Clinical Protocol Version 2.0

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Protocol Title: Karma Creme-1: A double-blind, placebo-controlled, three-armed, pilot study of the effects, safety and tolerability of topical endoxifen in women within the karma cohort

NCT: 04616430

Karma CREME-1: A double-blind, placebo-controlled, three-armed, pilot study of the effects, safety and tolerability of topical endoxifen in healthy women

Investigational Medical Product: Topical endoxifen

EudraCT: 2018-000573-72
Protocol: ATOS-010

Version: 2.0

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PROTOCOL REVISION HISTORY

Version	Date	Revised by	Description of change	Refers to chapter/page
1.0	20180306	NA		NA
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PROTOCOL SYNOPSIS

Study Title Karma CREME-1: A double-blind, placebo-controlled, three armed, pilot study of the effects, safety and tolerability of topical endoxifen in healthy women	
Study code: ATOS-010	**EudraCT No:** 2018-000573-72
Coordinating Investigator/Principle Investigator Per Hall	
Study centre Karma Study Centre/Breast and Mammography screening unit, Södersjukhuset, Stockholm, Sweden	
Study period Estimated date of study open for enrolment: April 2018 Estimated date of first participant enrolled, May 2018 Estimated date of last participant completed, March 2019	**Phase of development** Phase 2

Objectives and endpoints

Primary objective: Breast Density Reduction

- To determine the effect size of breast density between topical placebo and two doses of topical endoxifen. The effect size will permit sample size calculations for statistical significance in a future phase III trial.

Primary endpoint:

- Change, on an individual level, in mammographic breast density, measured at 3 and 6 months after study entry (= baseline screening mammography).

Secondary objective: Tolerability and Safety

- Assess tolerability and safety of topical endoxifen

Secondary endpoints:

- Determine dose dependent differences in compliance, side effects and local tolerability measured through questionnaires
- Determine dose dependent differences in laboratory assessments such as liver function tests (ALAT, ASAT, ALP, Bilirubin), coagulation function (INR, aPTT), sex hormone binding globulin (SHBG)

Tertiary objective:

- Determine if plasma levels of endoxifen influence primary and secondary endpoints

Tertiary endpoints:

- Determine if plasma level concentrations of endoxifen are related to primary and secondary endpoints

Investigational Medicinal Product (IMP)

The IMP, topical endoxifen and its matching placebo, are formulated from widely used for both cosmetics and pharmaceutical topical constituents: Transcutol™ (2-(2-Ethoxyethoxy)ethanol); isopropanol, Crodamol™ GTCC (a fully saturated emollient triester) and mineral oil. The active IMP also contains endoxifen, the strength of which is based on Z-endoxifen content.

Study design

Randomized, double-blinded, three-armed, placebo controlled pilot study

Group	IMP			Assessments
	Dose mg/day*	Frequency	Duration	
1	0	Daily	6 months	0, 3, 6 months: • Safety Labs • Mammogram 3, 6 months: • Endoxifen levels 0, 1, 3, 6 months • Questionnaires
2	10	Daily	6 months	
3	20	Daily	6 months	

- A daily dose = 2 sachets/day in total which is the equivalent to1 sachet/breast/day

Number of participants planned

90 participants will be randomized to one of three groups with 30 participants per group

Diagnosis and main eligibility criteria

Healthy post-menopausal women participating in mammographic screening program at SöS Bröstcentrum with a measurable mammographic density, i.e., ≥ 4.5 % density (volumetric) measured by Volpara. No history of coagulopathies, cardio-vascular disorders and cancer.

Duration of treatment

6 months

Duration of participants involvement in the study

6 months of exposure to active compound or placebo

Efficacy assessments

Mammographic density after 3 and 6 months.

Safety assessments

The safety profile of each individual and dose group will be determined by clinical assessment, laboratory findings and participant reports. Laboratory findings and AEs will be followed throughout the study period. A Data and Safety Monitoring Board will provide safety oversight of the study.

Statistical methods

Karma CREME-1, is a pilot study conducted to aid the design of a larger future trial. As such, the pilot study is not powered to show statistical significant reductions in breast density in the treatment arms compared to the control arm. Rather, results of the pilot study will be qualitatively presented and assessed, which will aid in making decisions about dosing, study length, and sample size for the larger trial.

Efficacy: Assess change in mammographic density from baseline to 3 and 6 months and from 3 to 6 months of study drug administration.

Tolerability: Assess the grade, severity and frequency of side effects

Safety: rank adverse events by severity, grade, interventions, and resolution.

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or term	Explanation
AE	Adverse event
BMI	Body mass index
CRF	Case report form
CRO	Contract Research Organisation
CTA	Clinical Trial Agreement or Clinical Trial Application
eCRF	Electronic Case Report Form
DCIS	Ductal Carcinoma In Situ
DDP	Data Display Plan
DMP	Data Management Plan
DSMB	Data and Safety Monitoring Board
FAP	Full Analysis Population
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
ICF	Informed Consent Form
ICH	International conference on harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IMPD	Investigational Medicinal Product Dossier
MedDRA	Medical Dictionary for Regulatory Activities
PP	Protocol Population
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SP	Safety Population
SUSAR	Suspected Unexpected Serious Adverse Event
SöS BC	Södersjukhuset Bröstcentrum
QC	Quality Control
QP	Qualified Person. A legally defined and certified Quality Assurance professional that ensures each lot of product complies with its specification and has been made according to good manufacturing practice.

2 ETHICS

2.1 Ethical and Regulatory review

Necessary approvals of the Study Protocol, the Participant Information and Informed Consent Form (ICF) must be obtained before enrolment of any participant into the study. Furthermore, it is the responsibility of the Sponsor to keep the applicable Independent Ethics Committee (IEC) informed of any Suspected Unexpected Serious Adverse Reactions (SUSARs) and any substantial amendments to the protocol during the study period. The written approval from the IEC, including a study identification and the date of approval, will be filed by the Karma Group at the Karolinska Institutet and at the study site at Södersjukhuset Bröstcentrum (SöS BC) together with a list of the IEC members, their titles or occupation, and their institutional affiliations.

2.2 Ethical conduct of the study

The study will be conducted according to the protocol and in line with applicable regulations, i.e. LVFS 2011:19, ICH GCP and the latest version of the declaration of Helsinki.

2.3 Participant information and consent

It is the responsibility of the Investigator to give each participant, adequate verbal and written information regarding the objectives and the procedures of the study as well as any risks or inconvenience involved before including the participant in the study. The participant should be informed that by signing the ICF she authorises monitor(s), auditor(s), the IEC and the Regulatory Authorities to have direct access to the participant's medical records for verification of clinical study procedures. The women must be informed about the right to withdraw from the study at any time and that participation is on a voluntarily basis. The participant should be allowed sufficient time for consideration of the proposal.

It is the responsibility of the Investigator to obtain signed informed consent from all participants before including them in the study. The ICF must be signed and dated before any study-specific procedures are performed, including screening procedures. In case of possible future audits/inspections, the Investigator must file the signed ICF.

The final version of the participant information and ICF is submitted to the IEC and concerned Regulatory Authorities and must not be changed without permission from Sponsor and the local IEC.

2.4 Participant data protection

The Investigator must file a participant identification list that includes sufficient information to link records, i.e., the electronic Case Report Form (eCRF) and clinical records. This list must be preserved for possible future inspections/audits.

The participants will be informed that the data will be stored and analysed by computer, that Swedish and local regulations for the handling of computerised data will be followed and that identification of individual participant data will only be possible for the Investigator.

Representatives of the Karma Group including a Contract Research Organisation (CRO), and/or regulatory authorities will inform the participants about the possibility of inspections/audits of relevant parts of the clinical records. Authorisation to direct access to the participant's clinical records, as described above, is given by signing the ICF.

3 ADMINISTRATIVE STRUCTURE

Qualified investigators under the sponsorship of Atossa Genetics and the Karma Group will conduct the study. The name and contact details of the responsible persons at Karma Group and the CRO will be listed in the Investigator Site File provided at the site.

Role	Name	Contact	Location
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4 INTRODUCTION

Breast cancer is by far the most common cancer among women in the world and a continuing increase is seen, particularly so in the developing world. Currently there are few efforts taken to reduce the *incidence* of breast cancer, that is, to prevent the disease. The major research focuses are early detection (screening) and therapy. Adjuvant therapy (administrated to patients without a measurable tumour burden in order to decrease risk of recurrence of the disease) has been used for decades and has dramatically improved survival [Pan, 2017]. Some of the drugs used in the adjuvant setting has also been used for prevention. Aromatase inhibitors and selective estrogen receptor modulators (SERMs), e.g., tamoxifen, has been shown to reduce the incidence of breast cancer in healthy individuals. Four studies have shown that 20 mg of oral tamoxifen in healthy women can reduce the incidence of breast cancer by nearly 50% [Visvanathan, 2013]. Tamoxifen has therefore been approved by the FDA for prevention since the 1990s.

Despite the fact that tamoxifen has been found to reduce the incidence of breast cancer in healthy women, it is rarely prescribed for this use. The reluctance of physicians to prescribe and for women to use oral tamoxifen for prevention is likely due to the perceived and real risks of side effects. Hot flushes, and other vasomotor symptoms, which can be severe, are barriers to acceptance. Rare and serious side effects are endometrial cancer and venous embolism.

One possible way of reducing side effects is to lower tamoxifen doses, under the assumption that lower dose is required for prevention than for curative treatment. We therefore launched the Karisma-2 trial (Karisma-2, Eudra CT 2016-000882-22) in the end of 2016. In short, in the Karisma2 trial we test if lower doses of tamoxifen (10, 5, 2.5, 1 mg) has the same effect (measured as a decrease in mammographic density, please see below) as the established 20 mg dose. The trial is ongoing and approximately 800 participants (as of February 2018) of the 1440 women have been recruited. Recruitment is planned to end December 2018.

Another way to reduce side effects is to, instead of using tamoxifen, introducing the tamoxifen metabolite endoxifen. As a prodrug, tamoxifen has to be metabolized and endoxifen is considered the main active metabolite of tamoxifen [Lim, 2005]. By using endoxifen as a topical application the systemic side effects can be reduced [Lee, 2015].

In a collaboration with Atossa Genetics Inc., a US company that has developed endoxifen for topical application, topical endoxifen will be tested to determine if it reduces mammographic density, compared to a placebo group, with acceptable tolerability and safety.

This pilot study, which is the first launched phase 2 study of topical endoxifen, is named Karma CREME-1 and it will be conducted in accordance with the ICH GCP guidelines, the principals of which have their origins in the Declaration of Helsinki.

5 STUDY RATIONALE

5.1 Background

Karma CREME-1 will consist of 90 healthy women that will be recruited from the mammography screening program at Södersjukhuset, Stockholm. Since 2010, The Karma Group have invited women to the Karma project, aiming to reduce breast cancer by a preventive approach. The Karma cohort was created between 2010-2013 and consists of 71,000 Swedish women. All women invited for screening mammography in Lund, Helsingborg and at Södersjukhuset, were invited to the Karma Study Centers. If agreeing to join the study, participants signed an informed consent, donated blood and answered a comprehensive questionnaire on lifestyle factors [Gabrielsson, 2017].

In the ongoing Karisma 2 trial, all women attending mammography screening at Södersjukhuset are invited, not only Karma participants. The Karma CREME-1 trial should be viewed as an extension of the

Karisma-2 trial with a possible further reduction of side effects through even lower plasma concentrations of the active metabolites of tamoxifen.

5.2 Topical administration rationale

Intravenous, intramuscular and oral administration of a medication gives *systemic* effects which means that the entire body could affected by the drug. In contrast, a topical application has the potential to reduce the systemic effect without reducing the local effect.

There are theoretical reasons for using a topical endoxifen since it has a potential to be enriched in the breast tissue. The breast gland has developed from an apocrine gland and could thus be seen as part of the skin and any substance would therefore be more likely to penetrate the skin [Ackerman, 2007]. Secondly, there is an abundance of lymph and blood vessels in the breast gland that should increase the uptake [Suami, 2008]. Thirdly, type of tissue influence the uptake of tamoxifen metabolites. When the tamoxifen metabolite afimoxifene was applied in the lower part of the body and over the breast, the concentration in the underlying tissue was 10 times higher in the breast than the adipose tissue of the belly [Suami, 2008]. Probably an effect of the affinity of afimoxifene to the estrogen receptor.

5.3 Endoxifen rationale

As a prodrug, tamoxifen has to be metabolized and rely on the activity of its metabolites for clinical effects. Effects and side effects of tamoxifen is the sum of tamoxifen and all its metabolites. Endoxifen has an estrogen receptor affinity exceeding that of the parent drug tamoxifen and is considered the main active metabolite of tamoxifen. It has for long been known that the affinity of endoxifen to the estrogen receptor is approximately 100 times higher than that of tamoxifen [Katzenellenbogen, 1984].

5.3.1 Topical endoxifen - Phase 1 data

Atossa Genetics Inc., has performed two clinical endoxifen phase 1 studies, one with endoxifen as an oral compound and one with endoxifen as a topical compound. The topical phase 1 study is described in detail in the Investigators Brochure.

In the phase 1 topical endoxifen study, 25 healthy individuals received topical endoxifen at doses 0, 2, 6 and 10 mg/day. None of them experienced side-effects normally linked to tamoxifen, and thereby possibly endoxifen, exposure. There were no reports of hot flushes, vaginal discharge, mood swings, fatigue or breast pain/tenderness. These symptoms are associated with tamoxifen use and seen in more than 50% of the Karisma-2 participants. What was reported in the topical endoxifen phase 1 study was for tamoxifen atypical, non-dose dependent experiences of abnormal dreams, hypersomnia, vomiting and headache.

In the phase 1 topical endoxifen study, serum concentrations of endoxifen were low even for the highest dose group, 10 mg/day of daily topical endoxifen. Most measured samples were below or slightly above the limit of detection/quantitation. The mean concentration in the 10 mg group was 1.0 ng/mL and the maximum 5.0 ng/mL. Concentrations were too low to perform any pharmacokinetic analyses. Furthermore, there were no clinically significant safety signals (no measurable influence on coagulation system, liver function or sex hormone binding globulin) in any of the subjects receiving topical endoxifen.

In conclusion, topical endoxifen (at doses 0, 2, 6 and 10 mg/day) was well tolerated when administered daily for 28 days to 25 healthy volunteers. There were no dose-related or treatment-related trends in any of the safety and tolerability endpoints.

5.3.2 Plasma endoxifen levels after exposure to oral tamoxifen

Endoxifen concentrations in blood in patients taking oral tamoxifen has been measured in numerous studies. Most studies describe a wide variation of plasma concentrations of tamoxifen and its metabolites. The inter-individual variation of tamoxifen metabolism is supposedly caused by genetic

factors and different methods used to determine the concentration. In a recent study, concentrations of endoxifen were measured in plasma specimens from 281 breast cancer patients treated with tamoxifen [Woo, 2017]. The average exposure to 20 mg of tamoxifen was 125 days (range 56 – 340 days). For endoxifen the mean was 25.0 ng/mL and range 11.4 – 44.8 ng/mL. Most of the variation was explained by polymorphisms in key metabolizing genes suchas CYP2D6.

A meta analyses gathered published data covering 13,001 breast cancer patients using tamoxifen [Hwang, 2017]. CYP2D6 poor metabolizers were compared to extensive metabolizers and the mean endoxifen concentrations were significantly lower in poor metabolizers, 8.8±7.2 versus 22.3±11.8 ng/mL ($p<0.05$). In all, 39 women (19 premenopausal and 20 postmenopausal women) on adjuvant tamoxifen treatment (20 mg/d) for early breast cancer had endoxifen levels measured using ultra-performance liquid chromatography with a mass spectrometry detection [Fotoohi, 2016]. Plasma concentrations of endoxifen range from 3.2 to 19 ng/mL, with a mean of 10.4 ng/mL.

Twenty-four Karma Cohort participants that developed breast cancer during follow up (data not published) and were put on 20 mg of tamoxifen had tamoxifen metabolites measured in 2016. The average endoxifen plasma levels were 7.4 ng/mL (range 1.8 – 12.2) and the median 9.4 ng/mL.

From this we assume that the systemic endoxifen concentrations from topical administration of endoxifen is approximately 5-10% of the endoxifen plasma levels seen after 20 mg of oral tamoxifen. This is most likely the reason why few dose-dependent side effects, typically linked to tamoxifen, were seen in the topical endoxifen phase 1 trial.

5.4 Dosing Rationale

If topical endoxifen is actively enriched in the breast tissue and if concentrations are sufficient to influence the breast parenchyma, that is, the dense part of a mammogram, has not been studied. The influence of another metabolite of tamoxifen, afimoxifene, has been reported in some few studies. It should be noted that the affinity of endoxifen to the estrogen receptor is higher than that of another tamoxifen metabolite, afimoxifene.

In a randomised controlled trial 45 breast cancer patients were treated with topical administration of afimoxifene in the period between diagnosis and surgery. The effect measure was cell proliferation in the breast gland [Rouanet, 2005]. Patients were divided in to five groups, placebo, topical afimoxifene in doses 1, 2, and 4 mg/day, and 20 mg of oral tamoxifen. No effect on epithelial cell proliferation was seen in patients on placebo and 1 mg/day. These groups did not report any side effects. Proliferation was significantly reduced in the groups on 2 and 4 mg/day of afimoxifene and oral tamoxifen 20 mg compared to the placebo group. No difference in reduction in proliferation was seen between the three groups that responded to therapy. There was no significant difference in side effects in the three response groups despite the fact that the plasma concentration of afimoxifene was less than 10% of that of oral tamoxifen.

There are two known studies that tested the effect of topically administrated afimoxifene on mammographic density. None of these studies are published but preliminary results show that a significant reduction in density was seen without reports on side effects [Bua, 2004; Le Nestour, 2009].

Topically administered tamoxifen metabolites seems to influence the breast parenchyma but we do not know the dose needed. The tested doses in the topical endoxifen phase 1 trial generated few, if any, treatment related side effects and very low concentrations of plasma endoxifen. We therefore want to test the breast parenchymal effect of a total daily dose of 10 mg (5 mg/breast) and 20 mg (10 mg/breast) of topical endoxifen.

5.5 Mammographic density

In a conventional breast cancer prevention study the outcome would be number of breast cancers in each arm given a predefined time period. Such a study requires a long follow-up and a very large

number of participants. An alternative is to use mammographic density change as a proxy for therapy response.

Mammographic density is the white part of the mammogram and consist of glandular and connective tissue. The black, non-radiolucent part is fat. The more glandular and more connective tissues, the whiter the breast, and thus, the higher the risk of breast cancer [Boyd, 2007]. Factors that influence risk of breast cancer are known to influence density. Hormone replacement therapy increases density and risk of breast cancer [Brand, 2013], while tamoxifen has the opposite effect [Li, 2013].

In addition to be a excellent marker of risk, mammographic density has been shown to be a reliable proxy for therapy response. Mammographic density has been assessed in a nested case-control study within the IBIS-1 study, a randomised prevention study of tamoxifen vs. placebo. The density decrease, over the first 18 months, in 123 women diagnosed with breast cancer, was compared to 942 women without breast cancer [Cuzick, 2011]. Forty-eight per cent of the women treated with tamoxifen experienced a 10% or greater reduction in breast density and had a 63% reduction in breast cancer risk compared to women in the placebo group. In contrast, those who took tamoxifen but experienced less than a 10% reduction in breast density had no risk reduction.

Within the Karma group a parallel study was conducted including breast cancer patients who were treated with adjuvant tamoxifen therapy [Li, 2013]. Forty-eight per cent of the women experienced a decrease in density of > 20 % over a 12 month period and had a reduced breast cancer recurrence of 50%. These findings are fully supported by a very recent finding by a US group [Nyante, 2015].

In clinical practice mammographic density is measured using BI-RADS. BI-RADS categorizes breast into four categories: entirely fatty (BI-RADS A), scattered areas of fibroglandular density (BI-RADS B), heterogeneously dense (BI-RADS C) and extremely dense breast (BI-RADS D). The BI-RADS measurement is done by the radiologist by looking at the mammogram. BI-RADS measurements are very crude and highly reader dependent. To avoid time consuming and reader dependent measures of risk the Karma research group have developed the computerized measurement tool Stratus [Eriksson, 2018].

Stratus is an automated tool that is not dependent on reader skills or experience. The unique features of Stratus is that it enables *comparison of mammographic density changes over time* without being restricted to type of mammogram or technical differences between images. An image from one and the same women are not always comparable since not the same extent of the breast is seen in the image. In order to reduce this technical problem, images has to be aligned before density measures are performed. Stratus includes an alignment protocol that makes images from the same individual comparable and reduced the non-biological variability between mammograms. Stratus has successfully been used in the Karisma trials. In short, Stratus will assess therapy response without being influenced by type of image and the alignment protocol will reduce the non-biological variability between mammograms.

Even though Stratus has shown to reduce most of the differences between images through the alignment protocol, minute differences could still influence results. In order to reduce any possible biological difference between images of the same woman, the study is restricted to postmenopausal women that, per definition, have no influence of density related to hormone change during the menstruation cycle.

5.6 Study duration

The Karisma-1 pilot trial (Eudra CT2014-005-005-20) preceded the Karisma-2 trial. The major focus of the pilot trial was to estimate time to mammographic density change. In all, 32 healthy women completed the 6 month trial and were exposed to 10 or 20 mg/day of oral tamoxifen.

The results of the Karisma-1 trial showed a mammographic density decrease after the full study period of 6 months, of about 50% for one quarter of the participants. For another quarter of the participants

a ≈ 20% mammographic density decrease was seen. The remaining 50% of the participants did not experience any change in mammographic density.

Table 1 displays the change in mammographic density among the 32 patients seen after 3, 6 and 9 month of follow up. The biggest decrease is seen the first 3 months and the decrease continues even after the treatment was stopped at 6 months.

Table 1*. Mean percent dense area and density change from baseline in percent in the Karisma-1 pilot study (n=32), in relation to months in study.*

	0 month	**3 months**	**6 months**	**9 months**
Mean % dense area	17.6	15.8	15.3	14.6
Mean % change from baseline	-	-1.8	-2.3	-3.0

The results of the Karisma-1 pilot trial show that 3 months of oral tamoxifen exposure is enough to significantly influence mammographic density. Since it could be that the uptake of topical endoxifen, in contrast to oral tamoxifen, is slower, the treatment period in Karma CREME-1 trial has been set to 6 months, with mammograms and density measurements performed at 3 and 6 months.

5.7 Conclusion

The ability of oral tamoxifen to reduce breast cancer risk is well-accepted and proven. The tamoxifen metabolite endoxifen has the highest affinity for the estrogen-receptor of the tamoxifen metabolites. The ability of topical endoxifen to penetrate the skin of the breast was demonstrated in the phase 1 study of topical endoxifen without safety or tolerability signals. Topical endoxifen, at doses 10 and 20 mg/day will therefore be tested using mammographic density change as the outcome. The arguments for topical endoxifen are:

1. Endoxifen has the highest affinity of all the tamoxifen metabolites to the estrogen-receptor.
2. The liver is not required to metabolize endoxifen and interference with the coagulation pathway system and liver function is less likely to occur.
3. From a theoretical pint of view, endoxifen applied to the skin covering the breast could be enriched in the breast tissue because the high affinity to the estrogen receptor and the vascularisation of the breast epithelium.
4. Directed delivery to the breast with limited systemic exposure may result in better tolerability and compliance.

6 BENEFIT-HARM ASSESMENT

6.1 Background

In a broader sense, ethical considerations in clinical trials should focus on answering the question – does knowledge generated through the trial outweigh the possible harms inflicted on the participants? The most important task is to take the safety of study participants in to consideration. Breast cancer incidence has increased rapidly over the last generations and currently one women per minute is diagnosed with breast cancer in Europe. It could therefore be argued that efforts taken to reduce the number of breast cancers are much needed. Tamoxifen has been used for adjuvant therapy for breast cancer for several decades and the side effects of tamoxifen are well-known. Side effects ranges from menopausal symptoms and mood swings to increased risks of endometrial cancer and thromboembolism. Tamoxifen has also been found to reduce the number of newly diagnosed cancers in perfectly healthy women but is not used to any larger extent due to the risk of bothersome as well as potentially very serious side-effects. Little is known about the side effects of endoxifen. Therefore, a conservative approach must be to assume that the toxicity of endoxifen is identical to that of

tamoxifen and that there is a dose dependency is used. The following sections discuss the potential risks associated with exposing healthy volunteers to topical endoxifen and the associated mitigation strategies. Possible benefits of participating in the trial are also described, as well as benefit-harm assessment of frequent mammograms.

6.2 Safety

The most serious side effects of tamoxifen are thromboembolic events, endometrial cancer, sarcoma of the uterus and liver damage such as cirrhosis and steatosis. Markers of the coagulation system, liver function and levels of sex hormone binding globulin (SHBG) were therefore tested in the phase I topical endoxifen trial. Comparing levels before trial initiation and at 28 days of exposure to the study drug revealed no influence on these parameters, not even in the highest dose (10 mg) category. For more detailed information on the phase 1 results, please see Investigator Brochure.

During pregnancy, tamoxifen and its metabolites interact with rapidly growing and developing embryonic or foetal tissues. Tamoxifen exposure during pregnancy could lead to congenital malformations, spontaneous abortions and even foetal deaths.

6.2.1 Risk mitigation strategy -Safety

The phase 1 data does not indicate a systemic influence on the systems but since it cannot entirely be ruled out that there is an effect on the coagulation system, liver function or SHBG, markers of their function will be measured at 3 and 6 months in this phase 2 study.

Patients with a previous cardiovascular event will be excluded from the study. Blood pressure will be measured before entering the study and women with a blood pressure >140/90 mm Hg will not be included in the trial. Possible signs of vaginal bleeding will be addressed immediately. Since only postmenopausal women will be included, pregnancy related safety issues are not a concern.

6.3 Tolerability

Theoretically, topical endoxifen could give two kind of side effects, local and systemic. The local problems emanate from the application of the solution to the skin of the breast. The systemic effects from circulating plasma endoxifen and are measured as experienced side effects through using self-reported answers to a Functional Assessment of Cancer Therapy – Endocrine Subscale (FACT-ES) questionnaire. The comprehensive questionnaire covers all the well-known side effects seen for tamoxifen, such as physical, social, emotional and functional wellbeing. Additional concerns are hot flushes, night and cold sweats, vaginal discharge, etc.

6.3.1 Local side effects

Local irritation, redness and itching, were the most commonly reported symptoms in the topical endoxifen phase 1 trial, which mostly spontaneously resolved during treatment but in one case lead to the discontinuation of the study drug. Mild itching, pain and redness was seen in all dose categories, even placebo. Moderate problems were seen in 4 individuals in the highest dose group and in one participant in the lowest dose group. No severe skin problems were reported.

A self-administered assessment was performed daily by the women as to local tolerance. **Table 2** shows the results of the assessments. As can be seen, most problems were scored as mild, some few moderate and none as severe. It turned out that the majority of the reports (41%) of burning, itching, and particularly irritation was reported by one study subject.

Table 2. Results of Local Tolerance Self-assessment

Parameter	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n
Redness	662 (98.5)	10 (1.5)	0 (0.0)	0 (0.0)	672
Burning	669 (99.6)	3 (0.4)	0 (0.0)	0 (0.0)	672
Pain	661 (98.4)	10 (1.5)	1 (0.1)	0 (0.0)	672
Itching	651 (96.9)	16 (2.4)	5 (0.7)	0 (0.0)	672
Irritation	651 (96.9)	20 (3.0)	1 (0.1)	0 (0.0)	672

6.3.1.1 Risk mitigation strategy - Local side effects

It is important that participants are encouraged to only apply the product to intact and not to broken skin. Should local symptoms emerge, consultation with the study staff should be made to determine if continued participation is warranted. The participants will also be asked to:

- Not expose the treated skin to sunlight (natural or artificial), as the photosensitivity properties of the product have not been established
- Avoid skin to skin transfer if possible, at least 30 minutes after application
- Avoid exercise, swimming or bathing for at least 30 minutes after application

6.3.2 Systemic side effects

In the topical endoxifen phase 1 study systemic side effects were measured using the FACT-ES. The most common side–effects of tamoxifen and thereby possibly endoxifen are hot flushes, amenorrhea, altered menses, vaginal discharge, depression, mood swings, nausea, oedema, fatigue and breast pain/tenderness. None of these symptoms were seen among the 25 participants of the phase 1 trial.

What was seen was abnormal dreams, hypersomnia, vomiting and headache, however, not in a dose-dependent manner. The group that had most participants experiencing side effects was the placebo group and the most common symptom in this group was headache. As can be seen in **Table 3** there were reports of mild to moderate symptoms from a variety of organs but, with the exception of skin problems, there does not seem to be a dose dependency. The table gives the number of individuals reporting problems.

Table 3. Number of individuals reporting treatment emergent adverse events by severity and dose in the topical endoxifen phase 1 trial

System Organ Class, Preferred Term	Severity	Active Cohort				Total Placebo (n = 7)	All Subjects (n = 25)
		2 mg (n = 6)	6 mg (n = 6)	10 mg (n = 6)	Total Active (n = 19)		
Infections and infestations							
	Moderate					1 (14%)	1 (14%)
	Mild	1 (17%)	1 (17%)	3 (50%)	5 (28%)	-	5 (20%)
Psychiatric disorders							
	Mild	2 (33%)	-	-	2 (11%)	-	2 (8%)
Nervous system disorders							
	Moderate	-	1 (17%)	-	1 (6%)	2 (29%)	3 (12%)
	Mild	1 (17%)	-	1 (17%)	2 (11%)	1 (14%)	3 (12%)
Vascular disorders							
	Mild	-	-	-	-	1 (14%)	1 (4%)
Gastrointestinal disorders							
	Moderate	-	1 (17%)	-	1 (6%)	1 (14%)	2 (8%)
	Mild	-	2(33%)	-	2 (11%)	1 (14%)	3 (12%)
Skin and subcutaneous tissue disorders							
	Mild	-	1 (17%)	2 (33%)	3 (17%)	-	3 (12%
Reproductive system and breast disorders							
	Moderate	1 (17%)	-	-	1 (6%)	-	1 (4%)
	Mild	-	-	-	-	1 (14%)	1 (4%)
General disorders and administration site conditions							
	Mild	-	-	-	-	1 (14%)	1 (4%)
Investigations							
	Mild	-	-	1 (17%)	1 (6%)	-	1 (4%)
Injury, Poisoning and procedural complications							
	Moderate	-	1 (17%)	-	1 (6%)	-	1 (4%)
	Mild	1 (17%)	1 (17%)	-	2 (11%)	-	2 (8%)

6.3.2.1 Risk mitigation strategy - Systemic side effects

Participants will be informed to immediately contact the Karma Study Centre if they suspect side effects. As within the ongoing dose determination study, Karisma-2 where the aim is to test the effect of low dose tamoxifen, participants have the options of reporting side effects via telephone, mail, internet or the so called Karmapp. Participants get help at the centre in downloading the app at inclusion. Participants are encouraged to report side effects month 1, 3 and 6. They are also encouraged to spontaneously report any problems that could be related to the therapy.

In the Karisma-2 trial, study personal take turns carrying a study mobile phone and participants can reach the Karma Trial Centre during office hours. Exactly the same strategy for reporting side effects will be used in the topical endoxifen phase 2 trial as in the Karisma-2 trial. Participants reporting severe side effects are immediately contacted and discontinuation discussed. So far, 16% of the participants of the Karisma-2 trial have left the study because of side effects.

6.4 Benefit-harm assessment of frequent mammograms

Eligible study participants will only be women that have negative screening mammograms before entering the study, i.e., no abnormalities have been identified. The participants will have extra mammograms taken at 3 and 6 months after study entry. In order to reduce radiation exposure, the mammograms consist of 2 images instead of 4, which are standard at a screening examination. The examinations are performed on a low-dose screening modality and the total effective radiation dose

is less than 0.2 mSv. The mean value of a conventional x-ray examination is 1 mSv. The Radiation Protection Board of Södersjukhuset has approved the Karma CREME-1 study.

The images will be used for density measurement but radiologist will also screen them for abnormalities as in clinical practice. It could be that cancers are diagnosed at these extra visits, which should be seen as something that benefits the study participants.

If a suspected alteration is seen at baseline mammogram, the women will be excluded from the study and receive the normal diagnostic routine work-up for a suspected breast cancer, that is, additional ultrasound examination and a possible fine needle biopsy.

6.5 Possible benefits of participation in the trial

Participants of the trial will all be Karma Cohort participants and recruited from the national mammography screening program at the Breast Centre at Södersjukhuset. In addition to their screening mammogram they will have the following examinations:

- Blood pressure will be measured
    - A substantial number of women with hypertension have been found in the Karisma-2 trial, even women with pressures that needed acute referral for medical attention.
- Markers of coagulation system, liver function and SHBG will be measured
    - If any clinically significant abnormal values are found, participants will discontinue their participation in the trial
- Additional two mammograms at months 3 and 6
    - One participant in the Karisma-2 trial had a breast cancer diagnosed at the 6 months follow up. According to the radiologist, the mammographic density had decreased in a manner that made it possible to identify the cancer. Due to the seriousness of this event, the randomization code was broken, revealing that the participant had been randomized to a daily dose of 1 mg tamoxifen.

7 SAFETY, TOLERABILITY, EFFICACY AND LABORATORY ASSESSMENTS

7.1 Safety Assessment

- Monitoring and recording Adverse Events (AE) and Serious Adverse Events (SAE). Participant that reports of adverse events will be followed and appropriate medical action taken, (e.g., examination, telephonic contact, etc.) as warranted. Participants can contact Karma Study Centre through phone, mail, visit or using the application Karmapp. Reported Adverse Events defined as AE of interest, for example, severe intensity grade or signs of severe events (see section 10.4 AE of interest) will alert Investigator in the eCRF system for immediate action. This approach was successfully used in the Karisma-1 and 2 trials.
- A Data and Safety Monitoring Board (DSMB) will monitor the safety of the study according to the guidelines described in the DSMB charter. Monitoring will also be executed by an external monitor according to a monitoring plan.
- Blood tests for liver function and coagulation function will be obtained at baseline, 3 and 6 months (see section below, laboratory assessment, for specific test information).
- Participants will be provided a wallet sized Participant card containing essential information about the study and contact information to Karma Study Centre (see appendix).
- Participants will be trained and encouraged to report any symptoms or changes they experience.

7.2 Tolerability Assessments

Tolerability will be assessed as a function of two doses of endoxifen dose or placebo. In Karma CREME-1, questionnaires will be used to evaluate general symptoms (Memorial Symptom Assessment Scale), specific symptoms of anti-hormonal treatment (FACT-ES), compliance of medicine intake (Morisky scale). In addition to the revised FACT-ES questionnaire, specific skin-related questions will also be employed to assess local tolerability. Qualitative data will be collected through interviews with some of the participants to get their experiences particularly regarding the IMP in order to design next study for optimal feasibility.

7.3 Efficacy Assessments

Mammographic density will be measured at baseline and after 3 and 6 months. In the Karma CREME-1 study both Volpara and Stratus will be used to analyse the mammographic changes as described in chapter 5 Study Rationale; section 5.5 Mammographic density.

7.4 Laboratory Assessments

Blood tests for safety

Blood tests such as liver function tests (ALT, AST, ASP, Bilirubin), Sex Hormone Binding Globulin (SHBG) and coagulation parameters (INR, aPTT), will be analysed. The analyses will be performed within the routine care at Karolinska University Laboratory. These blood tests will be performed at baseline and at 3 and 6 months following study entry. Abnormal laboratory findings and liver and coagulation parameters changing after baseline will call for attention in the eCRF and alert Investigator for judgment and possible action.

Endoxifen in plasma

It is expected that the topical administration will yield substantially reduced blood levels of endoxifen compared to oral tamoxifen dosing (see section 5.3.2 Plasma endoxifen levels after exposure to tamoxifen). In the phase 1 study of topical endoxifen, low levels of endoxifen were observed in some participants in a dose-dependent manner. The metabolic analyses for Karma CREME-1 will be performed at Clinical Pharmacology, Karolinska University Hospital, Huddinge, with a validated method also used in the Karisma-2 trial.

8 STUDY OBJECTIVES AND ENDPOINTS

8.1 Primary objective: Breast Density Reduction

- Primary objective is to determine the effect size of the breast density change between topical placebo and two doses of topical endoxifen. The effect size will permit sample size calculations for statistical significance in a future phase III trial.

8.1.1 Primary endpoint

- Primary endpoint is to determine change, on an individual level, in mammographic breast density, measured at 3 and 6 months after study entry (=baseline screening-mammography).

8.2 Secondary objective: Tolerability and Safety

- Secondary objective is to assess tolerability and safety of topical endoxifen

8.2.1 Secondary endpoints

- Determine dose dependent differences in compliance, side effects and local tolerability measured through questionnaires

- Determine dose dependent differences in laboratory assessments such as liver function tests (ALAT, ASAT, ALP, Bilirubin), coagulation function (INR, aPTT), sex hormone binding globulin (SHBG)

8.3 Tertiary objective

- The tertiary objective is to determine if plasma levels of endoxifen influence primary and secondary endpoints

8.3.1 Tertiary endpoint

- Tertiary endpoint is to determine if plasma level concentrations of endoxifen are related to primary and secondary endpoints

9 STATISTICAL METHODS AND CONSIDERATIONS

Karma CREME-1 is an exploratory pilot study conducted to aid the planning of a larger phase 2 trial. As such, the pilot study is not powered to show statistical significant reductions in breast density in the treatment arms compared to the control arm. Rather, the pilot study will give qualitative results, which will aid in making decisions about dosing, study length, and sample size for the phase II trial.

The pilot study's inclusion criteria will be the same as in the planned full study, but compliance is expected to be higher since the population is small and there will be a large number of contact points with each study participant. Furthermore, in the pilot study only Karma Cohort participants will be invited. The participants have shown that they are more willing to be recruited in the ongoing oral tamoxifen Karisma-2 trial than the ordinary screening attendant. Data from this pilot study will be used to adequately power a future, larger study.

9.1 Statistical methods and determination of sample size

All analyses will be performed after the study is completed and the database is released. All statistics, including tables, figures and listings, will be performed using SAS®, Version 9.3, and R, Version 3.x. The statistical analysis are described in detail in the Statistical Analysis Plan (SAP) including a Data Display Plan (DDP), which will be in a final draft version prior to study start and finalized and approved before database lock.

9.1.1 Demographics and baseline data

All data will be presented using descriptive statistics. Continuous variables will be summarized using number of women, mean, standard deviation (for symmetric distributions), interquartile range (for skewed distributions), median, minimum and maximum. Categorical variables will be summarized using the number and percentage of women.

9.1.2 Analysis of the primary endpoint (effectiveness)

The analysis of the primary endpoint qualitatively and quantitatively summarize difference in density change between baseline and at 3 and 6 months follow-up between the three arms. More specifically, the difference in density between baseline and at 3 and 6 months follow-up, respectively, for women in the placebo arm (ΔD_p) and in the two endoxifen arms (ΔD_{e1} and ΔD_{e2}), will be computed. Subsequently, the difference between ΔD_p and ΔD_{e1} as well as ΔD_p and ΔD_{e2} (at both 3 and 6 months) will be assessed.

The primary analysis will be performed on an intention to treat (ITT) basis, and a per protocol (PP) analysis will be performed as a secondary analysis. Women who stop using topical endoxifen will be encouraged to remain in the study and come in for an exit mammography. The density measured in these mammograms will be used in the analyses of the ITT population. Our experience from the Karisma-2 study is that virtually all women accept an exit mammography if choosing to withdraw from the study. However, women who drop out of the study and do not come in for additional

mammography appointments will be assumed to not have any density reduction for the ITT analysis. Sensitivity analyses where density for women who drop out is imputed based on age and density at baseline will also be performed.

Since this is a pilot study, which is not powered for showing statistical significance when testing for differences in mammographic density reduction between the treatment arms and the control arm, a simple criterion based on the difference in the mean of the density reduction across the two treatment arms and the density reduction in the control arm will be used instead. The concept *mt* is define as the mean of the reduction in mammographic density across all women in the two treatment arms (n=60) and the *mc* to be the mean on the reduction in mammographic density in the control arm (n=30). The result of the trial as *mt* minus *mc* will be summarized.

9.1.3 Trial operating characteristics

Simulations to assess the operating characteristics of the pilot study were performed. The simulations aimed at using the best data currently available to estimate the likely outcomes in the pilot study.

As a basis for the simulations, a dataset of 4,288 women aged 40-74 sampled from the Karma Cohort was used. Each woman had Stratus measured density from two mammograms taken at two different points in time (approximately two years in between the two time points as this is the screening interval in the Swedish national screening program). Summary statistics of the density at the two time points:

Time point 1: 25.5% (mean), 18.9% (median), IQR 8.3-35.2, 0.1 (min), 99.2 (max)

Time point 2: 23.3% (mean), 18.7% (median), IQR 8.3-34.4, 0.1 (min), 99.8 (max)

Women with BI-RADS categories B, C, and D will be invited to the Karma CRÈME-1 study. All women with a BI-RADS A density, which corresponds to women with a STRATUS density measures of 2% or lower (n=240), were removed from the dataset. The remaining women were used for simulations.

The following assumptions were used for all simulations:

- Age: 40-74
- BI-RADS: B, C, and D
- The density for women in the control arm is only affected by the natural reduction in density that typically comes with increased age. For simulations under the null, this applied also to the treatment arms
- 65% of the women in the treatment arm are good compliers and are assumed to get the whole density reduction that topical application of endoxifen can induce.
- 25% of the women in the treatment arm are poor compliers and are assumed to get half of the density reduction that topical application of endoxifen can induce.
- 10% of the women in each arm drop out of the study. It was assumed that the probability of dropout is proportional to the density reduction a given woman gets from the treatment (this is consistent with previous data that shows that it primarily is women who get a density reduction of tamoxifen who also experience side effects).
- The density reduction that topical application of endoxifen induces is proportional to each woman's density at baseline.
- Comparison between treatment and control arm will be done using a Wilcoxon test in the full phase II trial using a two-sided alpha=0.05 to declare statistical significance.

The assumption about the effect size (anticipated density reduction by using topical endoxifen) was then varied in different simulations according to the following:

- No or very little density reduction by using topical endoxifen (null hypothesis):

- 0% density reduction
- 1% density reduction
- 2% density reduction

- A clinically meaningful density reduction (alternative hypothesis):
  - Best guess. The density reduction by using topical application of endoxifen was assumed to the reduction seen in the pilot study of the Karisma-1 (oral tamoxifen, 10 and 20 mg) trial, i.e. 12% of the baseline density (range 1-19%).
  - Slightly smaller effect size than our best guess. Assuming the density reduction to be 10%
  - Slightly larger effect size than our best guess. Assuming the density reduction to be 14%

Given the dataset from the Karma Cohort and the assumptions listed above, the likely results from the pilot trial were simulated. Briefly, a trial cohort of 3x30 women by drawing women from the Karma Cohort and applying the density reduction in the treatment arm according to the assumptions above was repeatedly (N_{sim}=1000) simulated. Based on the results from the pilot trial, a decision on how to perform a larger, adequately powered study will be taken. Since the pilot study is not designed to show statistically significant results in terms of differences in density reductions between the three trial arms, a simple criterion based on the differences in mean density reductions between the placebo and treatment arms will be used for deciding about performing a larger trial. Whatever criterion picked, there will be non-zero probabilities of the pilot leading to false negative or false positive results. **Tables 4 and 5** summarize these probabilities for different choices of criteria.

Table 4. The table shows the probabilities of the pilot trial showing a false negative result based on different criteria for declaring a positive result from the pilot study. Simulations performed under the alternative hypothesis of a clinically meaningful reduction in density induced by topical application of endoxifen.

Criterion	Density Reduction		
	10%	12%	14%
mt-mc > 0%	10%	7%	3%
mt-mc > 1%	27%	20%	16%
mt-mc > 2%	52%	43%	33%
mt-mc > 3%	74%	66%	59%

Table 5. The table shows the probabilities of the pilot trial showing a *false positive* result based on different criteria for declaring a positive result from the pilot study. Simulations performed under the null hypothesis of no or only a very small reduction in density induced by topical application of endoxifen

Criterion	Density Reduction		
	10%	12%	14%
mt-mc > 0%	50%	56%	57%
mt-mc > 1%	24%	33%	35%
mt-mc > 2%	8%	16%	17%
mt-mc > 3%	2%	5%	5%

Based on these simulations of the operating characteristics of the trial, the criterion mt-mc > 0% as a criterion for a positive result from the pilot trial and for moving forward with a larger trial with adequate power for showing a statistically significant density reduction from topical endoxifen will be used.

9.1.4 Analysis of the secondary outcome

Estimate dose dependent differences in compliance, side effects and local tolerability and laboratory results.

9.1.5 Analysis of the tertiary outcome

Estimate if plasma level concentrations of endoxifen are related to primary and secondary endpoints.

9.1.6 Interim analysis

No interim analyses will be performed.

10 INVESTIGATIONAL PLAN

10.1 The Karma Study Centre

Women participating in the Karma CREME-1 study will conduct all study specific activities, except the mammography, at the Karma Study Centre. The Karma Study Centre is located in the facilities of Södersjukhuset Breast Centre (SöS Bröstcentrum) at Södra station, where mammographic examinations are conducted, and is daily staffed with two full time employed nurses and one full time employed investigator

10.2 Selection of study population

Eligible women will be identified from those women invited for mammography screening at SöS Bröstcentrum.

The rationale to exclude women with the lowest density is based on experience from the Karma Group previous study of mammographic density reduction in patients on tamoxifen. In that study the researchers had to exclude women with the lowest density since density change was not possible to measure in women with very low density. The lower cut off for inclusion is set to 4.5% density, measured by Volpara. The 4.5% level corresponds to the clinically used BI-RADS score A.

The rationale to exclude premenopausal women is to avoid natural fluctuations of mammographic density related to the changing hormone levels associated with the menstrual cycle.

10.3 Inclusion criteria

To participate, the women must meet the following inclusion criteria:

- Attending the national mammography screening program, i.e., aged 40-74 and have performed a screening mammogram maximum 3 months prior to study inclusion
- Mammographic density ≥4.5 % density (volumetric) measured by Volpara, at the screening mammogram performed in connection to baseline (maximum 3 months prior to inclusion). The threshold value of 4.5% corresponds to the clinically used BI-RADS score A
- Postmenopausal, defined as no period of menstruation during last 12 months independent of any hormonal treatment
- Informed consent must be signed before any study specific assessments are performed

10.4 Exclusion criteria

To participate, the women must not meet any of the exclusion criteria listed below at entry of the study nor under time of treatment.

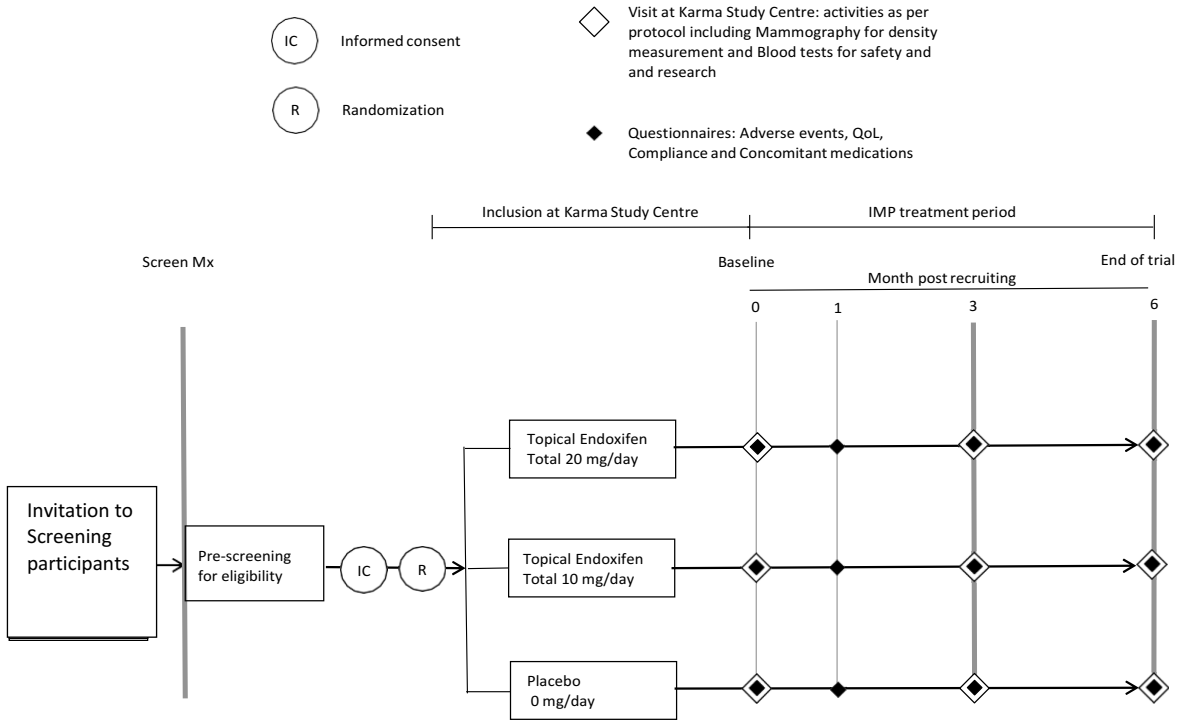
Criteria related to study design

- Any previous or current diagnosis of breast cancer (including carcinoma *in situ*).
- Any previous diagnosis of cancer with the exception of non-melanoma skin cancer and in situ cancer of the cervix.
- A history of major surgery of the breast, e.g., reduction or enlargement, which might affect density measurements.
- Mammographic BI-RADS *malignancy* code 3, or above, at baseline mammography, or at mammography during time of treatment. Recall for additional examinations due to technical problems with the mammogram is accepted.
- Currently using estrogen and progesterone based hormone replacement therapy (oral or patches). Local estrogen treatment is accepted (ex. Vagifem).
- Non-medical approved drugs against hot-flashes including phytoestrogen.

Criteria related to safety

- A history of thromboembolic disease such as embolus, deep vein thrombosis, stroke, TIA or myocardial infarction.
- Known APC (Activated Protein C)-resistance, an inherited haemostatic disorder.
- Women who have an increased risk of venous thrombosis due to immobilization, e.g., using wheelchair.
- Known uncontrolled diabetes.
- Hypertension at baseline, defined as systolic pressure higher than 140 mm Hg and diastolic higher than 90 mm Hg
- Prescribed and regular use of anticoagulants (defined as substances included in group B01A in the ATC-system)
- Not able to understand the study information and/or informed consent.

10.5 Overall study design



10.5.1 Invitation

Women invited for ordinary mammography screening to Södersjukhuset Bröstcentrum will receive an invitation to participate in Karma CREME-1. The invitation includes a comprehensive study information about Karma CREME-1 (see Study file; Studieinformation Karma CREME-1). In connection to the screening examination, interested women are invited to visit the Karma Study Centre (located within the screening facilities) to declare their interest of participation and to get further information about the study

10.5.2 Pre-screening of eligibility of participation

At Karma Study Centre:

- Karma nurse checks that the potential participant has read the study information, answers any questions, then confirms that potential participant fully understands the information.
- Screening for eligibility commences with blood pressure measurement.
- Volpara density measurement are performed and automatically retrieved from the performed mammogram in order to see that women meet inclusion criteria for density (≥4.5 % volumetric density).
- If it at this stage turns out that the woman doesn't meet inclusion criteria or meet any of the exclusion criteria, she will be given an explanation from investigator why she can't participate. A record of non-participation is done in the Study file screening-list.

10.5.3 Baseline (Month 0)

Meeting with Investigator

- The investigator will explain the nature and aim of the study, its procedures, possible side effects, requirements, restrictions and answer any questions.
- The study participant and the responsible investigator signs and dates the informed consent.
- A woman fulfilling the inclusion and exclusion criteria will be randomized to either placebo or any of two active substances.
- The woman will receive a sufficient amount of IMP for daily application for at least 3 months.
- Screening form, randomisation number and other study specific information will be filled in by investigator in the eCRF.

Procedures at baseline

After meeting with the investigator, the ICF is signed and randomization is performed, the following will be obtained:

- A total of 19.2 ml blood will be collected. 9.2 ml blood will be analysed for liver function tests, sex hormones and coagulation markers. 10 ml will be stored as a back-up sample for baseline measurements
- The participants will be asked to answer Karma CREME-1 baseline web-based questionnaire (see Study file; Questionnaires in Karma CREME-1)
- Measurement of weight and length
- Instructions are given on how to apply the topical endoxifen and what restrictions the participant shall adhere to (see Study file; Instruktioner Endoxifen kutan lösning)
- Instructions are given on how to report events and how to use the Karmapp

10.5.4 1 month after baseline (+2/-1 weeks)

- Karma CREME-1 follow up questionnaire including general symptoms, tamoxifen related symptoms, skin-related symptoms, compliance and health care contact connected to possible side effects

10.5.5 3 months after baseline (+/- 2 weeks)

- Mammogram (one image per breast only for density measurement purposes)
- A total of 19.2 ml blood will be collected. 9.2 ml blood will be analysed for liver function tests, sex hormones and coagulation markers. 10 ml will be used to measure for endoxifen markers
- The women will return empty sachets and secondary boxes for drug accountability. The women will receive a sufficient amount of IMP for daily application for at least 3 months
- Karma CREME-1 follow up questionnaire including general symptoms, tamoxifen related symptoms, skin-related symptoms, compliance and health care contact connected to possible side effects

10.5.6 6 months after baseline (+/- 2 weeks), visit at Karma Study Centre, end of study:

- Mammogram (one image per breast only for density measurement purposes)
- In total 19.2 ml blood will be collected. 9.2 ml blood will be analysed for liver function tests, sex hormones and coagulation markers. 10 ml will be used to measure for endoxifen markers in blood.

- Karma CREME-1 follow up questionnaire including general symptoms, tamoxifen related symptoms, compliance and health care contact connected to possible side effects
- Measurement of weight
- The women will return empty sachets and secondary boxes for drug accountability.
- The women will be informed that the study period has ended and she will receive the ordinary invitations to mammography within the national screening program in the future. When the trial is closed, information will be sent out to all participants with information about study results including dose and density change.

10.5.7 In between regular visits at the Karma Study Centre

The participants can at any time in between regular visit at the Karma Study Centre contact the Karma personal with questions and issues regarding adverse events, compliance and concomitant medications. The Karma personal will give participants fast access to health care in case of need. Contact channels are phone, mail, visit or the application Karmapp designed for the study.

10.5.8 Reminders

Women will receive SMS reminders regarding their upcoming appointment and/or web-questionnaire to complete.

Women not showing up at regular visits at the Karma Study Centre or fail to submit follow-up questionnaires will be contacted to ensure compliance and to ensure that no adverse events have occurred.

10.6 Criteria for discontinuation and handling of drop-outs

The participant should be excluded from the study if, in the opinion of the Investigator, it is medically necessary, or if it is the expressed wish of the participant. Women are free to discontinue their participation in the study at any time.

A withdrawn participant is not allowed to re-enter into the study. The criteria for withdrawal are the following:

- Participant wishes to discontinue
- Participant fulfil any, in the protocol defined, exclusion criteria
- Unacceptable adverse event/side effect
- Non-compliance with the study protocol
- Participant refuses to cooperate
- Other medical reasons

Irrespective of the reason for withdrawal and whenever possible, the participant should be encouraged to return for a clinical visit at the time of or soon after discontinuation and complete all evaluations which may be necessary to assure that the participant is free from any untoward effects and to perform appropriate follow-up for any continuing medical event.

There is also a scientific value to continue investigating the effects of topical endoxifen after the participant discontinues her treatment. Women that drop out after 1 week or more, will therefore be asked to perform exit examination; follow-up questionnaire, blood sampling and exit-mammogram. The time limit of exit exams is set to 2 weeks after the participant has stopped the medication. The women are asked, in all cases, to return the remaining IMP to Karma Study Centre.

Withdrawals will not be replaced. Inclusion stops when 90 participants have been included irrespective of numbers of drop outs.

10.7 Treatments

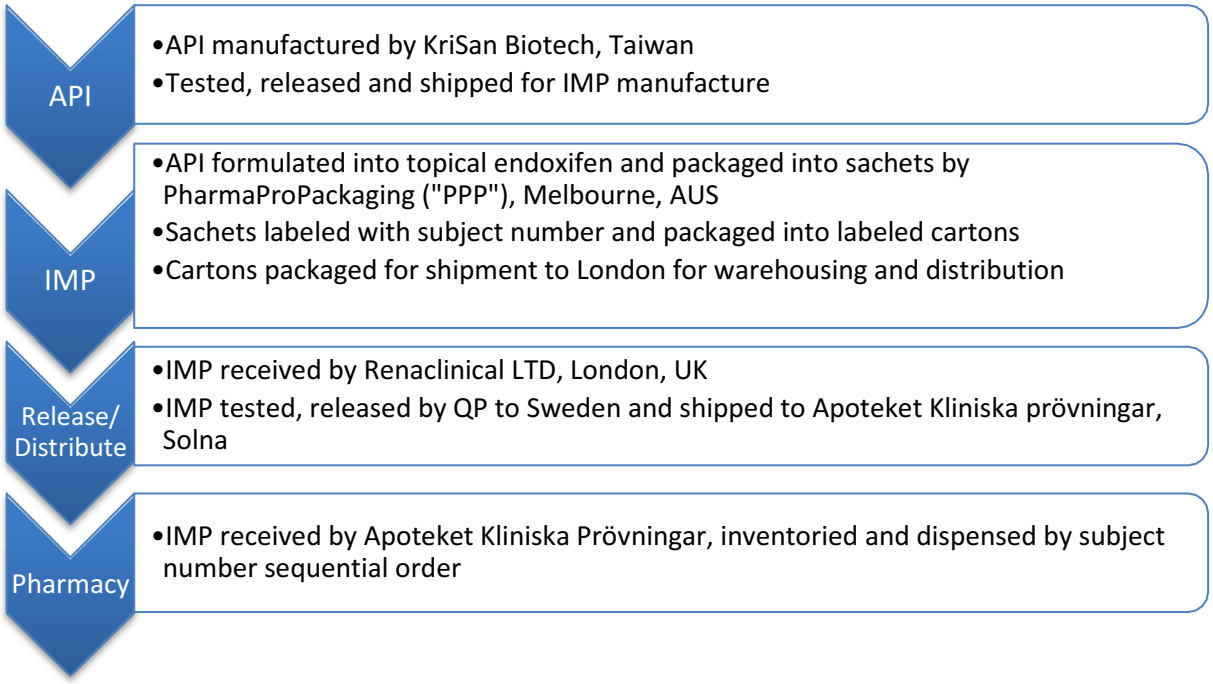
10.7.1 Identity of Investigational Medicinal Product (IMP)

The IMP, Topical endoxifen and its matching placebo, are formulated from widely used for both cosmetics and pharmaceutical topical constituents: Transcutol™ (2-(2-Ethoxyethoxy)ethanol); isopropanol, CrodamolTM GTCC (a fully saturated emollient triester) and mineral oil. The active IMP also contains endoxifen, the strength of which is based on Z-endoxifen content.

The formulated product is dispensed into single-dose (a dose defined as one administration per breast) and use "sachets". Each sachet is pliable and consists of laminated plastic and aluminum film. This configuration has been used for other topical pharmaceutical dosage units. Each sachet is fully sealed, labelled and sufficiently filled to deliver no less than 1.0 mL. Each sachet has a "nozzle" to facilitate the delivery of the product directly to the skin. It can be described as similar to a ketchup or mayonnaise packet for individual use at a restaurant (please also see more detailed description in the Investigator Brochure).

All investigational product (endoxifen and matching placebo) are manufactured according to Good Manufacturing Practice (GMP).

10.7.2 Flow of IMP from manufacturing to Investigators site



10.7.3 Packaging and labelling of IMP

The packaged Active Pharmaceutical Ingredient (API) is tested and released for shipment to PharmaProPackaging (PPP), Melbourne AUS, for drug product manufacture. Upon receipt by PPP, the identity of the API is confirmed, and used to manufacture the IMP, both the active and the placebo, and packaged into individual sachets according to GMPs. Each IMP is labelled with:

Each sachet (primary package) is labelled with:

- Atossa Genetics, USA
- 1 mL: 10 mg endoxifen or 5 mg endoxifen or placebo
- Topical, 1 sachet/breast /day
- Study: ATOS-010

- Rand.id: KCxxxx-x
- Batch Nr: xxx/xxx

Labelling is performed throughout the manufacturing process to limit the potential for mix-ups, in accordance with Good Manufacturing Practices (GMP).

Secondary packaging is labelled with same information as above with the additional information:

- Only for Clinical trial use
- Contains 184 sachets 1ml/sachet
- Storage instructions
- Sponsor: Atossa Genetics Inc. (contact information)
- Contact information Principal Investigator
- Expiry date: mm/yyyy

Size of labels and precise Swedish wording is to be found in Enclosure Labels in application to MPA.

10.7.4 Storage of IMP

When released the IMP will be stored at Apoteket Kliniska prövningar, Karolinska Sjukhuset, Solna.

They will store the IMP in the containers in which they are received from the Sponsor's supplier at room temperature. Extreme temperatures (hot, cold) should be avoided and the drug kept away from children.

10.7.5 Doses and treatment regimens

Participants will be randomized into one of three groups:

- Topical endoxifen, total 20 mg/day (10 mg/breast/day)
- Topical endoxifen, total 10 mg/day (5 mg/breast/day)
- Placebo 0 mg

Each participant will apply the contents of two sachets to each breast (one sachet/breast) each day for 6 months.

10.7.6 Investigational Medicinal Product accountability

The IMP will be dispensed to the study participant at baseline. A sufficient amount will be provided for at least 3 months. The number of sachets given out will be recorded in both CRF and in the Product Accountability log in the Study file. Participants are requested to bring back the empty sachets at the planned visits by 3 and 6 months or, by discontinuation, at time of exit examination. Any unused sachets will be saved for drug accountability and sent for destruction or to the manufacturer for analyses if directed by the sponsor.

10.7.7 Method of assigning participants to treatment groups

- A sequential list of participant identifiers (Rand.id) will be generated by the Investigator, and provided to the sponsor.
- Renaclinical LTD London will populate the sequential list of Rand.id and link dose of IMP (0 mg, 5 mg/sachet or 10 mg/sachet) to Rand.id in a randomized manner. A Randomization list is subsequently created.
- Renaclinical will provide the Randomization list directly to the pharmacy (Apoteket AB, Sjukhusapoteket Linköping) in a secured fashion, to be opened in case of a safety emergency.

- Renaclinical will also provide the Randomization list directly to PPP for blinded labelling and packaging.
- The IMP will be imported and received by Renaclinical. Once released by the QP, it will be sent to Apoteket Kliniska prövningar, Solna.
- IMP will be delivered to study site (Karma Study Centre) already randomized, packed and marked in a sequential order. The IMP will be provided to each participant in numerical order.
- The Investigator link the Rand.id to participant in the eCRF and Drug accountability log

Researchers do not have access to the Randomization list. In case of an emergency, the entire list will not be released, rather the treatment assigned for a specifically identified participant.

10.7.8 Blinding

The study is a double-blind, placebo controlled randomized study and neither the investigators, sponsor nor the participants will know who is on active treatment or placebo.

The randomization code (emergency envelope) is held by Apoteket AB, Sjukhusapoteket Linköping. The treatment code can only be broken if an investigator considers there is a valid medical or safety reason to break the blinding (see section 14.2 Emergency un-blinding, for further instructions). The Investigator must have a reason to break the blinding, for example when the studied drug is likely to have a significant effect on the clinical management of the study participant. When the code is broken for an individual participant, a notification must be made in the eCRF, and to the Principle Investigator and the Sponsor.

The study is also blinded for those responsible for mammographic density measurements.

10.7.9 Prior and concomitant therapy

All concomitant therapy must be recorded in the eCRF. No other drug under investigation may be used concomitantly with the study medication.

Although endoxifen is one of the first pass metabolites of tamoxifen, conditions that require medications metabolized by the P450 pathway should be carefully monitored during this study.

10.7.10 Prohibited medications

- Estrogen and progesterone based hormone replacement therapy (other than local), are not allowed during the study or used at study enrolment. Rationale for prohibition is potential interference with outcome measurements.
- Prescribed and regular use of anticoagulants (defined as substances included in group B01A in the ATC-system) are not allowed during the study or at time of study enrolment. Prescription of anticoagulants indicates that person is at risk of thrombosis. The literature and tamoxifen product information also describe concomitant use of tamoxifen and warfarin as a contraindication, since this combination may result in an increase in the anticoagulation and the risk of bleeding complications. Since the exact mechanism triggering this effect is not clear, the Sponsor declares the same precautions regarding endoxifen.
- Non-medical approved drugs against hot-flushes including phytoestrogen are not allowed during the study or used at study enrolment. Rationale for prohibition is potential interference with outcome measurements.

10.7.11 Treatment compliance

Compliance will be assessed throughout the study by: *i*) calculating the number of sachets remaining at the visits to the Karma Study Centre and comparing with the expected usage; and *ii*) by web-

questionnaires targeting adherence to therapy. The participant is defined as “compliant” if more than 80% of the sachets are used.

A maximum of 14 days of coherent treatment interruption is allowed. Longer time period than that must be seen as discontinuation of treatment.

11 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

Any untoward medical occurrence in a participant, who has received IMP, will be registered. The occurrence does not necessary have to have a causal relationship with the IMP. An AE can therefore be any significant change, unfavourable and/or unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

11.1.2 Serious Adverse Event

An SAE is any untoward medical occurrence or event, at any dose, that:

- Results in death
- Is life threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

or

- Other important medical event (example of such events are convulsions that do not result in hospitalization)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardises the participant’s health or may require intervention to prevent one of the other outcomes listed in the definitions above. These AEs should also usually be considered as *serious.*

It is important to distinguish between serious and severe adverse events. Severity is a measure of intensity whereas seriousness is defined by the criteria in the previous sections. An adverse event of severe intensity need not necessarily be considered serious. For example, nausea, which persists for several hours, may be considered severe nausea but not a serious adverse event. On the other hand, a stroke resulting only in limited degree in disability may be considered a mild stroke but would be considered a serious adverse event.

11.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a suspected unexpected serious adverse reaction, potentially causally related to the investigational medicinal product, and will be reported to the appropriate IEC and Regulatory Authorities.

11.2 Registration and Assessment of AEs

Adverse Events will be collected through the web-based questionnaire each study participant must complete at a regular basis (month 1, 3 and 6) after study entry during the study period. Additionally, the participants are encouraged to report AEs anytime (24 hours/day and 7 days/week) to the Karma

Study Centre by contacting through phone, mail, visit or using the application Karmapp. All AEs, serious and non-serious, will be recorded in the eCRFs.

11.3 Eliciting and recording of AEs

Adverse Events will be collected through the web-based questionnaire each study participant must complete at a regular basis (month 1, 3 and 6) after study entry during the study period. Additionally, the participants are encouraged to report AEs anytime (24 hours/day and 7 days/week) to the Karma Study Centre by contacting through phone, mail, visit or using the application Karmapp. All AEs, serious and non-serious, will be recorded in the eCRFs.

11.4 AEs of Interest

11.4.1 Definition of AE of interest

AEs reported after study entry via questionnaire (not Baseline questionnaire), telephone, mail, visit or via the Karmapp, with high level of intensity ("quite a bit " or "very much") are considered as AE of Interest. These AEs are flagged for in the CRM system (eCRF) as a point of action for investigators to assess causality to IMP and eventual action for follow-up.

As an AE of interest is also included:

- All AEs registered in eCRF as free text
- Vaginal bleeding; Intensity grade 3 of 5 (“somewhat”)
- Laboratory measurements (liver function tests and / or coagulation) outside reference limits or major changes since last measurement
- Contact taken with health care

A total of 52 pre-defined AEs is listed in the eCRF, free text excluded (Se Study file: Sources to Questionnaires in Karma CREME-1)

11.4.1.1 Assessment of AE of interest

In addition to pre-defined AEs, the ability to include free text to capture events outside of the pre-defined symptoms. These answers are continuously monitored by Karma staff in order to take immediate action if there are any signs of adverse events of interest or possible serious adverse event. Potential serious adverse events are signs of thromboembolism or vaginal bleedings.

An alarm system in the eCRF will alert personnel at the Karma Study Centre when an AE of interest is recorded to permit a rapid evaluation and to ensure appropriate follow up is performed throughout the study period.

All AEs of interest will be coded according to Medical Dictionary for Regulatory Activities - MedDRA. The Investigator will perform the coding.

The following evaluations are to be done by the Investigator about the AE of interest:

- **Description of the AE**. Describe each symptom and if possible include the diagnosis for description of the event.
- **Intensity** (if the intensity changes during the period of the AE the maximum intensity should be recorded)
  - Mild - symptoms which are easily tolerated (acceptable)
  - Moderate - symptoms which interfere with usual activity (disturbing)
  - Severe - symptoms which give incapacity to do usual activity (unacceptable)
- **Duration of the AE** (start - end)

- **Seriousness**
  - Yes or No, see definition of a SAE for seriousness, as of above.
- **Action taken due to the AE**
  - None
  - IMP stopped
  - Additional details on action taken, including diagnostic procedures, will be recorded for any women with vaginal bleeding or discharge. Any women who report abnormal vaginal bleeding or discharge or pelvic pain or pressure, will be promptly investigated. This also applies to participants with suspected signs of thromboembolism. It is not mandatory that the study code is broken in such cases, but this may be done if requested by the treating physician, necessary for further treatment.
- **Causality rating** with investigational medicinal product
  - Not related: Indicates that the AE is definitely not related to the study drug.
  - Unlikely: The adverse onset and the medicinal product administration is such that the medicinal product is not likely to have any reasonable association to the AE.
  - Possible: The participant ´s clinical status or the medicinal product could have produced the AE.
  - Probable: The AE follows a reasonable temporal sequence from the time of administration of the medicinal product, abates upon discontinuation of the medicinal product and cannot be reasonably explained by the known characteristics of the participant ´s clinical status.
  - Not assessable: There is not sufficient information to assess causality between the medicinal product and the suspected reaction.
- **Outcome of the AE** – follow until an outcome can be defined
  - Recovered/Resolved
  - Recovered/Resolved with sequelae
  - Recovering/Resolving
  - Not recovered/Not resolved
  - Fatal
  - Unknown

11.5 Reporting of SAEs and SUSARs to Sponsor and Authorities

11.5.1 Reporting of SAEs

All SAEs must be reported by the Investigator using phone, text, email or FAX within 24 hours from the Investigator's knowledge of the event to the Sponsor regardless of the time that may have elapsed from the time the event occurred to when the Investigator first learns of it. The initial report should contain as a minimum the following information:

- Participant identification
- Treatment specification
- Diagnosis or symptoms

- Name of the original reporter
- Date and time

An SAE report form must also be completed, signed by the Investigator and submitted to the Sponsor within 24 hours after the initial information was received. Additional information can be provided in follow-up reports, but it is critical to ensure the initial report is made as soon as possible. Apart from the information above, this follow-up report should also contain the following information:

- Assessment of intensity
- Assessment of causality

11.5.2 Reporting of SUSARs

SAEs that are both unexpected and assessed as related to IMP(s), i.e., SUSARs, should be reported by the Sponsor to the appropriate IEC and Regulatory Authorities. In Karma CREME-1, the Karolinska Trial Alliance (KTA) has the authorization from Sponsor to report SUSAR to the Investigator, Sponsor, regulatory health authorities, the IEC and DSMB

The Sponsor (or authorised agent) must report all SUSARs that were life threatening or resulted in death, to the authority and to the IEC within 24 hours, and if necessary complete the follow up report within the following 8 days. Other SUSARs should be reported within 15 days.

11.6 Duration of observation of AE/SAE

AE/SAE will be recorded from the moment the participant gives her informed consent to participation in the study, until the participant undergoes the final examination planned in the study and results from examination are evaluated. AEs reported up to 2 weeks after last day of treatment will be assessed according to protocol. AE/SAE that are persisting at the end of the study will be followed up and evaluated.

11.7 Follow-up of unresolved AE

If a participant is withdrawn due to an AE, or if an AE persists at the end of the study treatment period, this should be followed up until the condition has ceased, becomes stable or chronic, or until the participant is under professional medical care and a potential causality between IMP and the AE has been penetrated. An outcome assessment should be performed when an AE persists.

12 DATA QUALITY ASSURANCE

12.1 Electronic Case Report Forms (eCRFs)

The site personnel will enter the information required for the study in the eCRF. Data will also be imported from web questionnaire, medical records, laboratory findings and measurements of mammographic density.

12.2 Monitoring

The Karma CREME-1 study will be monitored according to ICH-GCP guidelines, Regulatory requirements and the study specific Monitoring plan. The Karma CREME-1 study will be monitored by an independent Monitor according to ICH GCP Guidelines. Study conductance, personnel training, source data and adherence to the study protocol will be monitored. Findings will be provided to the investigator such that corrective measures can be taken. Investigator will grant monitor, or certain regulatory personal, access to source data/medical records.

12.3 Data Monitoring and Safety Board (DSMB)

A chartered DSMB will be utilized to provide safety oversight of all study participants. Evaluations and assessments of adverse reactions, any safety trends or concerns, etc., will be reviewed as defined in the DSMB Charter

12.4 Source data

Source data will be handled according to regulatory requirements. A source data location list will be kept at the investigational site for definition of source data.

Mammograms will be retained as interpreted via the software as well as a raw electronic file.

12.5 Audit and inspections

The study site may be requested to participate in a quality audit by the Sponsor or someone appointed for this task by the Sponsor. A Regulatory Authority may request to inspect the study site. The procedures of such a visit would be similar to those of a monitoring visit, and data already checked by the Monitor may be checked again. The Investigator is required to inform Karma CREME-1 study staff immediately of a request to inspect by a Regulatory Authority. The investigator and other relevant personnel must be available during the audit/inspection and must devote sufficient time.

12.6 Changes in the approved Study Protocol

Study procedures must not be changed without the agreement of the Investigator and Sponsor and indicated as such by an approved amendment to the protocol.

Any substantial change (e.g., procedure changes increased blood sample volumes or frequencies; number of participants, study drug, etc.) to the approved Final Study Protocol will be documented in a written, signed, and revision numbered Protocol Amendment. Any proposed substantial change to the Final Study Protocol must be discussed with and approved by Sponsor and Investigator before submitted to IEC and Regulatory Authority for approval, according to applicable national regulations.

12.7 Data Management

A quality control (QC) of data will be performed to ensure that data entry and verification have been performed correctly in accordance to pre-defined instructions. The QC will be performed as described in the Data Management Plan (DMP). Audit trails will be used to ensure data changes are attributable. The QC will be performed and documented before data is declared clean.

13 STUDY MANAGEMENT

13.1 Study time table - End of study

The study will be open for inclusion from April 2018 and inclusion will continue for three months (with a stop of inclusion during summer vacations), or until 90 participants are enrolled. All attempts will be made to fully enrol the study prior to the beginning of summer vacation. If this is not achieved, then the last participant would enter into the study by the end of September 2018 and be followed for 6 months, that is, March 2019.

End of study is defined as when last participant fulfil study-period (6 months) + 2 weeks window of self-reporting of AEs.

13.2 Insurance/indemnity

All participants are insured against injuries received in connection with the trial by the Patient Injury Act insurance (Patientförsäkringslagen). Atossa Genetics shall maintain commercial liability insurance covering injuries to participants that are caused by study drug (equivalent to that of the Swedish Pharmaceutical Insurance Scheme “LFF”). Such insurance shall be underwritten by a nationally-

recognized insurance carrier with coverage of at least US $1 million per occurrence and US $2 million aggregate. The insurance shall cover Atossa Genetics' liability under law and generally accepted liability standards within the pharmaceutical industry towards any third parties, including participating women, as Sponsor of the study.

Atossa Genetics agrees to indemnify (legal and financial coverage) and hold the Investigator free of harm from any claim, whether based on legal principles or on generally accepted liability standards within the pharmaceutical industry, made against him by reason of personal injury, including death, to any person arising out of or connected with the performance of the study to the extent that the injury is not caused by:

1) Failure by the Investigator to adhere to the terms of the Protocol;

2) Failure by the Investigator to comply with any applicable governmental regulations; or

3) Malpractice, negligence or wilful malfeasance by the Investigator.

The Principal Investigator agrees to notify Atossa Genetics whenever he becomes aware of a claim or action, and to co-operate with and to authorize Atossa Genetics to carry out sole management of such claim or action. Atossa Genetics will provide the Principal Investigator with application forms in case of insurance claims.

13.3 Study agreements

The Principal Investigator at the investigational site must comply with all the terms, conditions, and obligations of the Clinical Study Agreement (CTA) for this study.

13.4 Criteria for termination of the study

The Karma CREME-1 study personnel reserve the right to discontinue the study at any time, but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the Principal Investigator must contact all participating women within 2 weeks and inform the women as well as perform relevant assessments, preferably according to the scheme for the final assessments. All delivered and unused study products and other study materials must be returned and all eCRFs completed as far as possible.

The sponsor (or the authorised agent) will also notify the IEC and the competent authority (Medical Products Agency) of any decision of premature termination of the study, within 2 weeks after such a decision.

13.5 Reporting of results and publication policy

Agreements on publications and dissemination is described in the site clinical trial agreement (CTA).

13.6 Record retention

The Investigator must arrange for retention at the investigational site of a list of the women and their identifying code, participant files and other study documents. The archiving period must be adapted to regulations in force but should not be shorter than ten years after the termination of the study and the presentation of the final report.

It is the responsibility of the Karma CREME-1 study personnel to inform the Investigator/institution as to when these documents no longer need to be retained

13.7 Disclosure and confidentiality

Agreements on Back- and Foreground Intellectual Property is described in the CTA.

14 EMERGENCY PROCEDURES

14.1 Emergency contacts

In case of a medical emergency, contact Karma CREME-1 study personnel:

- Per Hall, Responsible Medical Officer, Coordinating and Principal Investigator

Mobile +46733960590, email: per.hall@ki.se

- Mattias Hammarström, Clinical Trial Manager

Mobile +46737121476, email: Mattias.Hammarstrom@ki.se

14.2 Emergency un-blinding for safety reason

The randomization code (emergency envelope) is held by Apoteket AB Linköping, wich provide a 24/7 service for emergency un-blinding. In case of an emergency where, in the opinion of the Principal Investigator, discontinuation of the study treatment is not sufficient and the study treatment must be un-blinded in order to evaluate further course of action, the Investigator should contact Apoteket AB, Linköping (phone numbers and routines are to be found in the Study Site File) to initiate participant un-blinding. In the event the blind is broken, notify the Sponsor as soon as possible. The date, time, and reason for un-blinding must be documented in the appropriate section of the eCRF, and in the source document.

14.3 Procedures in case of medical emergency

The Investigator is responsible for ensuring that there are procedures and expertise available to cope with medical emergencies during the study. The study is performed at Södersjukhuset and any acute medical illness should be dealt with at the hospital.

14.4 Procedure in case of overdose

Overdosing topical endoxifen may increase the pharmacological side effects of the drug. Any study participant with a suspected or confirmed overdose of topical endoxifen should contact the Karma Study Centre. The Karma personal will in turn contact the Swedish Poison Information Centre.

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16 SIGNATURE PAGES

Principal Investigator

Study title:

Karma CREME-1: A double-blind, placebo-controlled, three-armed, pilot study of the effects, safety and tolerability of topical endoxifen in healthy women

By signing this page I acknowledge that I have read and understood the study protocol "Karma CREME-1: A double-blind, placebo-controlled, three-armed, pilot study of the effects, safety and tolerability of topical endoxifen in healthy women".

I also agree by signing this page that I will conduct the study in accordance with the procedures specified in the protocol and in line with applicable regulations, i.e. LVFS 2011:19, ICH GCP and the latest version of the declaration of Helsinki.

Coordinating Investigator and Principal Investigator, Södersjukhuset

Per Hall		20180416
Name	*Signature*	*Date*

Sponsor

Study title:

Karma CREME-1: A double-blind, placebo-controlled, three-armed, pilot study of the effects, safety and tolerability of topical endoxifen in healthy women

By signing this page I acknowledge that I have read and understood the study protocol "Karma CREME-1: A double-blind, placebo-controlled, three-armed, pilot study of the effects, safety and tolerability of topical endoxifen in healthy women".

I also agree by signing this page that the Sponsor will conduct the study in accordance with the procedures specified in the protocol, and in line with applicable regulations, i.e. LVFS 2011:19, ICH GCP and the latest version of the declaration of Helsinki.

Representative of Sponsor; Atossa Genetics Inc.

Janet R. Rea	Janet R Rea	16 April 2018
Name	*Signature*	*Date*

17 LIST OF APPENDECIES

A. Schedule of events

B. Participant card

17.1 Appendix A: **Schedule of Events in Karma CREME-1**

	Months				
	0	1	3	6	ET/W*
Key Tasks	SCREEN (BASELINE)	IMP Administration Period			
Informed Consent	x				
Physical Exam	x		x	x	x
Height	x				
Weight	x		x	x	x
Blood Pressure	x				
Mammography	*a*		x	x	x
MD Eligibility	x				
MD Efficacy			x	x	x
Blood sampling	x		x	x	x
Safety**	x		x	x	x
Back up sample	x				
Endoxifen metabolites			x	x	x
Randomise to dose group	x				
Administration of IMP	x		x		
Questionnaires	x	x	x	x	x
Adverse Event Assessment* **		x	x	x	x

*ET/W: Early Termination or withdrawal

a –from routine screening

**** Blood Sampling Safety:**

- Liver function test(ALAT, ASAT, ALP, Bilirubin)
- Coagulation function (INR, aPTT)
- Sex Hormone Binding Globulin (SHBG)

***** Adverse Event Assessment**

- Continuously from day 1 of IMP medication

17.2 Appendix B: **Participation Card**

Deltagarkort för klinisk forskningsstudie
Protokoll Karma CREME-1

Innehavaren av detta kort deltar i en klinisk forskningsstudie där Endoxifen-gel för utvärtes bruk utvärderas för förebyggande av bröstcancer. Studien innehåller en placeboarm och 2 aktiva armar (5mg/bröst/dag och 10mg/bröst/dag). Om information om studieläkemedlet är nödvändig för fortsatt vård av patienten ber vi er kontakta prövaren (meddelande kan lämnas dygnet runt),
Tel 08- 524 823 39

Studieläkemedel: Endoxifen kutan lösning

Protokoll Karma CREME-1

Studiedeltagarens namn: _____

Studiedeltagarens födelsedatum: _____

Prövarens namn: _____

Prövare kontaktinformation: Karma Studiecenter SöS Bröstcentrum
, Stockholm Sweden.
Tel: +46-8-524 823 39
karmastudien@ki.se

Version 1.0, 20180212