

Pharmacokinetic Dose-Scheduling Study of Hedgehog Pathway Inhibitor Vismodegib (GDC-0449) in Patients with Locally Advanced or Metastatic Solid Tumors

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Abstract

Purpose: This study was designed to evaluate whether less frequent dosing [three times per week (TIW) or once weekly (QW)] of 150 mg vismodegib following a loading dose [150 mg once daily (QD) for 11 days] would result in similar safety, tolerability, and steady-state levels of total and unbound vismodegib as continuous QD dosing.

Experimental Design: Sixty-seven patients with advanced solid tumors were stratified by baseline plasma alpha 1-acid glycoprotein (AAG) levels and randomized to one of three vismodegib 150 mg regimens: QD ($n = 23$), TIW ($n = 22$), or QW ($n = 22$) for up to 42 days after an 11-day loading phase (150 mg QD). Total and unbound (dialyzed) plasma vismodegib concentrations were determined by LC-MS/MS.

Results: The most frequently reported adverse events were consistent with those in prior monotherapy trials, with similar incidence and severity regardless of dosing schedule. After the 150 mg QD loading phase, a concentration-dependent change in protein binding (3-fold increase in vismodegib fraction unbound) was observed at steady state compared with single dose. Mean total and unbound vismodegib steady-state concentrations were lower after TIW and QW than QD dosing, with an average intrasubject decrease of 50% and 80%, respectively, for unbound drug. Mechanism-based PK model simulations accurately and prospectively predicted the PK results.

Conclusions: Vismodegib 150 mg TIW or QW failed to achieve unbound plasma concentrations previously associated with efficacy in patients with advanced basal cell carcinoma and medulloblastoma, even after a QD loading dose period. The 150 mg QD regimen is appropriate for vismodegib based on its clinical activity, tolerability, and favorable unbound concentrations. *Clin Cancer Res*; 17(17); 5774–82. ©2011 AACR.

Introduction

Aberrant hedgehog pathway activation has been implicated in a number of cancers (1–9). Vismodegib (GDC-0449; 2-chloro-N-[4-chloro-3-(pyridin-2-yl)phenyl]-4-[methylsulfonyl]benzamide) is a potent small molecule inhibitor of the hedgehog signaling pathway and is being developed for treatment of various cancers (10–13). Vismodegib binds to and inhibits smoothed, a 7-transmembrane hedgehog pathway signaling protein. Activity of vismodegib was first shown *in vivo* in preclinical models of

medulloblastoma (14), colon, and pancreatic tumors (9). Data from these studies were used to establish a target plasma concentration of vismodegib to meet, or exceed, the unbound IC_{95} for *Gli1* inhibition (0.042–0.068 $\mu\text{mol/L}$; ref. 15). In a phase I study for patients with advanced malignancies, vismodegib was well tolerated, with pharmacodynamic (PD) evidence of hedgehog pathway inhibition via *GLI1* suppression, and tumor regressions in patients with basal cell carcinoma and medulloblastoma (10, 11, 13).

In general, the pharmacokinetics (PK) of vismodegib are similar between healthy volunteers and cancer patients, with minor differences attributed to differences in amount and variability of plasma proteins. Vismodegib showed an unexpected PK profile upon oral daily dosing in healthy volunteers, with high, sustained micromolar plasma levels, and an estimated terminal half-life of 10 to 14 days (16). In a phase I study with continuous once daily dosing, total and unbound steady-state plasma concentrations in patients were typically achieved within 7 to 14 days of dosing; increasing the daily dose from 150 to 270 or 540 mg did not result in higher plasma concentrations,

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Translational Relevance

Vismodegib (GDC-0449), a small-molecule hedgehog pathway inhibitor, has shown encouraging antitumor activity in advanced basal cell carcinoma and medulloblastoma and has a unique pharmacokinetic (PK) profile showing nonlinearity with regard to dose and time. This clinical trial was designed to compare the effect of different dosing schedules on the safety and steady-state plasma PK profiles of total and unbound vismodegib. We found that 150 mg vismodegib three times a week or once weekly was associated with a marked decrease in unbound steady-state vismodegib concentrations relative to a once daily regimen, which could compromise therapeutic activity. These findings were compared with simulations from a mechanism-based PK model for validation purposes and dosage justification.

suggestive of nonlinear PKs with regard to dose and time (13). Furthermore, vismodegib levels were strongly correlated with alpha 1-acid glycoprotein (AAG) levels, showing parallel fluctuations of AAG and total drug over time and consistently low unbound drug levels. This unique PK profile was shown to be due to high-affinity reversible binding to AAG and binding to albumin (17), in addition to nonlinear absorption and slow metabolic elimination (18). A mechanism-based conceptual PK model was developed to provide a quantitative description of the observed vismodegib phase I data (18).

Due to the nonlinearity in vismodegib PKs after daily dosing, it was of interest to determine whether less frequent dosing could result in similar steady-state levels of total and unbound vismodegib to those obtained with daily dosing. The objectives of this phase Ib study were to evaluate the safety, tolerability, and relative effect of different dosing schedules on the steady-state PKs of total and unbound vismodegib. A vismodegib dose of 150 mg was administered either once daily (QD), three times per week (TIW), or once weekly (QW) after an 11-day loading dose (150 mg QD) in patients with advanced solid tumors that were refractory to treatment or for whom no standard therapy existed. A secondary objective was to assess the PKs of unbound vismodegib for 72 hours after a single dose. This study was conducted to provide insight into the optimal dosage of vismodegib for ongoing and future clinical studies.

Materials and Methods

Subject eligibility

All patients were at least 18 years of age and had histologically documented, incurable, locally advanced, or metastatic solid malignancy that had progressed after first-line and second-line therapy or for which there was no appropriate standard therapy. Patients with basal cell

carcinoma (BCC) were excluded from this study unless they did not qualify for another open vismodegib clinical trial. Patients had Eastern Cooperative Oncology Group performance status less than or equal to 1. Women of childbearing potential had a documented negative serum pregnancy test. Exclusion criteria included untreated central nervous system malignancies or treated brain metastases that were not radiographically stable for 3 or more months, active infection requiring i.v. antibiotics, inability to swallow pills, clinically important history of liver disease, any medical condition or diagnosis that would likely impair absorption of an orally administered drug, pregnancy or lactation, treatment with strong CYP450 inhibitors and inducers, and any other conditions that would contraindicate investigational drug use in the opinion of the investigator. The study was approved by a local Human Investigations Committee. All patients provided written informed consent according to Federal and Institutional Guidelines before study procedures began.

Study design

This phase Ib study was a 2-part, randomized, open-label, multicenter design in which all patients received a daily 150 mg loading dose for 11 days (loading phase), followed by a 150 mg maintenance dose administered QD, TIW (Monday, Wednesday, Friday), or QW (Monday). Considering the potential effect of AAG on the PKs of total and unbound vismodegib, patients were stratified according to baseline AAG concentration [low (≤ 100 mg/dL), mid-range (> 100 mg/dL to ≤ 150 mg/dL), or high (> 150 mg/dL)] and then randomized to 1 of 3 treatment arms to receive vismodegib QD, TIW, or QW (randomization ratio of 2:3:3).

Vismodegib was taken at approximately the same time each day on an empty stomach (nothing but water for 2 hours before and 1 hour after drug administration). Dose modification from assigned regimen or treatment interruption was not allowed before day 57. On study visit days, patients received vismodegib at the clinic. In part 1, all patients received a single dose of vismodegib on day 1. No drug was taken on days 2 or 3. Starting on day 4, daily doses of vismodegib were administered to all patients for 11 days to bring patients to steady state (loading phase). In part 2, patients received vismodegib QD, TIW, or QW as a maintenance dose for up to an additional 42 days. The study schema is shown in Figure 1.

Accrual to the TIW or QW arms could be closed before day 57 if available PK and/or efficacy data suggested that TIW or QW dosing was futile. If the QW arm was closed to enrollment, patients currently receiving QW dosing could cross over to receive QD dosing for the remainder of the study, and subsequent patients would be stratified based on baseline AAG levels and randomized to the 2 remaining study arms. If the TIW arm was closed to enrollment, the QW arm would also be closed; patients currently receiving TIW or QW dosing could cross over to receive QD dosing for the remainder of the study.

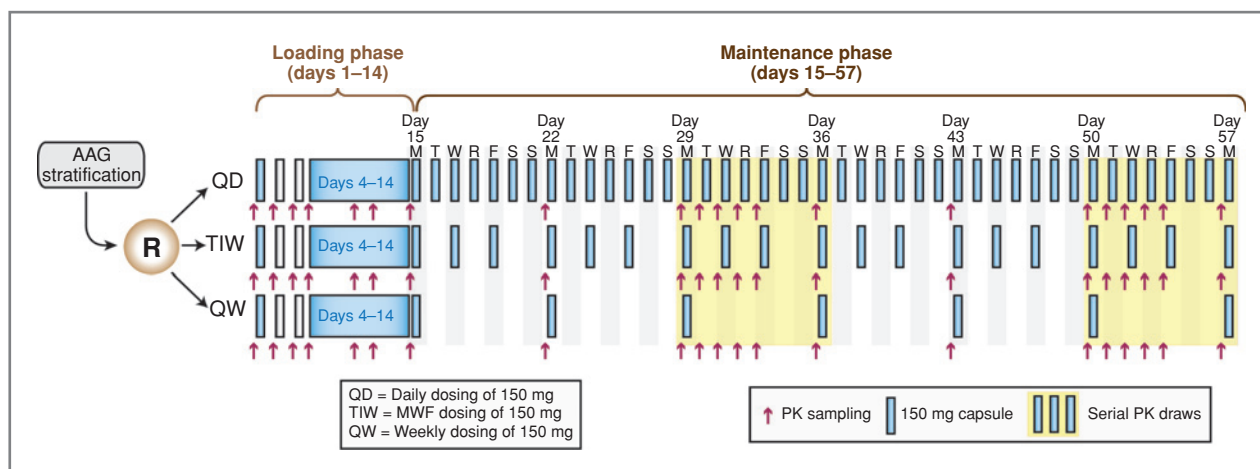


Figure 1. Schematic depicting subject stratification, randomization, dosing, and PK sampling.

Safety and PK assessments

The safety and tolerability of vismodegib were assessed by collecting the incidence, nature, and severity of adverse events, including clinically significant changes in vital signs or abnormalities in safety-related laboratory parameters. Severity was determined based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0.

The same sampling times were used for blood sample collection for the assessment of vismodegib (total and unbound) and AAG concentrations. In part 1, blood samples for plasma PK analyses were collected on day 1 before dosing and at 1, 2, 4, 6, and 24 hours after dosing. Blood samples for plasma PK analyses were also collected on day 3 (48 hours), and before dosing on day 4 (72 hours), day 8, and day 10. In part 2, blood samples for PK analyses were collected weekly, before dosing on days 15, 22, 29, 36, 43, 50, and 57. In addition, on days 29 and 50, PK samples were drawn at 1, 2, 4, and 6 hours after dosing, and daily morning samples corresponding to 24, 48, 72, and 96 hours after the first dose of each week.

Total and unbound plasma levels of vismodegib were determined using liquid chromatography–tandem mass spectrometry (16). Unbound vismodegib was measured in ultrafiltrate from plasma samples that underwent equilibrium dialysis (18). AAG levels in serum were determined by immunonephelometry using a standard clinical laboratory procedure.

Individual patient vismodegib PK parameter values for total and unbound plasma concentration–time data were derived using noncompartmental methods (WinNonlin version 5.2.1, Pharsight Corp.). Trough concentration at steady state was estimated as the average of trough values on days 29 to 57. The relationship between total plasma or unbound vismodegib concentration and AAG level was explored graphically and by linear regression analysis for each dosing schedule using the average steady-state trough vismodegib concentration and average AAG concentration from day 29 through day 57. A previously developed

mechanism-based PK model was used to prospectively simulate the impact of dosing schedule on the PKs of vismodegib during study conduct (prior to observation of actual PK results) and predict vismodegib PK profiles for lower daily doses (18).

Results

Safety

Vismodegib was generally well tolerated in this study, and the overall rate and severity of adverse events was similar across dose groups. All but one patient experienced at least one adverse event while on study. The most common adverse event was nausea (30 patients; 47.6%). A total of 24 patients (38.1%) experienced grade 3 to 5 adverse events on study (Table 1), but only 1 event in 1 patient was considered related to vismodegib (i.e., grade 3 hyponatremia).

Twenty-two patients (34.9%) experienced serious adverse events, the most common of which was intestinal obstruction (3 patients; 4.8%). No serious adverse event was considered to be related to vismodegib. No pattern of clinically significant change was identified for any of the hematologic, chemistry, or urinalysis parameters measured.

PKs

The average maximum plasma concentration (C_{max}) of total and unbound vismodegib was observed at 48 hours and maintained through 72 hours after a single 150 mg vismodegib dose. Total and unbound plasma concentrations seemed to be at steady state within 11 days (i.e., by day 15) of continuous once daily dosing of 150 mg vismodegib (loading phase). During the 6-week multiple-dose period following the loading phase, total and unbound plasma vismodegib concentrations were maintained with the QD dosing schedule. Total plasma vismodegib concentrations declined in a dosing frequency-related fashion, with the greatest decline observed in the

Table 1. Adverse events are summarized by dosing schedule

	Summary of adverse events			
	QD (n = 20)	TIW (n = 21)	QW (n = 22)	Total (n = 63)
All treatment-emergent adverse events	20 (100)	20 (95.2)	22 (100.0)	62 (98.4)
Grade 3–4 treatment-emergent adverse events	8 (40.0)	8 (38.1)	8 (36.4)	24 (38.1)
Deaths	2 (10.0)	0 (0.0)	0 (0.0)	2 (3.2)
Treatment-emergent serious adverse events	6 (30.0)	8 (38.1)	8 (36.4)	22 (34.9)
Adverse events leading to treatment discontinuation	1 (5.0)	3 (14.3)	5 (22.7)	9 (14.3)

NOTE: Two patients in the QD dose group died within 30 days of discontinuing study treatment. The cause of death for both patients was considered to be disease progression. Values in parenthesis are given in percentage.

QW group (Fig. 2A). Patients in the TIW and QW groups seem to have attained a new steady state for total plasma vismodegib levels by day 29 (Fig. 2A). A similar pattern was observed for unbound vismodegib compared with total plasma vismodegib concentrations, although the magnitude of the decrease in the TIW and QW groups was more pronounced for unbound than for total drug concentrations (Fig. 2B). A new steady state for unbound plasma vismodegib concentrations seems to have been achieved

between days 29 and 36 for the TIW and QW groups (Fig. 2B).

By day 57, the total steady-state plasma vismodegib concentration had declined by 24% and 46%, on average, compared with the concentration on day 15 for the TIW and QW groups, respectively. Compared with day 15 (after 11 days of continuous QD dosing), the total steady-state plasma vismodegib concentration on day 57 had decreased by more than 50% in almost half the patients in the QW

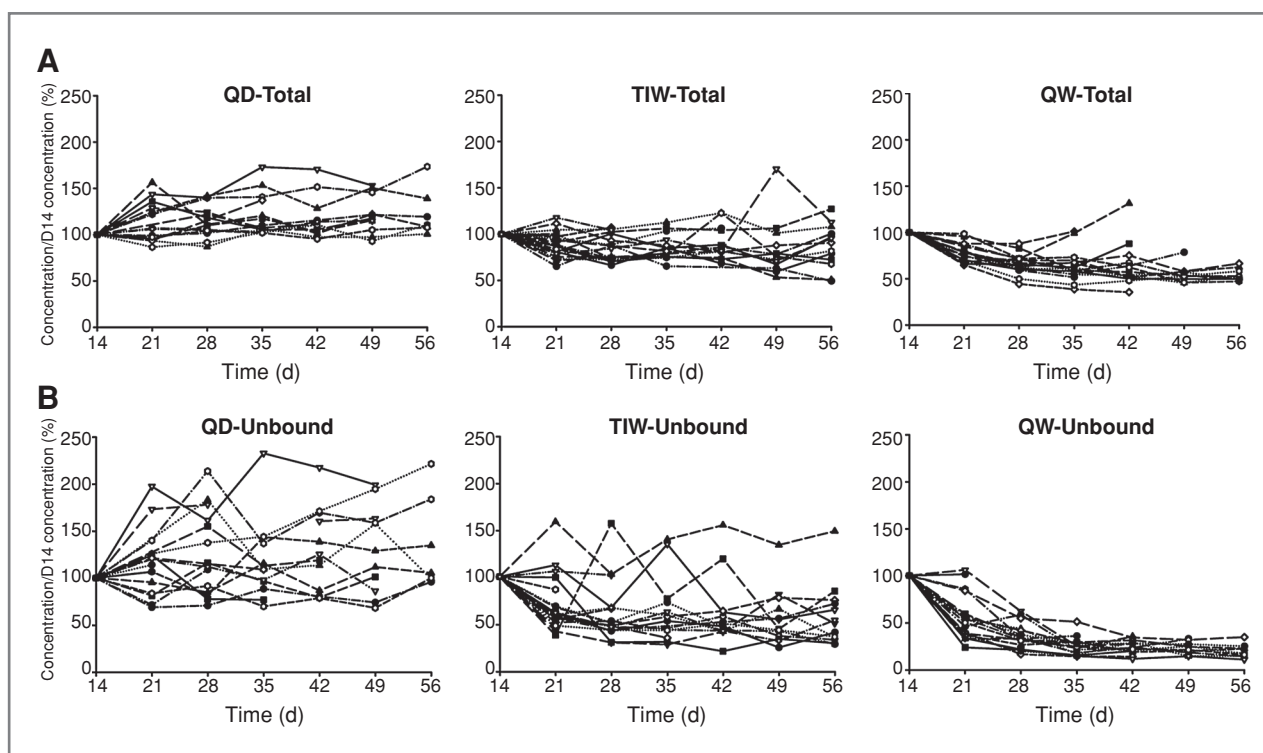


Figure 2. Percent ratio of total (A) or unbound (B) plasma vismodegib trough concentration at each sampling time to the concentration on PK day 14 (study day 15) for 150 mg vismodegib administered QD, TIW, and QW. By day 57, total plasma vismodegib concentrations decrease by 24% (3%–51%) [mean (range)] with TIW schedule and by 46% (34%–53%) with QW schedule. Extent of decrease is nonlinear (less than in proportion to decrease in dose). By day 57, unbound plasma vismodegib concentrations decrease by 50% (15%–72%) with TIW schedule and by 80% (65%–89%) with QW schedule.

group. The observed decline in unbound steady-state plasma vismodegib concentration from day 15 to 57 was even more pronounced, with an average decrease of 50% and 80%, respectively, for the TIW and QW groups. These differences were in accordance with the change in dose (57% and 86% lower weekly dose for TIW and QW compared with QD). Approximately half the patients in the TIW group and all patients in the QW group had a more than 50% decrease in unbound steady-state plasma vismodegib levels.

Within the respective dosing schedules, similar mean C_{max} and area under the concentration-time curve (AUC_{29-36} and AUC_{50-57}) values were observed for the 2 extensive PK intervals (days 29–36 and days 50–57) for both total and unbound drug, consistent with attainment of new steady state by day 29 to 36 for all dosing schedules. For total vismodegib concentrations, mean (\pm SD) C_{max} and AUC values on days 50 to 57 were highest for the QD group ($33.9 \pm 12.2 \mu\text{mol/L}$ and $5,240 \pm 2,010 \mu\text{mol/L}\cdot\text{h}$, respectively), with slightly lower values in the TIW group ($28.6 \pm 13.8 \mu\text{mol/L}$ and $4,070 \pm 1,780 \mu\text{mol/L}\cdot\text{h}$, respectively) and even lower values in the QW group ($18.2 \pm 4.23 \mu\text{mol/L}$ and $2,660 \pm 666 \mu\text{mol/L}\cdot\text{h}$, respectively). Average total vismodegib steady-state trough values for days 29 to 57 exhibited the same dosing schedule-related trends as observed for C_{max} and AUC. For unbound vismodegib, the mean C_{max} and AUC values for the TIW and QW groups were considerably lower (up to 53% for TIW and up to 74% for QW) than those in the QD group for both PK intervals days 29 to 36 and days 50 to 57. Average unbound steady-state trough concentrations over these periods were lower for the TIW and QW groups compared with the QD group, in accordance with the observed differences in C_{max} and AUC.

Mean total and unbound plasma concentration-time profiles were similar and fairly constant over the 24-hour period on day 29 and day 50 for all 3 dosing schedules, further showing attainment of steady state by day 29. Accordingly, mean total and unbound AUC_{0-24} values were also similar between days 29 and 50. The mean vismodegib AUC_{0-24} values were lower in the TIW and QW groups than in the QD group, with greater differences observed for unbound than for total drug.

Total vismodegib steady-state trough concentrations and AAG levels were strongly correlated for the QD and TIW groups and were somewhat less correlated for the QW group (Supplementary Fig.S1A in the Supplementary Appendix). There was no correlation between the analogous unbound vismodegib concentrations and AAG, as expected (Supplementary Fig. S1B in the Supplementary Appendix).

The fraction unbound of vismodegib increased markedly with QD dosing in almost all patients, with a 3-fold higher average fraction unbound at steady state (0.00653 ± 0.00286) than after a single dose (0.00253 ± 0.00144 ; Fig. 3). In the one subject for whom a significant drop in fraction unbound was observed, the AAG level had increased relative to baseline.

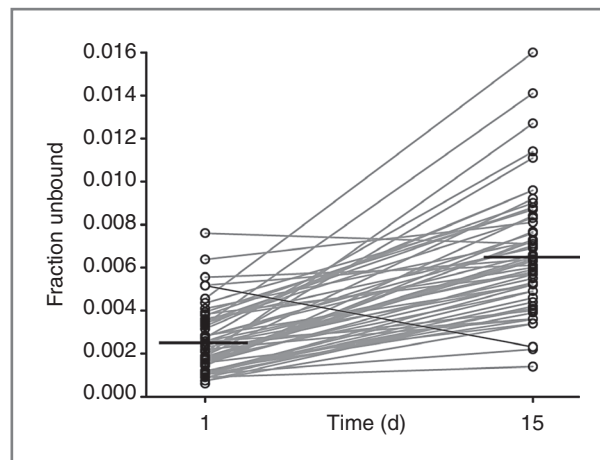


Figure 3. Vismodegib fraction unbound after a single dose (average of all samples through 24 hours) and after 11 days of once daily vismodegib dosing (single sample after the loading phase). The mean value is depicted by the solid horizontal bar. The mean (\pm SD) fraction unbound increases from 0.00253 ± 0.00144 (single dose) to 0.00653 ± 0.00286 (steady state). The subject with a marked decrease in vismodegib fraction unbound (black line) had an elevated AAG level on day 15.

Steady-state unbound vismodegib concentrations for the 3 dosing regimens in this study were compared with the target IC_{95} values for *Gli1* inhibition ($0.068 \mu\text{mol/L}$ for patient-derived colorectal cancer xenograft models and $0.042 \mu\text{mol/L}$ for a *Ptch*^{+/-} allograft model of medulloblastoma exhibiting mutational activation of the Hh pathway; ref. 15). As shown in Figure 4, only the QD regimen provided unbound steady-state vismodegib concentrations in excess of the target IC_{95} values for *GLI1* inhibition in all subjects. Although the TIW regimen had

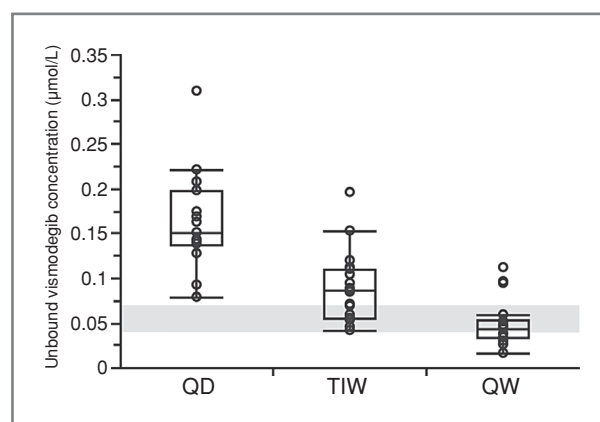


Figure 4. Unbound steady-state trough vismodegib concentrations (average of days 29–57) for each dosing regimen. The line inside the box represents the median value, the top and bottom box limits represent the 25th and 75th percentiles, and the top and bottom bars represent 1.5 * (the interquartile range). The horizontal lines represent the IC_{95} values for *Gli1* inhibition (top line: $0.068 \mu\text{mol/L}$ for patient-derived colorectal cancer xenograft models; lower line: $0.042 \mu\text{mol/L}$ for a *Ptch*^{+/-} allograft model of medulloblastoma). With QD dosing the mean unbound vismodegib steady-state trough concentration is only 2.4- to 3.9-fold above the IC_{95} values.

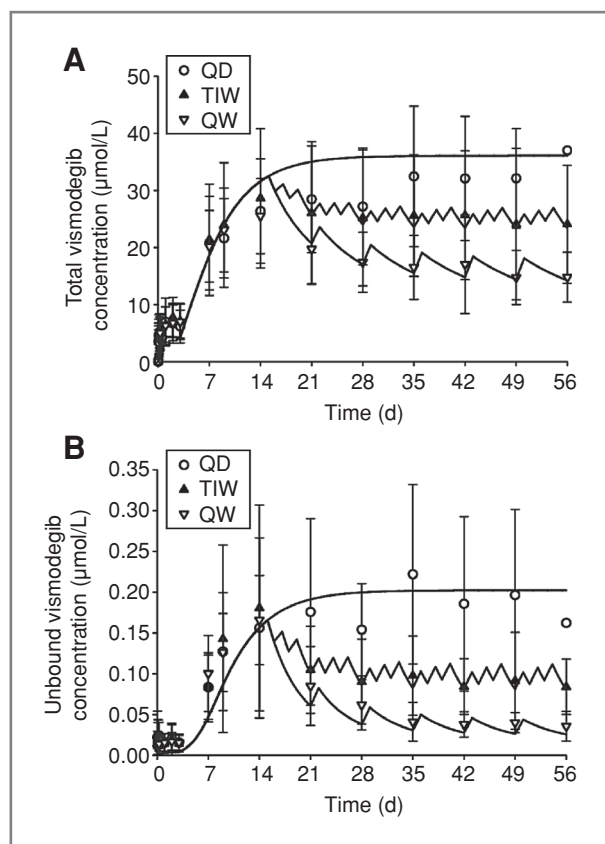


Figure 5. Observed mean (symbol) and SD (bar) and model-predicted (solid lines) total (A) and unbound (B) vismodegib concentrations for QD regimen (open circles), TIW regimen (closed triangles), and QW regimen (open inverted triangles). The mechanistic PK model accurately and prospectively described vismodegib PK with alternate regimens.

a mean unbound steady-state vismodegib concentration ($0.088 \mu\text{mol/L}$) which was greater than the target IC_{95} values, almost half the subjects in this group had concentrations below the more conservative target ($0.068 \mu\text{mol/L}$). The mean unbound steady-state vismodegib concentration in the QW group ($0.0489 \mu\text{mol/L}$) was close to the lowest target IC_{95} for *Gli1* inhibition, with the majority of the subjects in this dosing regimen having unbound drug concentrations below the target.

PK modeling and simulation

A previously developed mechanistic PK model based on phase I data was used to simulate vismodegib PK profiles with the alternative dosing regimens in this study (Supplementary Fig. S2 in the Supplementary Appendix; ref. 18). This model incorporates 3 main hypotheses [saturable absorption, higher affinity plasma protein binding to AAG than human serum albumin (HSA), and slow intrinsic clearance] to explain the key properties of vismodegib PKs: nonlinearity, long half-life, and a strong correlation between total vismodegib and AAG concentrations. AAG and HSA were both incorporated with fast equilibrium binding to vismodegib. AAG bind-

ing is low capacity and high affinity, while HSA binding is high capacity and low affinity. As shown in Figure 5A and B, the previous PK model prospectively predicted the decrease in total vismodegib concentration with TIW and QW dosing and the larger decrease for unbound as compared with total concentrations with these alternative regimens, prior to observation of actual PK results from the current study. The decline in unbound steady-state vismodegib concentrations between day 57 of the maintenance phase and day 15 of the loading phase was greater than that in total concentrations, with an observed intra-subject decrease (mean \pm SD) of $50\% \pm 20\%$ and $24\% \pm 18\%$, respectively, for unbound and total concentrations with the TIW regimen and $80\% \pm 7\%$ and $46\% \pm 7\%$, respectively, for unbound and total concentrations with the QW regimen.

The mechanistic PK model was extended to explore the effect of lower once daily vismodegib doses on total and unbound concentrations. As shown in Figure 6A, simulated total vismodegib concentrations decreased in a dose-related fashion from 150 to 25 mg. Unbound vismodegib

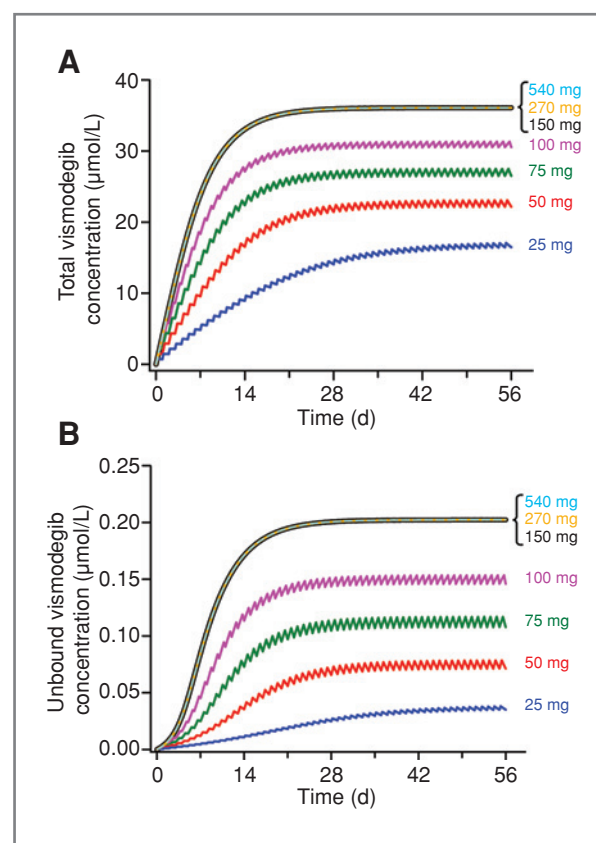


Figure 6. Simulated total (A) and unbound (B) vismodegib concentration-time profiles after once daily dosing of 25 mg (blue), 50 mg (red), 75 mg (green), 100 mg (magenta), 150 mg (black), 270 mg (yellow), and 540 mg (aqua). Doses lower than 150 mg QD lead to markedly lower unbound vismodegib concentrations. No further increase in vismodegib exposure occurs at doses higher than 150 mg QD (black, yellow, and aqua lines overlap).

levels were predicted to decrease more than the total concentrations at the analogous lower daily doses (Fig. 6B). These results are predicted by the saturable absorption and saturable AAG-binding components in the model. At doses lower than 150 mg, absorption is no longer saturated, but AAG binding is at least partially saturated at steady state (although less saturated than at 150 mg). In addition, due to saturated absorption and protein binding, no further increases in total or unbound vismodegib concentrations were predicted for doses greater than 150 mg, which is in agreement with observed phase I results (13).

Discussion

Vismodegib was generally well tolerated in this phase Ib study with adverse events of similar incidence and severity among dose groups. Twenty-four patients (38.1%) experienced grade 3 to 5 adverse events, which were primarily due to the underlying disease and/or disease progression in this advanced cancer patient population; only 1 event (hyponatremia) in 1 patient was considered related to vismodegib. No reported serious adverse events were considered related to vismodegib. These findings confirm the favorable safety profile of vismodegib after 150 mg QD dosing as no dose-limiting toxicities are observed with this dosage regimen based on findings from the current and previous studies (13).

Due to the long single dose half-life and the nonlinearity in vismodegib PKs after daily dosing, this study was designed to determine whether less frequent dosing could result in similar steady-state levels of total and unbound vismodegib to those obtained with daily dosing. TIW and QW dosing schedules were chosen based upon the single dose half-life and because each represented a potentially suitable alternative to QD dosing from the perspective of patient compliance. The PK profiles of vismodegib in patients after a single 150 mg dose of vismodegib and after once daily dosing with 150 mg vismodegib were consistent with previous findings (13). Both total and unbound plasma vismodegib concentrations reached mean peak levels at 48 hours that were maintained through 72 hours after a single dose of vismodegib, and steady state was achieved within 11 days of continuous once daily dosing. When the dosing schedule was altered to TIW or QW, total plasma vismodegib levels decreased compared with QD dosing. The magnitude of the observed change in total concentrations was less than dose proportional, consistent with nonlinear PKs. The decrease in unbound plasma vismodegib concentrations with less frequent dosing was more pronounced than for total drug and was proportional to the decrease in weekly dose, suggestive of linear PK of unbound vismodegib.

Unbound steady-state vismodegib concentrations were 60% and 85% lower for the TIW and QW dose groups, respectively, relative to the QD dose group. Such decreases may be associated with loss of vismodegib activity based on findings from preclinical models. Inte-

grated PK/PD modeling of vismodegib in xenograft models has revealed a steep relationship between pathway modulation (*Gli1* inhibition) and antitumor effect, suggesting that even small reductions in exposure could lead to dramatic loss in vismodegib activity (15). Furthermore, the 150 mg QD regimen has shown activity in patients with advanced BCC (13). Integration of the preclinical concentration–response relationship, human efficacy data, and PK results of this dose scheduling study in cancer patients suggests that patients receiving 150 mg vismodegib on a TIW or QW regimen could be at risk of not achieving unbound drug concentrations associated with maximum clinical benefit.

There is no evidence that a dose greater than 150 mg daily would provide additional efficacy, especially considering that exposure does not increase with higher vismodegib doses (13). Our mechanistic PK model based on phase I data accurately describes the atypical PK of vismodegib (18). The predictability of this model was further supported by the prospective simulation of total and unbound plasma vismodegib PK profiles which were consistent with observations for different dosing schedules in the current study. The intermittent dosing schedules with 150 mg is somewhat representative of PK from lower dose levels with a daily schedule (less daily input and lower plasma concentration range), which provides confidence for using the mechanistic PK model to predict plasma vismodegib concentrations for once daily doses less than 150 mg. Overall, the simulation results indicate that, while total drug concentrations decrease relative to 150 mg QD at steady state, there is a more pronounced impact on unbound concentrations, similar to observations in the current study with less frequent dosing and therefore lower weekly doses. Unbound vismodegib concentrations change in proportion to dose at daily doses lower than 150 mg. For example, a daily dose of 75 mg QD would yield steady-state unbound plasma concentrations that are 47% lower than those achieved with 150 mg QD, consistent with linear PK for unbound drug.

In some cases, unwanted drug effects (e.g., toxicities) can be ameliorated by decreasing drug exposure. The most frequently reported adverse events that seem to be associated with vismodegib seem to be on-target toxicities (dysgeusia, alopecia, muscle spasms, fatigue, and nausea). As the adverse events and efficacy associated with vismodegib are probably a result of interaction with the same pathway, decreasing vismodegib exposure to avoid adverse events by lower or less frequent dose regimens may have a negative impact on efficacy.

Serum AAG concentrations remained relatively constant in all dose groups during the course of the study, thus maintaining the even stratification of AAG levels among dose groups and thereby minimizing any potential influence of AAG fluctuations on the extent of protein binding of vismodegib. As previously observed, total vismodegib and AAG concentrations were strongly correlated with QD dosing in this study (18). This strong correlation was maintained with the TIW dosing schedule. However, a

weaker correlation between total vismodegib and AAG levels was observed for the QW dosing schedule, which may be due to less saturated AAG binding compared with more frequent dosing. The large decreases in unbound vismodegib concentrations after TIW and QW dosing are also consistent with a decreased saturation of AAG binding. The weaker correlation between total vismodegib and AAG with an intermittent dosing schedule (relative to QD), and the large decrease of unbound concentration were predicted by our mechanistic PK model after incorporation of saturable AAG binding. The apparent time dependent PK with continuous once daily vismodegib dosing is explained by the change in fraction unbound, thereby resulting in concentration-dependent (nonlinear) PK that is likely responsible for the increase in vismodegib clearance after repeated dosing. Therefore, the half-life of vismodegib is shorter after multiple dosing than after a single dose, and steady-state drug concentrations are attained earlier and are lower than expected. Although not necessarily similar mechanistically, this phenomenon has been observed for other compounds, particularly those with a long single-dose half-life, resulting in an effective or operational half-life that is considerably shorter than the measured half-life after a single dose (19).

Vismodegib fraction unbound is believed to be dependent on AAG saturation which occurs as the vismodegib concentration increases with repeated daily dosing, resulting in establishment of equilibrium with HSA (17). Fraction unbound remains low due to binding to HSA which serves as a low affinity, high capacity drug-binding protein relative to AAG due to its high level in plasma (Supplementary Fig. S3 in the Supplementary Appendix).

In conclusion, the results of this study provide important insights on the concentration-dependent changes in the PKs of vismodegib and validate a previously developed mechanistic PK model. The 150 mg vismodegib QD schedule has been generally well tolerated to date and shown to be active in patients with advanced BCC. Any reduction in vismodegib dose or frequency of dosing could put patients at risk of suboptimal exposure of unbound drug. Therefore, these findings support the use of a 150 mg once daily vismodegib regimen for future clinical trials.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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