BMJ Open

Phase I dose-escalation study to evaluate the safety of SH003 in patients with solid cancer: a study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019502
Article Type:	Protocol
Date Submitted by the Author:	06-Sep-2017
Complete List of Authors:	Cheon, Chunhoo Kang, Sohyeon; Kyung Hee University Ko, Youme Kim, Mia; Kyung Hee University Jang, Bo-Hyoung Shin, Yong-Cheol Ko, Seong-Gyu; Kyung Hee University,
Keywords:	Herbal medicine < THERAPEUTICS, ONCOLOGY, COMPLEMENTARY MEDICINE

Phase I dose-escalation study to evaluate the safety of SH003 in patients with solid cancer: a study protocol

Chunhoo Cheon[1], Sohyeon Kang[1], Youme Ko[1], Mia Kim[2], Bo-Hyoung Jang[1], Yong-Cheol Shin[1] and Seong-Gyu Ko[1§]

[1] Department of Korean Preventive Medicine, Graduate School, Kyung Hee University, Seoul, Republic of Korea

[2] Department of Cardiovascular and Neurologic disease (Stroke center), College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

[§]Corresponding author

Email addresses:

CC: pm.thehoo@gmail.com

SK: kangsohyeon@gmail.com

YK: ymymko84@gmail.com

MK: hyuntemia@hanmail.net

BHJ: bhjang@khu.ac.kr

YCS: syc99@khu.ac.kr

SGK: epiko@khu.ac.kr

Correspondence to

Professor Seong-Gyu Ko; epiko@khu.ac.kr, 26, Kyungheedae-ro, Dongdaemun-gu, Seoul, 02447, Korea Tel. +82-2-961-9278

Word count: 2,556

Abstract

Introduction

Cancer is a major health problem worldwide and the leading cause of death in many countries. The number of patients with cancer and socioeconomic costs of cancer continues to increase. SH003 is a novel herbal medicine consist of Astragalus membranaceus, Angelica gigas, and Trichosanthes Kirilowii Maximowicz. Preclinical studies showed that SH003 has therapeutic effectiveness of anticancer. The aim of this study is to determine the maximum tolerated dose of SH003 in patient with solid cancer.

Methods and analysis

This study is an open-label, dose escalation trial evaluating the safety and tolerability of SH003. The traditional 3+3 dose escalation design will be implemented. Patients with solid cancer will be recruited. According to dose level, the patients will receive 1 to 3 tablets of SH003 three times a day for 3 weeks. The toxicity will be evaluated using common terminology criteria for adverse events (CTCAE). Dose-limiting toxicities are defined Grade 3 or higher adverse events based on CTCAE. Maximum tolerated dose will be determined by the highest dose at which no more than 1 of 6 patients has dose-limiting toxicity.

Ethics and dissemination

This study has been approved by the institutional review board of the Ajou University Hospital (reference AJIRB-MED-CT1-16-311). The results of this study will be disseminated through a scientific journal and conference.

Trial registrations

ClinicalTrials.gov NCT03081819

Strengths and limitations of this study

▪ This is the first human study to examine the safety and feasibility of SH003 for patients with solid cancer.

▪ The present study is the first Phase I study to determine maximum tolerated dose of herbal medicine in Korea.

▪ Limitations of this study is that pharmacokinetic and pharmacodynamics studies could not be conducted due to the nature of the drug.

Introduction

Cancer which is the disease caused by an uncontrolled division of abnormal cells in a part of the body is a leading cause of death global, to the amount of 8.8 million deaths in 2015[1]. The economic cost of cancer is increasing. In 2010, the total economic cost of cancer was calculated at approximately 1.16 trillion US dollars[2]. In Korea, there were 1.46 million patients with cancer and 9.57% of people aged 65 and older were patients with cancer[3]. Korea National Health Insurance Service reported that socioeconomic cost of cancer was more than 12.1 billion US dollars in 2012, it is 43.2% of the socioeconomic costs of the five major causes of death[4].

Although many investigation and development of several anticancer drugs, the global market for cancer treatment is continuing to grow due to unmet need. Under this circumstance, many herbal medicines have received attention as new anticancer drugs.

SH003 is a mixed herbal extract containing Huang-Qi (*Astragalus membranaceus*), Dang-Gui (*Angelica gigas*), and Gua-Lou-Gen (*Trichosanthes Kirilowii Maximowicz*), which are based on the principle of traditional Korean medicine. Huang-Qi has been reported to be effective in cancer treatment in many previous studies[5]. Dang-Gui enhances chemosensitivity in ovarian cancer cells by inhibition of P-glycoprotein expression[6]. Gua-Lou-Gen also showed anti-tumor activity on cancer cell[7]. According to the theoretical frameworks of

Korean medicine, the effect of Huang-Qi is tonifying qi, Dang-Gui has the function of tonifying blood, and Gua-Lou-Gen has effects of disperse swelling and expel pus[8]. Therefore, the combination of those herbs is expected to be effective in the treatment of cancer patients. It has been reported that SH003 suppresses breast cancer growth and metastasis by inducing autophagy[9] and inhibiting STAT3-IL-6 signaling[10], represses tumor angiogenesis by inhibiting VEGF-induced VEGFR2 activation[11], and induces apoptotic cell death of prostate cancer cells by inhibiting ERK2-mediated signaling[12].

SH003 has never been used in human before, therefore, in the present study, we designed a phase I dose-escalation study to evaluate the maximum tolerated dose (MTD) of SH003 in patients with solid cancer.

Methods

Study design

A Phase I dose escalation study will be conducted at the Ajou University Hospital in Suwon, Republic of Korea. Any participants who fulfilling the eligibility criteria will be enrolled. The enrolled participants will be assigned to one of the three groups: 1,200 mg, 2,400 mg, and 4,800 mg of SH003 per day. Each participant will be examined for signs and symptoms of any adverse events during the study period. Figure 1 shows the schematic flow of the present study. Protocol amendments are not expected. However if it is essential, any change in the study protocol will be informed to the entire investigators in a conference. All modifications will be included in the final manuscript.

Recruitment

Subjects will be recruited as follows. Patients who visit the trial site and meet the criteria will be recommended to participate in the trial by the physician in charge of the study. Detailed information on the trial including study period, purpose of study, inclusion and exclusion criteria, and intervention will be provided by the investigators.

Participants

Inclusion criteria

Participants will be included when they meet the following criteria: 19 years and older; patients with histologically or cytologically confirmed solid cancer; metastatic or unresectable and for which standard curative measures do not exist or are no longer effective; ECOG Performance Status ≤ 2; life expectancy estimated to be at least 12 weeks; at least 4 weeks since prior chemotherapy or surgery, with recovery to haemoglobin ≥8g/dL, platelet ≥ 75,000/㎕, absolute neutrophil count ≥1,500/㎕; participants who can swallow tablet; ability to understand and willingness to sign a written informed consent document

Exclusion criteria

The exclusion criteria are as follows: known hypersensitivity to any study drug component, including *Astragalus membranaceus*, *Angelica gigas*, or *Trichosanthes Kirilowii Maximowicz*; patient with acute or chronic infections requiring treatment (active HAV, HBV, HCV, HIV, TB); eGFR < 60ml/min, AST, ALT, total bilirubin ≥ 2.5 times institutional upper limit of normal (ULN); patient with uncontrolled cardiovascular diseases (unstable angina, heart failure, myocardial infarction, hypertension that remains uncontrolled: 140/90 mm Hg or higher); patient with active cytomegalovirus infection within 4 weeks; patient who experienced major surgery on cerebrovascular disease such as acute coronary syndrome,

stroke, etc. within 1 year; pregnant or lactating females, women of childbearing potential; patient who do not agrees to use effective means of contraception and not to donate sperm during the trial and up to 1 month after final administration; patient who are taking anticoagulants or anticonvulsants; any psychological, sociological, or geographical condition that could potentially interfere with compliance with the study protocol; patient who participated other clinical trials of medicine or medical devices within 1 month.

Subject withdrawal criteria

The participants who meet the criteria as follows will be discontinued from the study: receive other treatment for anti-cancer purposes; participant's withdrawal of consent; occurrence of a serious adverse event related to investigational drug; occurrence of other significant protocol violations during the trial including detection of eligibility violations; investigator's decision to terminate the process for the sake of the participant's health. The participant who has been withdrawn regardless of the investigational product will be replaced by a new participant.

Sample size

The present study is a dose-escalation study that examine the MTD of SH003 for patient with solid cancer. Thus, dose escalation rules for the traditional 3 + 3 design will be adopted[13]. Three patients are initially enrolled into a starting dose cohort. If there is no dose-limiting toxicity (DLT) observed in any of these participants, the study proceeds to enroll additional participants into the next higher dose cohort. If one participant develops a DLT at a specific dose, an additional three participants are enrolled into that same dose cohort. Development of DLTs in more than 1 of 6 participants in a specific dose suggests that the MTD has been exceeded, and further dose escalation will be stopped. The present study plans to escalate the

dose of SH003 up to three times. Thus, at least 3 up to 18 participants will be recruited for the study. Three to six participants will be allocated to the each dose of SH003.

Allocation

The study participants who satisfy the eligibility criteria will be assigned to each cohort in sequence which they are recruited. After one cohort has been recruited, the participant enrolment will be suspended until the end of the study of the cohort to check whether DLT occurred in the cohort. The recruitment and dose of the following cohort will depend on the outcome of the previous cohort.

Treatment protocol

The participants will receive SH003 for three weeks. They will orally take 1 to 3 tablets with water three times a day after meals for 3 weeks according to their dose level. The daily doses were determined based on repeated dose toxicity test and in vivo efficacy study [10]. The participants will be required to return remains of investigational products for calculating the compliance. During the study, the participants will be prohibited to receive other treatment for cancer including chemotherapy and radiotherapy.

Interventions

Hanpoong Pharm and Foods Co., Ltd., the pharmaceutical company, produces the SH003 in accordance with Korea Good Manufacturing Practice (KGMP) standards. SH003 used in the present study is a pale yellow to brown and rectangular tablet. One tablet (total of 800 mg) including 400mg of solid extract from Astragalus membranaceus · Angelica gigas · Trichosanthes Kirilowii Maximowicz (1:1:1) 30% ethanol extract.

Primary outcome measurement

The primary outcome in the present study is the adverse events (AEs) with grade 3 or 4 throughout the study period measured by national cancer institute (NCI) common terminology criteria for adverse events (CTCAE) v4.03 [14]. CTCAE is a sort of list of AE commonly occurred in oncology. Each AE term has a grading scale which indicates the severity of AE. The AE will be measured by a trained investigator at every visit according to standard operating procedures (SOPs).

Secondary outcome measurement

Secondary outcome measurements include the AEs regardless of grade throughout the study period measured by NCI CTCAE v4.03 and change in tumour size on computed tomography (CT) imaging. The study schedule is detailed in Table 1.

Table 1 - Study schedule of SH003 Phase I study (4 weeks)

	STUDY PERIOD				
	Enrolment	Treatment Period			Close-out
TIMEPOINT	Day -7	Day 0	Day 8	Day 22	Day 29
Eligibility screen	X				
Informed consent	X				
Allocation		X			
SH003		←	—	→	
Demographic characteristic	X				
Physical examination	X	X	X	X	X
Vital signs	X	X	X	X	X
Laboratory test	X		X	X	X
Electrocardiography	X			X	
Pregnancy test	X				
Medical/drug use history	X				
Smoking and drinking history	X				
Computed tomography	X				X
Compliance calculation			X	X	
Concomitant medication	X	X	X	X	X
Adverse event			X	X	X

Safety outcomes

All variables related to the safety of participant including vital signs, physical examination, hematologic test, biochemical test, urine test and adverse events will be documented on the case report form (CRF) at every visit. If the adverse event is severe and associated with the investigational product, the participant will be withdrawn from the study, and then the appropriate therapy will be given to him or her. Any loss caused by the present study will be reimbursed by insurance.

Outcomes analysis

Determination of maximum tolerated dose

MTD will be defined as that dose level at which more than 1 out of 6 patients exhibit dose limiting toxicity during the 4 weeks of trial period. In the present study, the highest dose among three dose groups of 1200 mg, 2400 mg and 4800 mg per day with less than one patient with dose limiting toxicity will be determined as the MTD of SH003.

All analyses of data from the present study will be descriptive as the study has no inferential analysis and general hypothesis test. The continuous variables will be displayed as the mean and range, and the categorical variables will be displayed as the numbers. After completion of each cohort's study period, an analysis will be conducted to determine the subsequent dose level.

Data and safety monitoring

To maintain the quality of the present study, monitoring will be conducted by the contract research organization (CRO). The institution participating in the present study will be monitored while this trial is in progress using SOPs. For data quality improvement, double data entry and range checks for data values will be done. Suspected unexpected serious

adverse reactions will be reported to institutional review board (IRB) and regulatory authorities in Republic of Korea within 24 hours.

Ethics and dissemination

The present study has been approved by the IRB of the Ajou University Hospital (reference AJIRB-MED-CT1-16-311). The current protocol version is 1.1. A written informed consent will be obtained from each participant prior to commencement of the trial procedure by the investigator. Informed consent for the research use of human biological material will be also obtained for collection, storage and use of blood samples from participants. The trial will be performed in compliance with the Helsinki Declaration and according to Good Clinical Practice as described by the Korea Food and Drug Administration.

The confidentiality of personal information of patients will be protected. Each participant will be given a study identification number at the study enrolment. During the trial period, data will be dealt by the study identification number. During and after the study, all the records will be kept secure in a locked cabinets or password protected computer files. Only participating investigators will have the authority to access to the data. The results of this study will be disseminated through academic journal or scientific conference.

Discussion

The present study investigates the tolerability and safety of SH003 in patient with solid cancer. Globally, 8.2 million deaths from cancer in 2012, and cancer is also the leading cause of mortality in Korea.[15 16] Thus, development of anti-cancer drugs is also active in Korea. Among total 628 cases of investigational new drug (IND) approval in 2016, the number of

anti-cancer drugs was the highest as 202 cases.[17] Nevertheless there is little IND approval for new herbal medicine as anti-cancer drug. In this situation, SH003 received IND approval from MFDS to begin phase I trial as anti-cancer drug.

In addition to the effect of tumour size reduction, SH003 has shown several potential as an anti-cancer agent in preclinical studies. Combination of SH003 and paclitaxel enhanced apoptotic cell death of paclitaxel-resistant breast cancer cells by inhibition of multidrug resistance protein 1 (MDR1) expression.[18] Decursin in Dang-Gui, one of the constituent herbs of SH003, inhibited doxorubicin-resistant ovarian cancer cell proliferation and induced apoptosis.[6] Combination of SH003 and doxorubicin showed synergistic effect in triple negative breast cancer (TNBC) treatment.[19] Therefore, those studies suggest that SH003 could be used for an anti-MDR tumour agent and combination therapy with conventional chemotherapy drugs. SH003 showed efficacy in various cancers including breast cancer, ovarian cancer and prostate cancer. Thus, further clinical studies are necessary to evaluate the effectiveness for various cancers.

The present study has its own significance. First, it is the first Phase I dose-escalation study to determine MTD for new herbal medicine in Korea. There were several studies that investigated anti-cancer effect of herbal medicine. Most of them were preclinical studies or clinical trials to evaluate effectiveness of established herbal medicine in cancer patients.[20-23] Second, the present study will investigate the effect of SH003 on the changes in tumour size for planning further studies to evaluate efficacy.

Limitations of the present study are that the number of dose level is relatively small and the study does not include pharmacokinetics and pharmacodynamics research. Due to the nature of the formulation, the dose exceeding 4 tablets is inconvenient and may reduce the patient compliance, so the upper limit of dose level was determined as 4,800 mg per day, the third dose level. The effective dose estimated from preclinical studies was also considered.[10] Since

most herbal medicine, including SH003 is composed of complex compounds, thus PK and PD study is not easy[24]. Based on *in vivo* PK studies currently being performed, further human studies should be conducted.

Although the present study also has a few limitations, this study would serve as a first-in-human trials to plan therapeutic exploratory trials of SH003 on patient with cancer. To the best of our knowledge, this is the first Phase I study on herbal medicine in Korea. We expect that the present study could contribute to promoting the development of new herbal medicine.

Authors' affiliations

[1] Department of Korean Preventive Medicine, Graduate School, Kyung Hee University, 26, Kyungheedae-ro, Dongdaemun-gu, Seoul, Republic of Korea

[2] Department of Cardiovascular and Neurologic disease (Stroke center), College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

Acknowledgements

We wish to acknowledge Hanpoong Pharm. & Foods Co. Ltd. for providing investigational product support.

Contributors

CC, SK and YK have written the first manuscript for this trial and they will contribute to monitoring this trial. MK, BHJ and YCS have edited the first manuscript. SGK has conducted all the procedures for this protocol. All authors have read and approved the final manuscript.

Funding

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number : HI11C2110). The management, analysis and reporting of study will be conducted independently by the study investigators.

Competing interests

None declared.

Patients consent

Obtained

Ethics approval

The Institutional Review Board of the Ajou University Hospital approved the study (reference AJIRB-MED-CT1-16-311).

Provenance and peer review

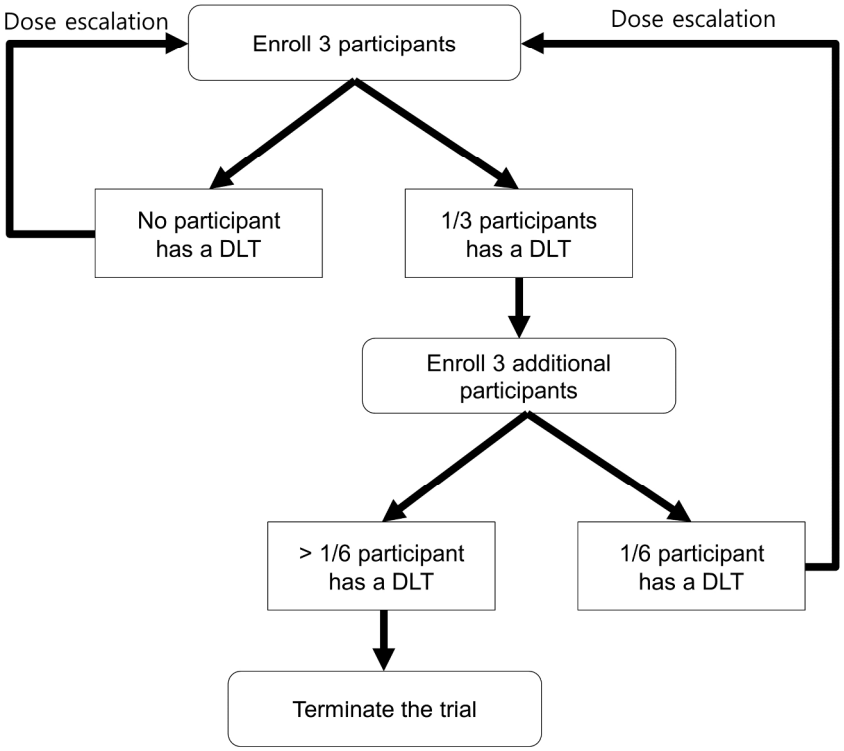
Not commissioned; externally peer reviewed.

References

1. World Health Organization. Cancer, fact sheet. Updated February 2017 ed: World Health Organization, 2017.
2. World Health Organization. World cancer report 2014: Lyon: International Agency for Research on Cancer, 2014.
3. National Cancer Center. National Cancer Information Center 2017 [Available from: http://www.cancer.go.krJuly 2017.

4. Hyun KR, Lee SM. Analysis of Socioeconomic Costs of Five Major Diseases. *Health insurance & policy* 2014;13(2):91-107.
5. Auyeung KK, Han QB, Ko JK. Astragalus membranaceus: A Review of its Protection Against Inflammation and Gastrointestinal Cancers. *Am J Chin Med* 2016;44(1):1-22. doi: 10.1142/s0192415x16500014 [published Online First: 2016/02/27]
6. Choi HS, Cho SG, Kim MK, et al. Decursin in Angelica gigas Nakai (AGN) Enhances Doxorubicin Chemosensitivity in NCI/ADR-RES Ovarian Cancer Cells via Inhibition of P-glycoprotein Expression. *Phytother Res* 2016;30(12):2020-26. doi: 10.1002/ptr.5708 [published Online First: 2016/09/09]
7. Li J, Li H, Zhang Z, et al. The anti-cancerous activity of recombinant trichosanthin on prostate cancer cell PC3. *Biol Res* 2016;49:21.
8. National College of Korean Medicine Publication Committee on Joint Textbook. Herbology. Seoul, Korea: Younglimsa 2016.
9. Choi YK, Cho SG, Choi YJ, et al. SH003 suppresses breast cancer growth by accumulating p62 in autolysosomes. *Oncotarget* 2016 doi: 10.18632/oncotarget.11393 [published Online First: 2016/08/25]
10. Choi YK, Cho SG, Woo SM, et al. Herbal extract SH003 suppresses tumor growth and metastasis of MDA-MB-231 breast cancer cells by inhibiting STAT3-IL-6 signaling. *Mediators Inflamm* 2014;2014:492173.
11. Choi HS, Kim MK, Lee K, et al. SH003 represses tumor angiogenesis by blocking VEGF binding to VEGFR2. *Oncotarget* 2016;7(22):32969-79.
12. Choi YJ, Choi YK, Lee KM, et al. SH003 induces apoptosis of DU145 prostate cancer cells by inhibiting ERK-involved pathway. *BMC Complement Altern Med* 2016;16(1):507.
13. Storer BE. An evaluation of phase I clinical trial designs in the continuous dose-response setting. *Stat Med* 2001;20(16):2399-408. [published Online First: 2001/08/21]
14. U.S.Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) v4.03: National Institutes of Health National Cancer Institute, 2010.
15. International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidnece, Mortality and Prevalence Worldwide in 2012: World Health Organization; 2012 [Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx accessed 2015.07.04 2015.
16. National Cancer Center. Cancer Facts & Figures 2014. In: Welfare MoH, ed.: Ministry of Health & Welfare, 2014.
17. Ministry of Food and Drug Safety. MFDS, Results of the Investigational New Drug approval status 2016. In: MFDS, ed. Osong, Korea: Ministry of Food and Drug Safety, 2017.
18. Choi HS, Cho SG, Kim MK, et al. SH003 enhances paclitaxel chemosensitivity in MCF-7/PAX breast cancer cells through inhibition of MDR1 activity. *Mol Cell Biochem* 2017;426(1-2):1-8. doi: 10.1007/s11010-016-2875-y [published Online First: 2016/11/18]
19. Woo SM, Kim AJ, Choi YK, et al. Synergistic Effect of SH003 and Doxorubicin in Triple-negative Breast Cancer. *Phytother Res* 2016;30(11):1817-23. doi: 10.1002/ptr.5687 [published Online First: 2016/11/05]
20. Kim HY, Kim J, Ha Thi HT, et al. Evaluation of anti-tumorigenic activity of BP3B against colon cancer with patient-derived tumor xenograft model. *BMC Complement Altern Med* 2016;16(1):473.

21. Choi BY, Joo JC, Lee YK, et al. Anti-cancer effect of Scutellaria baicalensis in combination with cisplatin in human ovarian cancer cell. *BMC Complement Altern Med* 2017;17(1):277.
22. Lee SI, Bae JA, Ko YS, et al. Geijigajakyak decoction inhibits the motility and tumorigenesis of colorectal cancer cells. *BMC Complement Altern Med* 2016;16(1):288.
23. Jeong JS, Ryu BH, Kim JS, et al. Bojungikki-tang for cancer-related fatigue: a pilot randomized clinical trial. *Integr Cancer Ther* 2010;9(4):331-8. doi: 10.1177/1534735410383170 [published Online First: 2010/11/10]
24. Liu WJH. Traditional Herbal Medicine Research Methods: Identification, Analysis, Bioassay, and Pharmaceutical and Clinical Studies: Wiley 2011.



Study flow chart. SH003

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	___Appendix__
Protocol version	3	Date and version identifier	_____11____
Funding	4	Sources and types of financial, material, and other support	_____13_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____13_____
	5b	Name and contact information for the trial sponsor	_____13_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____13_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____NA_____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	4

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A single-arm, open-label, dose-escalation Phase I study to evaluate the safety of an herbal medicine SH003 in patients with solid cancer: a study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019502.R1
Article Type:	Protocol
Date Submitted by the Author:	31-Jan-2018
Complete List of Authors:	Cheon, Chunhoo; Kyung Hee University, Department of Korean Preventive Medicine Kang, Sohyeon; Kyung Hee University, Department of Korean Preventive Medicine Ko, Youme; Kyung Hee University, Department of Korean Preventive Medicine Kim, Mia; Kyung Hee University, Department of Cardiovascular and Neurologic disease (Stroke center) Jang, Bo-Hyoung; Kyung Hee University, Department of Korean Preventive Medicine Shin, Yong-Cheol; Kyung Hee University, Department of Korean Preventive Medicine Ko, Seong-Gyu; Kyung Hee University, Department of Korean Preventive Medicine
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Oncology
Keywords:	Herbal medicine < THERAPEUTICS, ONCOLOGY, COMPLEMENTARY MEDICINE

A single-arm, open-label, dose-escalation Phase I study to evaluate the safety of an herbal medicine SH003 in patients with solid cancer: a study protocol

Chunhoo Cheon[1], Sohyeon Kang[1], Youme Ko[1], Mia Kim[2], Bo-Hyoung Jang[1], Yong-Cheol Shin[1] and Seong-Gyu Ko[1§]

[1] Department of Korean Preventive Medicine, Graduate School, Kyung Hee University, Seoul, Republic of Korea

[2] Department of Cardiovascular and Neurologic disease (Stroke center), College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

[§]Corresponding author

Email addresses:

CC: hreedom35@gmail.com

SK: kangsohyeon@gmail.com

YMK: ymymko84@gmail.com

BHJ: bhjang@khu.ac.kr

YCS: syc99@khu.ac.kr

SGK: epiko@khu.ac.kr

Correspondence to

Professor Seong-Gyu Ko; epiko@khu.ac.kr, 26, Kyungheedae-ro, Dongdaemun-gu, Seoul, 02447, Korea Tel. +82-2-961-9278

Word count: 2,732

Abstract

Introduction

Cancer is a major health problem worldwide and the leading cause of death in many countries. The number of patients with cancer and socioeconomic costs of cancer continues to increase. SH003 is a novel herbal medicine consisting of *Astragalus membranaceus*, *Angelica gigas*, and *Trichosanthes Kirilowii Maximowicz*. Preclinical studies have shown that SH003 has therapeutic anticancer effects. The aim of this study is to determine the maximum tolerated dose of SH003 in patients with solid cancers.

Methods and analysis

This study is an open-label, dose-escalation trial evaluating the safety and tolerability of SH003. The traditional 3+3 dose-escalation design will be implemented. Patients with solid cancers will be recruited. According to dose level, the patients will receive 1 to 3 tablets of SH003 3 times-a-day for 3 weeks. Toxicity will be evaluated using common terminology criteria for adverse events (CTCAE). Dose-limiting toxicities are defined as Grade 3 or higher adverse events based on CTCAE. The maximum tolerated dose will be determined by the highest dose at which no more than 1 of 6 patients experiences dose-limiting toxicity.

Ethics and dissemination

This study has been approved by the institutional review board of the Ajou University Hospital (reference AJIRB-MED-CT1-16-311). The results of this study will be disseminated through a scientific journal and a conference.

Trial registrations

ClinicalTrials.gov NCT03081819

Strengths and limitations of this study

- This is the first human study to examine the safety and feasibility of administering SH003 to treat patients with solid cancers.
- The present study is the first Phase I study to determine the maximum tolerated dose of an herbal medicine in Korea.
- Limitations of this study are that pharmacokinetic and pharmacodynamic studies could not be conducted due to the nature of the drug.

INTRODUCTION

Cancer, which is caused by an uncontrolled division of abnormal cells in a part of the body, is a leading cause of death globally, accounting for 8.8 million deaths in 2015.[1] Moreover, the economic cost of cancer is increasing. In 2010, the total economic cost of cancer was calculated at approximately 1.16 trillion US dollars.[2] In Korea, there were 1.46 million patients with cancer, and 9.57% of people aged 65 and older were patients with cancer.[3] The Korea National Health Insurance Service reported that the socioeconomic cost of cancer was more than 12.1 billion US dollars in 2012, which accounted for 43.2% of the socioeconomic costs of the five major causes of death.[4]

Although many investigations and development of several anticancer drugs have been conducted, the global market for cancer treatment is continuing to grow due to unmet needs. Therefore, many herbal medicines have received attention as potential new anticancer drugs. SH003 is a mixed herbal extract containing Huang-Qi (*Astragalus membranaceus*), Dang-Gui (*Angelica gigas*), and Gua-Lou-Gen (*Trichosanthes Kirilowii Maximowicz*), which are traditionally used in Korean medicine. Huang-Qi has been reported to be effective in cancer treatment in many previous studies.[5] Dang-Gui enhances chemosensitivity in ovarian cancer cells by inhibition of P-glycoprotein expression.[6] Gua-Lou-Gen has shown anti-tumour activity in cancer cells.[7] According to the theoretical framework of Korean medicine, Huang-

Qi has the effect of tonifying qi, Dang-Gui has the function of tonifying blood, and Gua-Lou-Gen has the effects of disperse swelling and expel pus.[8] Therefore, the combination of those herbs is expected to be effective in the treatment of cancer patients.

It has been reported that SH003 suppresses breast cancer growth and metastasis by inducing autophagy[9] and inhibiting STAT3-IL-6 signaling.[10] Moreover, it represses tumour angiogenesis by inhibiting VEGF-induced VEGFR2 activation,[11] and induces apoptosis of prostate cancer cells by inhibiting ERK2-mediated signalling.[12] *In vivo* xenograft studies have reported that SH003 inhibits tumour growth and metastasis,[10] as well as VEGF-induced tumour angiogenesis[11] without detectable toxicity, and SH003 in combination with doxorubicin has shown a synergistic effect in treating triple-negative breast cancer (TNBC).[13] Moreover, no toxicity was detected in the efficacy studies. In one toxicity test, hypertrophy of the liver was observed; however, it was deemed to be a reversible change with no toxicological significance.[9] However, an herbology textbook has mentioned that components of SH003 should be used with caution in patients with diarrhoea.[8]

SH003 has never been tested in humans before; therefore, we have designed a Phase I dose-escalation study to evaluate the maximum tolerated dose (MTD) of SH003 in patients with solid cancers.

METHODS

Study design

A Phase I dose-escalation study will be conducted at the Ajou University Hospital in Suwon, Republic of Korea. Any participants fulfilling the eligibility criteria will be enrolled. The enrolled participants will be assigned to one of three groups receiving 1200 mg, 2400 mg, and 4800 mg doses of SH003 per day. These doses represent the measurement of active ingredients found in a half of one tablet. The dose escalation will follow the modified

Fibonacci sequence. The dose will be increased twice by 100% of the preceding dose. Each participant will be examined for signs and symptoms of any adverse events (AEs) during the study period. Figure 1 shows the schematic flow of the present study. Protocol amendments are not expected; however if they are essential, any changes in the study protocol will be provided to the all investigators via a conference. All modifications will be included in the final manuscript. The present study was begun in March 2017 and is currently in progress.

Recruitment

Subjects will be recruited as follows. Patients who visit the trial site and meet the inclusion criteria will be recommended to participate in the trial by the physician in charge of the study. Detailed information on the trial, including the study period, purpose of the study, inclusion and exclusion criteria, and interventions, will be provided by the investigators.

Participants

Inclusion criteria

Participants meeting the following criteria will be included: those 19 years-of-age and older; patients with histologically or cytologically confirmed solid cancers; metastatic or unresectable cancers for which standard curative measures do not exist or are no longer effective; those with ECOG Performance Status ≤ 2; life expectancy estimated to be at least 12 weeks; those who have not received chemotherapy or surgery within the last 4 weeks; those with recovery to haemoglobin ≥8 g/dL, platelets ≥ 75,000/μL, and absolute neutrophil count ≥1,500/μL ; those patients with the ability to swallow tablets, as well as those with the ability to understand the study and who are willing to sign a written informed consent document.

Exclusion criteria

Patients with the following will be excluded: those with known hypersensitivity to any study drug component, including *Astragalus membranaceus*, *Angelica gigas*, and *Trichosanthes Kirilowii Maximowicz*; patients with acute or chronic infections requiring treatment (active hepatitis A, B, and C viruses, human immunodeficiency virus, tuberculosis); estimated glomerular filtration rate (eGFR) < 60ml/min, aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥ 2.5 times the institutional upper limit of normal (ULN); patients with uncontrolled cardiovascular diseases (unstable angina, heart failure, myocardial infarction, hypertension that remains uncontrolled: 140/90 mm Hg or higher); patients with active cytomegalovirus infection within the past 4 weeks; patients who have experienced major surgery on cerebrovascular disease such as acute coronary syndrome, stroke, etc., within the past year; pregnant or lactating females and women with childbearing potential; patients who do not agree to either use effective means of contraception or not to donate sperm during the trial and up to 1 month after final administration; patients who are taking anticoagulants or anticonvulsants; those with any psychological, sociological, or geographical conditions that could potentially interfere with their compliance to the study protocol, and, finally, patients who have participated in other clinical trials of medicine or medical devices within the past month.

Subject withdrawal criteria

The participants who meet the following criteria will be discontinued from the study: those who receive other treatments for anti-cancer purposes; participants who withdraw their consent; those who experience serious AEs related to the investigational drug; those with significant protocol violations during the trial, including detection of eligibility violations;

those patients who the investigator decides to terminate for their health. The participant who has been withdrawn regardless of the investigational product will be replaced by a new participant.

Sample size

The present study is a dose-escalation study that examines the MTD of SH003 for patients with solid cancers. The, dose-escalation rules for the traditional 3 + 3 design will be adopted.[14] Three patients will be initially enrolled into a starting dose cohort. If there is no dose-limiting toxicity (DLT) observed in any of these participants, the study will proceed to enrol additional participants into the next higher dose cohort. If one participant develops a DLT at a specific dose, an additional three participants will be enrolled into the same dose cohort. Development of DLTs in more than 1 of 6 participants at a specific dose will suggest that the MTD has been exceeded, and further dose escalation will be stopped. The present study plans to escalate the dose of SH003 up to three times. Thus, at least 3, and up to 18 participants, will be recruited for the study. Three to six participants will be allocated to each dose of SH003.

Allocation

The study participants who satisfy the eligibility criteria will be assigned to each cohort in the order they are recruited. After one cohort has been recruited, the participant enrolment will be suspended until the end of the study for that cohort to determine whether DLT has occurred. The recruitment and dose of the following cohort will depend on the outcome of the previous one.

Treatment protocol

The participants will receive SH003 for three weeks. They will orally take 1 to 3 tablets with water three times a day after meals for 3 weeks according to their dose level. It should be noted that no abnormal findings related to the investigational product were observed in either the single-dose toxicity study or the repeated-dose toxicity study. Therefore, the no observed adverse effect level (NOAEL) of the investigational product was determined to be 2500 mg/kg for rats. According to the FDA guideline, the maximum recommended starting dose for adults is 2400 mg per day based on a safety factor of 10.[15] Based on the toxicity and efficacy study results, the starting dose was determined to be 1200 mg per day for this study.[10] The participants will be required to return unused investigational products for calculating their compliance. During the study, the participants will be prohibited from receiving other treatments for cancer, including chemotherapy and radiotherapy.

Interventions

The pharmaceutical company Hanpoong Pharm and Foods Co. Ltd. (Jeonju, Republic of Korea), produces the SH003 in accordance with Korea Good Manufacturing Practice (KGMP) standards. The SH003 used in the present study is a pale yellow-to-brown rectangular tablet. One tablet (total of 800 mg) includes 400mg of solid extracts from *Astragalus membranaceus* · *Angelica gigas* · *Trichosanthes Kirilowii Maximowicz* (1:1:1) 30% ethanol extract.

Primary outcome measurement

The primary outcome in the present study will be determined by the number of 3 or 4 AEs throughout the study period as measured by the National Cancer Institute (NCI; Bethesda, MD USA) common terminology criteria for adverse events (CTCAE) v4.03.[16] CTCAE is a collection of AEs that commonly occur in oncology. Each AE listed has a grading scale

indicating its severity. The AEs for this study will be measured by a trained investigator at every patient visit, in accordance with standard operating procedures (SOPs). The expected dose-limiting toxicities include diarrhoea, increases in ALT, and/or AST, febrile neutropenia, and a decreased platelet count.

Secondary outcome measurement

Secondary outcome measurements include the AEs, regardless of grade, throughout the study period as measured by the NCI CTCAE v4.03 as well as changes in tumour size as assessed by computed tomography (CT) imaging. The study schedule is detailed in Table 1.

Table 1 - Study schedule of SH003 Phase I study (4 weeks)

	STUDY PERIOD				
	Enrolment	Treatment Period			Close-out
TIMEPOINT	Day -7	Day 0	Day 8	Day 22	Day 29
Eligibility screen	X				
Informed consent	X				
Allocation		X			
SH003		←	—	→	
Demographic characteristic	X				
Physical examination	X	X	X	X	X
Vital signs	X	X	X	X	X
Laboratory test	X		X	X	X
Electrocardiography	X			X	
Pregnancy test	X				
Medical/drug use history	X				
Smoking and drinking history	X				
Computed tomography	X				X
Compliance calculation			X	X	
Concomitant medication	X	X	X	X	X
Adverse event			X	X	X

Safety outcomes

All variables related to the safety of participants, including vital signs, physical examination, hematologic, biochemical, and urine tests, and AEs will be documented on the case report form (CRF) at every visit. If an AE is severe and associated with the investigational product, the participant will be withdrawn from the study and appropriate therapy will be provided to them. Any loss caused by the present study will be reimbursed by insurance.

Outcomes analysis

Determination of maximum tolerated dose

MTD will be defined as the dose just below the lowest dose level at which more than 1 out of 6 patients exhibit DLT during the 4 weeks of the trial period. In the present study, the highest dose among the three dose groups (1200 mg, 2400 mg or 4800 mg per day) with one patient or less experiencing DLT will be determined as the MTD of SH003.

All analyses of data from the present study will be descriptive, as the study includes no inferential analysis and general hypothesis testing. The continuous variables will be displayed as the median and range, and the categorical variables will be displayed as the absolute and relative frequencies. After completion of each cohort's study period, an analysis will be conducted to determine the subsequent dose level.

Data and safety monitoring

To maintain the quality of the present study, monitoring will be conducted by the Contract Research Organization (CRO). The institution participating in the present study will be monitored while this trial is in progress through use of SOPs. For data quality improvement, double data entry and range checks for data values will be performed. Suspected and

unexpected serious adverse reactions will be reported to the institutional review board (IRB) and regulatory authorities in the Republic of Korea within 24 hours.

Ethics and dissemination

The present study has been approved by the IRB of the Ajou University Hospital (reference AJIRB-MED-CT1-16-311). The current protocol version is 1.1. Written informed consent will be obtained from each participant prior to commencement of the trial procedure by the investigator. Informed consent for the research use of human biological material will also be obtained for collection, storage, and use of blood samples from participants. The trial will be performed in compliance with the Helsinki Declaration and according to Good Clinical Practice as described by the Korea Food and Drug Administration.

Confidentiality of patients' personal information will be protected. Each participant will be given a study identification number upon enrolment. During the trial period, data will be dealt with by using study identification numbers. During and after the study, all records will be kept in secure locked cabinets or in password-protected computer files. Only participating investigators will have the authority to access the data. The results of this study will be disseminated through an academic journal publication or a scientific conference.

DISCUSSION

The present study will investigate the tolerability and safety of administering SH003 to treat patients with solid cancers. Globally, there were 8.2 million reported deaths from cancer in 2012, and cancer is also the leading cause of mortality in Korea.[17 18] Thus, development of anti-cancer drugs is active in Korea. Among a total of 628 cases of investigational new drug

(IND) approvals in 2016, the number of anti-cancer drugs was the highest, at 202 cases.[19] Nevertheless, there have been few IND approvals for new herbal medicines as anti-cancer drugs. In this situation, SH003 received IND approval from the Korean Ministry of Food and Drug Safety (MFDS) to begin a Phase I trial testing it as anti-cancer drug.

In addition to the effect of tumour size-reduction, SH003 has shown much potential as an anti-cancer agent in preclinical studies. The combination of SH003 and paclitaxel has been shown to enhance apoptotic cell death in paclitaxel-resistant breast cancer cells by inhibition of multidrug resistance protein 1 (MDR1) expression.[20] Decursin in Dang-Gui, one of the constituent herbs of SH003, has been shown to inhibit doxorubicin-resistant ovarian cancer cell proliferation and induce apoptosis.[6] The combination of SH003 and doxorubicin has shown synergistic effects in TNBC treatment.[13] Those studies suggest that SH003 could be used as an anti-MDR tumour agent and in combination with conventional chemotherapy drugs. SH003 has shown efficacy in treating various cancers, including breast, ovarian, and prostate cancers. Thus, further clinical studies are necessary to evaluate its effectiveness in treating various cancers.

The present study is particularly significant. First, it is the only Phase I dose-escalation study conducted to date to determine the MTD for a new herbal medicine in Korea. While there have been several studies that investigated the anti-cancer effect of herbal medicine, most of these were preclinical studies or clinical trials to evaluate the effectiveness of established herbal medicine in treating cancer patients.[21-24] Second, the present study will investigate the effect of SH003 on changes in tumour size for planning further studies to evaluate its efficacy. Limitations of the present study are that the number of dose levels is relatively small and the study does not include pharmacokinetics (PK) and pharmacodynamics (PD) research. Due to the nature of the formulation, a dose exceeding 4 tablets would be inconvenient and may reduce patient compliance, thus the upper limit of dose level was determined as 4800 mg per

day, the third dose level in this study. The effective dose estimated from preclinical studies was also considered.[10] Most herbal medicines, including SH003, are composed of complex compounds, and thus, PK and PD studies are not easy.[25] Therefore, it is difficult to collect PK evidence on dose and frequency of administration of herbal medicines. Based on *in vivo* PK studies on SH003 currently being performed, further human studies will need to be conducted. Although the present study has a few limitations, it serves as the first in-human trial to explore the use of SH003 to treat patients with cancer. Moreover, to the best of our knowledge, this is the first Phase I study of an herbal medicine in Korea. We, therefore, expect that the present study could promote the overall development of new herbal medicines to treat cancer and other devastating diseases.

Authors' affiliations

[1] Department of Korean Preventive Medicine, Graduate School, Kyung Hee University, 26, Kyungheedae-ro, Dongdaemun-gu, Seoul, Republic of Korea

[2] Department of Cardiovascular and Neurologic disease (Stroke center), College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

Acknowledgements

We wish to acknowledge Hanpoong Phar. & Foods Co. Ltd. for providing investigational product support.

Contributors

CC, SK and YK have written the first manuscript for this trial and they will contribute to monitoring this trial. MK, BHJ and YCS have edited the first manuscript. SGK has conducted all the procedures for this protocol. All authors have read and approved the final manuscript.

Funding

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number : HI11C2110). The management, analysis and reporting of study will be conducted independently by the study investigators.

Competing interests

None declared.

Patients consent

Obtained

Ethics approval

The Institutional Review Board of the Ajou University Hospital approved the study (reference AJIRB-MED-CT1-16-311).

Provenance and peer review

Not commissioned; externally peer reviewed.

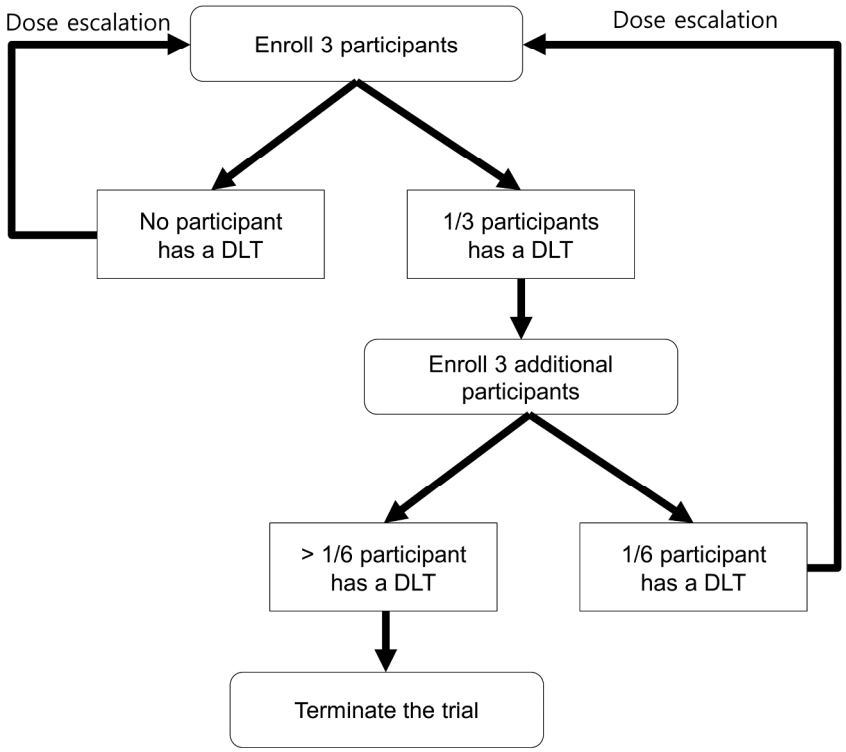
References

1. World Health Organization. Cancer, fact sheet. Updated February 2017. World Health Organization, 2017.
2. World Health Organization. World cancer report 2014. Lyon: International Agency for Research on Cancer, 2014.
3. National Cancer Center. National Cancer Information Center 2017. http://www.cancer.go.kr (accessed July 2017)
4. Hyun KR, Lee SM. Analysis of Socioeconomic Costs of Five Major Diseases. *Health insurance & policy* 2014;13(2):91-107.
5. Auyeung KK, Han QB, Ko JK. Astragalus membranaceus: A Review of its Protection Against Inflammation and Gastrointestinal Cancers. *Am J Chin Med* 2016;44(1):1-22.
6. Choi HS, Cho SG, Kim MK, et al. Decursin in Angelica gigas Nakai (AGN) Enhances Doxorubicin Chemosensitivity in NCI/ADR-RES Ovarian Cancer Cells via Inhibition of P-glycoprotein Expression. *Phytother Res* 2016;30(12):2020-26.
7. Li J, Li H, Zhang Z, et al. The anti-cancerous activity of recombinant trichosanthin on prostate cancer cell PC3. *Biol Res* 2016;49:21.
8. National College of Korean Medicine Publication Committee on Joint Textbook. Herbology. Seoul, Korea: Younglimsa 2016.
9. Choi YK, Cho SG, Choi YJ, et al. SH003 suppresses breast cancer growth by accumulating p62 in autolysosomes. *Oncotarget* 2016;8(51):88386-88400.
10. Choi YK, Cho SG, Woo SM, et al. Herbal extract SH003 suppresses tumor growth and metastasis of MDA-MB-231 breast cancer cells by inhibiting STAT3-IL-6 signaling. *Mediators Inflamm* 2014;2014:492173.
11. Choi HS, Kim MK, Lee K, et al. SH003 represses tumor angiogenesis by blocking VEGF binding to VEGFR2. *Oncotarget* 2016;7(22):32969-79.
12. Choi YJ, Choi YK, Lee KM, et al. SH003 induces apoptosis of DU145 prostate cancer cells by inhibiting ERK-involved pathway. *BMC Complement Altern Med* 2016;16(1):507.
13. Woo SM, Kim AJ, Choi YK, et al. Synergistic Effect of SH003 and Doxorubicin in Triple-negative Breast Cancer. *Phytother Res* 2016;30(11):1817-23.
14. Storer BE. An evaluation of phase I clinical trial designs in the continuous dose-response setting. *Stat Med* 2001;20(16):2399-408.
15. U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. Rockville, MD. USA: Food and Drug Administration, 2005.
16. U.S.Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) v4.03: National Institutes of Health National Cancer Institute, 2010.
17. International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidnece, Mortality and Prevalence Worldwide in 2012. World Health Organization, 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
18. National Cancer Center. Cancer Facts & Figures 2014. Ministry of Health & Welfare, 2014.
19. Ministry of Food and Drug Safety. MFDS, Results of the Investigational New Drug approval status 2016. Ministry of Food and Drug Safety, 2017.

20. Choi HS, Cho SG, Kim MK, et al. SH003 enhances paclitaxel chemosensitivity in MCF-7/PAX breast cancer cells through inhibition of MDR1 activity. *Mol Cell Biochem* 2017;426(1-2):1-8.
21. Kim HY, Kim J, Ha Thi HT, et al. Evaluation of anti-tumorigenic activity of BP3B against colon cancer with patient-derived tumor xenograft model. *BMC Complement Altern Med* 2016;16(1):473.
22. Choi BY, Joo JC, Lee YK, et al. Anti-cancer effect of Scutellaria baicalensis in combination with cisplatin in human ovarian cancer cell. *BMC Complement Altern Med* 2017;17(1):277.
23. Lee SI, Bae JA, Ko YS, et al. Geijigajakyak decoction inhibits the motility and tumorigenesis of colorectal cancer cells. *BMC Complement Altern Med* 2016;16(1):288.
24. Jeong JS, Ryu BH, Kim JS, et al. Bojungikki-tang for cancer-related fatigue: a pilot randomized clinical trial. *Integr Cancer Ther* 2010;9(4):331-8.
25. Liu WJH. Traditional Herbal Medicine Research Methods: Identification, Analysis, Bioassay, and Pharmaceutical and Clinical Studies: Wiley 2011.

List of Figure

Figure 1. Study flow chart



Study flow chart. SH003

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Appendix
Protocol version	3	Date and version identifier	11
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	4

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A single-arm, open-label, dose-escalation Phase I study to evaluate the safety of an herbal medicine SH003 in patients with solid cancer: a study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019502.R2
Article Type:	Protocol
Date Submitted by the Author:	28-Feb-2018
Complete List of Authors:	Cheon, Chunhoo; Kyung Hee University, Department of Korean Preventive Medicine Kang, Sohyeon; Kyung Hee University, Department of Korean Preventive Medicine Ko, Youme; Kyung Hee University, Department of Korean Preventive Medicine Kim, Mia; Kyung Hee University, Department of Cardiovascular and Neurologic disease (Stroke center) Jang, Bo-Hyoung; Kyung Hee University, Department of Korean Preventive Medicine Shin, Yong-Cheol; Kyung Hee University, Department of Korean Preventive Medicine Ko, Seong-Gyu; Kyung Hee University, Department of Korean Preventive Medicine
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Oncology
Keywords:	Herbal medicine < THERAPEUTICS, ONCOLOGY, COMPLEMENTARY MEDICINE, Clinical trials < THERAPEUTICS

A single-arm, open-label, dose-escalation Phase I study to evaluate the safety of an herbal medicine SH003 in patients with solid cancer: a study protocol

Chunhoo Cheon[1], Sohyeon Kang[1], Youme Ko[1], Mia Kim[2], Bo-Hyoung Jang[1], Yong-Cheol Shin[1] and Seong-Gyu Ko[1§]

[1] Department of Korean Preventive Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

[2] Department of Cardiovascular and Neurologic disease (Stroke center), College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

[§]Corresponding author

Email addresses:

CC: hreedom35@gmail.com

SK: kangsohyeon@gmail.com

YMK: ymymko84@gmail.com

BHJ: bhjang@khu.ac.kr

YCS: syc99@khu.ac.kr

SGK: epiko@khu.ac.kr

Correspondence to

Professor Seong-Gyu Ko; epiko@khu.ac.kr, 26, Kyungheedae-ro, Dongdaemun-gu, Seoul, 02447, Korea Tel. +82-2-961-9278

Word count: 2,845

Abstract

Introduction

Cancer is a major health problem worldwide and the leading cause of death in many countries. The number of patients with cancer and socioeconomic costs of cancer continues to increase. SH003 is a novel herbal medicine consisting of *Astragalus membranaceus*, *Angelica gigas*, and *Trichosanthes Kirilowii Maximowicz*. Preclinical studies have shown that SH003 has therapeutic anticancer effects. The aim of this study is to determine the maximum tolerated dose of SH003 in patients with solid cancers.

Methods and analysis

This study is an open-label, dose-escalation trial evaluating the safety and tolerability of SH003. The traditional 3+3 dose-escalation design will be implemented. Patients with solid cancers will be recruited. According to dose level, the patients will receive 1 to 3 tablets of SH003, 3 times-a-day for 3 weeks. Toxicity will be evaluated using common terminology criteria for adverse events (CTCAE). Dose-limiting toxicities are defined as Grade 3 or higher adverse events based on CTCAE. The maximum tolerated dose will be determined by the highest dose at which no more than 1 of 6 patients experiences dose-limiting toxicity.

Ethics and dissemination

This study has been approved by the institutional review board of the Ajou University Hospital (reference AJIRB-MED-CT1-16-311). The results of this study will be disseminated through a scientific journal and a conference.

Trial registrations

ClinicalTrials.gov NCT03081819

Strengths and limitations of this study

- This is the first human study to examine the safety and feasibility of administering SH003 to treat patients with solid cancers.
- The present study is the first Phase I study to determine the maximum tolerated dose of an herbal medicine in Korea.
- Limitations of this study are that pharmacokinetic and pharmacodynamic studies could not be conducted due to the nature of the drug.

INTRODUCTION

Cancer, which is caused by an uncontrolled division of abnormal cells in a part of the body, is a leading cause of death globally, accounting for 8.8 million deaths in 2015.[1] Moreover, the economic cost of cancer is increasing. In 2010, the total economic cost of cancer was calculated at approximately 1.16 trillion US dollars.[2] In Korea, there were 1.46 million patients with cancer, and 9.57% of people aged 65 and older were patients with cancer.[3] The Korea National Health Insurance Service reported that the socioeconomic cost of cancer was more than 12.1 billion US dollars in 2012, which accounted for 43.2% of the socioeconomic costs of the five major causes of death.[4]

Although many investigations and development of several anticancer drugs have been conducted, the global market for cancer treatment is continuing to grow due to unmet needs. Therefore, many herbal medicines have received attention as potential new anticancer drugs. SH003 is a mixed herbal extract containing Huang-Qi (*Astragalus membranaceus*), Dang-Gui (*Angelica gigas*), and Gua-Lou-Gen (*Trichosanthes Kirilowii Maximowicz*), which are traditionally used in Korean medicine. Huang-Qi has been reported to be effective in cancer treatment in many previous studies.[5] Dang-Gui enhances chemosensitivity in ovarian cancer cells by inhibition of P-glycoprotein expression.[6] Gua-Lou-Gen has shown anti-tumour activity in cancer cells.[7] According to the theoretical framework of Korean medicine, Huang-

Qi has the effect of tonifying qi, Dang-Gui has the function of tonifying blood, and Gua-Lou-Gen has the effects of disperse swelling and expel pus.[8] Therefore, the combination of those herbs is expected to be effective in the treatment of cancer patients.

It has been reported that SH003 suppresses breast cancer growth and metastasis by inducing autophagy[9] and inhibiting STAT3-IL-6 signaling.[10] SH003 inhibits cell proliferation and induces apoptosis without an effect on normal cell viability.[10] Moreover, it represses tumour angiogenesis by inhibiting VEGF-induced VEGFR2 activation.[11] VEGF-induced phosphorylation of VEGFR2 is blocked by SH003 interrupting VEGF binding to VEGFR2. SH003 induces apoptosis of prostate cancer cells in a dose-dependent manner. [12] This is due to the intracellular mechanisms that SH003 inhibits ERK2-mediated signalling. *In vivo* xenograft studies have reported that SH003 inhibits tumour growth and metastasis,[10] as well as VEGF-induced tumour angiogenesis[11] without detectable toxicity, and SH003 in combination with doxorubicin has shown a synergistic effect in treating triple-negative breast cancer (TNBC).[13] The combinational treatment induces apoptotic cell death and suppresses tumour growth. Moreover, no toxicity was detected in the efficacy studies. In one toxicity test, hypertrophy of the liver was observed; however, it was deemed to be a reversible change with no toxicological significance.[9] However, an herbology textbook has mentioned that components of SH003 should be used with caution in patients with diarrhoea.[8]

SH003 has never been tested in humans before; therefore, we have designed a Phase I dose-escalation study to evaluate the maximum tolerated dose (MTD) of SH003 in patients with solid cancers.

METHODS

Study design

A Phase I dose-escalation study will be conducted at the Ajou University Hospital in Suwon, Republic of Korea. Any participants fulfilling the eligibility criteria will be enrolled. The enrolled participants will be assigned to one of three groups receiving 1200 mg, 2400 mg, and 4800 mg doses of SH003 per day. These doses represent the measurement of active ingredients found in a half of one tablet. The dose escalation will follow the modified Fibonacci sequence. The dose will be increased twice by 100% of the preceding dose. Each participant will be examined for signs and symptoms of any adverse events (AEs) during the study period. Figure 1 shows the schematic flow of the present study. Protocol amendments are not expected; however if they are essential, any changes in the study protocol will be provided to the all investigators via a conference. All modifications will be included in the final manuscript. The present study was begun in March 2017 and is currently in progress.

Recruitment

Subjects will be recruited as follows. Patients who visit the trial site and meet the inclusion criteria will be recommended to participate in the trial by the physician in charge of the study. Detailed information on the trial, including the study period, purpose of the study, inclusion and exclusion criteria, and interventions, will be provided by the investigators.

Participants

Inclusion criteria

Participants meeting the following criteria will be included: those 19 years-of-age and older; patients with histologically or cytologically confirmed solid cancers; metastatic or unresectable cancers for which standard curative measures do not exist or are no longer effective; those with ECOG Performance Status ≤ 2; life expectancy estimated to be at least 12 weeks; those who have not received chemotherapy or surgery within the last 4 weeks;

those with recovery to haemoglobin ≥8 g/dL, platelets ≥ 75,000/μL, and absolute neutrophil count ≥1,500/μL ; those patients with the ability to swallow tablets, as well as those with the ability to understand the study and who are willing to sign a written informed consent document.

Exclusion criteria

Patients with the following will be excluded: those with known hypersensitivity to any study drug component, including *Astragalus membranaceus*, *Angelica gigas*, and *Trichosanthes Kirilowii Maximowicz*; patients with acute or chronic infections requiring treatment (active hepatitis A, B, and C viruses, human immunodeficiency virus, tuberculosis); estimated glomerular filtration rate (eGFR) < 60ml/min, aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥ 2.5 times the institutional upper limit of normal (ULN); patients with uncontrolled cardiovascular diseases (unstable angina, heart failure, myocardial infarction, hypertension that remains uncontrolled: 140/90 mm Hg or higher); patients with active cytomegalovirus infection within the past 4 weeks; patients who have experienced major surgery on cerebrovascular disease such as acute coronary syndrome, stroke, etc., within the past year; pregnant or lactating females and women with childbearing potential; patients who do not agree to either use effective means of contraception or not to donate sperm during the trial and up to 1 month after final administration; patients who are taking anticoagulants or anticonvulsants; those with any psychological, sociological, or geographical conditions that could potentially interfere with their compliance to the study protocol, and, finally, patients who have participated in other clinical trials of medicine or medical devices within the past month.

Subject withdrawal criteria

The participants who meet the following criteria will be discontinued from the study: those who receive other treatments for anti-cancer purposes; participants who withdraw their consent; those who experience serious AEs related to the investigational drug; those with significant protocol violations during the trial, including detection of eligibility violations; those patients who the investigator decides to terminate for their health. The participant who has been withdrawn regardless of the investigational product will be replaced by a new participant.

Sample size

The present study is a dose-escalation study that examines the MTD of SH003 for patients with solid cancers. The, dose-escalation rules for the traditional 3 + 3 design will be adopted.[14] Three patients will be initially enrolled into a starting dose cohort. If there is no dose-limiting toxicity (DLT) observed in any of these participants, the study will proceed to enrol additional participants into the next higher dose cohort. If one participant develops a DLT at a specific dose, an additional three participants will be enrolled into the same dose cohort. Development of DLTs in more than 1 of 6 participants at a specific dose will suggest that the MTD has been exceeded, and further dose escalation will be stopped. The present study plans to escalate the dose of SH003 up to three times. Thus, at least 3, and up to 18 participants, will be recruited for the study. Three to six participants will be allocated to each dose of SH003.

Allocation

The study participants who satisfy the eligibility criteria will be assigned to each cohort in the order they are recruited. After one cohort has been recruited, the participant enrolment will be

suspended until the end of the study for that cohort to determine whether DLT has occurred. The recruitment and dose of the following cohort will depend on the outcome of the previous one.

Treatment protocol

The participants will receive SH003 for three weeks. They will orally take 1 to 3 tablets with water three times a day after meals for 3 weeks according to their dose level. It should be noted that no abnormal findings related to the investigational product were observed in either the single-dose toxicity study or the repeated-dose toxicity study. Therefore, the no observed adverse effect level (NOAEL) of the investigational product was determined to be 2500 mg/kg for rats. According to the FDA guideline, the maximum recommended starting dose for adults is 2400 mg per day based on a safety factor of 10.[15] Based on the toxicity and efficacy study results, the starting dose was determined to be 1200 mg per day for this study.[10] The participants will be required to return unused investigational products for calculating their compliance. During the study, the participants will be prohibited from receiving other treatments for cancer, including chemotherapy and radiotherapy.

Interventions

The pharmaceutical company Hanpoong Pharm and Foods Co. Ltd. (Jeonju, Republic of Korea), produces the SH003 in accordance with Korea Good Manufacturing Practice (KGMP) standards. The SH003 used in the present study is a pale yellow-to-brown rectangular tablet. One tablet (total of 800 mg) includes 400mg of solid extracts from *Astragalus membranaceus · Angelica gigas · Trichosanthes Kirilowii Maximowicz* (1:1:1) 30% ethanol extract.

Primary outcome measurement

The primary outcome in the present study will be determined by the number of 3 or 4 AEs throughout the study period as measured by the National Cancer Institute (NCI; Bethesda, MD USA) common terminology criteria for adverse events (CTCAE) v4.03.[16] CTCAE is a collection of AEs that commonly occur in oncology. Each AE listed has a grading scale indicating its severity. The AEs for this study will be measured by a trained investigator at every patient visit, in accordance with standard operating procedures (SOPs). The expected dose-limiting toxicities include diarrhoea, increases in ALT, and/or AST, febrile neutropenia, and a decreased platelet count.

Secondary outcome measurement

Secondary outcome measurements include the AEs, regardless of grade, throughout the study period as measured by the NCI CTCAE v4.03 as well as changes in tumour size as assessed by computed tomography (CT) imaging. The study schedule is detailed in Table 1.

Table 1 - Study schedule of SH003 Phase I study (4 weeks)

	STUDY PERIOD				
	Enrolment	Treatment Period			Close-out
TIMEPOINT	Day -7	Day 0	Day 8	Day 22	Day 29
Eligibility screen	X				
Informed consent	X				
Allocation		X			
SH003		←	—	→	
Demographic characteristic	X				
Physical examination	X	X	X	X	X
Vital signs	X	X	X	X	X
Laboratory test	X		X	X	X
Electrocardiography	X			X	
Pregnancy test	X				
Medical/drug use history	X				
Smoking and drinking history	X				
Computed tomography	X				X
Compliance calculation			X	X	
Concomitant medication	X	X	X	X	X
Adverse event			X	X	X

Safety outcomes

All variables related to the safety of participants, including vital signs, physical examination, hematologic, biochemical, and urine tests, and AEs will be documented on the case report form (CRF) at every visit. If an AE is severe and associated with the investigational product, the participant will be withdrawn from the study and appropriate therapy will be provided to them. Any loss caused by the present study will be reimbursed by insurance.

Outcomes analysis

Determination of maximum tolerated dose

MTD will be defined as the dose just below the lowest dose level at which more than 1 out of 6 patients exhibit DLT during the 4 weeks of the trial period. In the present study, the highest dose among the three dose groups (1200 mg, 2400 mg or 4800 mg per day) with one patient or less experiencing DLT will be determined as the MTD of SH003.

All analyses of data from the present study will be descriptive, as the study includes no inferential analysis and general hypothesis testing. The continuous variables will be displayed as the median and range, and the categorical variables will be displayed as the absolute and relative frequencies. After completion of each cohort's study period, an analysis will be conducted to determine the subsequent dose level.

Data and safety monitoring

To maintain the quality of the present study, monitoring will be conducted by the Contract Research Organization (CRO). The institution participating in the present study will be monitored while this trial is in progress through use of SOPs. For data quality improvement, double data entry and range checks for data values will be performed. Suspected and

unexpected serious adverse reactions will be reported to the institutional review board (IRB) and regulatory authorities in the Republic of Korea within 24 hours.

Ethics and dissemination

The present study has been approved by the IRB of the Ajou University Hospital (reference AJIRB-MED-CT1-16-311). The current protocol version is 1.1. Written informed consent will be obtained from each participant prior to commencement of the trial procedure by the investigator. Informed consent for the research use of human biological material will also be obtained for collection, storage, and use of blood samples from participants. The trial will be performed in compliance with the Helsinki Declaration and according to Good Clinical Practice as described by the Korean Ministry of Food and DrugSafety (MFDS). Confidentiality of patients' personal information will be protected. Each participant will be given a study identification number upon enrolment. During the trial period, data will be dealt with by using study identification numbers. During and after the study, all records will be kept in secure locked cabinets or in password-protected computer files. Only participating investigators will have the authority to access the data. The results of this study will be disseminated through an academic journal publication or a scientific conference.

Patient and public involvement

Patients or public were not involved to design the present study, and will not involve in the recruitment to and conduct of the study. So far, there is no established plan for announcement the results of the study to study participants.

DISCUSSION

The present study will investigate the tolerability and safety of administering SH003 to treat patients with solid cancers. Globally, there were 8.2 million reported deaths from cancer in 2012, and cancer is also the leading cause of mortality in Korea.[17 18] Thus, development of anti-cancer drugs is active in Korea. Among a total of 628 cases of investigational new drug (IND) approvals in 2016, the number of anti-cancer drugs was the highest, at 202 cases.[19] Nevertheless, there have been few IND approvals for new herbal medicines as anti-cancer drugs. In this situation, SH003 received IND approval from the Korean MFDS to begin a Phase I trial testing it as anti-cancer drug.

In addition to the effect of tumour size-reduction, SH003 has shown much potential as an anti-cancer agent in preclinical studies. The combination of SH003 and paclitaxel has been shown to enhance apoptotic cell death in paclitaxel-resistant breast cancer cells by inhibition of multidrug resistance protein 1 (MDR1) expression.[20] Decursin in Dang-Gui, one of the constituent herbs of SH003, has been shown to inhibit doxorubicin-resistant ovarian cancer cell proliferation and induce apoptosis.[6] The combination of SH003 and doxorubicin has shown synergistic effects in TNBC treatment.[13] Those studies suggest that SH003 could be used as an anti-MDR tumour agent and in combination with conventional chemotherapy drugs. SH003 has shown efficacy in treating various cancers, including breast, ovarian, and prostate cancers. Thus, further clinical studies are necessary to evaluate its effectiveness in treating various cancers. The pharmacological action of SH003 has not yet been fully elucidated. Thus, preclinical studies for SH003 will also continue to be conducted and the results will be published.

The present study is particularly significant. First, it is the only Phase I dose-escalation study conducted to date to determine the MTD for a new herbal medicine in Korea. While there have been several studies that investigated the anti-cancer effect of herbal medicine, most of

these were preclinical studies or clinical trials to evaluate the effectiveness of established herbal medicine in treating cancer patients.[21-24] Second, the present study will investigate the effect of SH003 on changes in tumour size for planning further studies to evaluate its efficacy. Changes in tumour size, that is objective response, are not a common outcome measurement for phase I study, but have been included in the present study, expecting that the results would provide helpful information to plan further studies.

Limitations of the present study are that the number of dose levels is relatively small and the study does not include pharmacokinetics (PK) and pharmacodynamics (PD) research. Due to the nature of the formulation, a dose exceeding 4 tablets would be inconvenient and may reduce patient compliance, thus the upper limit of dose level was determined as 4800 mg per day, the third dose level in this study. The effective dose estimated from preclinical studies was also considered.[10] Most herbal medicines, including SH003, are composed of complex compounds, and thus, PK and PD studies are not easy.[25] Therefore, it is difficult to collect PK evidence on dose and frequency of administration of herbal medicines. Based on *in vivo* PK studies on SH003 currently being performed, further human studies will need to be conducted. Although the present study has a few limitations, it serves as the first in-human trial to explore the use of SH003 to treat patients with cancer. Moreover, to the best of our knowledge, this is the first Phase I study of an herbal medicine in Korea. We, therefore, expect that the present study could promote the overall development of new herbal medicines to treat cancer and other devastating diseases.

Authors' affiliations

[1] Department of Korean Preventive Medicine, College of Korean Medicine, Kyung Hee University, 26, Kyungheedae-ro, Dongdaemun-gu, Seoul, Republic of Korea

[2] Department of Cardiovascular and Neurologic disease (Stroke center), College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

Acknowledgements

We wish to acknowledge Hanpoong Phar. & Foods Co. Ltd. for providing investigational product support.

Contributors

CC, SK and YK have written the first manuscript for this trial and they will contribute to monitoring this trial. MK, BHJ and YCS have edited the first manuscript. SGK has conducted all the procedures for this protocol. All authors have read and approved the final manuscript.

Funding

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number : HI11C2110). The management, analysis and reporting of study will be conducted independently by the study investigators.

Competing interests

None declared.

Patients consent

Obtained

Ethics approval

The Institutional Review Board of the Ajou University Hospital approved the study

(reference AJIRB-MED-CT1-16-311).

Provenance and peer review

Not commissioned; externally peer reviewed.

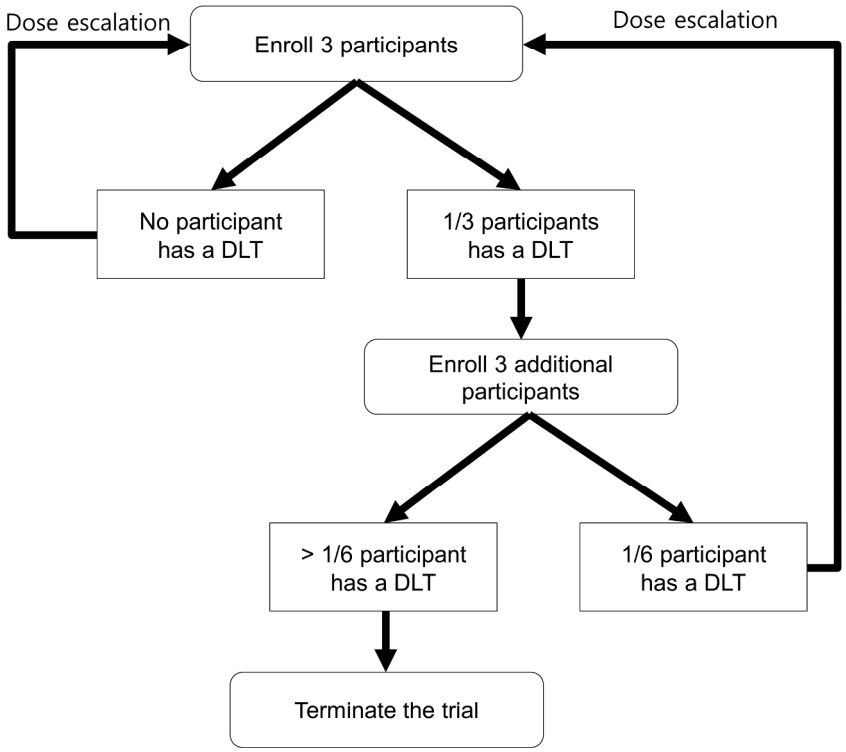
References

1. World Health Organization. Cancer, fact sheet. Updated February 2017. World Health Organization, 2017.
2. World Health Organization. World cancer report 2014. Lyon: International Agency for Research on Cancer, 2014.
3. National Cancer Center. National Cancer Information Center 2017. http://www.cancer.go.kr (accessed July 2017)
4. Hyun KR, Lee SM. Analysis of Socioeconomic Costs of Five Major Diseases. *Health insurance & policy* 2014;13(2):91-107.
5. Auyeung KK, Han QB, Ko JK. Astragalus membranaceus: A Review of its Protection Against Inflammation and Gastrointestinal Cancers. *Am J Chin Med* 2016;44(1):1-22.
6. Choi HS, Cho SG, Kim MK, et al. Decursin in Angelica gigas Nakai (AGN) Enhances Doxorubicin Chemosensitivity in NCI/ADR-RES Ovarian Cancer Cells via Inhibition of P-glycoprotein Expression. *Phytother Res* 2016;30(12):2020-26.
7. Li J, Li H, Zhang Z, et al. The anti-cancerous activity of recombinant trichosanthin on prostate cancer cell PC3. *Biol Res* 2016;49:21.
8. National College of Korean Medicine Publication Committee on Joint Textbook. Herbology. Seoul, Korea: Younglimsa 2016.
9. Choi YK, Cho SG, Choi YJ, et al. SH003 suppresses breast cancer growth by accumulating p62 in autolysosomes. *Oncotarget* 2016;8(51):88386-88400.
10. Choi YK, Cho SG, Woo SM, et al. Herbal extract SH003 suppresses tumor growth and metastasis of MDA-MB-231 breast cancer cells by inhibiting STAT3-IL-6 signaling. *Mediators Inflamm* 2014;2014:492173.
11. Choi HS, Kim MK, Lee K, et al. SH003 represses tumor angiogenesis by blocking VEGF binding to VEGFR2. *Oncotarget* 2016;7(22):32969-79.

12. Choi YJ, Choi YK, Lee KM, et al. SH003 induces apoptosis of DU145 prostate cancer cells by inhibiting ERK-involved pathway. *BMC Complement Altern Med* 2016;16(1):507.
13. Woo SM, Kim AJ, Choi YK, et al. Synergistic Effect of SH003 and Doxorubicin in Triple-negative Breast Cancer. *Phytother Res* 2016;30(11):1817-23.
14. Storer BE. An evaluation of phase I clinical trial designs in the continuous dose-response setting. *Stat Med* 2001;20(16):2399-408.
15. U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. Rockville, MD. USA: Food and Drug Administration, 2005.
16. U.S.Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) v4.03: National Institutes of Health National Cancer Institute, 2010.
17. International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidnece, Mortality and Prevalence Worldwide in 2012. World Health Organization, 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
18. National Cancer Center. Cancer Facts & Figures 2014. Ministry of Health & Welfare, 2014.
19. Ministry of Food and Drug Safety. MFDS, Results of the Investigational New Drug approval status 2016. Ministry of Food and Drug Safety, 2017.
20. Choi HS, Cho SG, Kim MK, et al. SH003 enhances paclitaxel chemosensitivity in MCF-7/PAX breast cancer cells through inhibition of MDR1 activity. *Mol Cell Biochem* 2017;426(1-2):1-8.
21. Kim HY, Kim J, Ha Thi HT, et al. Evaluation of anti-tumorigenic activity of BP3B against colon cancer with patient-derived tumor xenograft model. *BMC Complement Altern Med* 2016;16(1):473.
22. Choi BY, Joo JC, Lee YK, et al. Anti-cancer effect of Scutellaria baicalensis in combination with cisplatin in human ovarian cancer cell. *BMC Complement Altern Med* 2017;17(1):277.
23. Lee SI, Bae JA, Ko YS, et al. Geijigajakyak decoction inhibits the motility and tumorigenesis of colorectal cancer cells. *BMC Complement Altern Med* 2016;16(1):288.
24. Jeong JS, Ryu BH, Kim JS, et al. Bojungikki-tang for cancer-related fatigue: a pilot randomized clinical trial. *Integr Cancer Ther* 2010;9(4):331-8.
25. Liu WJH. Traditional Herbal Medicine Research Methods: Identification, Analysis, Bioassay, and Pharmaceutical and Clinical Studies: Wiley 2011.

List of Figure

Figure 1. Study flow chart



Study flow chart. SH003

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Appendix
Protocol version	3	Date and version identifier	11
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	4

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A single-arm, open-label, dose-escalation Phase I study to evaluate the safety of an herbal medicine SH003 in patients with solid cancer: a study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019502.R3
Article Type:	Protocol
Date Submitted by the Author:	24-May-2018
Complete List of Authors:	Cheon, Chunhoo; Kyung Hee University, Department of Korean Preventive Medicine Kang, Sohyeon; Kyung Hee University, Department of Korean Preventive Medicine Ko, Youme; Kyung Hee University, Department of Korean Preventive Medicine Kim, Mia; Kyung Hee University, Department of Cardiovascular and Neurologic disease (Stroke center) Jang, Bo-Hyoung; Kyung Hee University, Department of Korean Preventive Medicine Shin, Yong-Cheol; Kyung Hee University, Department of Korean Preventive Medicine Ko, Seong-Gyu; Kyung Hee University, Department of Korean Preventive Medicine
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Oncology
Keywords:	Herbal medicine < THERAPEUTICS, ONCOLOGY, COMPLEMENTARY MEDICINE, Clinical trials < THERAPEUTICS

A single-arm, open-label, dose-escalation Phase I study to evaluate the safety of an herbal medicine SH003 in patients with solid cancer: a study protocol

Chunhoo Cheon[1], Sohyeon Kang[1], Youme Ko[1], Mia Kim[2], Bo-Hyoung Jang[1], Yong-Cheol Shin[1] and Seong-Gyu Ko[1§]

[1] Department of Korean Preventive Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

[2] Department of Cardiovascular and Neurologic disease (Stroke center), College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

[§]Corresponding author

Email addresses:

CC: hreedom35@gmail.com

SK: kangsohyeon@gmail.com

YMK: ymymko84@gmail.com

BHJ: bhjang@khu.ac.kr

YCS: syc99@khu.ac.kr

SGK: epiko@khu.ac.kr

Correspondence to

Professor Seong-Gyu Ko; epiko@khu.ac.kr, 26, Kyungheedae-ro, Dongdaemun-gu, Seoul, 02447, Korea Tel. +82-2-961-9278

Word count: 3,064

Abstract

Introduction

Cancer is a major health problem worldwide and the leading cause of death in many countries. The number of patients with cancer and socioeconomic costs of cancer continues to increase. SH003 is a novel herbal medicine consisting of *Astragalus membranaceus*, *Angelica gigas*, and *Trichosanthes Kirilowii Maximowicz*. Preclinical studies have shown that SH003 has therapeutic anticancer effects. The aim of this study is to determine the maximum tolerated dose of SH003 in patients with solid cancers.

Methods and analysis

This study is an open-label, dose-escalation trial evaluating the safety and tolerability of SH003. The traditional 3+3 dose-escalation design will be implemented. Patients with solid cancers will be recruited. According to dose level, the patients will receive 1 to 4 tablets of SH003, 3 times-a-day for 3 weeks. Toxicity will be evaluated using common terminology criteria for adverse events (CTCAE). Dose-limiting toxicities are defined as Grade 3 or higher adverse events based on CTCAE. The maximum tolerated dose will be determined by the highest dose at which no more than 1 of 6 patients experiences dose-limiting toxicity.

Ethics and dissemination

This study has been approved by the institutional review board of the Ajou University Hospital (reference AJIRB-MED-CT1-16-311). The results of this study will be disseminated through a scientific journal and a conference.

Trial registrations

ClinicalTrials.gov NCT03081819

Strengths and limitations of this study

- This is the first human study to examine the safety and feasibility of administering SH003 to treat patients with solid cancers.
- The present study is the first Phase I study to determine the maximum tolerated dose of an herbal medicine in Korea.
- Limitations of this study are that pharmacokinetic and pharmacodynamic studies could not be conducted due to the nature of the drug.

INTRODUCTION

Cancer, which is caused by an uncontrolled division of abnormal cells in a part of the body, is a leading cause of death globally, accounting for 8.8 million deaths in 2015.[1] Moreover, the economic cost of cancer is increasing. In 2010, the total economic cost of cancer was calculated at approximately 1.16 trillion US dollars.[2] In Korea, there were 1.46 million patients with cancer, and 9.57% of people aged 65 and older were patients with cancer.[3] The Korea National Health Insurance Service reported that the socioeconomic cost of cancer was more than 12.1 billion US dollars in 2012, which accounted for 43.2% of the socioeconomic costs of the five major causes of death.[4]

Although many investigations and development of several anticancer drugs have been conducted, the global market for cancer treatment is continuing to grow due to unmet needs. Therefore, many herbal medicines have received attention as potential new anticancer drugs. SH003 is a mixed herbal extract containing Huang-Qi (*Astragalus membranaceus*), Dang-Gui (*Angelica gigas*), and Gua-Lou-Gen (*Trichosanthes Kirilowii Maximowicz*), which are traditionally used in Korean medicine. Huang-Qi has been reported to be effective in cancer treatment in many previous studies.[5] Dang-Gui enhances chemosensitivity in ovarian cancer cells by inhibition of P-glycoprotein expression.[6] Gua-Lou-Gen has shown anti-tumour activity in cancer cells.[7] According to the theoretical framework of Korean medicine, Huang-

Qi has the effect of tonifying qi, Dang-Gui has the function of tonifying blood, and Gua-Lou-Gen has the effects of disperse swelling and expel pus.[8] Therefore, the combination of those herbs is expected to be effective in the treatment of cancer patients.

It has been reported that SH003 suppresses breast cancer growth and metastasis by inducing autophagy[9] and inhibiting STAT3-IL-6 signaling.[10] SH003 inhibits cell proliferation and induces apoptosis without an effect on normal cell viability.[10] Moreover, it represses tumour angiogenesis by inhibiting VEGF-induced VEGFR2 activation.[11] VEGF-induced phosphorylation of VEGFR2 is blocked by SH003 interrupting VEGF binding to VEGFR2. SH003 induces apoptosis of prostate cancer cells in a dose-dependent manner. [12] This is due to the intracellular mechanisms that SH003 inhibits ERK2-mediated signalling. *In vivo* xenograft studies have reported that SH003 inhibits tumour growth and metastasis,[10] as well as VEGF-induced tumour angiogenesis[11] without detectable toxicity, and SH003 in combination with doxorubicin has shown a synergistic effect in treating triple-negative breast cancer (TNBC).[13] The combinational treatment induces apoptotic cell death and suppresses tumour growth. Moreover, no toxicity was detected in the efficacy studies. In one toxicity test, hypertrophy of the liver was observed; however, it was deemed to be a reversible change with no toxicological significance.[9] However, an herbology textbook has mentioned that components of SH003 should be used with caution in patients with diarrhoea.[8]

SH003 has never been tested in humans before; therefore, we have designed a Phase I dose-escalation study to evaluate the maximum tolerated dose (MTD) of SH003 in patients with solid cancers.

METHODS

Study design

A Phase I dose-escalation study will be conducted at the Ajou University Hospital in Suwon, Republic of Korea. Any participants fulfilling the eligibility criteria will be enrolled. The enrolled participants will be assigned to one of three groups receiving 1200 mg, 2400 mg, and 4800 mg doses of SH003 per day. These doses represent the measurement of active ingredients found in a half of one tablet. The dose escalation will follow the modified Fibonacci sequence. The dose will be increased twice by 100% of the preceding dose. Each participant will be examined for signs and symptoms of any adverse events (AEs) during the study period. Figure 1 shows the schematic flow of the present study. Protocol amendments are not expected; however if they are essential, any changes in the study protocol will be provided to the all investigators via a conference. All modifications will be included in the final manuscript. The present study was begun in March 2017 and is currently in progress.

Recruitment

Subjects will be recruited as follows. Patients who visit the trial site and meet the inclusion criteria will be recommended to participate in the trial by the physician in charge of the study. Detailed information on the trial, including the study period, purpose of the study, inclusion and exclusion criteria, and interventions, will be provided by the investigators.

Participants

Inclusion criteria

Participants meeting the following criteria will be included: those 19 years-of-age and older; patients with histologically or cytologically confirmed solid cancers; metastatic or unresectable cancers for which standard curative measures do not exist or are no longer effective; those with ECOG Performance Status ≤ 2; life expectancy estimated to be at least 12 weeks; those who have not received chemotherapy or surgery within the last 4 weeks;

those with recovery to haemoglobin ≥8 g/dL, platelets ≥ 75,000/μL, and absolute neutrophil count ≥1,500/μL ; those patients with the ability to swallow tablets, as well as those with the ability to understand the study and who are willing to sign a written informed consent document.

Exclusion criteria

Patients with the following will be excluded: those with known hypersensitivity to any study drug component, including *Astragalus membranaceus*, *Angelica gigas*, and *Trichosanthes Kirilowii Maximowicz*; patients with acute or chronic infections requiring treatment (active hepatitis A, B, and C viruses, human immunodeficiency virus, tuberculosis); estimated glomerular filtration rate (eGFR) < 60ml/min, aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥ 2.5 times the institutional upper limit of normal (ULN); patients with uncontrolled cardiovascular diseases (unstable angina, heart failure, myocardial infarction, hypertension that remains uncontrolled: 140/90 mm Hg or higher); patients with active cytomegalovirus infection within the past 4 weeks; patients who have experienced major surgery on cerebrovascular disease such as acute coronary syndrome, stroke, etc., within the past year; pregnant or lactating females and women with childbearing potential; patients who do not agree to either use effective means of contraception or not to donate sperm during the trial and up to 1 month after final administration; patients who are taking anticoagulants or anticonvulsants; those with any psychological, sociological, or geographical conditions that could potentially interfere with their compliance to the study protocol, and, finally, patients who have participated in other clinical trials of medicine or medical devices within the past month.

Subject withdrawal criteria

The participants who meet the following criteria will be discontinued from the study: those who receive other treatments for anti-cancer purposes; participants who withdraw their consent; those who experience serious AEs related to the investigational drug; those with significant protocol violations during the trial, including detection of eligibility violations; those patients who the investigator decides to terminate for their health. The participant who has been withdrawn regardless of the investigational product will be replaced by a new participant.

Sample size

The present study is a dose-escalation study that examines the MTD of SH003 for patients with solid cancers. The, dose-escalation rules for the traditional 3 + 3 design will be adopted.[14] Three patients will be initially enrolled into a starting dose cohort. If there is no dose-limiting toxicity (DLT) observed in any of these participants, the study will proceed to enrol additional participants into the next higher dose cohort. If one participant develops a DLT at a specific dose, an additional three participants will be enrolled into the same dose cohort. Development of DLTs in more than 1 of 6 participants at a specific dose will suggest that the MTD has been exceeded, and further dose escalation will be stopped. The present study plans to escalate the dose of SH003 up to three times. Thus, at least 3, and up to 18 participants, will be recruited for the study. Three to six participants will be allocated to each dose of SH003.

Allocation

The study participants who satisfy the eligibility criteria will be assigned to each cohort in the order they are recruited. After one cohort has been recruited, the participant enrolment will be

suspended until the end of the study for that cohort to determine whether DLT has occurred. The recruitment and dose of the following cohort will depend on the outcome of the previous one.

Treatment protocol

The participants will receive SH003 for three weeks. They will orally take 1 to 4 tablets with water three times a day after meals for 3 weeks according to their dose level. It should be noted that no abnormal findings related to the investigational product were observed in either the single-dose toxicity study or the repeated-dose toxicity study. Therefore, the no observed adverse effect level (NOAEL) of the investigational product was determined to be 2500 mg/kg for rats. According to the FDA guideline, the maximum recommended starting dose for adults is 2400 mg per day based on a safety factor of 10.[15] Based on the toxicity and efficacy study results, the starting dose was determined to be 1200 mg per day for this study.[10] The participants will be required to return unused investigational products for calculating their compliance. During the study, the participants will be prohibited from receiving other treatments for cancer, including chemotherapy and radiotherapy.

Interventions

The pharmaceutical company Hanpoong Pharm and Foods Co. Ltd. (Jeonju, Republic of Korea), produces the SH003 in accordance with Korea Good Manufacturing Practice (KGMP) standards. The SH003 used in the present study is a pale yellow-to-brown rectangular tablet. One tablet (total of 800 mg) includes 400mg of solid extracts from *Astragalus membranaceus · Angelica gigas · Trichosanthes Kirilowii Maximowicz* (1:1:1) 30% ethanol extract.

Primary outcome measurement

The primary outcome in the present study will be determined by the number of 3 or 4 AEs throughout the study period as measured by the National Cancer Institute (NCI; Bethesda, MD USA) common terminology criteria for adverse events (CTCAE) v4.03.[16] CTCAE is a collection of AEs that commonly occur in oncology. Each AE listed has a grading scale indicating its severity. The AEs for this study will be measured by a trained investigator at every patient visit, in accordance with standard operating procedures (SOPs). The expected dose-limiting toxicities include diarrhoea, increases in ALT, and/or AST, febrile neutropenia, and a decreased platelet count.

Secondary outcome measurement

Secondary outcome measurements include the AEs, regardless of grade, throughout the study period as measured by the NCI CTCAE v4.03 as well as changes in tumour size as assessed by computed tomography (CT) imaging. The study schedule is detailed in Table 1.

Table 1 - Study schedule of SH003 Phase I study (4 weeks)

	STUDY PERIOD				
	Enrolment	Treatment Period			Close-out
TIMEPOINT	Day -7	Day 0	Day 8	Day 22	Day 29
Eligibility screen	X				
Informed consent	X				
Allocation		X			
SH003		←	—	→	
Demographic characteristic	X				
Physical examination	X	X	X	X	X
Vital signs	X	X	X	X	X
Laboratory test	X		X	X	X
Electrocardiography	X			X	
Pregnancy test	X				
Medical/drug use history	X				
Smoking and drinking history	X				
Computed tomography	X				X
Compliance calculation			X	X	
Concomitant medication	X	X	X	X	X
Adverse event			X	X	X

Safety outcomes

All variables related to the safety of participants, including vital signs, physical examination, hematologic, biochemical, and urine tests, and AEs will be documented on the case report form (CRF) at every visit. If an AE is severe and associated with the investigational product, the participant will be withdrawn from the study and appropriate therapy will be provided to them. Any loss caused by the present study will be reimbursed by insurance.

Outcomes analysis

Determination of maximum tolerated dose

MTD will be defined as the dose just below the lowest dose level at which more than 1 out of 6 patients exhibit DLT during the 4 weeks of the trial period. In the present study, the highest dose among the three dose groups (1200 mg, 2400 mg or 4800 mg per day) with one patient or less experiencing DLT will be determined as the MTD of SH003.

All analyses of data from the present study will be descriptive, as the study includes no inferential analysis and general hypothesis testing. The continuous variables will be displayed as the median and range, and the categorical variables will be displayed as the absolute and relative frequencies. After completion of each cohort's study period, an analysis will be conducted to determine the subsequent dose level.

Data and safety monitoring

To maintain the quality of the present study, monitoring will be conducted by the Contract Research Organization (CRO). The institution participating in the present study will be monitored while this trial is in progress through use of SOPs. For data quality improvement, double data entry and range checks for data values will be performed. Suspected and

unexpected serious adverse reactions will be reported to the institutional review board (IRB) and regulatory authorities in the Republic of Korea within 24 hours.

Ethics and dissemination

The present study has been approved by the IRB of the Ajou University Hospital (reference AJIRB-MED-CT1-16-311). The current protocol version is 1.1. Written informed consent will be obtained from each participant prior to commencement of the trial procedure by the investigator. Informed consent for the research use of human biological material will also be obtained for collection, storage, and use of blood samples from participants. The trial will be performed in compliance with the Helsinki Declaration and according to Good Clinical Practice as described by the Korean Ministry of Food and Drug Safety (MFDS). Confidentiality of patients' personal information will be protected. Each participant will be given a study identification number upon enrolment. During the trial period, data will be dealt with by using study identification numbers. During and after the study, all records will be kept in secure locked cabinets or in password-protected computer files. Only participating investigators will have the authority to access the data. The results of this study will be disseminated through an academic journal publication or a scientific conference.

Patient and public involvement

Patients or public were not involved to design the present study, and will not involve in the recruitment to and conduct of the study. So far, there is no established plan for announcement the results of the study to study participants.

DISCUSSION

The present study will investigate the tolerability and safety of administering SH003 to treat patients with solid cancers. Globally, there were 8.2 million reported deaths from cancer in 2012, and cancer is also the leading cause of mortality in Korea.[17 18] Thus, development of anti-cancer drugs is active in Korea. Among a total of 628 cases of investigational new drug (IND) approvals in 2016, the number of anti-cancer drugs was the highest, at 202 cases.[19] Nevertheless, there have been few IND approvals for new herbal medicines as anti-cancer drugs. In this situation, SH003 received IND approval from the Korean MFDS to begin a Phase I trial testing it as anti-cancer drug.

In addition to the effect of tumour size-reduction, SH003 has shown much potential as an anti-cancer agent in preclinical studies. The combination of SH003 and paclitaxel has been shown to enhance apoptotic cell death in paclitaxel-resistant breast cancer cells by inhibition of multidrug resistance protein 1 (MDR1) expression.[20] Decursin in Dang-Gui, one of the constituent herbs of SH003, has been shown to inhibit doxorubicin-resistant ovarian cancer cell proliferation and induce apoptosis.[6] The combination of SH003 and doxorubicin has shown synergistic effects in TNBC treatment.[13] Those studies suggest that SH003 could be used as an anti-MDR tumour agent and in combination with conventional chemotherapy drugs. SH003 has shown efficacy in treating various cancers, including breast, ovarian, and prostate cancers. Thus, further clinical studies are necessary to evaluate its effectiveness in treating various cancers. The pharmacological action of SH003 has not yet been fully elucidated. Thus, preclinical studies for SH003 will also continue to be conducted and the results will be published.

The present study is particularly significant. First, it is the only Phase I dose-escalation study conducted to date to determine the MTD for a new herbal medicine in Korea. While there have been several studies that investigated the anti-cancer effect of herbal medicine, most of

these were preclinical studies or clinical trials to evaluate the effectiveness of established herbal medicine in treating cancer patients.[21-24] Second, the present study will investigate the effect of SH003 on changes in tumour size for planning further studies to evaluate its efficacy. Changes in tumour size, that is objective response, are not a common outcome measurement for phase I study, but have been included in the present study, expecting that the results would provide helpful information to plan further studies.

Limitations of the present study are that the number of dose levels is relatively small and the study does not include pharmacokinetics (PK) and pharmacodynamics (PD) research. Due to the nature of the formulation, a dose exceeding 4 tablets would be inconvenient and may reduce patient compliance, thus the upper limit of dose level was determined as 4800 mg per day, the third dose level in this study. The effective dose estimated from preclinical studies was also considered.[10] Most herbal medicines, including SH003, are composed of complex compounds, and thus, PK and PD studies are not easy.[25] Therefore, it is difficult to collect PK evidence on dose and frequency of administration of herbal medicines. Based on *in vivo* PK studies on SH003 currently being performed, further human studies will need to be conducted. One of the constituents of SH003, *Angelica gigas*, contains decursin and decursinol angelate, which are characterising compounds of *Angelica gigas* according to the Korean Pharmacopoeia.[26] Decursin and decursinol angelate have been reported to have anti-tumor activities.[27] *Astragalus membranaceus*, another constituent herb of SH003, contains calycosin and formononetin.[28, 29] Anti-tumor effect of calycosin and formononetin has also been reported.[30 31] Therefore, it is reasonable to conduct a pharmacokinetic studies on SH003 using decursin, calycosin, and formononetin as marker compounds. Although it has not yet published, plasma concentrations monitoring of decursin, decursinol angelate, decursinol, calycosin, and formononetin after the administration of SH003 in rat have conducted. In the study, decursin and decursinol angelate showed very low bioavailability, presumably because

of the rapid conversion of decursin and decursinol angelate to decursinol in body,[32 33] and decursinol showed a higher plasma concentration than the other components. Therefore, it suggest that decursinol could be used as a major marker compound in pharmacokinetic study of SH003. Based on these results, a clinical pharmacokinetic study of SH003 is being planned. Although the present study has a few limitations, it serves as the first in-human trial to explore the use of SH003 to treat patients with cancer. Moreover, to the best of our knowledge, this is the first phase I study of an herbal medicine in Korea. We, therefore, expect that the present study could promote the overall development of new herbal medicines to treat cancer and other devastating diseases.

Authors' affiliations

[1] Department of Korean Preventive Medicine, College of Korean Medicine, Kyung Hee University, 26, Kyungheedae-ro, Dongdaemun-gu, Seoul, Republic of Korea

[2] Department of Cardiovascular and Neurologic disease (Stroke center), College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

Acknowledgements

We wish to acknowledge Hanpoong Phar. & Foods Co. Ltd. for providing investigational product support.

Contributors

CC, SK and YK have written the first manuscript for this trial and they will contribute to monitoring this trial. MK, BHJ and YCS have edited the first manuscript. SGK has conducted all the procedures for this protocol. All authors have read and approved the final manuscript.

Funding

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number : HI11C2110). The management, analysis and reporting of study will be conducted independently by the study investigators.

Competing interests

None declared.

Patients consent

Obtained

Ethics approval

The Institutional Review Board of the Ajou University Hospital approved the study (reference AJIRB-MED-CT1-16-311).

Provenance and peer review

Not commissioned; externally peer reviewed.

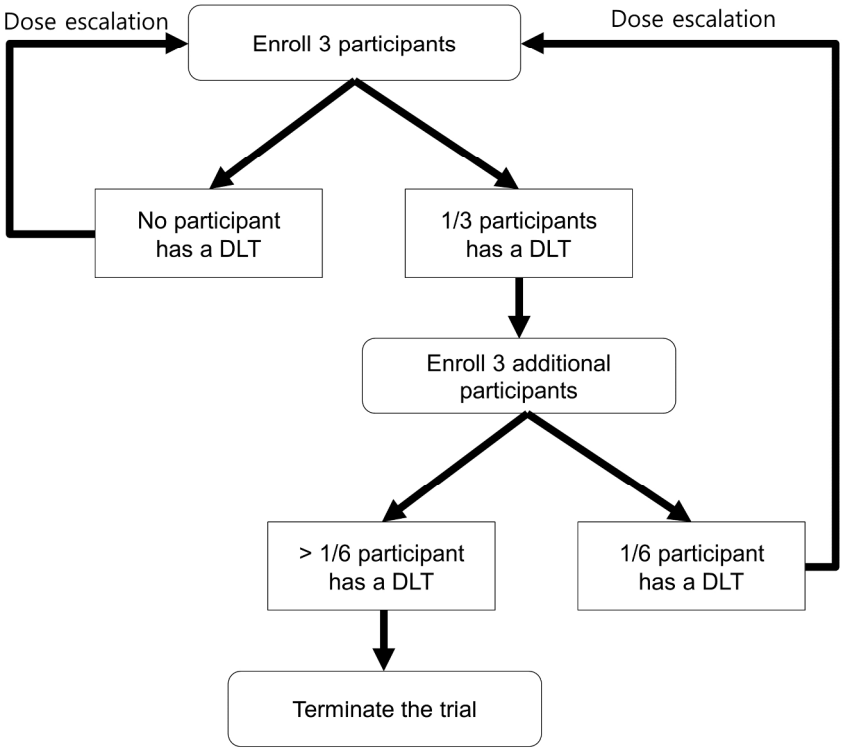
References

1. World Health Organization. Cancer, fact sheet. Updated February 2017. World Health Organization, 2017.
2. World Health Organization. World cancer report 2014. Lyon: International Agency for Research on Cancer, 2014.
3. National Cancer Center. National Cancer Information Center 2017. http://www.cancer.go.kr (accessed July 2017)
4. Hyun KR, Lee SM. Analysis of Socioeconomic Costs of Five Major Diseases. *Health insurance & policy* 2014;13(2):91-107.
5. Auyeung KK, Han QB, Ko JK. Astragalus membranaceus: A Review of its Protection Against Inflammation and Gastrointestinal Cancers. *Am J Chin Med* 2016;44(1):1-22.
6. Choi HS, Cho SG, Kim MK, et al. Decursin in Angelica gigas Nakai (AGN) Enhances Doxorubicin Chemosensitivity in NCI/ADR-RES Ovarian Cancer Cells via Inhibition of P-glycoprotein Expression. *Phytother Res* 2016;30(12):2020-26.
7. Li J, Li H, Zhang Z, et al. The anti-cancerous activity of recombinant trichosanthin on prostate cancer cell PC3. *Biol Res* 2016;49:21.
8. National College of Korean Medicine Publication Committee on Joint Textbook. Herbology. Seoul, Korea: Younglimsa 2016.
9. Choi YK, Cho SG, Choi YJ, et al. SH003 suppresses breast cancer growth by accumulating p62 in autolysosomes. *Oncotarget* 2016;8(51):88386-88400.
10. Choi YK, Cho SG, Woo SM, et al. Herbal extract SH003 suppresses tumor growth and metastasis of MDA-MB-231 breast cancer cells by inhibiting STAT3-IL-6 signaling. *Mediators Inflamm* 2014;2014:492173.
11. Choi HS, Kim MK, Lee K, et al. SH003 represses tumor angiogenesis by blocking VEGF binding to VEGFR2. *Oncotarget* 2016;7(22):32969-79.
12. Choi YJ, Choi YK, Lee KM, et al. SH003 induces apoptosis of DU145 prostate cancer cells by inhibiting ERK-involved pathway. *BMC Complement Altern Med* 2016;16(1):507.
13. Woo SM, Kim AJ, Choi YK, et al. Synergistic Effect of SH003 and Doxorubicin in Triple-negative Breast Cancer. *Phytother Res* 2016;30(11):1817-23.
14. Storer BE. An evaluation of phase I clinical trial designs in the continuous dose-response setting. *Stat Med* 2001;20(16):2399-408.
15. U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. Rockville, MD. USA: Food and Drug Administration, 2005.
16. U.S.Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) v4.03: National Institutes of Health National Cancer Institute, 2010.
17. International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidnece, Mortality and Prevalence Worldwide in 2012. World Health Organization, 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
18. National Cancer Center. Cancer Facts & Figures 2014. Ministry of Health & Welfare, 2014.
19. Ministry of Food and Drug Safety. MFDS, Results of the Investigational New Drug approval status 2016. Ministry of Food and Drug Safety, 2017.

20. Choi HS, Cho SG, Kim MK, et al. SH003 enhances paclitaxel chemosensitivity in MCF-7/PAX breast cancer cells through inhibition of MDR1 activity. *Mol Cell Biochem* 2017;426(1-2):1-8.
21. Kim HY, Kim J, Ha Thi HT, et al. Evaluation of anti-tumorigenic activity of BP3B against colon cancer with patient-derived tumor xenograft model. *BMC Complement Altern Med* 2016;16(1):473.
22. Choi BY, Joo JC, Lee YK, et al. Anti-cancer effect of Scutellaria baicalensis in combination with cisplatin in human ovarian cancer cell. *BMC Complement Altern Med* 2017;17(1):277.
23. Lee SI, Bae JA, Ko YS, et al. Geijigajakyak decoction inhibits the motility and tumorigenesis of colorectal cancer cells. *BMC Complement Altern Med* 2016;16(1):288.
24. Jeong JS, Ryu BH, Kim JS, et al. Bojungikki-tang for cancer-related fatigue: a pilot randomized clinical trial. *Integr Cancer Ther* 2010;9(4):331-8.
25. Liu WJH. Traditional Herbal Medicine Research Methods: Identification, Analysis, Bioassay, and Pharmaceutical and Clinical Studies: Wiley 2011.
26. Ministry of Food and Drug Safety, The Korean Pharmacopoeia Eleventh Edition, Ministry of Food and Drug Safety, Seoul, Korea, 2017.
27. Lee S, Lee YS, Jung SH, et al. Anti-tumor activities of decursinol angelate and decursin from Angelica gigas. *Arch Pharm Res*. 2003;26(9):727-30.
28. Ma X, Tu P, Chen Y, et al. Preparative isolation and purification of two isoflavones from Astragalus membranaceus Bge. var. mongholicus (Bge.) Hsiao by high-speed counter-current chromatography. *J Chromatogr A*. 2003;992(1-2):193-7.
29. Wu J, Ke X, Ma N, et al. Formononetin, an active compound of Astragalus membranaceus (Fisch) Bunge, inhibits hypoxia-induced retinal neovascularization via the HIF-1α/VEGF signaling pathway. *Drug Des Devel Ther*. 2016;10:3071-3081.
30. Chen J, Hou R, Zhang X, et al. Calycosin suppresses breast cancer cell growth via ERβ-dependent regulation of IGF-1R, p38 MAPK and PI3K/Akt pathways. *PLoS One*. 2014;9(3):e91245.
31. Wu XY, Xu H, Wu ZF, et al. Formononetin, a novel FGFR2 inhibitor, potently inhibits angiogenesis and tumor growth in preclinical models. *Oncotarget*. 2015;6(42):44563-78.
32. Kim KM, Kim MJ, Kang JS. Absorption, distribution, metabolism, and excretion of decursin and decursinol angelate from Angelica gigas Nakai. *J Microbiol Biotechnol*. 2009;19(12):1569-72.
33. Zhang J, Li L, Hale TW, et al. Single oral dose pharmacokinetics of decursin and decursinol angelate in healthy adult men and women. *PLoS One*. 2015;10(2):e0114992.

List of Figure

Figure 1. Study flow chart



Study flow chart. SH003

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	___Appendix__
Protocol version	3	Date and version identifier	_____11____
Funding	4	Sources and types of financial, material, and other support	_____13_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____13_____
	5b	Name and contact information for the trial sponsor	_____13_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____13_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____NA_____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	4

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.