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Phase I and pharmacological study of the oral farnesyltransferase inhibitor SCH 66336 given once daily to patients with advanced solid tumours

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Abstract

A single-agent dose-escalating phase I study on the farnesyl transferase inhibitor SCH 66336 was performed to determine the safety profile and recommended dose for phase II studies. Plasma pharmacokinetics were determined as well as the SCH 66336-induced inhibition of farnesyl protein transferase *in vivo*. SCH 66336 was given orally once daily (OD) without interruption to patients with histologically-confirmed solid tumours. Routine antiemetics were not prescribed. 12 patients were enrolled into the study. Dose levels studied were 300 mg (6 patients) and 400 mg (6 patients) OD. Pharmacokinetic sampling was performed on days 1 and 15. Although at 400 mg OD only 1 patient had a grade 3 diarrhoea, 3 out of 6 patients interrupted treatment early due to a combination of various grade 1-3 toxicities (diarrhoea, uremiacreatinine, asthenia, vomiting, weight loss) indicating that this dose was not tolerable for a prolonged period of time. At 300 mg OD, the same pattern of toxicities was observed, but all were grade 1-2. Therefore, this dose can be recommended for phase II studies. Pharmacokinetic analysis showed that peak plasma concentrations as well as the AUCs were dose-related, with increased parameters at day 15 compared with day 1, indicating some accumulation upon multiple dosing. Plasma half-life ranged from 5 to 9 h and appeared to increase with increasing dose. Steady state plasma concentrations were attained by day 14. A large volume of distribution at steady state suggested extensive distribution outside the plasma compartment. There is evidence of inhibition of protein prenylation in some patients after OD oral administration of SCH 66336. SCH 66336 can be safely administered using a continuous oral OD dosing regimen. The recommended dose for phase II studies using this regimen is 300 mg OD.

Keywords: Farnesyltransferase inhibitor; SCH 66336; Pharmacokinetics; Pharmacodynamics

1. Introduction

Cellular Ras proteins, encoded by nuclear *ras* genes, are transducers of extracellular growth-promoting stimuli. Epidermal and platelet-derived growth factors bind to specific cell surface receptors. Receptor-bound tyrosine kinases subsequently promote the phosphorylation of guanosine 5′-diphosphate (GDP) from membrane-bound inactive Ras.GDP. As a result, Ras.guanosine 5′-triphosphate (GTP) is formed that subsequently activates intracellular effector pathways leading to cellular proliferation through activation of Raf-1 and MEKK on the one hand and, amongst others, effects on the actin cytoskeletal organisation through activation of cellular Rho on the other hand. Evidence exists that the antiproliferative effects of farnesyl transferase inhibitors do not depend solely on the inhibition of Ras and that the gain of alternate prenylated (geranylgeranylated)

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forms of the *Rho* protein Rho-B mediate cell growth inhibition [1].

The intracellular concentration of Ras.GTP is balanced by the activity of GTP-ase activating protein (GAP), which turns Ras.GTP back into the inactive RAS.GDP bound conformation. Ras is synthesised as a soluble and biologically inactive protein that undergoes several posttranslational modifications before being localised on the inner surface of the plasma membrane where it exerts its activity after being transformed to Ras.GTP. An essential step in the posttranslational processing of Ras is the addition of a farnesyl of C_{15} isoprenoid moiety from farnesyl diphosphate to the cysteine residue at the C-terminal side of Ras. The enzymatic process of the addition of farnesyl to Ras is called farnesylation, and farnesyl transferase is the crucial enzyme for this process. Famesylation is not an enzymatic process restricted to Ras, as other cellular proteins also have to be farnesylated before exerting their activity [2–11].

As farnesylation of Ras oncoproteins is the essential enzymatic step in the process of posttranslational activation, eventually resulting in autonomous and malignant growth and proliferation of cells and tissues harbouring the mutated *ras* phenotype, inhibiting this enzymatic step could theoretically result in the inhibition of this autonomous and malignant growth and proliferation. Thus, specific inhibitors of farnesyl transferase could possibly lead the way towards a specifically targeted treatment for a *ras* oncogene-dependent tumour.

Several specific inhibitors of farnesyl transferase have been developed. SCH 66336 ((11R) 4[2[4-(3,10-dibromo-8 - chloro - 6,11 - dihydro - 5H - benzo[5,6]cyclohepta[1,2b]-pyridin-11-yl)-1-pyperazinyl}-2-oxoethyl]-1-piperidine-carboxamide) (Fig. 1) is a tricyclic nonpeptidyl, non-sulphydryl farnesyl transferase inhibitor (FTI). Preclinical studies of SCH 66336 have been summarised elsewhere [12–20].

Preclinical chronic oral toxicity studies revealed dose-dependent myelosuppression, weight loss, diarrhoea, and vomiting in rats and monkeys (Schering Plough Research Institute, data not shown).

This clinical phase I, pharmacokinetic and pharmacodynamic study represents the administration of SCH 66336 in patients with advanced solid tumours using a continuous once daily (OD) oral dosing regimen. This study followed another phase I performed by our group using a continuous twice daily oral dosing regimen, which was published recently [12]. The rationale to study the OD schedule was to reduce the moderate SCH 66336 accumulation observed during the continuous twice daily schedule (with a prolonged plasma half-life) and eventually to alleviate the pattern of toxicities observed and to improve the dose intensity of the drug.

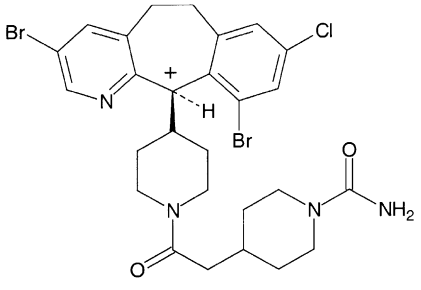

Fig. 1. Chemical structure of SCH 66336.

2. Patients and methods

2.1. Eligibility criteria

Patients with a cytologically- or histologically-confirmed diagnosis of a solid tumour that was refractory to standard treatment or for whom no standard therapy was available were eligible for this study. Patients with primary central nervous system neoplasm, known brain- or leptomeningeal metastases, or known bone marrow involvement were excluded. Further eligibility criteria included: age $\geqslant 18$ years; World Health Organization (WHO) performance status $\leqslant 2$; life expectancy of > 12 weeks; no anticancer therapy in the previous 4 weeks (6 weeks for nitrosoureas or mitomycin-C); no prior bone marrow or stem cell transplantation; no known HIV positivity or AIDS-related illness; adequate function of bone marrow (haemoglobin $\geqslant 6.2$ mmol/l, absolute neutrophil count $\geqslant 1.5\times10^9$ cells/l, platelets $\geqslant 100\times10^9$ cells/l), liver (bilirubin $\leqslant 25$ μmol/l, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) within 2.5 times the normal upper limit), and kidney (serum creatinine $\leqslant 140$ μmol/l); patients had to be able to take oral medication; patients were not allowed to have received more than two prior combination chemotherapy regimens or one prior combination regimen plus two single-agent regimens. Local ethics boards approved the protocol and informed consent brochures. All patients gave written informed consent at study entry.

2.2. Pretreatment assessment and follow-up studies

Prior to therapy, a complete medical history was taken and a physical examination was performed. A complete blood count (CBC), including white blood cell (WBC) differential, and serum chemistry including sodium, potassium, calcium, magnesium, phosphorus, urea, uric acid, creatinine, total protein, albumin, glucose, alkaline phosphatase, bilirubin, AST, ALT, γ-glutamyl transpeptidase and lactate dehydrogenase were performed. as were urine analysis, electrocardiogram (ECG) and chest X-ray. Because some visual proteins (i.e. rhodopsin kinase and transducin γ) are known to undergo farnesylation, patients were referred for ophthalmological examination including retinal photography

prior to treatment, after 4 and 8 weeks, and bimonthly thereafter. Weekly evaluations included history, physical examination, toxicity assessment according to the National Cancer Institute—Common Toxicity Criteria (NCI-CTC), version dated December 1994, CBC, serum chemistries, urine analysis and ECG. Tumour measurements were performed before treatment, at 4 and 8 weeks, and bimonthly thereafter and were evaluated according to the WHO criteria for response [13]. In cases of progressive disease, patients were taken off the study.

2.3. Drug administration

SCH 66336 is a crystalline solid containing one chiral centre. It was supplied as 25, 100 and 200 mg gelatin capsules by Schering-Plough Research Institute, Kenilworth, NJ, USA. The capsules were swallowed immediately after breakfast, with approximately 240 ml of non-carbonated water. On days of pharmacokinetic sampling, patients were administered standardised meals immediately prior to drug administration. SCH 66336 was taken for 28 consecutive days and was continued in cases of stable disease or disease remission after this period for as long as there was no disease progression and/or no unacceptable drug-related toxicity. Prophylactic antiemetics were not prescribed. SCH 66336 administration was immediately interrupted at the occurrence of dose-limiting toxicity (DLT).

2.4. Dosage and dose escalation

The starting dose of SCH 66336 was 300 mg OD. This dose was based upon the clinical results obtained from the continuous twice daily oral dosing study [12]. Dose escalation was performed according to the pattern of toxicities observed, At each dose level, a minimum of 3 patients had to have 28 days of treatment before escalation was allowed. Once DLT or significant toxicities were seen in 1 patient at a given dose level, at least 6 patients had to be treated at that dose level before a further dose escalation was allowed. DLT was defined as any grade $\geqslant 3$ non-haematological toxicity, or a serum creatinine elevation of $\geqslant 3$ times the upper limit of normal. Grade 3 fever in the absence of infection or grade 3 nausea or vomiting in patients not receiving adequate antiemetic treatment were not considered as DLT. Neutropenia or thrombocytopenia grade $\geqslant 3$ or grade 4 anaemia constituted haematological DLT. The maximum tolerated dose (MTD) was defined as the highest dose to be administered to a group of 6 patients producing tolerable, manageable and reversible, but DLT in at least 2 out of 6 patients. At the proposed dose for phase II studies, a maximum of 1 out of 6 patients was allowed to experience DLT. No intra-patient dose escalation was allowed.

2.5. Pharmacokinetic studies

For pharmacokinetic analysis, 6-ml blood samples were taken on day 1 via an intravenous cannula prior to administration, at 30, 60 and 90 min, and at 2, 4, 6, 8, 12, 14 and 24 h postdose. On day 15, blood samples were taken prior to the morning dosing, at 30, 60 and 90 min, and at 2, 4, 6, 8, 12 h postdose. On day 16, a sample was taken prior to the morning dose. If patients were on treatment after three 28-day cycles, optional pharmacokinetic blood samples were again obtained. Blood samples were collected in sodium heparin tubes and were immediately centrifuged at 3000 rpm for 15 min at 10 °C, after which plasma was divided into two aliquots of at least 1 ml and frozen at −70° C until analysis. Plasma samples were assayed by a specific and sensitive liquid chromatographic method with tandem mass spectrometric detection (LC-MS/MS) assay. The lower limit of quantitation of the assay was 1.0 ng/ml.

For each patient, the area under the plasma concentration versus time curve (AUC) was calculated by the trapezoidal rule and extrapolated to infinity by a linear regression analysis. The apparent total body clearance (CL/F) was calculated as dose/AUC. The apparent volume of distribution at steady state ($V_{d,ss}/F$) was calculated by a noncompartmental method based on the statistical moment theory [14]. The terminal disposition half-life ($T_{1/2}$) was calculated by dividing 0.693 by the fitted rate constant for drug elimination from the central compartment, estimated by linear-regression analysis of the final data points of the log-linear concentration–time plot. All data are presented as means ± standard deviations.

2.6. Pharmacodynamic study

Buccal smears for prelamin A determination obtained before therapy and again on day 15 (12 h after the last dose of SCH 66336) were air-dried and fixed in acetone within 3 h of harvest. Samples were stored in buffer A and subjected to the immunohistochemical assay. With each batch, A549 cells treated with SCH 66336 or diluant were included as positive and negative controls, respectively. The immunohistochemistry technique using a conventional fluorescence microscopy was described in detail elsewhere in Ref. [15].

3. Results

12 patients (8 males, 4 females), median age 61 years (range 41–77 years), were enrolled into the study. The patient characteristics are summarised in Table 1. Dose levels studied were 300 ($n = 6$) and 400 ($n = 6$) mg OD. The median duration of treatment was 55 days and 31 days for the 300 and 400 mg continuous OD schedule,

Table 1
Patient characteristics

Total entered	12
Male/female	8/4
Median age (range) (years)	61 (41–77)
Median WHO performance (range)	1 (0–1)
Prior therapy	
Chemotherapy (CT)	9
Radiotherapy + CT	3
Tumour type	
Colorectal	5
Kidney	2
Other	5

WHO, World Health Organization.

respectively. Table 2 summarises the treatment administration.

3.1. Haematological toxicity

Haematological toxicities were not observed at the dose level 300 mg, while the haematological toxicities observed at 400 mg OD are summarised in Table 3.

3.2. Non-haematological toxicity

The major non-haematological side-effects observed in this trial are summarised in Table 3. Toxicity was mainly gastrointestinal and consisted of watery diarrhoea, nausea, vomiting, anorexia and upper gastrointestinal/abdominal disturbances. In patients with diarrhoea, loperamide administered on an 'as-needed' basis resulted in the prompt relief of symptoms. At 300 mg OD, nausea and vomiting were usually mild, while at 400 mg OD, nausea and vomiting became more pronounced. Anorexia and weight loss (approximately 6 kg) mainly occurred at the highest dose level (400 mg). Almost all patients

Table 2
Treatment administration

Dose level (mg; OD)	300	400
Number of patients	6	6
Number of patients who completed[a]		
28 days of treatment	6	5
56 days of treatment	3	2
84 days of treatment	1	0
Number of completed courses/total started (course = 28 days)	10/14	7/11
Reason for drug discontinuation		
Progressive disease (PD)	5	3
Toxicity (T)	0	1
T (+PD)	1	2
Median no. of treatment days (range)	55 (28–86)	31 (12–57)

OD, once daily; no., number.
[a] Without interruption.

Table 3
Worst toxicities per patient

Dose level (mg)	300 (6 patients)			400 (6 patients)		
Toxicity grade	1	2	3	1	2	3
Diarrhoea	2	3	0	2	3	1
Nausea/vomiting	3/1	0/1	0	3/2	2/1	0
Neutropenia	0	0	0	1	0	1
Leucopenia	0	0	0	0	0	1
Uremia/creatinine	1/3	1/0	0	0/1	0/2	3/0
Fatigue, asthenia	1	4	0	2	1	1
UGI/abdominal symptoms	3/2	1/1	0	3/1	0	0

UGI symptoms, upper gastrointestinal symptoms.

experiencing weight loss had various concurrent gastrointestinal toxicities. Other toxicities consisted of grade 1–2 elevation of liver enzymes and reversible grade 1–2 elevated plasma creatinine levels recorded at the two dose levels studied. Creatinine and urea increase were mainly observed in parallel with diarrhoea (±anorexia ±vomiting) and were quickly reversible following intravenous (i.v.) hydration and drug discontinuation. Of note, no renal organic lesions were suspected from the urine biological tests.

Although at 400 mg continuous once daily, only 1 patient had a DLT (diarrhoea grade 3), 3 out of 6 patients interrupted treatment early due to a combination of various grade 1-3 toxicities (diarrhoea, uremia/creatinine, asthenia and vomiting) indicating that this dose was not tolerable for a prolonged period of time. This pattern of side-effects observed at 400 mg led us to stop the dose escalation and to recommend 300 mg OD continuous dosing for phase II studies.

Serial ECGs showed no relevant changes in any of the patients. Ophthalmological examinations revealed no retinal changes.

3.3. Pharmacokinetics

Pharmacokinetic studies were completed in all 12 patients. The plasma concentration versus time profiles of SCH 66336 were similar for all of the patients studied, with the mean curves shown in Fig. 2. The mean single- and multiple-dose pharmacokinetic parameters of SCH 66336 are summarised in Table 4. Significant inter-patient variability in pharmacokinetic parameters was apparent at the dose levels studied. The absorption of the drug was slow, and peak concentrations were reached 6–8 h after drug intake. Peak plasma concentrations as well as AUCs were dose-related. On days 1 and 15, there was a trend to an increasing plasma half-life with increasing the dose from 300 to 400 mg. The terminal disposition half-life was slightly different on days 1 and 15 within each group, although it is difficult to draw firm conclusions due to the limited number of patients. The apparent clearance was comparable between the

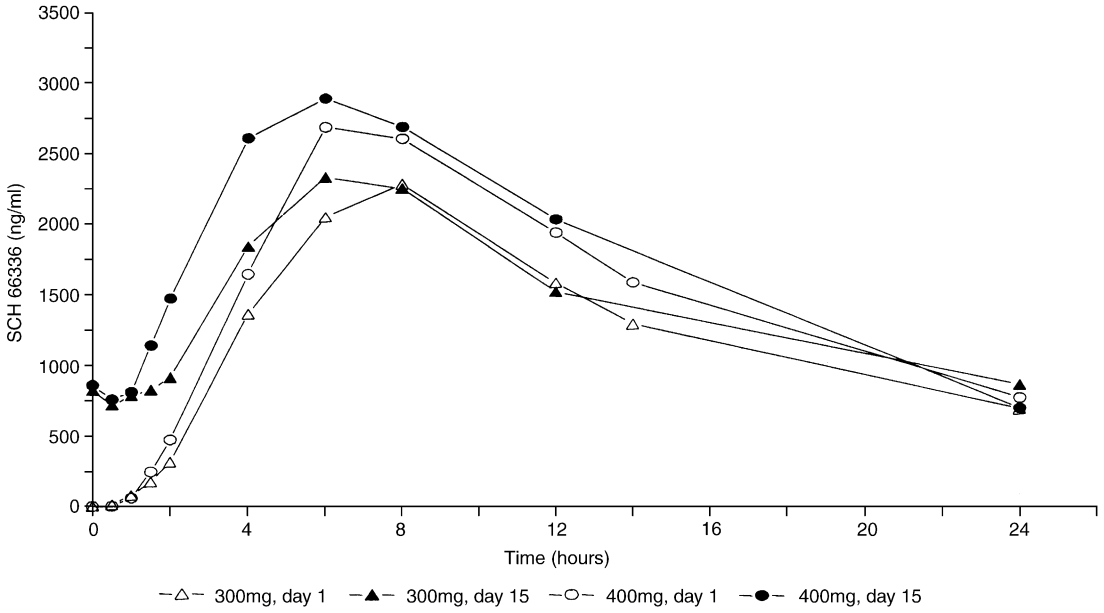

Fig. 2. Plasma SCH 66336 concentrations versus time profiles at 300 and 400 mg dose levels (days 1 and 15).

two dose levels on days 1 and 15. Accumulation after multiple dose administration ranged from 1.17-fold (day 15 of 300mg dose level) to 1.30-fold (day 15 of 400 mg dose level). Steady-state concentrations of SCH 66336 were attained by day 14. At 300 mg OD, trough plasma concentrations of SCH 66336 were shown to exceed 1.5 μM, which is above concentrations required *in vitro* to induce significant growth inhibition in colony assays against 20 various primary human tumour specimens.

3.4. Pharmacodynamics

To determine whether farnesyltransferase was inhibited in patients receiving SCH 66336, the presence of prelamin A was assessed in buccal mucosa cells using a histochemical assay described elsewhere [15]. Prelamin A was selected due to the absolute dependence of prelamin A proteolytic processing on farnesylation which is an obligatory prerequisite for the conversion of prelamin A to lamin A. When farnesylation is inhibited, prelamin A accumulates in cells. Before treatment with SCH 66336, none of the buccal smears contained detectable prelamin A. After treatment, prelamin A was readily detectable in a subset of the specimens. At the dose level 300 mg, 2/5 evaluable samples stained positive for prelamin A while at the dose level 400 mg 2/4 evaluable samples stained positive as determined by fluorescent microscopy (Fig. 3).

3.5. Response

No partial or complete responses were seen.

Table 4
Summary of SCH 66336 pharmacokinetic parameters[a]

Dose level (mg)	300		400	
Day	1	15	1	15
C_{max} (ng/ml)	2403 (913)	2382 (596)	2770 (803)	3130 (689)
T_{max}[b] (h)	8 (6–8)	6 (4–8)	6 (4–8)	4 (4–12)
AUC_{0-24} (ng h/ml)	30 066 (17 438)	34 850 (20 561)	36 335 (13 444)	42 876 (14 149)
$t_{1/2}$ (h)	6.55 (3.28)[c]	4.68 (1.59)[d]	8.64 (3.20)	6.08 (1.76)
Cl/F (ml/min)	236 (16.6)	183 (82)	221 (90.6)	174 (74.8)
Accumulation	–	1.17 (0.28)	–	1.30 (0.18)

C_{max}, peak plasma concentration; T_{max}, time to peak concentration; $t_{1/2}$, terminal disposition half-life; Cl/F, apparent clearance; AUC, plasma concentration versus time curve.

[a] Mean values ± standard deviations.

[b] Median (range).

[c] $n = 5$.

[d] $n = 4$.

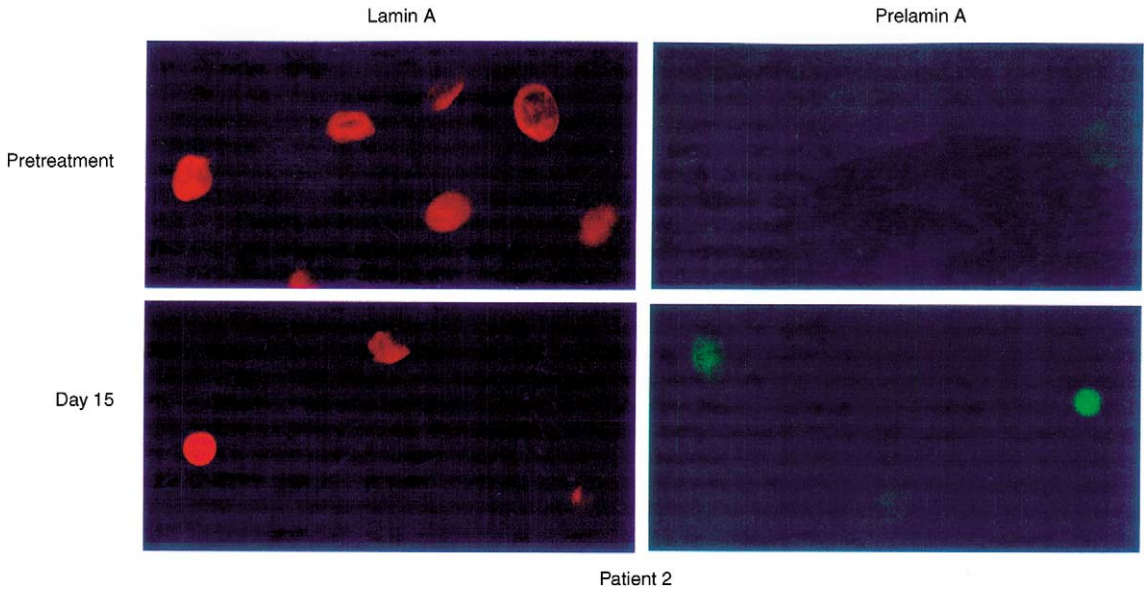

Fig. 3. Detection of prelamin A in buccal mucosa cells from patient 2 treated with SCH 66336 at the dose level of 300 mg once daily.

4. Discussion

We performed a phase I and pharmacokinetic study to explore the tolerability, maximum tolerated dose, pharmacokinetics and pharmacodynamics of the oral farnesyl transferase inhibitor SCH 66336. In this study using a continuous oral OD administration, side-effects attributable to the study drug were mainly non-haematological. While DLT included diarrhoea in only 1 patient out of 6 treated at 400 mg, various gastrointestinal side-effects associated with reversible renal toxicity, asthenia and weight loss led to early treatment interruption in 3 out of 6 patients treated at 400 mg OD. This pattern of toxicities was less pronounced at 300 mg OD, which was therefore considered to be the recommended dose for phase II studies.

Haematological toxicity of SCH 66336 in the current study consisted of uncomplicated and reversible neutropenia occurring at the highest dose level tested. At the recommended dose for phase II studies, 300 mg OD, myelosuppression did not occur. This parallels the experience in three other studies using different dosing regimens of SCH 66336 [12,15,16]. This finding, however, is in contrast to results obtained with another farnesyl transferase inhibitor. Out of three phase I studies [17–19] that have been reported on the farnesyl transferase inhibitor R115777, myelosuppression comprised the DLT in 2 [17,18].

The present study describes the pharmacokinetics of SCH 66336 when administered once daily. Accumulation after multiple dose administrations of SCH 66336 was 1.17- to 1.30-fold when administered OD at the two doses levels studied. These accumulation values appeared limited, but clinically did not alleviate toxicities and did not permit a better dose intensity than the twice daily (BID) schedule where continuous 200 mg BID was considered as the recommended phase II study [12]. Finally, we showed that SCH 66336 inhibited prelamin A farnesylation in some specimens treated at the two dose levels studied, providing evidence that farnesyltransferase was inhibited at clinically achievable doses.

In conclusion, this phase I and pharmacological study with oral SCH 66336 has shown that this farnesyl transferase inhibitor can be safely administered using a continuous OD dosing schedule. The recommended dose for phase II studies using this treatment schedule is 300 mg OD.

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