

## Phase 0 Clinical Chemoprevention Trial of the Akt Inhibitor SR13668

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### Abstract

SR13668, an orally active Akt pathway inhibitor, has demonstrated cancer chemopreventive potential in preclinical studies. To accelerate the clinical development of this promising agent, we designed and conducted the first-ever phase 0 chemoprevention trial to evaluate and compare the effects of food and formulation on SR13668 bioavailability. Healthy adult volunteers were randomly assigned to receive a single, 38-mg oral dose of SR13668 in one of five different formulations, with or without food. On the basis of existing animal data, SR13668 in a PEG400/Labrasol oral solution was defined as the reference formulation. Blood samples were obtained pre- and post-agent administration for pharmacokinetic analyses. Area under the plasma concentration–time curve ( $AUC_{0-\infty}$ ) was defined as the primary endpoint. Data were analyzed and compared using established statistical methods for phase 0 trials with a limited sample size. Participants ( $n = 20$ ) were rapidly accrued over a 5-month period. Complete pharmacokinetic data were available for 18 randomized participants.  $AUC_{0-\infty}$  values were highest in the fed state (range = 122–439 ng/mL  $\times$  hours) and were statistically significantly different across formulations ( $P = 0.007$ ), with Solutol HS15 providing the highest bioavailability. SR13668 time to peak plasma concentration (3 hours; range, 2–6 hours) and half-life were ( $11.2 \pm 3.1$  hours) were not formulation-dependent. Using a novel, highly efficient study design, we rapidly identified a lead formulation of SR13668 for further clinical testing. Our findings support application of the phase 0 trial paradigm to accelerate chemoprevention agent development. *Cancer Prev Res*; 4(3); 347–53. ©2011 AACR.

### Introduction

Cancer chemoprevention refers to the use of pharmaceutical or nutritional compounds to interrupt carcinogenesis at a preinvasive stage. Despite its strong potential, chemoprevention has achieved a relatively modest impact on clinical practice to date. Because chemoprevention agents are typically intended for chronic (or repeated) use by healthy individuals, the development process may

be more complex, and ultimately more costly, than for cancer treatment drugs (1). Thus, novel approaches to selecting lead candidate agents for subsequent clinical testing are highly desirable.

The exploratory IND, or "phase 0 trial", paradigm represents one strategy for accelerating development of chemoprevention agents. Phase 0 trials are designed to study investigational agents much earlier in clinical development than is possible with traditional phase I trials by defining essential preclinical toxicology data and doses that result in very limited human exposure (2). The goal of phase 0 studies is to assess the feasibility for further development of investigational agents.

Candidate agents derived from dietary sources should have a relatively wide therapeutic window, providing an excellent opportunity for phase 0 evaluation. Indole-3-carbinol (I3C) is a naturally occurring Akt inhibitor (3). Immunohistochemical studies have shown that Akt overexpression is a relatively early event in carcinogenesis, as evidenced by frequent detection of phospho-Akt in premalignant lung and colon lesions, with minimal or no expression in surrounding normal tissues (4, 5). I3C, which is extremely unstable under physiological conditions, produces 4 condensation products known to have anticancer

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**Prior Reports:** Data from this study have not been previously presented or published. Portions of the data included in this report were presented at: AACR 100th Annual Meeting, Apr 18–22, 2009, Denver CO and AACR International Conference on Frontiers in Cancer Prevention Research, Nov. 7–10, 2010, Philadelphia, PA

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**doi:** 10.1158/1940-6207.CAPR-10-0313

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activity (6). These 4 products were used to design a novel class of indole analogues as optimal Akt inhibitors (7). SR13668 represents the lead candidate compound.

SR13668 has improved *in vitro* and *in vivo* stability and activity as compared with I3C (7) and is not mutagenic (8). In early preclinical safety testing, no signs of toxicity were observed in rats administered a single oral dose of 1,000 mg/kg or multiple oral doses of 25 to 600 mg for 14 days (7). The no-adverse-event-level (NOAEL) in rats was 600 mg/kg or more. No adverse effects were observed in beagle dogs administered a single intravenous dose of 10 mg/kg or oral dose of 50 mg/kg. Although there is evidence that the P13K/Akt pathway plays a role in insulin-mediated regulation of glucose metabolism, no adverse effects on fasting glucose levels or body weight were seen in mice treated with SR13668 doses up to 500 mg/kg for 14 days.

SR13668 exhibited low oral bioavailability in initial pharmacokinetic studies performed with dogs and rats. Pharmacokinetic studies with rats found that the low apparent oral bioavailability of SR13668 when administered suspended in methyl cellulose (0.05%) could be increased more than 25-fold by modifying the formulation. SR13668 in 1:1 v/v Labrosol/PEG 400 resulted in oral bioavailability of  $25.4 \pm 3.8\%$  and  $27.7 \pm 3.9\%$  (30 mg/kg), for male and female rats, respectively (9). Similarly, pharmacokinetic studies with dogs and monkeys, where SR13668 was formulated in Solutol HS15, found substantial increases in oral bioavailability with levels of 14.6% and 7.3%, respectively, following doses of 90 mg/m<sup>2</sup> (10).

Because of its limited aqueous solubility and expected high permeability through biological membranes, SR13668 is predicted to be a Biopharmaceutics Drug Classification II compound that often exhibits dissolution rate limited oral absorption (11). Consistent with this classification, preclinical pharmacokinetic studies found low, but formulation-dependent bioavailability in rats, dogs, and monkeys. In addition, animal studies do not always predict drug disposition in humans. Therefore, formulation studies were undertaken to identify drug delivery vehicles that would increase the *in vivo* exposure of SR13668 in the intestinal lumen and maximize oral bioavailability. Based on the results of these studies, the current phase 0 study was conducted to determine the SR13668 formulation with the best oral bioavailability (coupled with adequate preliminary safety data) in humans, to further advance the clinical development of this promising agent.

## Participants and Methods

This study was conducted under an exploratory IND from the FDA (IND#103026; IND Sponsor: NCI Division of Cancer Prevention). All aspects of the study protocol were reviewed and approved by the Institutional Review Board for human research at Mayo Clinic in Rochester, Minnesota.

### Baseline evaluation

Study participants were recruited at a single institution (Mayo Clinic in Rochester, MN) and were required to

provide signed informed consent prior to enrollment. Eligibility criteria included: age 18 to 62 years, ECOG performance status 0, and adequate organ (serum sodium, potassium, alkaline phosphatase, ALT, direct bilirubin, and creatinine each 1.5 times or less upper limit of institutional normal range; fasting glucose < upper limit of institutional normal range) and bone marrow (hemoglobin  $\geq$  institutional lower limit of normal range; leukocytes  $\geq$  3,000/ $\mu$ L, absolute neutrophil count  $\geq$  1,500/ $\mu$ L, platelet count  $\geq$  100,000/ $\mu$ L) function at baseline. Women of childbearing potential were also required to document a negative pregnancy test prior to enrollment. Participants were asked to abstain from using alcoholic and caffeinated beverages for 24 hours or more prior to agent administration and until all blood and urine samples had been collected. Concomitant medications were recorded at baseline. Hormonal contraceptive agents were not allowed during the study.

### Study design and drug administration

A 2-stage design was adopted to study the effects of food and formulation on SR13668 bioavailability. Participants were administered a single, 38 mg (90  $\mu$ m) oral dose of SR13668 in 1 of 5 different formulations. Based on existing animal data, SR13668 in a PEG400/Labrosol (1:1 v/v) oral solution was defined as the reference formulation (formulation 1). Four self-emulsifying solid dispersion test formulations in capsules were also investigated: Solutol HS15 (formulation 2), Solutol HS15/Vitamin E TGPS (50/50 w/w%; formulation 3), Vitamin E TGPS (formulation 4), and Myrj 53 (formulation 5).

In stage I, participants were randomized to receive formulation 1 with or without food after an overnight fast of at least 10 hours in accordance with FDA guidance for food effect studies (12). The high-fat (approximately 50% of total caloric content) and high-calorie (approximately 800 to 1,000 calories) meal consisted of approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively and did not include grapefruit juice. Separate dietary conditions were evaluated in stage I only because any food effect was expected to act consistently across the test formulations. In stage II, participants were randomly assigned to receive formulations 2 to 5, using the preferred dietary condition identified in stage I. Pharmacokinetics data from participants assigned to the preferred dietary condition in stage I were combined with data from participants in stage II to permit increased efficiency for the formulation comparisons.

### Follow-up evaluation

Participants were contacted by telephone at 7 to 10 days and 30 ( $\pm$  3) days after completion of the pharmacokinetic analyses to inquire about concomitant medication use and adverse events. Additional blood samples were collected at 24 hours and 30 ( $\pm$  3) days after study agent administration for safety evaluation, including serum chemistry, fasting glucose, and complete blood count analyses. Additional follow-up measures were arranged by study staff, as needed, according to standard clinical practice.

## Formulation development

**Materials.** SR13668 was obtained from the National Cancer Institute. Methanol (Sigma-Aldrich); ethanol (AAPER Alcohol and Chemical Co.); Solutol HS15 (BASF); Vitamin E TPGS (Eastman Chemical Co.); Labrasol and Gelucire (Gattefossé); PEG-1000 and -2000 (Union Carbide); Myrj 52 and 53, corn oil, soybean oil, and sesame oil (Spectrum Chemical Co.) were used without further purification. Hard gelatin capsules were obtained from Capsugel.

**Solubility determination.** SR13668 was added to each vehicle in excess and allowed to equilibrate with stirring. For vehicles that were liquid at room temperature, equilibration was conducted at room temperature. For vehicles that were solids at room temperature, equilibration was carried out at 65°C to 70°C with vehicles in the liquid state. Once equilibrium between the solid and solution phases was achieved, the suspensions were centrifuged and the supernatant isolated for analysis of SR13668 concentration by comparison of UV absorption to external standards or by high-performance liquid chromatography (HPLC) with fluorescence detection using external standards.

**Formulation selection.** Self-emulsifying vehicles were selected for formulation studies based on the results of saturated solubility studies. SR13668 was dissolved in vehicle with stirring at concentrations ranging from 2 to 14 mg/gm of vehicle at 65°C to 70°C. Solutions containing 5 mg SR13668 per gram of formulation were poured into hard gelatin capsules by weight and allowed to solidify. Hard gelatin capsule formulations were stored in HDPE bottles at 25°C/60% relative humidity to assess stability.

Dissolution studies were performed using USP dissolution set up 2 and monitored by UV absorbance at 344 nm to measure SR13668 release.

## Pharmacokinetics

**Specimen collection.** Peripheral vein blood samples (6 mL) were collected into tubes containing sodium heparin, immediately mixed and chilled in an ice-water slurry. After centrifugation (15 minutes, 4°C, 3,000 rpm), the plasma layer was transferred to a polypropylene tube, capped, immediately frozen and stored at -70°C. Packed red blood cells were stored with the plasma samples. Specimens were drawn before SR13668 administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 20, and 24 hours postadministration. Urine samples were collected at baseline and for a 24-hour period after agent administration.

**HPLC assay.** SR13668 and SR13665 (internal standard) were provided by SRI International. Measurement of SR13668 in plasma and urine was performed using an HPLC assay with fluorescence detection (13). Standard curves were linear ( $r^2 > 0.99$ ) over the range of 0.5 to 200 ng/mL. Between-day coefficients of variation for the low (2 ng/mL), medium (20 ng/mL), and high (150 ng/mL) quality control samples were 2.76%, 2.78%, and 2.28% respectively.

**Pharmacokinetics data.** SR13668 plasma concentration-time data were analyzed by standard noncompart-

mental methods using the program WinNonlin Pro (Pharsight Corp.)

## Statistical analysis

Descriptive statistics and statistical plots were used to present overall and formulation-specific data. Area under the plasma concentration-time curve ( $AUC_{0-\infty}$ ) was defined as the primary endpoint. A parametric ANOVA model was used to compare pharmacokinetic parameters across all SR13668 formulations and Tukey's multiple comparison procedure was employed for pair-wise formulation comparisons. A nonparametric Wilcoxon rank-sum test was used as a complementary method for these comparisons. A preliminary power analysis showed that 3 participants per arm can detect an effect size of 1.27 with 80% power at the 5% significance level. However, the sample size of 3 subjects per arm was determined by clinical and practical considerations, rather than statistical considerations. With the limitation of small sample size, highest  $AUC_{0-\infty}$  (not necessarily statistically significant) was defined *a priori* as the major selection criterion for identifying a lead formulation for further development of SR13668. Formulations with  $AUC_{0-\infty}$  values within 20% of the highest value were also defined as possible candidate formulations. Plasma concentration was defined as a secondary selection criterion.

## Results

### Patients

Twenty participants were enrolled in this study between June 2009 and October 2009. Two of 8 participants enrolled in stage I did not complete the specimen collection, were deemed ineligible for the pharmacokinetics analysis and subsequently replaced. Twelve additional participants were enrolled in stage II, all of whom completed the study-related activities as planned. Demographic characteristics for the 18 evaluable participants are summarized in Table 1 (characteristics for the 2 replaced participants were not statistically different; data not shown).

**Table 1.** Demographic characteristics of evaluable participants ( $n = 18$ )

Age, median (range)	39 (18-58)
BMI, median (range)	25.4 (19.2-51.2)
Gender, $n$ (%)	
Female	7 (39)
Male	11(61)
Smoking Status, $n$ (%)	
Current	1 (6)
Former	2 (11)
Never	15 (83)

**Table 2.** Solubility of SR13668 in various vehicles

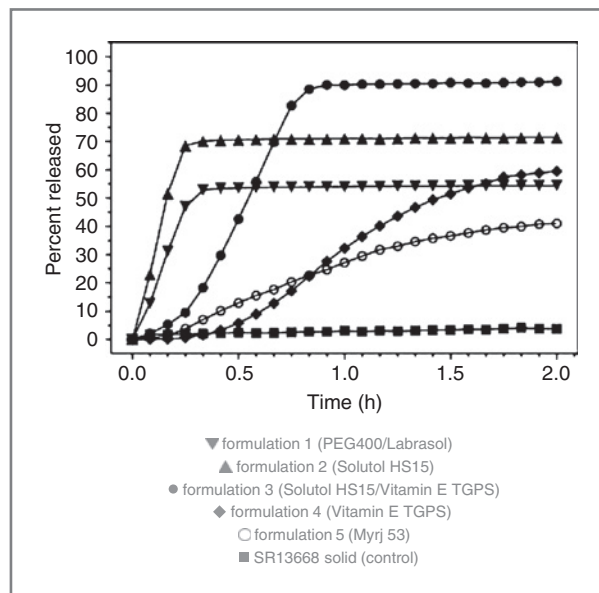
Vehicle	Temperature	Solubility, $\mu\text{g/mL}$
Corn Oil	Room	108
Ethanol	Room	148
Gelucire 44/14	65°C–70°C	4,260
Labrasol	Room	380
Methanol	Room	86
Myrj 52	65°C–70°C	6,700
Myrj 53	65°C–70°C	6,800
PEG-1000	65°C–70°C	8,150
PEG-2000	65°C–70°C	8,800
Sesame Oil	Room	47
Soybean Oil	Room	55
Vitamin E TPGS	65°C–70°C	5,500
Solutol HS15	65°C–70°C	7,950
Water	Room	0.01

### Formulation

Solubility data are summarized in Table 2. SR13668 has poor water solubility (10 ng/mL) and limited solubility in traditional solvents (86–148  $\mu\text{g/mL}$ ). Because of poor solubility in traditional vehicles and immediate precipitation when these solutions were mixed with water, self-emulsifying drug delivery systems (SEDDS) were investigated for SR13668. SEDDS vehicles such as Solutol HS15, Gelucire 44/14, Myrj 52 & 53, and Vitamin E TPGS increase apparent aqueous solubility by forming micelles when dissolved in water and are widely accepted in the pharmaceutical industry (14). These SEDDS vehicles provided solubilities of SR13668 in the 4 to 8 mg/mL range in the molten vehicles (Table 2) and were capable of holding SR13668 in solution for an extended period of time following dissolution (Fig. 1). Although formulation of SR13668 in SEDDS capsules greatly improved its solubility, a 38-mg dose still required a total of 8 capsules. No signs of degradation were observed during storage of these formulations in HDPE bottles at 25°C/60% RH over a 10-week period (data not shown).

### Pharmacokinetics

In stage I, the oral bioavailability of SR13668 in formulation 1 was greater under the fed versus fasting dietary state ( $P = 0.05$ , Wilcoxon rank-sum Test; Table 3). Therefore, the fed state was selected as the preferred dietary condition for stage II. The bioavailability of SR13668 administered as formulations 2, 3, 4, and 5 was then compared with the bioavailability of formulation 1 (Table 3). Statistically significant differences were observed across all formulations with respect to both  $\text{AUC}_{0-\infty}$  ( $P = 0.007$ ) and  $C_{\text{max}}$  ( $P = 0.001$ ). Overall, formulation 2 provided the highest bioavailability. The  $\text{AUC}_{0-\infty}$  for formulation 2 was higher than for all other formulations, and pair-wise comparisons were statistically



**Figure 1.** Release of SR13668 from the reference formulation and 4 self-emulsifying formulations in hard gelatin capsules, as a function of time using USP dissolution unit 2 at 37°C with paddles at 50 rpm and 900 mL water as the dissolution medium.

significant for formulations 4 ( $P = 0.01$ ) and 5 ( $P = 0.006$ ) but not formulations 1 ( $P = 0.09$ ) and 3 ( $P = 0.06$ ). Formulation 2 also exhibited a higher  $C_{\text{max}}$  than formulations 1, 3, 4, and 5 ( $P = 0.02, 0.007, 0.002, \text{ and } < 0.001$  for each pair-wise comparison, respectively). Formulation 1 provided the next largest  $\text{AUC}_{0-\infty}$ , but the observed value was 47% lower than the value achieved with formulation 2 and was also not significantly different from formulations 3, 4, or 5 ( $P > 0.05$  for each pair-wise comparison). Overall, peak plasma concentrations of SR13668 were achieved 3 hours (range, 2–6 hours) after dosing (Fig. 2). The half-life of SR13668 was  $11.2 \pm 3.1$  hours and was not formulation-dependent. Similar results were observed in the RBC fractions where SR13668 accumulated approximately 2.5-fold relative to plasma (Table 3).

### Adverse events

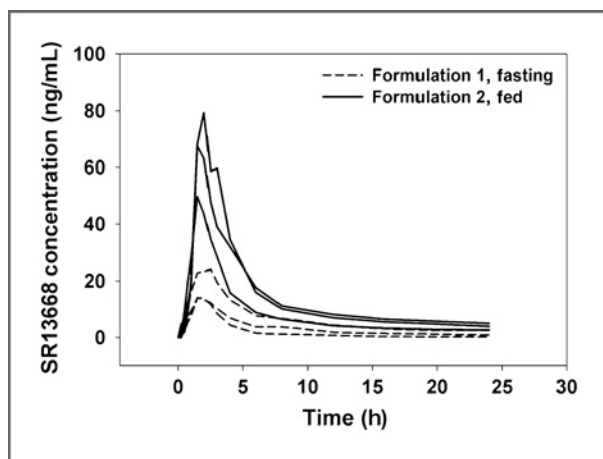
In stage I, 4 of the 6 (66%) participants (2 in each arm) experienced adverse events. Two participants (1 fed and 1 fasting) experienced grade 1 serum ALT elevation considered possibly related to treatment. One fasting participant experienced grade 1 hyperglycemia possibly related to treatment. One fed participant experienced grade 2 diarrhea 30 days after study agent administration, which was determined to be unrelated to treatment. Neither of the replaced participants experienced adverse events.

In stage II, 6 of 12 (50%) participants reported adverse events. Two events possibly related to treatment were reported. These included grade 1 nausea (formulation 3) and elevated lymphocytes (formulation 5). All other adverse events, including 3 reports of grade 1 headache (one assigned to formulation 3 and two participants

**Table 3.** Summary of SR13668 pharmacokinetic plasma parameter estimates<sup>a</sup>

Formulation	Formulation (dietary state)					Overall (Stage II)
	1 (fasting)	1 (fed)	2 (fed)	3 (fed)	4 (fed)	
	PEG400/Labrasol <sup>®</sup> (1:1 v/v) oral solution	PEG400/Labrasol <sup>®</sup> (1:1 v/v) oral solution	Solutol <sup>®</sup> HS15	Solutol <sup>®</sup> HS15/Vitamin E TGPS (50/50 w/w%)	Vitamin E TGPS	Myrij 53
n	3	3	3	3	3	3
T <sub>max</sub>						
Plasma	2.0 (1.5–2.5)	2.5 (1.5–3.0)	1.5 (1.5–2.0)	3.0 (2.0–4.0)	3.0 (3.0–6.1)	2.5 (1.5–6.1)
RBC	2.0 (1.5–2.0)	2.0 (1.5–2.0)	1.5 (1.5–2.0)	2.5 (2.0–4.0)	4.0 (2.5–4.0)	2.0 (1.5–4.0)
Half-life						
Plasma	7.9 (5.8–10.9)	7.2 (6.9–7.9)	13.0 (12.2–14.1)	11.2 (10.6–11.7)	9.0 (7.6–9.7)	16.2 (11.5–17.0)
RBC	11.8 (3.3–13.3)	8.8 (7.6–21.2)	13.6 (11.5–20.3)	11.6 (11.0–21.6)	16.9 (13.2–20.6)	12.3 (9.6–17.8)
C <sub>max</sub>						
Plasma	14.2 (14.1–24.1)	28.2 (23.2–47.5)	67.7 (49.7–79.3)	26.8 (16.3–36.7)	17.0 (15.2–26.1)	14.1 (7.9–17.6)
RBC	46.3 (22.9–62.3)	80.6 (68.7–124)	139 (82.2–220)	82.4 (54.2–103)	57.3 (50.2–74.9)	21.7 (14.3–38.0)
Ratio	2.6 (1.6–3.3)	2.6 (2.4–3.5)	2.1 (1.7–2.8)	3.1 (2.8–3.3)	3.3 (2.9–3.4)	1.8 (1.5–2.2)
AUC <sub>0–24 h</sub>						
Plasma	81.8 (49.2–159)	203 (168–273)	338 (212–350)	187 (134–210)	131 (121–177)	114 (75.0–117)
RBC	227 (88.3–385)	461 (405–534)	861 (348–890)	408 (318–507)	384 (168–458)	157 (124–188)
Ratio	2.4 (1.8–2.8)	2.0 (1.7–3.2)	2.5 (1.6–2.6)	2.4 (2.2–2.4)	2.6 (1.4–2.9)	1.7 (1.3–1.7)
AUC <sub>0–∞</sub>						
Plasma	91.2 (50.8–199)	221 (184–302)	419 (263–439)	225 (173–261)	149 (149–214)	160 (122–172)
RBC	301 (99.0–490)	547 (540–607)	1,030 (521–1,120)	492 (396–684)	636 (604–667)	206 (184–238)
Ratio	2.5 (1.9–3.3)	2.4 (1.8–3.3)	2.5 (2.0–2.5)	2.3 (2.2–2.6)	3.7 (2.8–4.5)	1.5 (1.1–1.7)

<sup>a</sup>Values shown are median (range) for T<sub>max</sub> (hours), half-life (hours), C<sub>max</sub> (ng/mL), AUC<sub>0–24 h</sub> (ng/mL × hours), and AUC<sub>0–∞</sub> (ng/mL × hours)



**Figure 2.** Representative plasma concentration–time participants administered formulation 1 (PEG400/Labrasol) in the fasting state ( $n = 3$ ; lowest bioavailability; dashed lines) or formulation 2 (Solutol HS15) in the fed state ( $n = 3$ ; highest bioavailability; solid lines).

assigned to formulation 5), grade 3 surgery (formulation 3), bruising (formulation 4), and dizziness (formulation 5), were deemed unlikely to be related to treatment.

## Discussion

This report describes, to our knowledge, results from the first phase 0 (exploratory IND) trial of a candidate chemopreventive agent in oncology. Participant accrual was accomplished over a relatively short time period (5 months from activation to closure) and a lead formulation for SR13668 was rapidly identified using pharmacokinetic data as the primary endpoint. Our study provides strong support for expanding the phase 0 trial paradigm beyond chemotherapy drug development.

SR13668 was developed utilizing a computer-assisted structural analysis of 4 active I3C metabolites. The resulting compound exhibited antitumor activity, but very low water solubility (7). As expected for Biopharmaceutics Drug Classification Class II drugs (11) that demonstrate dissolution rate limited absorption *in vivo*, SR13668 bioavailability was extremely low in preclinical species but was improved substantially by the surfactant-based formulation PEG400 Labrosol (1:1 v/v oral solution) (9). Formulation approaches to achieve the highest oral bioavailability of SR13668 in humans focused on suitable carriers for dissolved drug or increasing the dissolution rate. Formulation approaches further focused on the use of SEDDS, Generally Recommended as Safe (GRAS) that have been used in approved drug products to expedite advancement of the preferred formulation into subsequent phase I and II clinical trials. Of note, 4 SEDDS evaluated in our phase 0 trial all demonstrated SR13668 release and apparent solubility that were well in excess of the solid drug substance and were acceptable for *in vivo* evaluation. These results are remarkable in light of the poor solubility in water and limited solubility in traditional organic solvents.

The FDA guidance (2) for exploratory IND studies explores examples of clinical trials used to study drug pharmacokinetics, pharmacologic effects, and mechanism of action related to efficacy and further notes that other applications may be proposed. The recent report from Kummur and colleagues describes a phase 0 trial of a potential chemotherapy agent (ABT-888) among subjects with advanced malignancies, with pharmacodynamic modulation over a specified dose range defined as the primary endpoint (15). In contrast, our trial was designed to evaluate a candidate chemoprevention agent (SR13668) in healthy adult volunteers, with pharmacokinetic comparison across formulations defined as the primary endpoint. These 2 reports represent substantially different and complementary applications of the phase 0 trial design.

Statistical challenges for the design and analysis of phase 0 chemoprevention trials are similar to those encountered in phase 0 chemotherapeutic trials (16, 17). Application and interpretation of pharmacokinetics and/or pharmacodynamics data that are based on a relatively small number of study participants require careful planning and appropriate caution. In addition, biologically and statistically "significant" responses must be rigorously defined. In our phase 0 trial, pharmacokinetics data were chosen as the primary endpoint for investigating SR13668 bioavailability, as the major objective was to identify a preferred formulation for further development as a candidate chemoprevention agent. We adopted a flexible combination of biologic and statistical criteria for the selection of formulations to make this study not only scientifically sound but also clinically feasible in a phase 0 setting. The use of 2-stage design over factorial design for food effect and agent formulation also improved efficiency by reducing the necessary sample size.

Given that tobacco carcinogens have been shown to stimulate upregulation of the P13K/Akt pathway (18), coupled with the finding that SR13668 concentration was enhanced in pulmonary tissue following oral administration to rats (9), further development of this compound as a potential lung cancer chemoprevention agent may be worth pursuing. However, although formulation of SR13668 in a SEDDS vehicle greatly improved its solubility and bioavailability, administration of a 38-mg dose (1/50th of the rat NOAEL) still required ingestion of 8 capsules, which could adversely affect compliance with repeat or prolonged administration, particularly if substantially higher dosing is needed to achieve a pharmacologic response. Thus, additional data regarding the pharmacologic activity in humans would be important to fully evaluate the feasibility of successfully advancing SR13668 as a candidate chemoprevention agent. Alternatively, other approaches may be considered to enhance SR13668 bioavailability including assessment of vehicles that are not yet GRAS and/or consideration of water-soluble prodrugs. Additional computer-assisted structural analysis might also identify water-soluble analogues of SR13668 that maintain pharmacologic activity, while providing more efficient delivery.

In summary, based on our experience in this first-ever, phase 0 (exploratory IND) chemoprevention trial, pharmacokinetic analyses of different formulations represents an effective strategy to rapidly inform subsequent clinical testing. The inherent ethical issue of providing a microdose intervention with no anticipated clinical benefits is much less challenging in chemoprevention trials, which generally exclude patients with cancer or other unstable medical conditions. As noted by Murgo and colleagues (19) phase 0 trials can be designed to address several different pharmacologic endpoints, which should permit broad opportunities to accelerate chemoprevention agent development under this novel paradigm.

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## Acknowledgments

We thank the CTSA, Clinical Research Unit staff at Mayo Clinic Rochester for assistance and Colleen Garvey and Sharon Kaufman, for help with study administration and article preparation.

## Grant Support

Supported by NIH grants/contracts N01-CN-35000, CA15083-34C3, and UL1 RR024150

Received October 29, 2010; revised November 11, 2010; accepted November 30, 2010; published online March 3, 2011.