

EMPOWER Study: Study Protocol

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Prospective, controlled, non-interventional cohort study of Intrinsa use

<u>PROTOCOL DATE:</u>	Sep. 10, 2007
<u>DEVELOPMENT PHASE:</u>	Postmarketing study
<u>PRODUCTS:</u>	Intrinsa/Livensa (testosterone transdermal patch, 300 micrograms/24 hours)
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<u>PROTOCOL APPROVAL DATE:</u>	<i>Sep. 10, 2007</i>
<u>START OF PATIENT ENROLLMENT:</u>	Q4/2007
<u>LAST FOLLOW-UP:</u>	Q3/2015
<u>FINAL REPORT:</u>	Q4/2015

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
HSDD	Hypoactive Sexual Desire Disorder
IAB	Intrinsic Advisory Board
ITT	Intention to treat
P&GP	Procter & Gamble Pharmaceuticals, Inc.
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
WY	Women-years
ZEG	Centre for Epidemiology & Health Research (acronym for the German term 'Zentrum für Epidemiologie & Gesundheitsforschung')

Protocol Body

1. Introduction

Hypoactive sexual desire disorder (HSDD) is the persistent or recurrent deficiency or absence of sexual thoughts/fantasies and/or of desire or receptivity for sexual activity, which causes personal distress or interpersonal difficulties. In some menopausal women, a decrease in testosterone is associated with a loss of sexual desire, resulting in personal distress. This disorder can be effectively treated by administering testosterone at levels that are compatible with a woman's physiology.

Intrinsa is a transdermal patch that delivers 300 mcg of testosterone daily through the skin of the abdomen, providing women with testosterone levels that are within the physiological range for premenopausal women. It is indicated for the treatment of HSDD in women with bilateral oophorectomy and hysterectomy who are receiving concomitant estrogen therapy.

Data from placebo-controlled clinical trials for up to 12 months do not show any serious health concerns. Mild androgenic adverse effects have been observed in these trials, but most have not caused subjects to withdraw. However, these clinical trials have some limitations in quantifying risks that are rare in incidence and in establishing long-term effects of treatment. Cardiovascular and breast safety related to long-term testosterone administration are of particular interest.

The potential risks of cardiovascular and breast adverse effects related to testosterone treatment, which have been evaluated on the basis of retrospective cohort studies, observational data, and data from the literature, are currently assessed to be minimal. Procter & Gamble Pharmaceuticals, Inc. (P&GP) has established a comprehensive risk management plan including a number of post-authorization follow-up activities and studies to further supplement the current safety database. Results will be reported to European regulatory authorities within a predefined timeframe. The present study is part of this regulatory commitment. The primary outcome of interest from the regulatory authorities point of view is breast cancer.

In this prospective, controlled, non-interventional cohort study, information on selected safety outcomes (breast and other gynecological cancer, myocardial infarction and other cardiovascular events, and other serious adverse events¹) will be collected for a period of up to 8 years using a sample of women prescribed Intrinsa in a postmarketing, clinical practice setting. This study combines the strengths of the spontaneous reporting system (i.e., individual causality assessments) and epidemiological cohort studies (i.e., quantification of the incidence of events). Data generated by the study will be shared with regulatory authorities at intervals to be agreed upon.

¹ Serious adverse event means any adverse event that results in death, a life-threatening experience, inpatient hospitalization, persistent or significant disability/incapacity, or requires medical/surgical intervention to prevent one of said outcomes.

2. Study Objectives

The two main objectives of this study are as follows:

- to estimate the incidence of breast cancer, other gynecological cancer, myocardial infarction, other cardiovascular outcomes, and other rare serious adverse outcomes among Intrinsa users in actual clinical practice, and
- to compare these incidences with the incidences found in the comparison group of women with bilateral oophorectomy and hysterectomy using estrogen therapy. The primary variable for the statistical analysis is the breast cancer hazard ratio for Intrinsa users in comparison to users of estrogen therapy.

The secondary objectives of the study are:

- to analyze the Intrinsa utilization pattern in a study population that is representative for the users of this novel treatment,
- to characterize the baseline risk of Intrinsa users for breast cancer and cardiovascular diseases (lifetime history of co-morbidity, risk markers, co-medication, socio-demographic and lifestyle data), and
- to investigate the reversibility of specific androgenic outcomes (clitoromegaly and severe voice deepening) after stop of treatment.

3. Investigational Plan

3.1. Study Design

This will be a prospective, controlled, non-interventional long-term cohort study of women who are prescribed Intrinsa or estrogen therapy. The study will use a non-interference² approach to provide standardized, comprehensive, reliable information on these treatments in a routine clinical practice setting.

The two study cohorts will consist of new users of Intrinsa³ and estrogen therapy⁴, respectively. After study entry, cohort members will be followed for a period of five to eight years for rare serious safety outcomes. Regular, active contacts with the cohort members by the ZEG study team (= active surveillance) will provide the necessary information on health-related events or changes in health status. Additional follow-up procedures (cf. section 3.3.3) will be used to validate self-reported events.

² I.e., 1) all patients who are new users of study medication are eligible for enrollment if they give their informed consent; and 2) recruitment of patients should not influence the physician's prescribing, diagnostic, or therapeutic decisions.

³ In combination with estrogen therapy. If not indicated otherwise, the term "Intrinsa" is used in this document for the combination of Intrinsa and estrogen therapy. New users of Intrinsa are women 1) who start Intrinsa and estrogen therapy, 2) who start Intrinsa and continue to use estrogen therapy, or 3) who switch from a previously used androgen preparation that is not indicated for HSDD to Intrinsa and start or continue estrogen therapy.

⁴ Without simultaneous use of Intrinsa. If not indicated otherwise, the term "estrogen therapy" is used in this document for estrogen therapy without use of Intrinsa. New users of estrogen therapy are women 1) who start estrogen therapy or 2) who switch from one estrogen preparation to another estrogen preparation.

All cohort members will be contacted at 6 and 12 months after study entry, and then every 12 months⁵. By means of these contacts, almost all relevant clinical outcomes will be captured. However, laypersons often misclassify adverse events (e.g., pneumonia as “pulmonary embolism” or migraine attacks as “stroke” even if modern imaging procedures do not provide any indication of the perceived event). This type of inaccuracy in patient reports will require careful validation of the reported events. This will be accomplished by contacting the relevant physicians and by reviewing relevant source documents. Under routine medical conditions, clinical outcomes are not always confirmed by diagnostic procedures with high specificity. Therefore, reported serious clinical outcomes have to be classified as “confirmed” or “not confirmed” according to a predefined algorithm (cf. section 3.3.3). At the end of the study this classification will be verified by blinded independent adjudication (cf. section 3.3.3).

3.2. Selection of Study Population

Approximately 5,400 subjects per cohort will be recruited by participating physicians in order to provide 50,000 women-years (WY) of observation (cf. section 3.5.2), assuming a withdrawal rate of 10% per year.

The study will be conducted in Germany, the UK, Spain, France, and Italy. The study could be extended to other countries (e.g., Canada) based on the international registration and launch status of Intrinsa. Recruitment of cohort members will be conducted via existing networks of physicians (gynecologists in Germany, France, Spain and Italy, and general practitioners in the UK) who have participated in similar cohort studies in the past. In addition, new physicians will be identified by a variety of methods including general press releases and direct mailings. After the initial contact, physicians will be provided with an information package and asked whether they wish to participate in the recruitment of subjects for this study. Those expressing an interest will be sent subject information packages that include informed consent forms and contact information in case of questions. Physicians will be considered active in the study only after they have recruited their first subject.

Subjects will be considered for enrollment in this study after the participating physician has determined, based upon the SmPC product label, that Intrinsa or estrogen treatment is appropriate. There will be no inclusion/exclusion criteria other than the guidance provided by SmPC/local product label. I.e., all women with bilateral oophorectomy, hysterectomy, and HSDD who receive a new prescription for Intrinsa are to be asked by their physician if they are willing to participate. All women with bilateral oophorectomy and hysterectomy who receive a new prescription for estrogen therapy are also to be asked to participate. HSDD is not a mandatory criterion for enrollment into the estrogen therapy cohort. As this is a non-interventional study, the possibility to participate in the study should not be discussed with the patient before both - physician and patient - agree upon the prescription. The physician is to explain the nature of the study, its purpose and associated procedures, and the expected duration of follow-up for each woman prior to her entry into the study. Each woman is to have ample opportunity to ask questions and must be informed about her right to withdraw from the study at any time without disadvantage and without having to provide reasons for her decision. This information will be provided on an informed consent and data privacy form which must be

⁵ Planned follow-up for each individual patient is from 5 to 8 years (cf. section 3.3.2).

signed by all study participants. These documents are to be approved by the relevant local Ethics Committees and the relevant Data Privacy Office, if applicable.

The participating physician will be responsible for managing all subject care and will be instructed that treatment with Intrinsa should be consistent with the SmPC/local product label (e.g., Intrinsa users should return to the office for evaluation within 3 to 6 months of the initiation of treatment). If a physician enrolls a subject for whom Intrinsa is not indicated, this subject will still be eligible for study enrollment. Subjects who have been prescribed Intrinsa or estrogen therapy up to six months before they are asked to participate in the study may also be enrolled.

Once enrolled, a subject may discontinue use of study medication at any time. However, subjects will continue to be followed whether or not they remain on study medication, provided that they do not withdraw their consent. During the follow-up phase, subjects will be asked whether they have discontinued treatment with study medication. Information on the date and reason for discontinuation during the follow-up phase will also be collected.

It is expected that the baseline risks for breast cancer and cardiovascular diseases are balanced across the two cohorts or that differences between the cohorts are small enough to sufficiently limit their impact on the hazard ratios (cf. section 3.5) by adequate adjustment for confounders or by stratification. In the unlikely event that a comparison of baseline risks demonstrates major imbalances between the cohorts (e.g., much higher age or much longer use of estrogen therapy in the estrogen therapy cohort) in the early phase of the study a protocol amendment that could lead to more balanced baseline risks could be considered (e.g., introduction of an upper limit for age or duration of use for estrogen therapy users). The final decision on protocol amendments would have to be made by the Intrinsa Advisory Board (cf. section 8).

3.3. Data Collection and Study Procedures

The study will be divided into 2 phases: a clinic phase, which includes an initial consultation at baseline with a participating physician, and a follow-up phase, which includes two follow-up contacts within the first year, and then annual follow-up contacts for up to 8 years post-baseline. Visits and follow-up contacts are calculated in calendar months and years following the baseline visit. The schedule of study visits and follow-up contacts is presented in tabular form in Appendix 1.

3.3.1. Clinic Phase

Each physician's office will be provided with simple questionnaires for collecting data at baseline. The baseline visit will take place at the participating physician's office. All ovariectomized and hysterectomized women who receive a new prescription for Intrinsa or estrogen therapy are to be asked if they are willing to participate. Only after Intrinsa or estrogen therapy has been prescribed will the physician discuss the study with the subject. This ensures that participation in the study is not considered a requirement for treatment. After discussing the study details (including follow-up procedures and intervals, content and duration of follow-up contacts, use of data collected, etc.), each subject will be asked to provide written informed consent to participate in the study. If the subject needs time to consider participation, she will be

free to leave the physician's office with her prescription and take an appropriate period to decide whether to participate.

The informed consent will include permission for study data to be collected and analyzed and for contacts to be made by ZEG at intervals during the follow-up phase for collection of study information. Each subject will also be asked to provide information regarding alternative contacts (a close relative or friend, or primary care physician) if ZEG cannot reach the subject after several attempts. Permission for ZEG to contact a subject's primary care physician/attending physician(s) and to review applicable national health databases (where possible and permissible) for relevant subject information will also be sought. Follow-up frequency by ZEG will be explained, and the content of follow-up contacts will be described.

Confidentiality will be maintained throughout the study and no personal information will be shared with alternative contacts. P&GP will not have access to names, addresses, or alternative contact information for the subjects, and all individual subject data will remain anonymous. Personal and medical information will be recorded on separate documents. ZEG will ensure that access to personal information is restricted in accordance with data privacy rules.

The following information will be recorded at the baseline visit after the patient has provided written informed consent:

- study medication (Intrinsa/estrogen therapy),
- personal and demographic information,
- medical and gynecological history,
- family history of breast cancer and cardiovascular outcomes,
- history of estrogen use (including treatment dates),
- current estrogen use (including type of estrogen and treatment dates),
- history of androgen use (including tibolone and including treatment dates),
- other concomitant medications, and
- socio-demographic and lifestyle information.

Appointments for return visits should be made in compliance with the SmPC/local product label (e.g., according to the Intrinsa SmPC treatment response should be evaluated within 3-6 months of initiation).

3.3.2. Follow-Up Phase

ZEG will perform all follow-up activities during this phase of the study. All subjects who provide written informed consent will be contacted for follow-up regardless of the duration of treatment or whether they discontinue treatment with Intrinsa. Subjects who withdraw their consent for follow-up will not be contacted. P&GP will not have access to names, addresses, or alternative contact information for the subjects.

Follow-up questionnaires will be mailed to the study participants at 6 and 12 months after study entry, and then every year for up to 8 years to collect information regarding major safety outcomes. ZEG personnel will make initial contact with the subject 3 months after study entry to introduce themselves and to determine the subject's communication preferences during the

follow-up phase (i.e., time of day, day of week, telephone, e-mail, etc.). Additional contacts 18, 30, 42, 54, 66, 78, and 90 months after study entry will be used to facilitate subject retention and follow-up, if needed to achieve the targeted loss to follow-up rate (cf. section 3.3.4); however, these contacts will be brief and no other questions will be asked other than those regarding contact preferences. Subjects will be given a clear explanation of contact frequency at the time of informed consent.

The specific safety data to be collected during follow-up will focus on the following major safety outcomes: breast cancer and other gynecological cancer diagnoses or procedures, myocardial infarction and other cardiovascular diagnoses or procedures, death, and hospitalization.

Subjects who report any of these adverse outcomes will be asked to provide their primary care physician's/treating physician's name and address for further follow up. ZEG will contact the physician and inform him/her about the study objectives and will share the subject's informed consent to access her medical information. Follow up by ZEG will include obtaining hospital records and/or discharge summaries, medical history, Intrinsa treatment dates, and concomitant medication use (including past estrogen therapy). A qualified medical expert (i.e., pharmacovigilance physician) on the ZEG study team will assess the likelihood of a causal relationship to Intrinsa treatment for each serious or unexpected adverse drug reaction in accordance with a predefined algorithm (cf. Appendix 2).

In addition, the occurrence of specific androgenic outcomes (clitoromegaly and severe voice deepening) and their reversibility after stop of treatment will be investigated.

At each follow-up contact, subjects will be asked about their estrogen use and whether they continue to use the prescribed study medication.

3.3.3. Validation of Self-Reported Events

A self-administered questionnaire used by patients at short intervals is a very sensitive tool which captures almost all serious clinical outcomes. From a methodological point of view, it captures a much higher proportion of these outcomes than methods relying only on the prescribing gynecologist/primary care physician who often is not involved in the diagnosis and treatment of these outcomes. However, it must be considered that there is a significant difference between the rates of reported and validated events, because laypersons often misclassify adverse events. Therefore, validation of the self-reported events is of utmost importance.

Validation of self-reported events will start at the level of the local field organizations with a review of all subjective "events." This will be followed by a further review at the international coordinating center (ZEG).

If an adverse event is reported by a study participant, the subjectively perceived symptoms, the signs of disease and if possible the diagnoses as understood by the patient are to be recorded in the follow-up questionnaire. The name and address of the relevant physician (attending physician, physician responsible for the follow-up treatment after discharge from hospital, or primary care physician) are also documented.

Follow-up questionnaires containing information on such an event are to be immediately passed on to the medical reviewer group. If information is unclear or missing the woman will be contacted by phone, e-mail or other means. For many serious events it will be necessary to contact the diagnosing and/or treating physician for clarification and validation of the information received from the patient. This procedure is mandatory for all breast and other gynecological cancer cases, myocardial infarction and other cardiovascular SAEs,.

Under routine medical conditions, diagnosis of an SAE is not always confirmed by a diagnostic method with high specificity. Therefore, SAEs are classified by the investigators as “confirmed” or “not confirmed” according to a predefined algorithm (cf. Appendix 3).

In order to minimize classification bias - particularly if selectively affecting individual exposure cohorts - classification of self-reported breast and other gynecological cancers, myocardial infarction and other serious cardiovascular outcomes, into confirmed and not confirmed cases will be checked by three independent medical experts specializing in radiology/nuclear medicine, cardiology, and gynecology. They will review all available information on the reported outcomes. For this process, the brand names and composition of the treatments used by the reporting woman will be rendered anonymous. The adjudicators will perform the reviews independently of each other and without knowing the judgement of the other adjudicators or the investigators. Details of the procedure are given in Appendix 4.

3.3.4. Loss to Follow-Up

A low “lost to follow-up rate” will be essential for the validity of the study. In order to minimize loss to follow-up a multi-faceted, four-level follow-up process will be established. Level 1 activities include mailing of the follow-up questionnaire and – in case of no response – two reminder letters. If level 1 activities do not lead to a response, multiple attempts are to be made to contact the woman, friends, relatives and the Gynecologist/Primary Care Physician per phone. In parallel to these level 2 activities searches in national and international telephone and address directories are started (level 3 activities). If this is not successful, an official address search via the respective governmental administration will be conducted. This level 4 activity can provide information on new addresses (or emigration or death). If necessary, a search in the national death registers could be started at the end of the study to clarify the vital status of patients who are lost to follow-up after level 4 activities. The total loss to follow-up at the end of the study should be kept at less than 10% of the recruited population.

3.3.5. Subjects Previously Prescribed Intrinsa

Subjects who were prescribed Intrinsa or a new estrogen therapy for a period of six months or less before study entry may also be enrolled. Baseline data will be recorded retrospectively at study entry. The first follow-up questionnaire will be sent to these women six months after the start of treatment. Women who at baseline have used Intrinsa or the new estrogen therapy for more than six months are not eligible.

3.4. Data Management

When questionnaires are received from study participants, all pages are counted and date-stamped. Questionnaires are to be checked for correct subject identification number, missing pages, legibility, and incomplete information on the questionnaires (cf. section 3.3.4 ‘Loss to Follow-Up’). Missing pages, illegible or missing information are requested from the study participants prior to data entry of the respective questionnaire.

Data are entered by double data entry via formatted entry screens designed to reflect the appearance of the questionnaire. Discrepancies between first and second data entry are identified by comparison of the two entry files within the statistical software SAS. The decision on the true entry is done by the responsible data manager at ZEG. This may require direct contact with the study participant who filled in the questionnaire. Corrections will be made to the questionnaire only after contact with the study participant or her treating physician (cf. section 3.3.3 ‘Validation of Self-Reported Events’). All corrections are dated and initialed by the data manager who received the relevant new information (e.g., via direct contact or by a copy of medical reports/documents). The incorrect CRF entry will be crossed out; however, it must remain legible, and the correct entry will be placed next to it. The reason for any correction of medical data on the questionnaire must be documented.

Quality control of entered data will be supported by SAS plausibility programs which include range, coding, missing and date checks as well as cross-reference (consistency) checks between variables.

3.5. Statistical Methods

3.5.1. Statistical Analysis Plans

The final analyses will be based on ITT and “as treated” data sets using Cox regression models. Based on available data (cf. section 1) the a priori assumption is that use of Intrinsa is not associated with an increased risk of breast cancer. That is, a statistical comparison of Intrinsa and estrogen therapy, which according to the results of the WHI study of hysterectomized women did not show a heightened risk of breast cancer,⁶ is not expected to show a difference. Therefore, the Principal Investigator and the Intrinsa Advisory Board (cf. section 8) have chosen a non-inferiority design to investigate the breast cancer risk of Intrinsa. The primary analysis will be based on the comparison of the upper confidence limit for the point estimate of the breast cancer hazard ratio with the predefined non-inferiority limit (cf. section 3.5.2). Similar considerations apply to other myocardial infarction, other cardiovascular outcomes, and other rare serious adverse outcomes.

Crude as well as adjusted hazard ratios will be calculated. The appropriate confounding variables will be built into the model. Based on the expectation of a small absolute number of serious

⁶ The Women’s Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women’s Health Initiative randomized controlled trial. *JAMA*. 2004; 291:1701-1712

outcomes of interest the number of confounding variables will be limited to well established risk factors for these outcomes (e.g., age, BMI, duration of use, smoking, hypertension). The final decision on the confounding variables will be made by the Intrinsic Advisory Board (IAB). In addition, alternative analysis will be performed with other potential baseline risks to check the appropriateness of this decision.

A detailed statistical analysis plan will be developed by the Investigator during the first year after study start. This plan will include methodological details as well as a comprehensive set of mock tables for the presentation of the study results. The final analysis plan will be approved by the IAB before the first interim analysis of follow-up data. Changes of this document are to be approved by the IAB.

3.5.2. Power and Sample Size Considerations

Based on ZEG's experience with similar cohort studies it is expected that 3,000 to 5,000 European gynecologists and general practitioners can be motivated to participate in the study. If each of these physicians recruit one patient per cohort and year a total of 9,000 patients per cohort could be recruited over 3 years. However, in similar studies only 60% of the physicians who had agreed to participate actually recruited patients. Therefore, a total recruitment of 5,400 patients per cohort is expected.

The annual drop-out rate in similar studies has been approximately 10%. Based on this drop-out rate, a follow-up of all patients till the end of the 8th study year would result in more than 25,000 WY of observation per cohort (see table 1). To be on the safe side, however, the sample size calculations presented in this section are based on a drop-out rate of 20%. This would result in more than 18,000 WY of observation per cohort.

Roughly 50% of the participating physicians could probably be identified among the members of ZEG's physicians network. Other potential study centers will be informed about the study via advertisements in medical journals and targeted mailings inviting physicians to participate in the study. Several professional organizations (e.g., menopause societies, sexual medicine societies) are expected to support the study. Country-specific strategies to increase awareness of the study will be optimized, as appropriate for each country.

The breast cancer incidence is expected to be lower than the overall incidence of serious cardiovascular outcomes. Therefore, the power calculation is based on the expected breast cancer incidence. In addition, the sample size considerations for cardiovascular outcomes are given at the end of this section.

Table 1: Expected observation time per cohort

Assumptions: 5,400 patients per cohort recruited over 3 years; follow-up of all patients until the end of the 8th study year; individual follow-up for 5 to 8 years; drop-out rate of 10% per year

Time (y)	Sub-cohorts recruited during the					
	1 st study year		2 nd study year		3 rd study year	
	No. of women	Time of observation	No. of women	Time of observation	No. of women	Time of observation
1	1,701 [#]	851				
2	1,531	1,616	1,701 [#]	851		
3	1,378	1,454	1,531	1,616	1,701 [#]	851
4	1,240	1,309	1,378	1,454	1,531	1,616
5	1,116	1,178	1,240	1,309	1,378	1,454
6	1,004	1,060	1,116	1,178	1,240	1,309
7	904	954	1,004	1,060	1,116	1,178
8	814	859	904	954	1,004	1,060
WY (total)		9,281		8,422		7,468
WY (grand total)	25,171					

* Time after start of recruitment

The number of recruited women equals 1,800. However, the number of women at the end of the first year is lower because some women will drop out during the first year (monthly drop-out rate ~ 0.87%)

The age distribution of subjects who participated in four Intrinsa studies of surgically menopausal women with HSDD is shown in table 2. Applying age-specific breast cancer incidence rates (derived from the SEER Cancer Registry) to the expected number of subjects within each age category (see table 2) yields an overall breast cancer incidence of 229 cases/100,000 WY. In addition, it should be noted that the study population will age during the long-term follow-up. Overall, the breast cancer incidence is expected to be approx. 250 cases/100,000 WY.

Table 2: Age distribution of Intrinsa users and breast cancer incidence per age-group

Age	Proportion	Incidence (per 10 ⁵ WY)
< 39	11%	40
40-49	41%	160
50-59	41%	305
> 60	8%	420

To be on the safe side, however, the following power calculation is based on a conservative estimate of 200 breast cancer cases/100,000 WY. The study should be powered to test non-inferiority of Intrinsa treatment regarding breast cancer and serious cardiovascular outcome risk in comparison to women using estrogen therapy. Sample size calculations for a non-inferiority

test of two exponential survival curves^{7, 8} showed that 4,567 patients per cohort should be sufficient to reach this goal. These calculations are based on the following assumptions: 1) breast cancer incidence and incidence of serious cardiovascular outcomes are higher than 200 cases/100,000 WY; 2) $\alpha = 0.05$; 3) power $(1-\beta) = 0.90$; 4) non-inferiority limit on hazard ratio = 2; and 5) the size of the two cohorts is comparable.

Based on this calculation, the study is sufficiently powered to exclude a 2-fold breast cancer risk for Intrinsa users compared to estrogen therapy users in the event that

- the true breast cancer risk among Intrinsa users is not higher than among estrogen therapy users
- recruitment and drop-out rates are in line with the calculations given in the first two paragraphs of this section (3.5.2).

However, precise power calculations based on actual incidences and drop-out rates should be done on the basis of first year follow-up data. If these calculations do not confirm the assumed incidences and drop-out rates the Intrinsa Advisory Board may discuss the need to adapt patient numbers and follow-up times.

The sample size considerations regarding cardiovascular outcomes are based on the results of the Women's Health Initiative (WHI) study⁹ for estrogen-only therapy. The placebo group of women aged 50 – 59 showed an incidence for the composite outcome for cardiovascular disease (incl. coronary heart disease, stroke, and venous thromboembolism) of 530 outcomes/100,000 WY. The incidence for fatal and non-fatal myocardial infarction was 240 outcomes/100,000WY. A power calculation based on a conservative assumption of 200 myocardial infarctions/100,000 WY would lead to exactly the same sample size requirements as the calculations for breast cancer (see above). Overall, the study should be sufficiently powered to exclude a 2-fold risk of breast cancer, total cardiovascular disease, as well as myocardial infarction.

4. Ethical Conduct of the Study and Protecting Subject Privacy

The study will be conducted in a manner that is consistent with all relevant European and national guidelines and regulations for conducting studies with human subjects. Specifically, the latest version (2004) of the Helsinki Declaration¹⁰ and the guidelines for Good Epidemiological Practice (GEP)^{11, 12} will be observed. All steps will be taken to protect subject's privacy and all

⁷ Collett, D. Modelling Survival Data in Medical Research. Chapman & Hall 1994; Section 9.2

⁸ Benner A, Ortseifen C. Sample size software for equivalence trials of survival time data. <http://www.dhfz-heidelberg.de/biostatistics/benner/eqsurf.pdf> [online]

⁹ The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women's Health Initiative randomized controlled trial. JAMA. 2004; 291:1701-1712

¹⁰ Internationally recognized document defining the ethical principles of clinical research; it resulted from a series of meetings of the World Medical Association – an global organization representing physicians – between 1964 and 2004.

¹¹ 'Good Epidemiologic Practice (GEP) – Proper Conduct in Epidemiologic Research' issued by the European Epidemiology Federation in 2004

¹² 'Guidelines for Good Pharmacoepidemiology Practices (GPP)' issued by the International Society for Pharmacoepidemiology in 2004

relevant rules on data privacy will be followed. It will be ensured that subjects' names and addresses cannot be accessed by P&GP.

4.1. Institutional Review

Review of the study protocol will be obtained at central ethics committees in the appropriate geographies as required by local law. This non-interventional, observational study is part of the Intrinsic risk management program submitted to the central European regulatory agency (EMA) and, as such, will be reviewed by the appropriate regulatory body. Non-interventional studies are not within the scope of the European Clinical Trial Directive (2001/20/EC). Accordingly, clinical trial applications to individual European national authorities will not be filed. However, regional regulatory approval within certain European member states will be obtained as required by national regulations.

4.2. Subject Consent

Subjects will sign informed consent forms at baseline after reading a subject information sheet and discussing the study with the participating physician. The physician will describe the purpose of the study, the non-interventional character of the study, timing and expected content of follow-up phase contacts, and collection of alternative contact information. Consent will include permission to contact any treating physician to follow up on specific safety outcomes. Subjects will be informed that ZEG will contact them during the follow-up phase (5 to 8 years) to ask a predefined set of safety related questions or to update alternative contact information. Answers to these questions collected by ZEG will remain anonymous when forwarded to P&GP.

Subjects will be asked to provide personal contact information (e.g., telephone number, home and e-mail address) and information regarding alternative contacts (e.g., relative, friend, general practitioner) in case they cannot be reached. In the event that a subject cannot be reached during the follow-up phase, ZEG will attempt to reach an alternative contact to re-establish contact with the subject, or, in the event of a subject's death, to confirm the cause of death. Subjects may be contacted between two follow-up points to confirm that their personal contact information is correct.

Subjects retain the right to withdraw their consent at any time during the study. If they wish to withdraw consent during the follow-up phase, they may inform ZEG and no further direct contact will be made.

5. Publications

The final study protocol and the results of this study will be published. In accordance with the International Committee of Medical Journal Editors (ICMJE) initiative requiring prior entry of clinical studies in a public registry as a condition for publication, the study will be registered in the U.S. National Institutes of Health's protocol registration database (<http://ClinicalTrials.gov>).

6. Study Management

This study will be conducted in accordance with

- ‘Good Epidemiological Practice (GEP) – Proper Conduct in Epidemiologic Research’ issued by the European Epidemiology Federation in 2004
- ‘Guidelines for Good Pharmacoepidemiology Practices (GPP)’ issued by the International Society for Pharmacoepidemiology in 2004
- the ethical principles that have their origin in the Declaration of Helsinki.

7. Reporting of Serious Adverse Drug Reactions

ZEG will report all serious adverse events that are possibly related to the use of study medication to the relevant pharmaceutical companies. ZEG will not monitor whether these companies meet their obligation to report these events to the health authorities according to (inter)national rules.

8. Intrinsic Advisory Board

This study will maintain scientific independence from the Sponsor and will be governed by an independent Intrinsic Advisory Board (IAB). The IAB will be responsible for regular review and evaluation of safety data during study conduct as well as for review and approval of the study protocol, analysis plan, interim results, study report, and publications. P&GP will assure financing of the study. ZEG and its research team will be accountable to the Advisory Board in all scientific matters. The members of the IAB will be international experts in relevant scientific fields (e.g., epidemiology, gynecology, cardiology, statistics, endocrinology, and drug safety). The members will receive remuneration of expenses and an honorarium to compensate for loss of potential earnings during their work for the IAB. The members will not be involved in or paid for the operational conduct of the study.

9. Appendices

9.1. Appendix 1: Schedule of Study Procedures

Schedule of Study Procedures		
Study Procedures	Baseline	Follow-up 1 to 9 ^a
Informed consent	X	
Collect subject's regular and alternative contact information ^b	X	X
Personal and demographic information	X	
Medical and gynecological history	X	
History of estrogen use (including treatment dates)	X	
Document estrogen treatment dates (including type of estrogen)	X	X
Document Intrinsic treatment dates	X	X
Other concomitant medications	X	X
Document reasons for stopping study medication		X
Document all adverse events ^c		X
Document primary safety outcomes ^d		X
<p>^a Data will be collected 6, 12, 24, 36, 48, 60, (72, 84, and 96) months after study entry. The 72, 84, and 96-month follow-ups apply only to patients who are recruited during the first 2 study years.</p> <p>^b All contact information will be stored with ZEG.</p> <p>^c Serious adverse drug reactions should be documented on separate case report forms and reported to P&GP within 24 hours.</p> <p>^d Major safety outcomes include breast and other gynecological cancer diagnoses or procedures, myocardial infarction and other cardiovascular diagnoses or procedures, death, and hospitalization.</p>		

9.2. Appendix 2: Drug Relationship

Categories (Code)	Definition
no (1)	<p>The time course between administration of the study drug and occurrence or worsening of the adverse event rules out a causal relationship <u>and/or</u> another cause is confirmed and no indication of involvement of the study drug in the occurrence/worsening of the adverse event exists.</p>
unlikely (2)	<p>The time course between administration of the study drug and occurrence or worsening of the adverse event makes a causal relationship unlikely <u>and/or</u> the known effects of the study drug or of the substance class provide no indication of involvement in occurrence/worsening of the adverse event and another cause adequately explaining the adverse event is known <u>and/or</u> regarding the occurrence/worsening of the adverse event a plausible causal chain may be deduced from the known effects of the study drug or the substance class, but another cause is much more probable <u>and/or</u> another cause is confirmed and involvement of the study drug in the occurrence/worsening of the adverse event is unlikely.</p>
possible (3)	<p>Regarding the occurrence/worsening of the adverse event, a plausible causal chain may be deduced from the pharmacological properties of the study drug or the substance class, but another cause just as likely to be involved is also known <u>or</u> although the pharmacological properties of the study drug or the substance class provide no indication of involvement in the occurrence/worsening of the adverse event, no other cause gives adequate explanation</p>
probable (4)	<p>The pharmacological properties of the study drug or of the substance class <u>and/or</u> the course of the adverse event after dechallenge and, if applicable, after rechallenge <u>and/or</u> specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) suggest involvement of the study drug in the occurrence/worsening of the adverse event, although another cause cannot be ruled out.</p>
definite (5)	<p>The pharmacological properties of the study drug or of the substance class <u>and</u> the course of the adverse event after dechallenge and, if applicable, after rechallenge <u>and</u> specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) indicate involvement of the study drug in the occurrence/worsening of the adverse event and no indication of other causes exists.</p>

9.3. Appendix 3: Validation of Self-Reported Events

- Definite Event:
Confirmed by diagnostic measures with high specificity (e.g., phlebography for DVT, spiral CT for pulmonary embolism, cerebral MRT for cerebrovascular accidents, ECG with typical ST segment elevation for acute myocardial infarction, histology for gynecological cancer, two-sided blood pressure measurement with diastolic blood pressure of more than 120 mmHG for hypertensive crisis)
- Probable Event:
Absence of confirmation by a diagnostic measure with high specificity, but clinical diagnosis confirmed by a health professional or supported by diagnostic tests with low specificity (such as D-dimer for VTE or typical ECG/blood gas tests for PE). These cases are usually characterized by a subsequent specific therapy (such as fibrinolysis or long-term anticoagulant therapy). However, if the attending physician confirms that the diagnosis is correct, the event will be classified as a probable event even if specific treatment was not given.
- Event not confirmed:
 - Diagnosis reported by the patient is excluded by diagnostic procedures
 - A different medical condition is diagnosed by the attending physician
 - The woman did not contact a health professional to clarify her symptoms and no diagnostic measures were performed that could have clarified the diagnosis

Definite and probable events will be classified as 'confirmed events'.

9.4. Appendix 4: Blinded Adjudication

The following adjudication procedure will be established:

- 1) Independent adjudication by the individual specialists
- 2) Documentation of the individual assessments
- 3) Comparison of the individual assessments
- 4) Discussion of “split decisions” among the adjudicators without enforcement of a unanimous decision
- 5) Independent re-adjudication of the discussed cases by the individual adjudicators
- 6) Documentation of the individual assessments

Based on this procedure four different classification strategies will be possible

- I. Classification of the reported event according to the assessment of the majority of adjudicators before the discussion of “split decision” takes place (i.e., “majority vote” based on step 2 of the six-step procedure described above)
- II. Classification of the reported event according to the assessment of the majority of adjudicators after discussion of “split decision” takes place (i.e., majority classification based on step 6 of the six step procedure described above)
- III. Classification of the reported event as confirmed if at least one adjudicator had classified the event as confirmed before the discussion of split decisions took place (i.e., “worst case decision” based on step 2 of the six-step procedure described above)
- IV. Classification of the reported event as confirmed if at least one adjudicator had classified the event as confirmed after the discussion of split decisions took place (i.e., “worst case decision” based on step 6 of the six-step procedure described above)

The final analysis will be based on strategy III (worst case decision without discussion of split decisions) because it represents the most conservative approach. Alternative analyses will be possible on request of the Intrinsic Advisory Board or regulatory authorities.