INTRODUCTION

SCO-101 is an inhibitor of chloride channels (incl. the erythrocyte chloride conductance, volume-regulated anion channels and calcium-activated chloride channels),\(^1\)\(^-\)\(^3\) and was initially developed to treat patients with sickle cell anaemia. The chemical name is N-[4-Bromo-2-(1H-1,2,3,4-tetrazol-5-yl)phenyl]-N’-[3,5-bis(trifluoromethyl) phenyl]urea (Figure 1). The drug development was halted in 2003 because four phase 1 trials found a dose-dependent reversible increase in plasma unconjugated bilirubin which is incompatible with the high levels of bilirubin found in sickle cell anaemia patients. The results of these phase 1 trials, which were carried out by PAREXEL International, and under which SCO-101 was called NS3728...
or Endovion, were not published. The interest in SCO-101 was rekindled because SCO-101 was shown to inhibit the proliferation/migration of cancer cell lines, and recent pre-clinical cancer models indicate that it increases the potency of certain forms of cytotoxic chemotherapy and appears to revert chemoresistance to taxanes, topoisomerase I inhibitors, and the antiestrogens tamoxifen and fulvestrant. The reported mechanisms of action are inhibition of drug efflux pumps (ABCG2) and the Serine/Arginine-Rich Splicing Factor Kinase 1 (SRPK1) leading to increased accumulation of chemotherapy and thus increased cytotoxicity (data not shown).

SCO-101 is now in its first phase 2 clinical trial where patients with metastatic and drug-resistant colorectal cancer are included. De novo or acquired resistance to anticancer therapy, for example chemotherapy, endocrine therapy and/or biologicals, is the main reason for failure of anticancer treatment. With a worldwide annual death toll of 8.9 million in 2016 from cancer, and with a prediction of a further increase in cancer incidence over the next 15 years, there is a clear unmet need of novel effective treatment modalities. In due course, it is pertinent to disclose the results of the four phase 1 trials which were performed in 2002. The study objectives were to (a) determine the safety and tolerability of single and multiple once-daily oral doses, (b) determine the pharmacokinetics profiles, and (c) evaluate any marked differences in drug disposition between African American and Caucasian volunteers, between males and females, and between the fasted and fed state.

Thus, we present the results from four phase 1 trials of SCO-101 in healthy adult volunteers. Trial 1 assessed single oral dose pharmacokinetics in males, Trial 2 investigated repeated oral dose pharmacokinetics in males, Trial 3 assessed the impact of food on single-dose pharmacokinetics, and Trial 4 evaluated single oral dose pharmacokinetics in females.

2. **VOLUNTEERS, METHODS AND MATERIALS**

All procedures in the four trials were conducted according to United States (US) Food and Drug Administration (FDA) regulations and guidelines. FDA guidelines and regulations encompass all principles established by the Declaration of Helsinki (1989). The investigators complied with Good Clinical Practice. The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.

2.1 **Trial design/eligibility criteria**

Trials 1-4 were all single-centre, randomized trials carried out by the contract research organization PAREXEL. Double blinding and placebo control were applied in all trials. Included volunteers were allocated to either placebo, or from 5 to 200 mg SCO-101. For Trial 1, the planned number of volunteers was 48 divided in 6 dose cohorts. In each cohort, 6 volunteers were randomized to active drug and 2 to placebo. For Trial 2, the planned number of volunteers was 24 divided in three dose cohorts, also with 6 on SCO-101 and 2 on placebo in each. For Trials 3 and 4, the planned number of volunteers was 12 and 8, respectively. Inclusion and exclusion criteria varied little between the four trials. Inclusion criteria: (a) voluntary written and verbal consent, (b) healthy males or females using contraception—aged between 18 and 45 years, (c) no significant findings from medical history and physical examination, (d) body mass index less than or equal to 29 kg/m², (e) no clinically significant deviation from normal clinical biochemistry and haematology values (eg liver enzymes, bilirubin, creatinine, cholesterol, electrolytes, haemoglobin, white blood cell count and platelets), (f) negative results for hepatitis B and hepatitis C, and human immunodeficiency virus screening, and (g) clean urine and drug screen for recreational drugs and ethanol. Exclusion criteria: (a) history of drug hypersensitivity, (b) use of any prescription medication within 14 days, or use of any over-the-counter medication within 7 days prior to dosing (acetaminophen during the trial was permitted), (c) admission to drug and/or alcohol abuse, (d) tobacco use if greater than equivalent of 10 cigarettes per day, (e) abnormal electrocardiogram, (f) active malignant disease other than non-melanoma skin cancer and (g) donated blood within 30 days prior to study enrolment.

2.2 **Treatment plan**

The treatment plans were quite similar for all four trials. SCO-101 was administered according to dose as the

---

**FIGURE 1** Structural formula of SCO-101. Molecular weight is 495.19 g/mol
appropriate number of hard-shell immediate release gelatin capsules, or either 5 mg or 25 mg of SCO-101. Each oral dose was administered in the morning with 240 mL water (room temperature), after 8-10 hours of fasting. Ingestion was done under supervision. In Trial 3, volunteers randomized to the fed condition took SCO-101 after a standardized breakfast consisting of eggs, bacon, a muffin, potatoes, milk and apple juice (Figure 2).

2.3 | Safety assessment

Patient demographics were recorded during the inclusion phase in all the trials. Standard physical examination was carried out at inclusion, during the trial and at follow-up. Electrocardiogram (ECG) and vital signs including blood pressure, temperature, respiratory rate and pulse were monitored throughout the trials. All volunteers volunteered. All reported, observed and elicited adverse events were recorded regardless of relationship to SCO-101. The recorded events’ severity and relationship to SCO-101 was determined by the investigator using a probability algorithm by which events were categorized as either, probable, possible, unlikely, or not related to SCO-101. Briefly, the severity was categorized as mild, moderate and severe depending on if the adverse event did not interfere with, did interfere with, or made routine daily activities impossible. The relationship to SCO-101 was assessed by counting the number of the following conditions that would apply to the adverse event: (a) follows a reasonable temporal sequence after administration of SCO-101, (b) cannot be reasonably explained by known characteristics of the clinical state, environmental or toxic factors, (c) disappears or decreases on cessation or reduction in dose and reoccurs with re-exposure, (d) follows a known pattern of response to SCO-101, and (e) is associated with toxic levels of SCO-101 in the blood.

2.4 | Pharmacokinetic sampling and analyses

Blood samples for determining plasma concentrations of SCO-101 were taken pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36 and 48 hours after dosing with negligible variation between trials. Additional samples were taken after 96 and 144 hours in Trials 1 and 4. Approximately 5 mL blood was collected at each time point into lithium heparinized tubes and immediately placed in an ice-bath for up to 30 minutes before centrifugation and storage at −20°C until analyses. NS3728 was stable in human plasma during three freeze-thaw cycles and extracts of NS3728 in human plasma were stable for 120 hours when stored in autosampler at nominal 5°C. SCO-101 was determined in plasma by the department of Bioanalysis at NeuroSearch, Ballerup, Denmark. Samples were generally analysed within two days of receipt. Briefly, SCO-101 and internal standard (NS3736—a close structure analog to NS372814) were extracted from human plasma by precipitation using acetonitrile. The decanted supernatant was evaporated to dryness under nitrogen, then reconstituted with acetonitrile, followed by the addition of ammonium formate (5 mmol/L, pH 4.5) and directly injected onto the high-performance liquid chromatography system (Alliance 2790, Waters A/S). The column used was a YMC-basic 50 × 2.0 mm ID, 3.0 μm. Detection was performed by negative ion-spray mass spectrometry (Quattro Ultima, Micromass Ltd). Plasma concentrations were analysed using the non-compartmental approach in the software package WinNonlin version 3.1 (Pharsight Corporation), and reported graphically and with summary statistics including Cmax, terminal half-life, apparent oral clearance (CL/F) and area under the plasma-concentration time curve.

**FIGURE 2** Overview of trial pharmacokinetic sampling. Arrow—SCO-101 oral dose. Black bar—PK sampling.
2.4.1 Assay performance

Calibration of the assay was made with fresh calibration standards prepared in human plasma for each analytical run. The concentration range was from 1 to 1000 ng/mL, and good linearity ($r^2 > .996$; nine calibration points) was observed in all analytical batches.

Precision was measured using the coefficient of variation (CV). Accuracy is quoted as the measured concentration expressed as a percentage of the prepared concentration. At 2 ng/mL (QCL), precision was 2.8% and accuracy was 87.8%; at 80 ng/mL (QCM), precision was 1.1% and accuracy was 106.4%; at 800 ng/mL (QCH), precision was 2.9% and accuracy was 91.6%. In summary, the precision of the assay was less than 15% coefficient of variation, and the accuracy was between 85% and 115% of prepared concentration. Back-calculated concentrations of accepted standards in these batches were within 85%-115% of the theoretical value, which was the accepted deviation range for the highest standard. In the assay, the Lower Limit of Quantification (LLOQ) was 1 ng/mL and all pre-dose and placebo measurements were below the LLOQ.

For the measurement of the human plasma samples, at least four of the six quality control samples analysed in each batch of study samples should be within 85%-115% of their theoretical values. Two of the quality control samples may be outside these limits, but not both, at the same concentration. If dilutions were performed in the sample batch, at least one of the dilution quality control samples should satisfy the accuracy criteria; otherwise, all diluted samples within the batch were re-analysed. If an analytical batch was rejected on the basis of accuracy criteria, re-analysis of all study samples in the batch would take place.

2.5 Statistical methods

Data were log-transformed to ensure normal distribution, and an unpaired Student’s $t$ test was performed to assess statistically significant differences. A significance threshold of $P < .05$ was used.

3 RESULTS

3.1 Patient accrual and demographics

3.1.1 Trial 1

A total of 48 volunteers were enrolled in the trial as planned. Six cohorts with 8 volunteers each; 2 received placebo and 6 received SCO-101 (see Table 1). Five cohorts consisted
predominantly of African Americans. One cohort consisted predominantly of Caucasians. The volunteers received 5, 25, 50, 100 and 200 mg. The volunteers were generally well matched for baseline characteristics between the dose cohorts.

3.1.2 | Trial 2

A total of 24 volunteers were enrolled in the trial as planned, with 8 in each of the dose cohorts. In each cohort, 6 volunteers received SCO-101 and two received placebo. The volunteers received 10, 50 and 150 mg for 14 days. Two volunteers withdrew from the trial. Both belonged to the 10 mg cohort and had been randomized to placebo. The volunteers were generally well matched for baseline characteristics between the dose cohorts.

3.1.3 | Trial 3

Twelve volunteers were enrolled as planned and randomized to one of two sequences: fasted/fed or fed/fasted. Volunteers received a single dose of 100 mg SCO-101.

3.1.4 | Trial 4

Eight female volunteers were enrolled in the trial as planned. Two were randomized to placebo, and the rest received a single dose of SCO-101 of 100 mg.

3.2 | Safety

SCO-101 was generally tolerated well in all four trials. There were no deaths, and no serious adverse events in any of the trials and no volunteers in the active treatment groups were discontinued due to adverse events. With reference to the probability algorithm, there were two probable adverse events, which were cases of jaundice which both occurred in volunteers in the 150 mg dose cohort in Trial 2. Blood bilirubin unconjugated levels displayed a transient and relatively small dose-dependent increase in Trial 1. In Trial 2 (repeated dosing), bilirubin levels continued to rise through Day 14 (last day of dosing) and returned to normal levels before the follow-up observations approximately on day 24 (Figure 3).

The most frequently reported possible adverse event was headache, which generally resolved within a day without treatment. Other recorded possible adverse events were feeling cold, nasal congestion, somnolence, stiffness, constipation and pressure on chest, dry mouth, shortness of breath, back pain and abdominal pain. There was no perceptible effect on ECG parameters. Liver transaminases and creatinine remained stable and unremarkable in all volunteers in all trials.

3.3 | Pharmacokinetic analyses

The plasma-concentration time profiles for Trials 1-4 are shown in Figure 4A-F, and a summary of the derived pharmacokinetic parameters is shown in Tables 2 and 3. Extrapolated AUCs from \( t_{\text{last}} \) to infinity were between 0% and 9.7% for single-dose studies (studies 1, 3 and 4) and 0.4%-54.0% for steady state. The terminal part of the curve was approximately log linear over the entire dose range for both single dose and at steady state. \( T_{\text{max}} \) values showed little variation across trials. In Trial 1, \( C_{\text{max}} \) increased approximately 52-fold across the 40-fold dose range from 5 to 200 mg. The same pattern was apparent in Trial 2, where a 21-fold and a 36-fold increase were observed for the single dose and the repeated dosing regimen, respectively, across the 15-fold dose range. Area under the curve showed a similar pattern with a greater than proportional increase with increasing dose, and for repeated dose compared to single dose (Figure 5). The effect of food was demonstrated in Trial 3 for 100 mg SCO-101. \( C_{\text{max}} \) was 26% lower, and AUC\(_{\infty} \) was 29% lower in the fed compared to the fasted state. \( T_{\text{max}} \) was greater in the fed state as expected (Table 2). The effect of sex on SCO-101 pharmacokinetics was assessed by comparing data from Trial 4 (exclusively women) with the volunteers in Trial 1 who received 100 mg SCO-101. There was no statistically significant difference between AUC and \( C_{\text{max}} \) for males and females (\( P > .05 \)). There was also no statistically significant difference between AUC and \( C_{\text{max}} \) for African Americans and Caucasians (Figure 6; \( P > .05 \)).
We present data from four phase 1 trials of SCO-101 performed in 2002. Generally, SCO-101 is well tolerated. The plasma concentrations decline according to first-order elimination. Some dose dependency is apparent with decreased CL/F for increasing and repeated dosing. SCO-101 is now being investigated for efficacy as an enhancer or adjuvant in anticancer

**FIGURE 4** A, Plasma concentrations of SCO-101 for the dose escalating experiment (Trial 1). Lines represent cohort means. The two 100 mg cohorts represent the predominantly African American cohort (AA) and the Caucasian cohort (CAU), respectively. B, Plasma concentration of SCO-101 for the 10 mg cohort (Trial 2). Lines represent cohort means. C, Plasma concentration of SCO-101 for the 50 mg cohort (Trial 2). Lines represent cohort means. D, Plasma concentration of SCO-101 for the 150 mg cohort (Trial 2). Lines represent cohort means. E, Plasma concentration of SCO-101 for the fasted and fed cohorts (100 mg single dose) (Trial 4). The line represents the cohort mean. F, Plasma concentration of SCO-101 for the 100 mg female cohort (Trial 4). The line represents the cohort mean [Correction Statement: Correction added on 24 August 2020 after first online publication: Figures 4A and 4E were previously swapped and have been corrected in this version.]
### TABLE 2  PK parameters—single oral dose (Trial 1, 3 & 4)

| Group | Trial 1 | Trial 1 | Trial 1 | Trial 1 | Trial 1 | Trial 1 | Trial 3 | Trial 4a |
|-------|--------|--------|--------|--------|--------|--------|--------|--------|
|       | 5 mg (n = 6) | 25 mg (n = 6) | 50 mg (n = 6) | 100 mg (n = 6) | 200 mg (n = 6) | 100 mg (n = 12, fed) | 100 mg (n = 6) |
| C<sub>max</sub> (ng/mL) | 240 (207–379) | 1475 (1070–2690) | 3725 (2360–4430) | 8395 (4420–10 800) | 7495 (4590–8780) | 13 100 (9850–21 000) | 5485 (3330–8030) |
| t<sub>max</sub> (h) | 4 (2.5–5) | 4 (2.5–6) | 5 (4–6) | 4.5 (1.7–8) | 4 (4–8) | 4 (4–8) | 6 (5–8) |
| AUC<sub>∞</sub> (ng/mL* h) | 4301 (2429–4881) | 20 531 (11 891–116 530) | 62 037 (36 633–116 530) | 173 382 (112 350–317 732) | 162 562 (83 967–215 477) | 310 083 (239 790–480 655) | 73 129 (31 527–134 921) |
| CL/F (mL/h) | 1163 (1024–2059) | 1218 (465–2103) | 806 (429–1365) | 578 (315–890) | 615 (464–1191) | 645 (416–834) | 1370 (741–3172) |
| t<sub>1/2</sub> (h) | 13.6 (11.3–20.2) | 17.2 (10.2–25.9) | 12.9 (9.0–20.4) | 15.9 (11.7–18.4) | 14.2 (10.5–16.6) | 14.7 (9.7–19.2) | 8.1 (5.7–14.2) |
| AUC<sub>last</sub> (ng/mL* h) | 4276 (2284–4870) | 20 509 (11 859–115 677) | 61 936 (35 270–115 777) | 173 031 (111 901–316 774) | 162 396 (83 959–214 937) | 309 744 (239 256–480 504) | 70 675 (31 373–121 670) |

*Note:* Data are shown as median (range).

### TABLE 3  Pharmacokinetic parameters—repeated dosing (Trial 2)

|       | 10 mg (n = 6) | 50 mg (n = 6) | 150 mg (n = 6) |
|-------|---------------|---------------|---------------|
| Day 1 | Day 14        | Day 1 | Day 14        | Day 1 | Day 14 |
| C<sub>max</sub> (ng/mL) | 492 (392–545) | 543 (419–681) | 5550 (2370–4130) | 5140 (4480–6710) | 10 275 (7560–12 900) | 18 050 (10 600–37 600) |
| t<sub>max</sub> (h) | 4 (3–5) | 4 (3–5) | 3.5 (3–6) | 5 (3–6) | 3.5 (2.0–6.0) | 4 (3–8) |
| AUC<sub>∞</sub> (ng/mL* h) | 4748 (2226–7456) | 6710 (4111–8352) | 45 663 (40 153–60 925) | 92 686 (52 311–196 283) | 200 352 (92 522–285 890) | 462 322 (210 070–1 243 663) |
| CL/F (mL/h) | 2128 (1341–4473) | 1496 (1197–2433) | 1095 (821–1245) | 540 (255–956) | 749 (525–1621) | 329 (121–714) |
| t<sub>1/2</sub> (h) | 8.5 (7.5–12.9) | 10.3 (9.2–12.2) | 9.9 (6.1–13.3) | 10.7 (7.4–20.6) | 11.7 (5.8–16.5) | 17.0 (11.3–37.0) |
| AUC<sub>last</sub> (ng/mL* h) | 4684 (2191–7006) | 6491 (4052–7891) | 42 878 (39 979–56 277) | 84 094 (51 799–161 453) | 180 423 (92 165–255 272) | 397 479 (197 952–754 025) |

*Note:* Data are shown as median (range).
The molecule was discovered almost 20 years ago with an aim to treat sickle cell disease. SCO-101 was well tolerated but due to a reversible drug-induced increase in serum unconjugated bilirubin; further development was halted since sickle cell anaemia patients have increased bilirubin due to destruction of red blood cells and release of haemoglobin. Later pre-clinical studies have shown that SCO-101 inhibits the bilirubin uridine glucuronyl transferase (UGT-1A1), which is involved in bilirubin conjugation (NeuroSearch, unpublished data). In vitro analyses demonstrated an IC50 of 0.6 µmol/L, and in vivo studies showed that oral administration of SCO-101 to mice and monkeys appeared to result in elevated bilirubin, mainly due to a reversible inhibition of the UGT1A1 conjugating enzyme (data not shown). Because of the renewed interest in this drug, we find it relevant and interesting to document and publish the results of the four phase 1 trials that were conducted in 2002. The four trials all accrued the planned number of volunteers. SCO-101 was well tolerated with no serious adverse reactions recorded. Possible adverse reactions included jaundice, headache, constipation, shortness of breath and pain. There was no apparent relationship between adverse reactions and dose except for hyperbilirubinaemia. Two volunteers in the 150 mg dose cohort in Trial 2 developed hyperbilirubinaemia severe enough to manifest itself as jaundice. The levels of unconjugated bilirubin of the two volunteers continued to rise through day 14 and then return to normal levels at follow-up (approximately at day 24). These individual volunteers’ changes in unconjugated bilirubin, while accentuated, were consistent with the results observed in all the volunteers. The two volunteers had greater SCO-101 Cmax and AUC compared to all other volunteers in Trial 2. This indicated that the bilirubin increase might be dose-dependent. No parameters of hepatic toxicity (aminotransferases, alkaline phosphatase, conjugated bilirubin and albumin) were observed. Furthermore, no signs of haemolysis were observed. These isolated elevations in unconjugated bilirubin resemble that seen in Gilbert Syndrome, associated with reduced activity of bilirubin uridine glucuronyl transferase.

Plasma SCO-101 concentrations were analysed using the non-compartmental approach. The sampling period was adequate in all the trials. The terminal slope indicates no significant departure from first-order elimination. Half-lives ranged from 5.8 to 37.0 hours with no clear dose dependency. Drug exposure increased supra-proportionally with increasing dose. This suggests saturation at the level of the gut (ie efflux transporters) and/or liver (ie biotransformation)—effectively reducing the bioavailability (first pass effect)—thus affecting the apparent clearance, but with little impact on the terminal half-life. Along this line of reasoning, saturation of renal secretion is a less plausible explanation. However, we can only
speculate because no urine data are available from the studies. Both $C_{\text{max}}$ and AUC$_\infty$ were approximately 30% lower in the fed state compared to the fasted state. The most likely explanation being that food slightly reduces the absorption rate, but also the extent, that is the bioavailability. $C_{\text{max}}$ and AUC$_\infty$ were similar for females compared to males. African Americans had slightly greater apparent clearances than Caucasians, but the difference was not statistically significant.

In conclusion, we present the results from four phase I trials of the compound SCO-101. SCO-101 was discontinued as a drug against sickle cell anaemia, but the interest has since renewed because of pre-clinical results indicating that the molecule might be efficacious as an inhibitor of specific anticancer drug resistance mechanisms. The four trials demonstrate the safety and the pharmacokinetic properties of SCO-101 in healthy adult male and female volunteers. Scandion Oncology has initiated a phase 2 clinical study in patients with 5-Flurouracil, leucovorin plus irinotecan (FOLFIRI) resistant metastatic colorectal cancer (NCT04247256). The study consists of two parts. In part one, patients receive FOLFIRI plus escalating doses of SCO-101 in order to determine the maximum tolerated dose (MTD). In part two, the patients will receive FOLFIRI plus the MTD of SCO-101 in order to assess the safety, toxicity and the efficacy of the combination of SCO-101 and FOLFIRI.

CONFLICTS OF INTEREST

TK Bergmann has not received any honoraria for the work. However, Scandion Oncology A/S has compensated The University of Southern Denmark for the time spent on the project. TB Stage has done consulting for Pfizer and has received personal fees for teaching for Pfizer, Eisai and Novartis. TB Stage has not received any honoraria for the work. However, Scandion Oncology A/S has compensated The University of Southern Denmark for the time spent on the project. J Stenvang and N Brünner are employees, founders and stock owners in Scandion Oncology A/S. PM Vestlev and NL Roest are employees and stock owners in Scandion Oncology A/S. P Christophersen is employee, founder and stock owner in Saniona A/S, which possess a minority share part in Scandion Oncology. TA Jacobsen is an employee and stock owner in Saniona A/S, which possess a minority share part in Scandion Oncology A/S.

ORCID
Troels K. Bergmann https://orcid.org/0000-0001-8313-0721
Tore B. Stage https://orcid.org/0000-0002-4698-4389

REFERENCES
1. Hélix N, Strobaek D, Dahl BH, Christophersen P. Inhibition of the endogenous volume-regulated anion channel (VRAC) in HEK293 cells by acidic di-aryl-ureas. J Membr Biol. 2003;196:83-94.
2. Klausen TK, Bergdahl A, Hougaard C, Christophersen P, Pedersen SF, Hoffmann EK. Cell cycle-dependent activity of the volume- and Ca2+-activated anion currents in Ehrlich leette ascites cells. J Cell Physiol. 2007;210:831-842.
3. Poulsen KA, Andersen EC, Hansen CF, et al. Deregulation of apoptotic volume decrease and ionic movements in multidrug-re- sistant tumor cells: role of chloride channels. Am J Physiol Cell Physiol. 2010;298:C14-C25.
4. Schneider L, Klausen TK, Stock C, et al. H-ras transformation sensitizes volume-activated anion channels and increases migratory activity of NIH3T3 fibroblasts. Pflugers Arch. 2008;455:1055-1062.
5. Brünner N, Stenvang J, Popovic V, Budinska E. ABCG2 and TOP-1 as predictive biomarkers and targets for therapy in colon cancer. Ann Oncol. 2018;29:v61.
6. Bagger SO, Drejer J, Brünner N, Nielsen SL, Christoffersen P, Stenvang J. Abstract A144: Sensitization of docetaxel-resistant breast cancer cells to docetaxel by the VRAC modulator SCO-101. Mol Cancer Ther. 2018;17:A144.
7. Hansen SN, Westergaard D, Thomsen MBH, et al. Acquisition of docetaxel resistance in breast cancer cells reveals upregulation of ABCB1 expression as a key mediator of resistance accompanied by discrete upregulation of other specific genes and pathways. Tumour Biol. 2015;36:4327-4338.
8. Jensen NF, Stenvang J, Beck MK, et al. Establishment and characterization of models of chemotherapy resistance in colorectal cancer: towards a predictive signature of chemoresistance. Mol Oncol. 2015;9:1169-1185.
9. Brünner N, Boysen B, Jirus S, et al. MCF7/LCC9: an antiestrogen-resistant MCF-7 variant in which acquired resistance to the steroidal antiestrogen tamoxifen. Cancer Res. 1997;57:3486-3493.
10. Nohr-Nielsen A, Bagger SO, Brünner N, Stenvang J, Lund TM. Pharmacodynamic modelling reveals synergistic interaction between docetaxel and SCO-101 in a docetaxel-resistant triple negative breast cancer cell line. Eur J Pharm Sci. 2020;148:105315.
11. Housman G, Byler S, Heerboth S, et al. Drug resistance in cancer: an overview. Cancers. 2014;6:1769-1792.
12. Naghavi M, Abajobir AA, Abbafati C, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2014: an overview. Cancers. 2020;12:319.
13. Tveden-Nyborg P, Bergmann TK, Lykkefeldt J. Basic & Clinical Pharmacology & Toxicology Policy for Experimental and Clinical studies. Basic Clin Pharmacol Toxicol. 2018;123:233-235.
14. Schaller S, Henriksen K, Sveigaard C, et al. The chloride channel inhibitor NS3736 [corrected] prevents bone resorption in ovariec- tomized rats without changing bone formation. J Bone Miner Res Off J Am Soc Bone Miner Res. 2004;19:1144-1153.

How to cite this article: Bergmann TK, Stage TB, Stenvang J, et al. Four phase I trials to evaluate the safety and pharmacokinetic profile of single and repeated dosing of SCO-101 in adult male and female volunteers. Basic Clin Pharmacol Toxicol. 2020;127:329–337. https://doi.org/10.1111/bcpt.13466