacokinetics of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with locally advanced or metastatic solid tumors: the role of alpha-1-acid glycoprotein binding.* Clin Cancer Res, 2011. 17(8): p. 2512-20.**

25. **Lorusso, P.M., et al., *Pharmacokinetic dose-scheduling study of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with locally advanced or metastatic solid tumors.* Clin Cancer Res, 2011. 17(17): p. 5774-82.**
26. **LoRusso, P.M., et al., *Phase I trial of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with refractory, locally advanced or metastatic solid tumors.* Clin Cancer Res, 2011. 17(8): p. 2502-11.**

APPENDIX A: SCHEDULE OF STUDY ASSESSMENTS & PROCEDURES

STUDY ASSESSMENTS & PROCEDURES	SCREENING PHASE	TREATMENT PHASE (1 YEAR)												POST TREATMENT FOLLOW UP (2 YEARS)						
	BASELINE VISIT	1 MONTH POST DOSING	2 MONTH POST DOSING	3 MONTH POST DOSING	4 MONTH POST DOSING	5 MONTH POST DOSING	6 MONTH POST DOSING	7 MONTH POST DOSING	8 MONTH POST DOSING	9 MONTH POST DOSING	10 MONTH POST DOSING	11 MONTH POST DOSING	1 YEAR POST DOSING	1 MONTH POST TREATMENT	2 MONTH POST TREATMENT	3 MONTH POST TREATMENT	7 MONTH POST TREATMENT	1 YEAR POST TREATMENT	2 YEARS POST TREATMENT	DISCONTINUATION VISIT
		+/- 7 DAYS																		
Informed Consent & Screening	X																			
Review of Inclusion/Exclusion Criteria	X																			
Review of Medical Records, if applicable	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical/Dental History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographics (height, weight)	X																			
Urine Pregnancy Test, if female patient of child bearing potential		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test, if female patient of child bearing potential	X	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Oral Cavity Assessment (soft & hard tissues,	X	X		X			X						X				X	X	X	X
Physical Exam	X	X		X			X						X							X
Clinical Laboratories	X			X			X						X							X
Genetic Testing of Blood	X												X							X
Genetic Testing of the Tumor, if biopsy on excision	X												X							X
Vital Signs (BP, HR, temperature)	X	X		X			X						X				X	X	X	X
Verification of KCOT Diagnosis	X																			
Biopsy of Tumor, if applicable	X																			
Panoramic Radiograph	X	X		X			X						X				X	X	X	X
Volumetric CT Scan	X						X						X					X	X	X
Skin Examination for NBCCS-associated KCOT patients	X						X						X					X		X
Photographs of Skin Lesions, if applicable	X						X						X					X		X
Study Drug Administration – First Dose	X																			
Study Drug Dispense until next visit / Compliance with study drug	X	X	X	X	X	X	X	X	X	X	X	X	X							
Continuance Criteria/Study Reminders		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study completion, Discharge																				X

* Any positive urine pregnancy test must be confirmed by a serum pregnancy test.

APPENDIX B
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 child-bearing potential must use two methods of acceptable contraception including one highly effective method and a barrier method during Erivedge therapy and for 9 months after the final dose.

Acceptable forms of barrier contraception include the following:

- Latex, non-latex, or any other male condom (always used with spermicide)
- Diaphragm (always used with spermicide)

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

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

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 C
Gorlin Syndrome Diagnostic Criteria (if applicable)

Major Criteria	Minor Criteria
More than two histologically confirmed BCCs, or one under the age of 20 years	Macrocephaly determined after adjustment for height
Keratocystic odontogenic tumors (KOT) of the jaw proven by histology	Congenital malformations such as the following: cleft lip or palate, frontal bossing, strabismus, “coarse face,” or moderate or severe hypertelorism
Three or more palmar and/or plantar pits	Skeletal abnormalities such as the following: Sprengel’s deformity, marked pectus deformity, marked syndactyly of the digits, scoliosis
Bilamellar calcification of the falx cerebri (if less than 20 years old)	Radiological abnormalities such as the following: bridging of the sella turcica; vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defects of the hands and feet, or flame-shaped lucencies of the hands or feet
Fused, bifid, or markedly splayed ribs	Ovarian fibroma
First- degree relative with BCCNS	Medulloblastoma, menengioma
PTCH1 gene mutation in normal tissue	

Note: Diagnostic criteria are adapted from Kimonis VE, Goldstein AM, Pastakia B, et al. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. Am J Med Genet 1997;69:299-308.

APPENDIX D
NCI-CTCAE Grading System for Adverse Events Commonly Associated with Vismodegib Therapy

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alopecia	Hair loss of < 50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	Hair loss of ≥ 50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact	–	–	–
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	–	–	–

APPENDIX E

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-4630

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ]-[ ]-[ ]

SAE or Safety Reporting questions, contact Genentech Safety:

(888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET.

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APPENDIX F
Material Safety Data Sheet (MSDS)

The current Material Safety Data Sheet (MSDS) for ERIVEDGE® Capsules (150 mg) is available at:

http://www.gene.com/download/pdf/ErivedgeCapsules150mgMSDS.pdf