SCIENTIFIC DISCUSSION

1 Introduction

INTRINSA is a testosterone transdermal patch (also called a testosterone transdermal system, TTS). This is a thin, clear, 28cm^2 matrix patch which contains 8.4 mg testosterone and provides 300 micrograms/24 hours testosterone over a 3- to 4-day period when applied to intact abdominal skin.

The approved indication is: treatment of hypoactive sexual desire disorder (HSDD) in bilaterally oophorectomised and hysterectomised (surgically induced menopausal) women receiving concomitant estrogen therapy.

Lower free testosterone concentrations are seen in oophorectomised women with low libido compared to women with normal libido, but there is a great overlap in testosterone concentrations. At menopause, the production of oestrogen declines and the postmenopausal ovary secretes primarily androstenedione and testosterone. Total testosterone production decreases by around 25% after menopause. It has been estimated that oophorectomy in a postmenopausal woman would reduce her total testosterone production by around 50% and her total androstenedione production by around 20%.

Hypoactive sexual desire disorder (HSDD) is defined as 'a deficiency or absence of sexual fantasies and desire for sexual activity. The disturbance must cause marked distress or interpersonal difficulty and must not be better accounted for by another psychological disorder or medical condition'. In the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10; 2003) HSDD is listed under 'lack or loss of sexual desire' where 'loss of sexual desire is the principal problem and is not secondary to other sexual difficulties, such as erectile failure or dyspareunia'.

Estimates of the proportion of women having low sexual desire range from 7 to 33%. Studies conducted by the Applicant enrolling women with surgical menopause found that 46% of women aged 20-49 and 38% of women aged 50-70 reported decreased interest in sex after surgery. In addition to significant distress due to low desire, affected women can suffer from depression and anxiety and sexual dysfunction can significantly impair partner relationships and decrease quality of life.

2 Quality aspects

Introduction

Intrinsa contains testosterone as the active substance. It is presented as a matrix type transdermal patch with an area of 28 cm^2. Each patch contains 8.4 mg of testosterone and is designed to release 300µg of testosterone /24 hours over a 3 to 4 day period, when applied to intact abdominal skin.

It is a thin flexible patch and consists of three layers: a non-removable polyester protective film (backing layer), the adhesive matrix containing the active substance and a polyester removable protective layer (release liner). The backing layer is made of a translucent polyethylene (LDPE) polymer. The matrix layer contains the active substance, sorbitan oleate as a permeation enhancer and a pressure sensitive acrylic copolymer adhesive. The release liner consists of two overlapped siliconised polyester film liner strips, designed to be peeled off and discarded by the patient prior to applying the patch to the skin. Each transdermal patch is packed in a heat sealed sachet.

Active Substance

The chemical name of testosterone is 17β-hydroxyandrost-4-en-3-one. It is a well-known active substance monographed in the European as well as in the US Pharmacopoeia. Testosterone appears as white to nearly white crystals, or crystalline powder. It is practically insoluble in water and has no pronounced hygroscopic behaviour. The structure of the active substance has been characterised using NMR (^{1}H and ^{13}C), MS, IR elemental analysis and X-ray diffraction. Testosterone exhibits six chiral carbons, however it has been demonstrated that only one single enantiomer is present in the substance used for the manufacture of the Intrinsa transdermal patches. The IR spectra confirm the existence of only one crystal form.

The applicant has submitted information for two suppliers of testosterone. One of them has submitted a certificate of suitability to the monographs of the Eur. Pharmacopoeia and for this reason no further assessment except stability was performed. The other has submitted information concerning the details of the manufacture, controls and validation of the active substance in the form of an active substance master file (ASMF). The information mentioned below concerns only the active substance for which an ASMF has been submitted.

- Manufacture

The active substance is produced by a three-step synthesis starting from androstenedione. Androstenedione is a steroidal material produced by fermentation from phytosterols by a subclonal mutant strain of the wild type organism *Mycobacterium fortuitum*. It is also an intermediate in the natural degradation pathway of testosterone.
Detailed information has been submitted demonstrating that no impurities are present at significant level in the active substance, other than those described in the respective EP monograph for testosterone. A residual solvent evaluation conducted on ten production batches, demonstrates that the levels of all solvents evaluated were below the limits set by ICH guidelines.

- Specification

The active substance specification includes tests for appearance, identification (IR), assay (UV), related impurities (HPLC, TLC), residual solvents (GC), specific optical rotation (Ph. Eur) and loss on drying (Ph. Eur). The non-Ph.Eur. tests included in the specification (HPLC, GC) have been adequately described and validated in accordance with the ICH requirements.

Batch analysis data have been provided for three non-micronised and three supportive micronised batches. For the manufacture of the Intrinsa patches the non- micronised form is being used. In all cases the results met the pre-determined specifications.

- Stability

Stability studies have been performed to demonstrate the stability of testosterone, when stored at long-term conditions. Five batches of non-micronised active substance have been stored for up to 60 months at ambient conditions and one for 7 months at 25°C/60% RH. In addition six batches of micronised testosterone have been stored for up to 60 months at ambient conditions.
Despite the fact that there are some minor deviations from the ICH requirements, the stability data provided demonstrate that the active substance is stable when stored at room temperature/ambient relative humidity for the proposed shelf life.

Since the CEP submitted for testosterone provides no information on stability and no re-test period, the applicant has performed additional stability studies. Data have been obtained from batches stored at 15°C to 25°C (three batches) for 60 months, at 25°C ± 2°C/ 65% RH (two batches) for up to 36 months and at 45°C (three batches) for 6 months. In all cases no significant change has been observed in any specification parameter and for this reason the proposed re-test period was found to be acceptable.

Medicinal Product

- Pharmaceutical Development

Intrinsa is a matrix type transdermal patch. In these types of patches the active substance is dissolved directly in the adhesive, which is kept in contact with intact skin. The objectives in developing this product formulation were threefold: a) to provide sufficient blood levels of testosterone for effective therapy; b) to provide consistent delivery of testosterone over the dosing period; and c) to ensure acceptable adhesion to allow for continuous wearing over the dosing interval with minimal skin irritation. The matrix formulation is designed specifically to present a sufficiently high concentration of the active substance to the stratum corneum, which is the primary absorption-controlling factor.

Important factors in the development of matrix-type transdermal delivery systems include adhesive quality and skin tolerability, active ingredient concentration, skin permeability, skin flux enhancer concentration and compatibility, as well as stability. All of these factors were evaluated in the development of the drug product. Since testosterone is dissolved in the adhesive, the particle size and physical form of the active substance were not considered as critical.

The selection of the adhesive was based on in-vitro skin permeability studies in human cadaver skin and existing knowledge. The rate and extent of skin permeation is fundamentally associated with the concentration of the active ingredient in the matrix composition. The active substance concentration and patch size have been studied in relation to diffusion through skin both *in vitro* and *in vivo* (abdomen and buttocks from both men and women). It was determined that the selected concentration of testosterone in the matrix formulation is appropriate to provide sufficient skin flux to achieve the desired absorption rate from a patch of a reasonable total surface area. Special attention was given to the physical stability of the formulations with respect to crystal formation. No crystal formation was seen at any of the conditions or storage durations studied (room temperature for 17 months, and 40 and 45°C for 6 months). A number of potential skin permeation enhancers were examined for their effect on steady state flux of testosterone from matrix formulations. Based on preliminary skin flux studies and on its well-known skin tolerance, sorbitan oleate was selected.

The polymers used in the release liner and the backing film are suitable for pharmaceutical use and compatible with the adhesive solution.

The composition of the final formulation was selected based on the results of *in-vitro* skin permeability studies, the adhesive characteristics and stability studies. The proposed formulation has been found to provide a nominal transdermal delivery rate of testosterone 300 µg/day from a skin contact surface area of 28 cm^2 over a dosing duration of up to 4 days. The actual delivery rate is determined directly from human pharmacokinetic studies.

Process development has primarily been focused on optimisation of the individual steps and the definition of the critical ranges of the process parameters. Detailed optimisation data have been provided for the adhesive solution mixing (blade speed, mixing time), the coating process (line speed/web speed, oven temperatures), die cutting (machine tension, rotary die pressure) and the pouching process (heat seal die pressure, heat seal die temperature, heat seal die dwell time).

The patch formulation used in the phase III pivotal clinical trials is identical to the one intended for marketing.

In general the excipients of this formulation are commonly used. Sorbitan oleate is tested for compliance to pharmacopoeia monographs. It is stated to be of animal origin and a TSE certificate has been provided. The other excipients are tested for compliance to in-house monographs.

- Manufacture of the Product

The manufacturing process has been described in detail. It comprises of the following steps (1) mixing of adhesive, testosterone and sorbitan oleate to achieve the casting solution, (2) coating of the casting solution on the polyester release liner, drying of the casting solution on the liner, and laminating of a printed backing film onto the dried casting solution, (3) removal of the release liner, laminating of the same release liner or alternatively addition of a new one on the casting solution in an overlapping fashion/way, (4) die cutting and pouching of patches, and finally (5) packaging into a secondary packaging (carton).

All critical process parameters have been identified and controlled by appropriate in process controls. The validation report from several production scale batches demonstrates that the process is reproducible and provides a drug product that complies with the in-process and finished product specifications.

- Product Specification

The product specifications include tests by validated methods for the appearance, content uniformity (HPLC), assay (HPLC), identification (HPLC), degradation products (HPLC), residual solvents (GC), drug release (dissolution testing), adhesion to steel and release liner peel.

The specification and control tests applied for the finished product at time of release and throughout the life of the product, are in compliance with pharmacopoeial standards (including Ph Eur) and ICH guidelines. The limits for each specification test are supported by stability data.

Batch analysis data from nine batches of the finished product have been provided. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release and indicated that patches of consistent quality are obtained.

- Stability of the Product

Stability studies were carried out on 11 pilot scale batches of transdermal patches according to the ICH requirements. The batches were manufactured by the commercial process using active substance from both suppliers and stored in the intended primary package. Samples were stored at 25°C/60 % RH for up to 39 months, at 30°C/60 % RH for up to 13 months and in 40°C/75 % RH for 6 months.
The samples were tested according to the release specification (parameters, methods and acceptance criteria). In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Intrinsa is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is well characterised and documented. The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. The manufacturing process of the finished product is a standard process that has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

3 Non-clinical aspects

Introduction

INTRINSA is a transdermal patch containing the active substance testosterone (with a nominal testosterone release of 300 µg/day).

The non-clinical data on acute toxicity, carcinogenicity, genotoxicity, reproductive toxicity, and safety pharmacology were based on the literature.

Specific studies have been conducted to evaluate skin tolerability of INTRINSA. The non-clinical development programme has appropriately concentrated on skin tolerability of INTRINSA and the patch adhesive. All local tolerance studies performed or sponsored by the Applicant were conducted in compliance with GLP.

Pharmacology

- Primary and or secondary pharmacology

No data have been submitted.

- Safety pharmacology

There is a significant body of literature, both non-clinical and clinical, evaluating the effects of testosterone on a range of pharmacological endpoints. A range of dose levels and dose routes have been evaluated, and much of the work focuses on pharmacological effects in males. The doses used were generally much higher (i.e., in the male ranges) when compared to the claimed concentrations in the clinic with the testosterone transdermal system.

In **cardiovascular studies**, testosterone has been shown to have vasodilatory properties in a wide variety of vasculature and vascular beds.

There are no data on blood pressure effects in animals, but clinical studies have indicated this is not a concern.

Testosterone has recently been evaluated for its effects on cardiac electrophysiology. While it does block HERG channel *in vitro*, it does not show any consistent effect on QT interval prolongation in either animals or humans. It appears to reduce the potential for this effect produced by other drugs.

There were no published reports on **respiratory effects** of testosterone.

No specific information about the effects on the **central nervous system** was submitted.

Overall, non-clinical safety pharmacology findings raise no safety concerns for the use of transdermal testosterone in women at the low dose provided by the testosterone transdermal system.

- **Overall conclusions on pharmacology**

Testosterone is the predominant, naturally occurring androgenic hormone in mammals. The testosterone transdermal patch provides a low dose of testosterone (300 microgram/day) and the concentrations in the clinic are stated to be within the reference range for premenopausal women.

Literature reports provided the basis for assessment of endpoints not deliberately tested for in the clinic, *i.e.* safety pharmacology, which was adequately evaluated. This is appropriate in view of the substantial preclinical and clinical data relating to the pharmacodynamics and safety pharmacology of testosterone.

The above non-clinical safety pharmacology findings raise no safety concerns for the use of transdermal testosterone in women at the low dose provided by the testosterone transdermal system. The androgenisation in female animals by administered testosterone is addressed in the reproduction section.

Pharmacokinetics

No non-clinical pharmacokinetic study reports have been submitted. In addition, taking into consideration the extensive pharmacokinetic assessment included in the clinical programme, no sponsored non-clinical pharmacokinetic studies were conducted for ethical/animal welfare reasons.

The CHMP agreed with the Applicant that no key additional information to support this submission would be obtained from animal pharmacokinetic studies.

Toxicology

Also provided in this section is a review of toxicological evaluations conducted with the excipients used in the clinical formulation of the transdermal patch. The toxicity profile has been documented in applicant-sponsored studies and scientific literature.

- **Single dose toxicity**

No classical single dose study data are available in the literature. Literature reports involving single doses of testosterone propionate administered to rats did not result in a lethal toxic response.

- **Repeat dose toxicity**

Regarding repeat-toxicity the Applicant referred to two studies.

. The effects of repeat administration of testosterone propionate on muscle weight (i.e., to treat/reverse hypertrophy) have been examined in adult female rats, and it was noted that testosterone treatment had no effect on muscle weight or body weight.

- **Genotoxicity**

The genotoxicity profile of testosterone has been evaluated in a wide range of well designed (including all ICH endpoints) *in vivo* and *in vitro* studies reported in the literature.
Testosterone was reported as being non-mutagenic in a range of assays evaluating effects on chromosomes: in the Ames test in bacteria, in a mouse lymphoma assay and in chromosomal aberration tests (HeLa cells, human synovial cells, Chinese hamster Don cells) except in the Chinese hamster lung cells where a clastogenic response in was observed at the highest dose tested corresponding to cytotoxic dose levels. Three mouse micro nucleus tests were reported from different laboratories, and all were negative. An absence of DNA adducts was further reported.
In *in vivo* tests testosterone was non-mutagenic in two micronucleus tests in mice and in one chromosomal aberration test (sperm head morphology and chromosomal aberrations bone marrow) in rats.

The results of these studies consistently confirm the lack of a genotoxic effect with testosterone.

- **Carcinogenicity**

A substantial body of literature demonstrate that as expected for a hormonally active compound, tumour incidence can be increased in hormonally responsive organs and tissues including endometrium, mammary glands, and liver.

In 1987, the International Agency for Research on Cancer (IARC Supplement 7) concluded in the overall evaluation that androgenic (anabolic) steroids are probably carcinogenic in humans.

Testosterone is most probably associated with an increased risk for carcinogenicity through epigenetic mechanisms as genotoxicity data are overall negative. This would likely result in proliferative responses in organs with expressed receptors. In females these organs would include mammary tissue, the uterus, ovaries, and the liver. Studies also have shown that when co-administered with a carcinogen, testosterone at high doses is a promoter in rodent animal models. Testosterone was also evaluated in SHE cells for its transforming effects, and it was found to be weakly positive with no dose response. This finding was consistent with an epigenetic mechanism, and with promoter properties as the SHE assay can respond to both genotoxic and epigenetic carcinogens. It has been demonstrated that in male mice, hepatocarcinomas are androgen dependent, exemplifying the complex response of rodents to exogenous hormones.
Several publications have presented experimental data associated with changes following neonatal testosterone exposure. Overall, the exposure of young female animals to testosterone results in life-long changes characterised by androgenisation.

Consistent with other marketed testosterone products, statements about rodent carcinogenic data are included in the 5.3 section of the SmPC.

- **Reproduction Toxicity**

Extensive data are available on the reproductive and developmental effects of testosterone. Testosterone is a potent androgenic hormone and its effects on developing foetuses are pronounced and thus, developing foetuses should not be exposed to testosterone. Across multiple species, masculinisation of the foetus anatomically and increases in aggressive behaviour, are the end results of exposure to testosterone during neonatal development.

A NOEL of 0.1 mg testosterone propionate per rat, administered sc is reported in the literature. Assuming a rat weight of 300 g, this is a dose of 333 µg/kg/day. For comparison the daily dose of testosterone from the patch is 300 µg. Thus a 50 kg woman would be exposed to 6 µg/kg/day, over 50 fold less than the NOEL in rats.

No topical reproductive studies are reported in the literature.

- Toxicokinetic data

Literature data were submitted
- Local tolerance

Dermal irritation studies (rabbits) and skin sensitisation studies (guinea pigs) were conducted by the Applicant with the active testosterone transdermal system and placebo patches according to GLP principles.

Both patches were classified as moderate irritants. However some of the irritation was attributed to the trauma associated with removal of patches from the skin.

No evidence of delayed dermal contact skin sensitisation was seen in either of the performed studies with active testosterone transdermal or placebo patches in female guinea pigs.

Other toxicity studies

The components of the patch that will be in contact with skin during administration consist of an adhesive matrix that contains the active ingredient testosterone and the excipients sorbitan monooleate (permeation enhancer) and acrylic adhesive. All of the skin contacting ingredients were evaluated for dermal irritation and sensitization in rabbits and guinea pigs respectively using the clinically formulated patch. In addition, sorbitan monooleate has been evaluated separately in dermal irritation and sensitization studies in rabbits and guinea pigs as well as in single dose, repeat dose, and carcinogenicity studies in rats and rabbits following topical, ocular, and oral administration. The toxicity of the acrylic adhesive was investigated separately in a battery of studies including an *in vitro* biocompatibility study in mouse fibroblasts, a dermal irritation study in rabbits, a muscle implantation study in rabbits, and an oral systemic toxicity study in mice.

In conclusion sorbitan monooleate is considered to be a minimal skin irritant and did not irritate the eyes.

The applicant has conducted four studies with regard to the safety of the acrylic adhesive.
The toxicity of has also been investigated separately in an in *vitro* biocompatibility study in mouse fibroblasts, in a dermal irritation study in rabbits, in a muscle implantation study in rabbits, and in an oral systemic toxicity study in the mouse.

In conclusion, the acrylic adhesive is considered to be non-toxic and nonclinical data do not raise any safety concerns relevant to clinical use.

- **Antigenicity**

In a GLP dermal sensitization study in female guinea pigs, delayed contact hypersensitivity was not induced by any of the ingredients in the transdermal patch.

- **Immunotoxicity**

Hughes et al. (1995) reported in immune response studies that testosterone did not have a significant effect on the production of antibodies *in vivo* in response to sheep red blood cell (SRBCs), and did not cause human peripheral blood lymphocytes to produce inflammatory cytokines *in vitro.*

- **Dependence**

The testosterone transdermal patch delivers a low dose of 300 microgram/day testosterone, consequently it is not appropriate to perform such studies for this product.

- **Metabolites**

Testosterone and its metabolites are naturally occurring hormones. It is well recognised that both endogenous and exogenous testosterone are metabolised in the same way. There is sufficient clinical data both from the testosterone 300 µg transdermal patch clinical programme and in the literature to establish the safety profile of testosterone metabolites. Consequently no further non-clinical work was conducted by the Applicant.

- **Ecotoxicity/environmental risk assessment**

The Predicted Environmental Concentrations of testosterone in surface water (PEC) was calculated and literature was provided and support the applicant's conclusion that risks to the environment are unlikely from use of the patch is endorsed.

Discussion on the non-clinical aspects

Testosterone has been used and is used in several other products indicated for use in males. The current application concerns a testosterone 300 microgram transdermal patch, which is indicated for hypoactive sexual desire disorder (HSDD) in surgically menopausal women who are, by nature of their condition unable to become pregnant. The testosterone transdermal patch provides a low dose of testosterone (300 microgram/day) and the stated concentrations in the clinic are within the reference range for premenopausal women.

Published data provide an adequate basis for the assessment of the end-points not deliberately tested for in the clinic, *i.e.* acute toxicity, genotoxicity, carcinogenicity and reproductive toxicity.

Testosterone is not genotoxic, yet produces tumours in a range of organs, including endometrium, mammary gland, and liver, in rodents when administered at high doses.
Consistent with other marketed testosterone products, statements about rodent carcinogenic data are included in the 5.3 section of the SPC.

In addition it is also clear that testosterone can have adverse effects on the developing foetus and should not be used by women who are, or who are likely to become, pregnant or breast-feeding women. This is taken into account in Sections 4.6 and 5.3 of the SmPC.

New specific studies have been conducted to evaluate skin tolerability of the testosterone transdermal system itself and no evidence of delayed dermal contact sensitisation was observed in female guinea pigs. Primary skin irritation studies in rabbits indicated that the testosterone transdermal and the placebo patches were, at most, moderately irritating. Part of the irritation could have been caused by the fact that the patches were difficult to remove from the skin. However, since sufficient clinical data exist, there are no non-clinical concerns.

4 Clinical aspects

Introduction

INTRINSA is a testosterone transdermal patch (also called a testosterone transdermal system, TTS). This is a thin, clear, 28cm^2 matrix patch which contains 8.4 mg testosterone and provides 300 micrograms/24 hours testosterone over a 3- to 4-day period when applied to intact abdominal skin.

The approved indication is: treatment of hypoactive sexual desire disorder (HSDD) in bilaterally oophorectomized and hysterectomized (surgically induced menopausal) women receiving concomitant oestrogen therapy.

For the clinical trials programme of INTRINSA, three patient-based instruments were developed, the Sexual Activity Log© (SAL©), the Profile of Female Sexual Function© (PFSF©) and the Personal Distress Scale© (PDS©), in order to cover the frequency and quality of sexual activity, psychological aspects of sexuality and personal distress. Final versions of the PFSF, PDS, and SAL were evaluated in clinical studies, enrolling surgically menopausal women who met criteria for HSDD and age-matched control women who had intact ovaries and normal libido. All domains of the PFSF and PDS and all SAL endpoints were found to discriminate between women with low libido and age-matched healthy controls.

GCP

All Clinical trials were performed in accordance with GCP as claimed by the Applicant.

Pharmacokinetics

Testosterone is an endogenous well-known substance, used in several other products indicated for use in males. Studies investigating basic pharmacokinetic properties of testosterone (e.g. metabolism, elimination, interactions) have not been submitted. The main purpose of this pharmacokinetic assessment is to document the pharmacokinetic properties of INTRINSA TTS and to describe the plasma levels of testosterone achieved in females.

The testosterone transdermal system (TTS) contains 8.4 mg of testosterone and has been designed to provide systemic delivery of testosterone 300 µg/day from a 28-cm2-matrix formulation when applied to the abdomen for 3 to 4 days. This formulation was used in the majority of pharmacokinetic and safety and efficacy trials. The TTS is a three-layer drug in adhesive matrix design that consists of a translucent backing film, an adhesive matrix, and an overlapped-tab release liner that is removed prior to application.

The pharmacokinetics of testosterone from the patch has been evaluated in single and multiple dose studies, in standard pharmacokinetic and population pharmacokinetic studies, for durations of 4 days to 12 months, by application site (abdomen or buttocks), over a range of testosterone doses and by dose and route of concomitant estrogen therapy.

- Analytical methods

Serum samples were analysed for free, total, and bioavailable testosterone; SHBG; free and total dihydrotestosterone (DHT); free and total estradiol; estrone, dehydroepiandrosterone sulphate (DHEA-S) and androstenedione.

The analyses of total testosterone, total estradiol, and estrone were performed by radioimmunoassay (RIA) following sample extraction and column chromatography. The analysis of total DHT was performed by competitive single antibody RIA following sample extraction and column chromatography.

Percent free testosterone, percent free estradiol, and percent free DHT were determined by equilibrium dialysis using radiolabeled tracer techniques. The serum concentrations of free testosterone, free estradiol, and free DHT were calculated using the values for total concentration and percent free analyte. The percent bioavailable testosterone assay used ammonium sulfate to precipitate the fraction of total testosterone bound by SHBG. Bioavailable testosterone is the fraction of total testosterone remaining in the supernatant after the precipitation of SHBG-bound testosterone. The concentration of SHBG was determined using a sandwich immunoassay. Validation results have been presented for all relevant analytes.

Conventional non-compartmental methods have been used in most studies. Base-line adjusted levels of testosterone were generally used in the pharmacokinetic analyses.
A population pharmacokinetic approach was used on data from two Phase III studies.

- Absorption

Pharmacokinetic results after a single dose were available from a study performed in 30 surgically menopausal healthy women aged 40 to 70 years who were on a stable dose of oral estrogen therapy (Study 2003003). In each subject, a single 28-cm2 patch, designed to systemically deliver approximately 300 µg/day testosterone, was applied to the abdomen and worn for 96 hours. At the end of 96 hours, the used patch and any adhesive residue was collected for residual content analysis. In a subgroup of 12 subjects, serial serum samples were collected over the 24 hours prior to application of the patch and over 120 hours (with patch removed at 96 hours) after application of the patch. The samples were analysed for free and total testosterone. The results are shown below:

Figure 1. Mean total testosterone serum concentrations over time (Study 2003003)

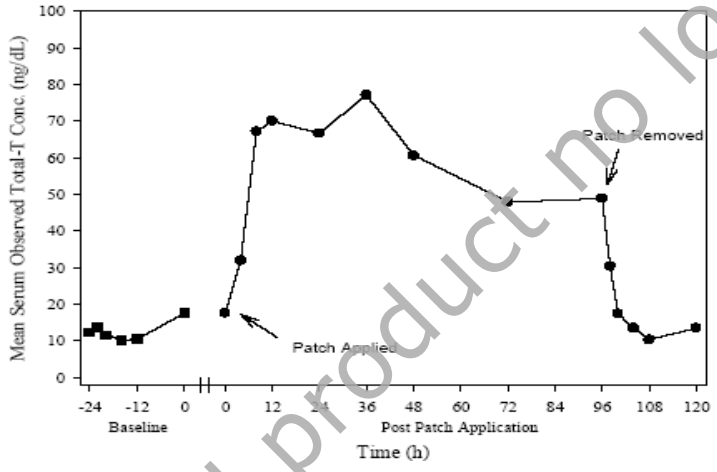


Table 1. Mean (SD) baseline-corrected PK parameters for total and free testosterone (Study 2003003)

Parameter	N	Free Testosterone	Total Testosterone
C_{max}	12	3.65 (2.73) pg/mL	81.3 (28.4) ng/dL
t_{max}	12	20.04 (13.52) hours	27.38 (25.21) hours
$t_{1/2,Z}$	9	2.35 (0.85) hours	2.17 (0.84) hours

The absolute bioavailability from the patch in comparison with i.v. administration has not been studied and there was no estimation of relative bioavailability in comparison with other administration routes for testosterone. However, data on absolute and relative bioavailability were not deemed necessary.

- Evaluation of the daily dose from the patch

An assessment of the daily dose of testosterone delivered from the patch has been made by two methods, by using systemic exposure/clearance principles or by using the depletion method.

All relevant studies have been performed with the product intended for marketing. Where the dose from the patch was estimated to be higher using the depletion method compared with the method based on systemic exposure and clearance several factors can affect the dose delivered to the patient and absorbed in comparison to the amount lost from the patch. The total amount in the patch is 8.4 mg, the estimated amount released per day corresponds to about 6% and errors in the estimations are likely. Therefore, from a pharmacokinetic point of view, the data using the systemic exposure method support a daily release of approximately 300 µg/day.

- Effect of application site on absorption

Absorption of testosterone from a 14-cm2 patch from the abdomen and from the buttocks was assessed in Study T98002. The steady-state pharmacokinetics of testosterone was assessed in surgically menopausal women. The application of the patch on the buttocks in comparison with the abdomen resulted in an approximately 12% lower exposure to free testosterone and 20% lower total testosterone, with 90% confidence intervals outside the commonly accepted 0.80-1.25 range for showing bioequivalence. Based on the results, all subsequent studies including the clinical safety and efficacy studies utilised the abdomen as the application site. Where the difference is small and possibly non relevant, the CHMP endorsed the recommendation to only use the abdomen and this is included in the SmPC.

- Distribution

No specific studies on distribution have been performed. Circulating testosterone in serum exists either tightly bound to SHBG (sex hormone binding globulin; a plasma protein synthesized in the liver that specifically binds steroid sex hormones) (approximately 65-80%), weakly and reversibly bound to serum albumin (approximately 20-30%) or as free testosterone (0.5-2%). The SHBG bound fraction is regarded as not contributing to biological activity. The albumin bound fraction and the unbound fraction are collectively termed "bioavailable" testosterone. Factors that affect SHBG concentrations also affect free testosterone concentrations.

- Elimination

No specific studies regarding elimination have been performed. Testosterone is extensively metabolised by cytochrome P450 3A4 (CYP3A4), aromatase, and 5-alpha-reductase. CYP3A4 metabolises testosterone primarily in the liver by conversion to various hydroxy steroids. The active metabolites of testosterone are DHT and estradiol. Testosterone is metabolised to DHT by steroid 5-alpha-reductase in many tissues, including skin. Testosterone is metabolised to estradiol by aromatase, in various tissues including adipose tissue. About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronide and sulfate conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the faeces, mostly in unconjugated form.

- Dose proportionality and time dependencies

Dose proportionality of the testosterone transdermal system was assessed in a multiple dose (150, 300 and 450 µg/day), open, randomised 3-period crossover study (2000155) in 18 surgically menopausal women on stable oral conjugated equine estrogens doses (0.625 mg/day or higher). Results showed the exposure to free and total testosterone tends to increase slightly less than proportionally. Considering that INTRINSA is available in only one strength, it is agreed that dose proportionality is not of major importance.

For time dependencies, in the pharmacokinetic studies, durations of exposure ranging from 7 days to 2 months of continuous dosing have been studied. In clinical studies, hormone levels after up to 52 weeks of treatment have been measured. Data from two phase IIb and two phase III studies were used.

Table 2. Single and multiple dose pharmacokinetic parameters of free and total testosterone as means (SD)

Analyte	Parameter	Units	Single dose (2003003)	3rd dose (2000155)
Free Testosterone	C_{max}	pg/mL	3.65 (2.7)	3.02 (2.0)
	AUC	pg.hr/mL	232 (173)	157 (79)
Total Testosterone	C_{max}	ng/dL	81 (29)	79 (39)
	AUC	ng.hr/dL	5243 (1629)	4272 (1689)

$AUC_{0-\infty}$ is reported for the single dose study and AUCτ is reported for the 3rd dose.

Study 2001134 (see Efficacy section) was a phase III, placebo controlled study to evaluate efficacy and safety of transdermal testosterone (300 µg/day) for 24 weeks and safety for a further 28-week open-label period in surgically menopausal women with HSDD on concurrent ERT. Serum samples for hormone analyses were collected at baseline, Week 12, 24, and 52.

Administration of the patch increased serum concentrations of free, total and bioavailable testosterone compared to baseline. Testosterone concentrations were higher (10-20%) at Week 12 compared to the average of concentrations at Week 24 and Week 52 visits. No changes in serum concentrations of SHBG, estradiol and estrone were observed.

Overall these data indicate that stable testosterone levels are achieved upon multiple dosing, with no unexpected accumulation up to 52 weeks of dosing.

- Inter-individual and intra-individual variability

The inter-individual variability (% CV) in C_{max} and AUC values ranges from 30% up to 75% for free and total testosterone. Data on intra-individual variability have not been presented. Factors affecting SHBG levels are expected to have an influence on the intra-individual variability.

The inter-individual variability is high, but not unexpected since steroids often show a high inter-individual variability in pharmacokinetics and the transdermal administration route may also contribute. However, the reference range for normal testosterone levels in premenopausal females also shows a wide range.

- Hormone levels in surgical menopausal women with HSDD (Phase III studies: 2001133, 2001134) by Oestrogen route of administration

About 74% of the patients in study 2001133 and about 80% of the patients in study 2001134 received oral estrogen concomitantly, and the remaining patients received estrogen transdermally.
Higher free testosterone levels in patients receiving transdermal oestrogen therapy were observed across several studies.

The serum concentrations of DHEA-S, androstenedione, free and total estradiol, and estrone, were similar between the treatment groups at baseline, and no appreciable changes in the concentrations of these hormones occurred following treatment with INTRINSA. In addition, treatment with INTRINSA for 52 weeks did not exhibit significant changes in SHBG serum concentrations. These results indicate that administration of INTRINSA for up to 52 weeks has no significant influence on serum concentrations of estrogens (free and total estradiol), SHBG, and adrenal precursors (DHEA-S and androstenedione) concentrations.

Consistent with the known effect of the route of ET on SHBG serum concentrations, patients on transdermal ET had lower median SHBG serum concentrations compared with patients on oral ET. However, patients on oral ET had a larger range of SHBG serum concentrations compared with patients on transdermal ET, and there was a wide overlap between the 2 ET groups in these concentrations.

Specifically, the subgroup of patients on transdermal ET exhibited relatively higher mean or median serum concentrations of free and bioavailable testosterone compared with patients on oral ET.
The mean or median total testosterone serum concentrations were similar for patients receiving either oral or transdermal ET. Patients on transdermal ET exhibited higher mean or median free and total estradiol and lower mean or median estrone serum concentrations compared with patients on oral ET.

Similar pharmacokinetic results were observed in Study 2001134.

In both studies 2001133 and 2001134, the mean free testosterone was similar at baseline in the placebo and INTRINSA group, and increased about 5 times only in the INTRINSA group at Week 24. However, in the 2001133 the mean free testosterone at Week 24 in patients receiving oral estrogen was 3.74 pg/ml and 6.23 pg/ml in the patient group receiving transdermal estrogen with a median of 3.05 and 5.55 pg/ml, respectively. Difference: 81%.

In study 20011134, the mean free testosterone at Week 24 in patients receiving estrogen orally was 3.75 pg/ml and 6.07 pg/ml in the patient group receiving transdermal estrogen with a median of 2.85 and 5.50 pg/ml, respectively. Difference: 92%.

The median free testosterone in the efficacy studies at week 24 with oral estrogen background was 2.9 pg/ml and in patients with transdermal estrogen background was 5.55 pg/ml.

The mean or median total testosterone was not different when patients received either oral or transdermal estrogen. Conversely, SHBG concentrations were markedly different in patients receiving concomitantly transdermal estrogen or oral estrogen and about two fold higher in patients receiving oral estrogen compared with transdermal estrogen.
In study 2001133 mean SHBG concentrations at Week 24 in patients receiving oral estrogen was 112 nmol/L and 53.8 nmol/L in the patient group receiving transdermal estrogen (median at week 24: 100.0 and 52.0 nmol/L, respectively). Similar results were observed in study 2001134.

Means of free estradiol, total estradiol, and estrone concentrations of the total study population in studies 2001133 and 2001134 were not changed during INTRINSA application. In patients, who received concomitantly transdermal estrogen the means of free estrogen and total estrogen concentrations were about 1.5-2.0-fold greater than those observed with concomitant oral estrogen .

The CHMP considered the approach of pooling the data of free testosterone from patients receiving oral estrogen or transdermal estrogen questionable, also based on the efficacy analysis by subgroups, which shows that the improvement of the primary endpoint was greater in patients receiving transdermal estrogen compared to those receiving oral estrogen (see Efficacy section).

In this view, the Applicant further clarified the free testosterone serum concentration within the subgroup of patients on oral oestrogen: in fact marked reduction of free testosterone only apply to women concomitantly treated by conjugate equine oestrogens (CEE), but not to non-CEE oral treatments. Pooled pharmacokinetic data from studies 2001133, 2001134, 1999068 and 1999092 indicated a free testosterone serum concentration at Week 24 of 3.6 pg/mL in CEE subset, versus 5.0 pg/mL in non-CEE subset (where transdermal treated women exhibited at Week 24 a mean value of 6.0 pg/mL). These hormonal values were approximately associated with efficacy results (see also the Efficacy section).

- Special populations

No specific studies have been performed in special populations. This is acceptable since testosterone is a well-known endogenous substance.

A population pharmacokinetic analysis in the target population was performed using serum total, free and bioavailable testosterone concentrations collected in two Phase III studies (2001133, 2001134). A total of 549 patients received active drug in these studies and were eligible for this analysis. Blood samples were collected at Week -4 (baseline Visit 2) and during Weeks 24 and 52 in Study 2001133.

An additional sample was collected at Week 12 in Study 2001134. Linear mixed-effect regression analysis was performed to explore relationships between serum free, total, bioavailable testosterone and various patient specific factors (covariates), including concomitant treatment with CYP3A4 inhibitors.

A significant relationship between total testosterone concentrations and body weight was shown: total testosterone concentration decreased as body weight increased. However, since no significant relationship was found between body weight and free testosterone levels the effect on total testosterone seems of limited clinical significance.

No effect of renal function on the testosterone levels was observed. This was expected, since testosterone is not primarily eliminated by renal excretion. Also, the majority of the patients had a normal renal function (mean CLcr 106 ml/min, CV 27%).

No patients with hepatic impairment were included in the population pharmacokinetic analysis and no specific study has been performed. Where severe hepatic impairment may have an effect on the pharmacokinetics of testosterone, specific data for this dosage form are deemed not necessary. The SPC describes a risk of oedema in patients with pre-existing renal or hepatic disease in section 4.4. It also stated that this is not expected with INTRINSA due to its low dose.

INTRINSA is only intended for treatment of females. The age range of the women included in the population analysis was quite narrow: 49 ± 7 years (mean ± SD). Within this range, age did not seem to affect the testosterone concentrations. Limited data are available in elderly women.

INTRINSA is not indicated for use in children or adolescents.

Overall the population pharmacokinetic analysis did not reveal any new or unexpected covariate relationships. A total of 52 patients were listed as taking CYP3A4 inhibitors during the time period that pharmacokinetic samples were collected. Where the population PK analysis wais negative, the subjects classified as taking CYP3A4 inhibitors did not seem to take potent inhibitors and the number of subjects taking inducers was too low. The observed lack of effect of CYP3A4 inhibitors should be treated with caution. This is taken into consideration in section 4.5 of the SmPC.

- Pharmacokinetic interaction studies

Two separate studies were performed to evaluate the effect of two oral (study T98003) or transdermal (study T98004) doses of E2 on the pharmacokinetic profiles of free and total testosterone.

Results showed that within the same administration route, the dose of concomitant estradiol treatment did not affect the exposure to free or total testosterone.

Specific interaction studies with CYP3A4 inhibitors were not performed (see above).

- Pharmacokinetics using human biomaterials

N/A

Pharmacodynamics

- Mechanism of action

Testosterone is well-known to be the primary androgenic hormone in both men and women. In women, it is produced both by the ovaries and the adrenal glands (100 to 400 µg/day). For women in whom the ovaries are removed, testosterone production is reduced by approximately 50%. In many of these patients, this reduction in endogenously produced testosterone is associated with low libido and resultant personal distress termed hypoactive sexual desire disorder (HSDD). Although HSDD is associated with low levels of circulating testosterone, low serum concentrations of testosterone alone

do not predict the presence or the severity of this disorder in women. The exact mechanism by which testosterone may affect sexual function in women is not known.

- Primary and Secondary pharmacology

No primary pharmacological studies were performed.

The physiologic actions of androgens in women have been inferred from developmental observations, androgen deficiency states, and correlational studies and by analogies to the actions of androgens in men and include:

Pubertal development: voice lowering, facial hair, body (pubic) hair, genital development;
Sexual function: libido (sexual desire}, arousal (genital blood flow}, and orgasmic response;
Anabolic effects: muscle mass, bone density, haematocrit;
Effects on mind: sense of energy (vitality), cognitive functions (spatial perception, memory), feeling of well-being (antidepressant effect);
Other actions: Stimulation of oil and sweat production, alterations of hair follicles on the scalp in a manner that promotes hair loss.

No secondary pharmacological studies were performed.

The CHMP agreed with the Applicant that the pharmacological effects of elevated levels of testosterone in women are known, and the early, reversible signs are readily monitored in the clinic.

- Relationship between plasma concentration and effect

No specific clinical studies were performed: a correlation between free testosterone and the primary efficacy endpoint (total satisfying sexual activity over 4 weeks) and the secondary efficacy endpoint (sexual desire over 4 weeks) was carried out for the main efficacy studies.

Clinical efficacy

The clinical development programme performed for the evaluation of efficacy of INTRINSA in the treatment of HSDD in SM women includes 3 Phase II studies (T96006, 1999068 and 1999092), and 2 Phase III studies (2001133 and 2001134). A subset of patients from the Phase III studies was evaluated in a clinical relevance study (CMKUS030993) to determine whether they experienced meaningful benefits during study participation.

- Clinical Program of Controlled Studies

Table 3. Studies Included in the Summary of Clinical Efficacy

Study Number	Phase/ Region	Study Design	Concomitant Estrogen Therapy	Testosterone Dose Groups mcg/day (ITT Patients)
Pivotal Phase III Studies				
2001133	III/ US, Canada, Australia	24-week randomized, DB, PC, efficacy and safety period followed by 28-week OL safety period in SM women	Oral or transdermal	0 (n = 279) 300 (n = 283)
2001134	III/ US, Canada, Australia	24-week randomized, DB, PC, efficacy and safety period followed by 28-week OL safety period in SM women	Oral or transdermal	0 (n = 266) 300 (n = 266)
Supporting Studies				
2001133/ 2001134 Persistence of Treatment Benefit	III/ US, Canada, Australia	13-week randomized, DB, PC follow-up period (Weeks 53-65) to evaluate persistence of treatment benefit in Studies 2001133 and 2001134 in SM women	Oral or transdermal	0 (n = 103) 300 (n = 102)
CMK US030993 Clinical Relevance	III/ US	One-on-one patient interviews about treatment experiences during 24-week DB period of Studies 2001133 and 2001134 in SM women	Oral or transdermal	0 (n = 68) 300 (n = 64)
Phase II Studies				
1999068	IIb/ US	24-week randomized, DB, PC, efficacy and safety period followed by 28-week DB, PC safety extension period in SM women	Oral	0 (n = 119) 150 (n = 107) 300 (n = 110) 450 (n = 111)
1999092	IIb/ EU, Australia	24-week randomized, DB, PC, efficacy and safety in SM women	Transdermal	0 (n = 39) 300 (n = 37)
T96006	IIa/ US	36-week randomized, DB, PC, 3-period crossover in SM women (n = 65)	Oral	0 150 300
Studies in Other Populations				
2002006	III/ US, Canada, Australia	24-week randomized, DB, PC, efficacy and safety in SM women	Oral estrogen and progestin	0 (n = 273) 300 (n = 276)

- Development of Psychometric Instruments

Prior to the start of the key Phase II & III studies (Studies 1999068, 1999092, 2001133, 2001134) the Applicant undertook qualitative and quantitative work (studies 1999069, 1999070 and 19999071) to develop three psychometric instruments that were capable to capture and quantify sexual activities in women:

The **Sexual Activity Log© (SAL©)** records the frequency of sexual activity, orgasm and satisfying sexual activity over the past seven days.

The **Profile of Female Sexual Function© (PFSF©)** is a comprehensive psychometric tool which assesses a woman's sexuality categorised in 7 domains; desire, arousal, pleasure, orgasm, sexual concerns, responsiveness and self image over the past 30 days.

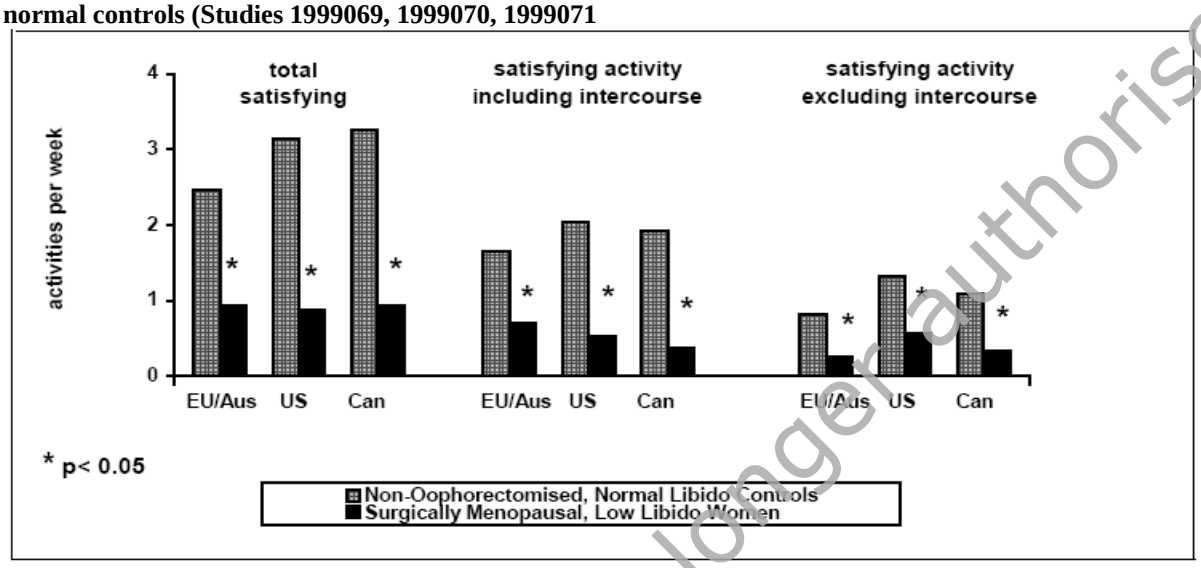
The **Personal Distress Scale© (PDS©)** measures distress associated with low libido in menopausal women over the past 30 days.

The three studies used for initial instrument development and validation were of essentially identical design (Studies 1999069, 1999070, 1999071). Each was a non-randomised, parallel group, multi-centre study of 4 weeks duration. The two groups in each study were hysterectomised/ oophorectomised women with low libido and women with intact ovaries with normal libido ('controls'). There was no clinical intervention in either group as the objectives were to assess the

validity and reliability of the psychometric instruments and to measure hormone levels in these groups. After study completion, as pre-planned, question reduction was undertaken through assessment of data quality, frequency distribution of question responses to assess clustering and discriminant and multivariate statistical analysis.

The SAL was demonstrated to be able to discriminate between low libido surgically menopausal women and normal libido controls. The discriminant ability was robust across the tested geographic areas.

Figure 2. Estimation of sexual activity in the previous 7 days in surgically menopaused women versus normal controls (Studies 1999069, 1999070, 1999071



PFSF was validated to discriminate between the low libido and control populations across its seven domains (sexual desire, arousal, orgasm, sexual pleasure, sexual concerns, sexual responsiveness and sexual self-image). The Sexual Desire domain contains questions that correspond most closely to the DSM-IV diagnostic category of hypoactive sexual desire disorder (HSDD). This domain shows good discrimination between groups across geographic areas.

Similarly the PDS was validated to discriminate between low libido and control populations, while keeping consistency across geographic areas.

Overall these 3 evaluation tools are considered capable to address the specific symptoms of menopausal women with HSDD. Their development was rigorous and validated across different geographic areas.

- Dose response studies

Dose finding studies were performed in a randomized, double-blind, placebo-controlled trial testing patches releasing 150, 300 and 450µg/24h of testosterone in women with HSDD (1999068). The doses 150 and 300µg/24h of testosterone were also tested in a randomized double-blind, placebo-controlled study with a cross-over design (T96006).

Dose-finding study 1999068

Results

Borderline significant linear dose effects were observed for PFSF Sexual Desire at week 24 and for the SAL (frequency of Satisfying Sexual Activity) at week 24. Pairwise comparisons of active treatment with placebo demonstrated a statistically significant change from baseline in the PSFS Sexual Desire score for the 300 µg/day group only. A statistically significant increase in the frequency of Satisfying Sexual Activity (SAL) was also observed for the 300 µg/day group compared with

placebo, whereas no statistically significant differences were observed for the 150 µg/day group or the 450 µg/day group.

Adverse events (AE) occurred with similar frequency in placebo and active treatment groups. Across the range of doses no positive AE dose-response was observed. The majority of the AEs reported were mild (57%) or moderate (38%) in severity. The most commonly reported AEs were application-site reactions (32%), respiratory infection (14%), acne (13%), and breast pain (12%), all similarly distributed among the treatment groups. There was some evidence of an androgenic effect (e.g., facial hair, slight decreases in HDL, and slight increases in LDL) with 450 µg/day testosterone. Serious safety risks, such as severe virilization (i.e., voice deepening or clitoromegaly), were not seen in any patient.

Dose-finding study T96006

Results
Although the instruments used to measure efficacy in this study were not those subsequently developed, the results showed a dose-response for efficacy, with the 300 µg /day testosterone dose demonstrating statistically significant mean increases over placebo for several study endpoints. No statistically significant improvements in the primary efficacy endpoints were observed for the 150 µg day dose. This study showed the potential for 300µg /day INTRINSA to improve sexual functioning in SM women with HSDD.

- Dose selection

Based on those studies, the 300µg/day does was found to be safe and effective and was therefore selected for further clinical trials.

- Main studies

The testing of the treatment principle with the selected dose of 300 µg was performed in 2 pivotal randomized, double-blind, placebo-controlled multinational clinical trials (2001133, 2001134).

The 2 studies were nearly identical in design (clinical laboratory tests differed slightly between the studies), each study being a 52-week, multicenter, multinational study that included a 24-week, randomized, double-blind, placebo-controlled, parallel-group design, efficacy and safety period, followed by a 28-week open label safety period, during which all patients received active treatment.

Study 2001133 & 2001134

METHODS

Study Participants

Study 2001133 enrolled 562 patients at 52 clinical sites in the US, Canada and Australia. Of those, 451 (80%) patients completed the efficacy and safety period through week 24. Study 2001134 enrolled 533 patients at 51 clinical sites in the US, Canada and Australia and of those 418 (78%) patients completed through week 24. Thus, 1095 patients were enrolled and 869 (79%) completed the efficacy period.

According to inclusion criteria, patients were healthy women, aged 20 – 70 years, who had undergone bilateral salpingo-oophorectomy and hysterectomy and met the diagnostic criteria for acquired HSDD, were in stable relationships in which partner factors would not preclude the possibility of demonstrating a treatment effect, were on stable regimens of approved oestrogen replacement therapies, and did not have any breast or cervical malignancies at baseline. Patients with psychological or physical factors, other than low testosterone, that could cause HSDD were excluded from participation. Potential study patients with medical conditions that might cause them to be at increased

risk (e.g., patients with diabetes, severe liver function abnormalities, or alcohol or substance abuse) were also excluded, as were patients taking drugs or nutritional supplements that were likely to affect sexual function.

Patients with low sexual desire and causing distress were initially identified by positive answering to a purpose screening questionnaire.

Treatment effects were measured by the SAL, PFSF, and PDS during the 24-week efficacy and safety period. The SAL was completed by patients at home on a weekly basis and returned to the clinical sites at the next scheduled visit. The PFSF and PDS were completed at the clinical sites at baseline and at scheduled visits at weeks 4, 8, 12, and 24. Safety was evaluated by monitoring adverse events (AEs) throughout the study, clinical laboratory measurements, vital signs, and physical examinations. Skin appearance at the most recent abdominal patch application site was evaluated at each clinic visit for patch site symptoms of irritation. Objective assessments of androgenic effects on the skin (increases in hair growth at the lip and chin, facial depilation, and degree of facial acne vulgaris) were also evaluated in each study. Serum samples were analyzed in each study for determination of free, total, and bioavailable testosterone; SHBG; free and total estradiol and estrone.

Treatments
Patients were stratified based on their use of oral or transdermal oestrogen and within each stratum, randomly assigned in a 1:1 ratio to receive 300µg/24h INTRINSA TTS or a placebo patch. The patch was applied to the abdomen twice weekly and worn for 3-4 days. With regard to oestrogen, more than 75% patients were using an oral oestrogen and, of those, around 60% used conjugated oestrogens.

Upon completion of the 24-week double-blind efficacy and safety period of the study, patients receiving placebo were switched to 300 µg/day INTRINSA, while the active cohort remained on active treatment. All patients were then followed for an additional 28 weeks for safety in an open label manner. The patients and study site personnel remained blinded to the initial randomized treatment throughout the remainder of each study.

Concomitant treatment with estrogens (ET): Patients were requested to maintain a stable dose of ET (oral or transdermal route of administration) throughout the study.

Objectives

The primary objective of each study was to assess the efficacy of INTRINSA 300 µg/day TTS versus placebo in treating Hypoactive Sexual Desire Disorder in surgically menopaused women on concomitant oral or transdermal estrogen therapy (ET), over 24 weeks, as captured by the SAL.

The secondary objectives of the study, listed in order of importance, were to assess the efficacy of INTRINSA versus placebo over 24 weeks in Sexual Desire, as measured by the PFSF, and Personal Distress as measured by the PDS score.

Outcomes/endpoints

The primary efficacy endpoint was the change from baseline in the 4-week frequency of total satisfying episodes at 24 weeks (sum of the weekly frequencies of total satisfying episodes from Weeks 21 through 24).

The secondary efficacy endpoints were the change from baseline of the sexual desire domain of the PFSF, personal distress (PDS), the remaining 6 domains of the PFSF, and the total activity and total orgasm endpoints of the SAL.

Statistical methods

The treatment effect of 300 µg/day INTRINSA was compared with that of placebo using an analysis of co-variance (ANCOVA) based on the ITT population. If model assumptions of normality or homo-scedasticity were severely violated, a Wilcoxon rank-sum test (WRS) was used to compare the

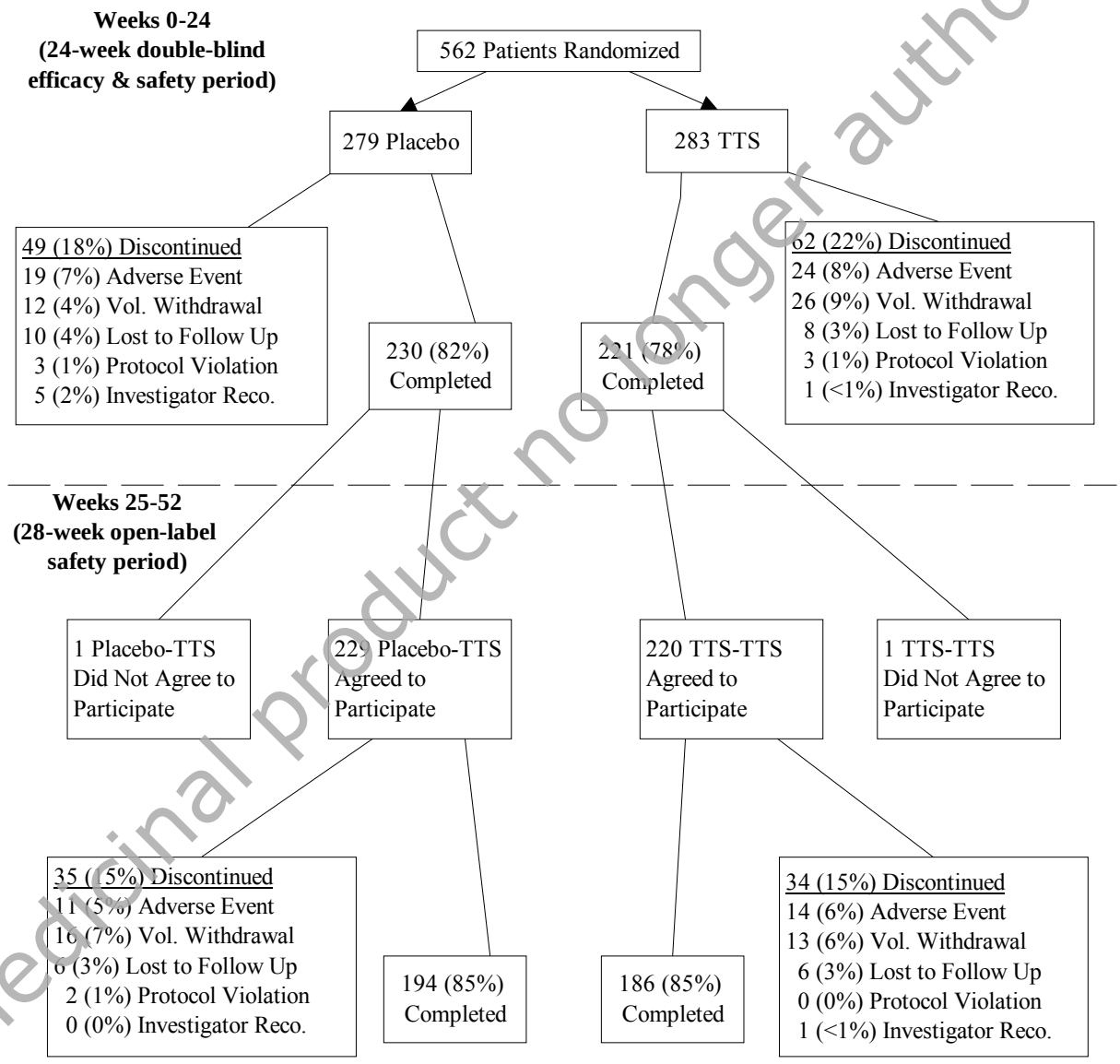
treatment effect of 300 µg/day INTRINSA versus placebo. To account for patients who did not complete 24 weeks of each study, a last observation carried forward (LOCF) approach was used. Comparisons of 300 µg/day INTRINSA with placebo for the secondary efficacy endpoints were performed in a manner similar to the primary efficacy analysis

RESULTS

Participant flow

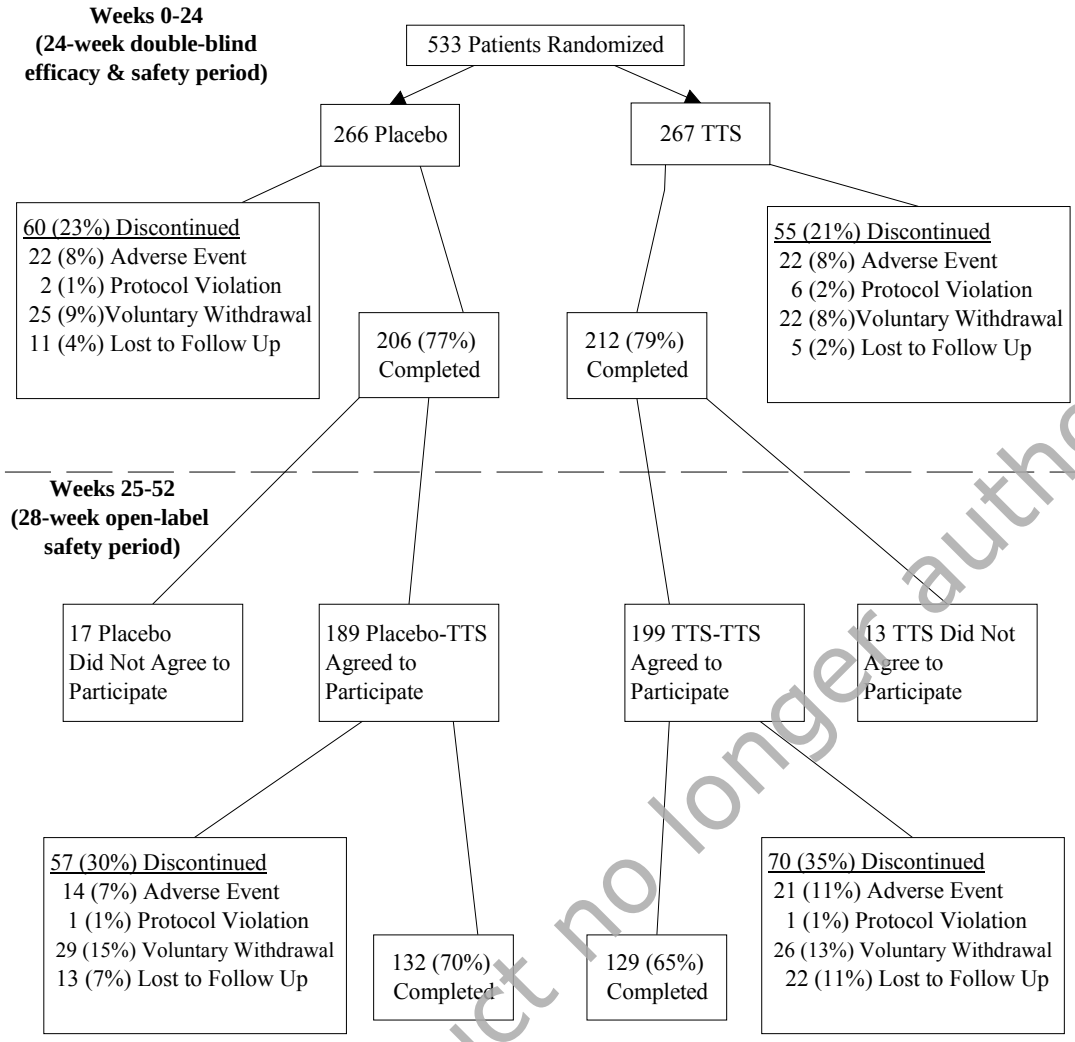
Study 2001133: Of the 888 patients who were screened for study, 326 were considered screening failures, 562 were randomly assigned to treatment and 451 completed 6 month treatment and 380 went on to complete the 28 week open label phase.

Figure 3. Study 2001133 Participant Flow



Study 2001134: Of the 835 patients who were screened for this study, 302 were considered screening failures, 533 were randomly assigned to treatment and 418 completed 6 month treatment and 261 went on to complete the 28 week open label phase.

Figure 4. Study 2001134 Participant Flow



Conduct of the study

Study 2001133 was amended in order to extend treatment for an additional 52 weeks to assess: overall safety of INTRINSA and persistence of treatment benefit in a subset of patients who responded to treatment during the previous 28-week OL period of the study; serum concentrations of free, total, and bioavailable testosterone; SHBG; and total DHT; androgenic effects and overall health in patients who decided not to receive an additional 52 weeks of treatment.

Baseline data

2001133: Age (mean age was 49 ±7.5 years), race/ethnicity (Caucasian 89%; Black 8%; Hispanic 3%); Body Mass Index was overall 28±6; years since oophorectomy 8.5±6.8. Marital status, weight, height, BMI, and length of relationship with partner were similar between the treatment groups at baseline. Overall, most patients at baseline were married to their partners (87%), and the length of the relationships with their partners averaged about 19 years.

2001134: Age (mean age was 48.9±7.5 years), race/ethnicity (90-92 % were Caucasian), Body Mass Index was overall 27.6±5.7; years since oophorectomy 9±7.3. Marital status, weight, height, BMI, and length of relationship with partner were similar between the treatment groups at baseline. Overall, most patients at baseline were married to their partners (87%), and the length of the relationships with their partners averaged approximately 18 years.

Treatments

Overall, 87% of patients in study 2001133 and 86% of patients in study 2001134 were compliant with treatment (during the time in which they were enrolled) during Weeks 1 through 12 and 13 through 24. The percentage of patients who were compliant with treatment within each interval of the 28-week open label safety period was 82% (2001133) and 69% (2001134).

Concomitant treatment with estrogens (ET)

In the pivotal clinical trials, around 25% of women were on transdermal and 75% of the women took oral oestrogens and of those, 60% took conjugated equine oestrogens (CEE) and around 40% took non-CEE. The percentage of patients on concomitant oral ET or transdermal ET was similar between the treatment groups for each ET route in both studies, as well as the percentage of patients taking conjugated oral estrogen therapies.

Numbers analysed

2001133: Of the 562 patients (placebo: n=279; INTRINSA 300 µg: n=283) included in the ITT population 82% of patients in the placebo group (230/279) and 78% of patients in the INTRINSA group (221/283) completed the 24 week study.
2001134: Of the 532 patients (placebo: n=266; INTRINSA 300 µg: n=267) included in the ITT population 77% of patients in the placebo group (206/266) and 79% of patients in the INTRINSA group (212/267) completed the 24 week study.

Outcomes and estimation

- **Results (Pivotal study 2001133)**

A statistically significant increase was observed in the primary efficacy endpoint (SAL, frequency of total satisfying episodes)) at Week 24 for the INTRINSA group compared with placebo both according to ANCOVA (adjusted mean difference = 1.15; p = 0.0003) and Wilcoxon rank sum test (mean difference = 1.11; p = 0.0011).

Table 4. Study 2001133 Change from baseline in 4-week Frequency of total satisfying episodes (SAL) at Week 24 (LOCF Intent-to-Treat Patients)

			Unadjusted Change from Baseline				Adjusted Change from Baseline[a]		
Treatment	n	Baseline Mean (SE)	Mean (SE)	Median (P25, P75)	Difference in Means (CI)	WRS p-value	Least-squares Means (SE)	Difference in Least-squares Means (CI)	ANCOVA p-value
Placebo	273	2.94 (0.19)	0.98 (0.19)	0.3 (-0.5,2.0)	1.11	0.0011	0.98 (0.25)	1.15	0.0003
TTS	276	2.82 (0.15)	2.10 (0.25)	1.0 (-0.3,3.5)	(0.50,1.73)		2.13 (0.24)	(0.54,1.77)	

The frequency of total satisfying episodes was based on the Sexual Activity Log (SAL), which recorded weekly sexual activity.
The last observation carried forward (LOCF) analysis at Week 24 was based on responses recorded on the last weekly SAL and the preceding 3 weekly SALs.
Difference corresponds to the difference in means between TTS and placebo and the 95% confidence interval (CI).
p-value corresponds to the test of the null hypothesis of no treatment difference.
n = number of patients with responses; SE = standard error; P25 = 25th percentile; P75 = 75th percentile; WRS = Wilcoxon Rank-Sum; ANCOVA = Analysis of Covariance;
TTS = 300 mcg/day testosterone transdermal system.
[a] Change from baseline adjusted for treatment, age, estrogen therapy route, pooled centers, and baseline rate of sexual activity.

As for the main secondary efficacy endpoints, patients who received INTRINSA experienced also significantly greater increase in sexual desire domain of PSFS and significantly greater decrease in personal distress (PDS) as compared with patients on placebo at Week 24.

Table 5. Study 2001133 Change from baseline in Sexual Desire (PSFS) at Week 24 (LOCF Intent-to-Treat Patients)

				Adjusted Change from Baseline[a]		
Treatment	n	Baseline Mean (SE)	Week 24/LOCF Least-squares Means (SE)	Least-squares Means (SE)	Difference in Least-squares Means (CI)	ANCOVA p-value
Placebo	269	20.82 (0.84)	27.20 (1.14)	6.90 (1.14)	4.95 (2.13,7.78)	0.0006
TTS	269	19.79 (0.78)	32.16 (1.12)	11.85 (1.12)		

The last observation carried forward (LOCF) analysis at Week 24 was based on responses recorded on the last Profile of Female Sexual Function (PFSF) evaluated.
Difference corresponds to the difference in means between TTS and placebo and the 95% confidence interval (CI).
p-value corresponds to the test of the null hypothesis of no treatment difference.
n = number of patients with responses; SE = standard error; ANCOVA = Analysis of Covariance; TTS = 300 mcg/day testosterone transdermal system.
[a] Change from baseline adjusted for treatment, age, estrogen therapy route, pooled centers, and baseline sexual desire.

Table 6. Study 2001133 Change from baseline in Personal Distress (PDS) at Week 24 (LOCF Intent-to-Treat Patients)

Treatment	n	Baseline Mean (SE)	Week 24/LOCF Least-squares Means (SE)	Adjusted Change from Baseline[a]		
				Least-squares Means (SE)	Difference in Least-squares Means (CI)	ANCOVA p-value
Placebo	266	62.57 (1.56)	47.37 (1.66)	-16.31 (1.66)	-7.25 (-11.37,-3.12)	0.0006
TTS	268	64.78 (1.52)	40.12 (1.63)	-23.55 (1.63)		

The last observation carried forward (LOCF) analysis at Week 24 was based on responses recorded on the last PDS evaluated.
Difference corresponds to the difference in means between TTS and placebo and the 95% confidence interval (CI).
p-value corresponds to the test of the null hypothesis of no treatment difference.
n = number of patients with responses; SE = standard error; ANCOVA = Analysis of Covariance; TTS = 300 mcg/day testosterone transdermal system.
[a] Change from baseline adjusted for treatment, age, estrogen therapy route, pooled centers, and baseline PDS.

Ancillary analyses

Responder analysis SAL

A responder was defined as a patient who had an increase from baseline of >1 episode per 4-week period. A significantly higher percentage of patients in the INTRINSA group responded to treatment compared with placebo: 46% in the INTRINSA group versus 35% in placebo. Other cut-off values (i.e., > 0, > 2, > 3 episodes per 4-week period) were also analysed on exploratory basis.

Table 7. Responder analysis SAL, using different cut-off points for the definition of a responder.

EOT Table 8
Change from Baseline in 4-week Frequency of Total Satisfying Episodes at Week 24 (LOCF): Responder Analysis (Intent-to-treat Patients)

Cut-off	Responders[a]		p-value[b]
	Placebo (n = 273) m (%)	TTS (n = 276) m (%)	
> 0	146 (53.5%)	175 (63.4%)	0.0196
> 1	95 (34.8%)	126 (45.7%)	0.0102
> 2	61 (22.3%)	105 (38.0%)	<0.0001
> 3	45 (16.5%)	74 (26.8%)	0.0036

Responder analysis PFSF

A responder was defined as a patient who had an increase of > 8.89 on the Sexual Desire domain score. An increase of 8.89 corresponds, on the average, to an increase of 1 unit (e.g., "seldom" to "sometimes") on 4 of the 9 items in the Sexual Desire domain. A significantly higher percentage of patients who received INTRINSA responded to treatment compared with placebo (51% in the INTRINSA group versus 35% in placebo.

Subgroup analyses

The SAL results in various subpopulations (patients categorized by disease severity, baseline hormone concentrations, and demographic and reproductive characteristics etc) showed a generally consistent treatment effect with INTRINSA relative to placebo.

Subgroup analysis by baseline SHBG

A statistically significant increase in the frequency of total satisfying episodes at Week 24 was observed in the INTRINSA group compared with the placebo group for patients with baseline SHBG serum concentrations ≤ 160 nmol/L using ANCOVA ($p < 0.0001$), but not at SHBG serum concentrations > 160 nmol/L at baseline. This subgroup represented 13% of the total study population.

A statistically significant increase in the PSFS Sexual Desire score at week 24 was observed in the INTRINSA group compared with placebo for patients with baseline SHBG serum concentrations < 160 nmol/L (adjusted mean difference = 6.54; p < 0.0001). Conversely, a statistically significant decrease in the Sexual Desire score PSFS at week 24 was observed in this subgroup (adjusted mean difference = -7.37; p = 0.0358).

Subgroup analysis by route and dose of oestrogen

Greater increases from baseline were observed in the INTRINSA group relative to placebo in the primary endpoint regardless of the route of oestrogen (transdermal p = 0.0045; oral p = 0.0154). However, the difference between the treatment groups was greater for patients on transdermal oestrogen (adjusted mean difference = 1.94) compared with patients on oral oestrogen (adjusted mean difference = 0.86). Greater differences between the treatment groups were observed for patients who received higher doses of oral (conjugated oestrogen equivalent > 0.625 mg) or transdermal (> 0.05 mg) oestrogen compared with lower doses for each route.

- **Results (Pivotal study 2001134)**

For SAL at week 24 (primary endpoint) the ANCOVA model assumption of normality was severely violated. Based on ANCOVA, the difference in adjusted means between the INTRINSA and placebo groups with regard to the change from baseline in the frequency of total satisfying episodes at week 24 was not statistically significant (adjusted mean difference = 0.65; p = 0.0816). Therefore, the Wilcoxon rank-sum test was used to compare treatment groups. A statistically significant increase was observed in the primary endpoint (SAL, frequency of total satisfying episodes)) at Week 24 for the INTRINSA group compared with placebo according to the Wilcoxon rank-sum test (mean difference = 0.83; p =0.0010).

Table 8. Study 2001133 Change from baseline in 4-week Frequency of total satisfying episodes (SAL) at Week 24 (LOCF Intent-to-Treat Patients)

Table 7
Change from Baseline in 4-week Frequency of Total Satisfying Episodes at Week 24 (LOCF)
(Intent-to-treat Patients)

			Unadjusted Change from Baseline				Adjusted Change from Baseline[a]		
Treatment	n	Baseline Mean (SE)	Mean (SE)	Median (P25, P75)	Difference in Means (CI)	WRS p-value	Least-squares Means (SE)	Difference in Least-squares Means (CI)	ANCOVA p-value
Placebo	255	3.19 (0.24)	0.73 (0.25)	0.0 (-1.0,1.1)	0.83 (0.07,1.58)	0.0010	1.08 (0.31)	0.65 (-0.08,1.39)	0.0816
TTS	258	3.04 (0.23)	1.56 (0.29)	0.9 (-0.5,3.0)			1.74 (0.31)		

For the secondary endpoint PFSF Sexual Desire at week 24, a statistically significant increase from baseline was observed for the INTRINSA group compared with placebo in sexual desire using ANCOVA (adjusted mean difference = 5.17; p = 0.0006).

For the next secondary endpoint, Personal Distress Score (PDSA), a statistically significant decrease was observed for the INTRINSA group compared with the placebo group at week 24 (p = 0.0091).

Responder analysis

For the Frequency of total satisfying episodes (SAL), responder analyses were based on the change from baseline at week 24. A significantly higher percentage of patients in the INTRINSA group responded to treatment compared with placebo.

EOT Table 8
Change from Baseline in 4-week Frequency of Total Satisfying Episodes at Week 24 (LOCF): Responder Analysis
(Intent-to-treat Patients)

	Responders[a]		
Cut-off	Placebo (n = 255) m (%)	TTS (n = 258) m (%)	p-value[b]
> 1	64 (25.1%)	109 (42.2%)	<0.0001

For the PFSF Sexual Desire score, Responder analyses were based on the change from baseline at week 24 (LOCF). A significantly higher percentage of patients who received INTRINSA responded to treatment compared with placebo.

Subgroup analyses

Subgroup analyses according SHBG serum concentration, gave results similar to study 2001133, with lower (SAL) or no efficacy (PSFS) for SHBG >160 nmol/L; greater efficacy (SAL) for patients on transdermal oestrogen (mean difference = 2.62) compared with patients on oral oestrogen (mean difference = 0.38). The Applicant subsequently clarified via additional subgroup analyses that *the efficacy of INTRINSA was affected by the type of oestrogen used with no significant difference compared to placebo in women on CEE.*

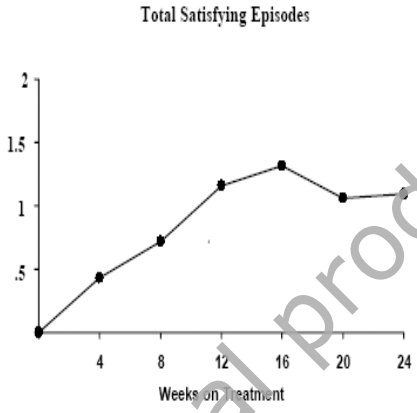
Other Secondary efficacy endpoints in Studies 2001133, 2001134 (Other SAL Endpoints, PFSF Domains)

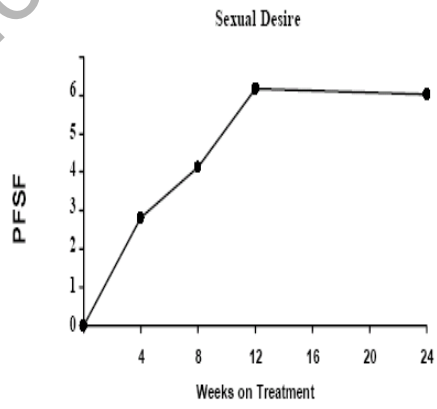
In study 2001133, significant increases from baseline were observed in the INTRINSA group compared with placebo at Week 24 for most of the SAL and for all PFSF domains at Week 24 (LOCF). Significant improvements were observed in study 2001134 for PFSF only (all domains).

- **Time of onset and duration of effect**

Onset and maintenance of efficacy for INTRINSA therapy over placebo was tested in the two pivotal trials.

Statistically significant treatment effects with INTRINSA compared with placebo in the mean change from baseline were observed beginning at weeks 5-8 based on ANCOVA and were sustained for the duration of the treatment period



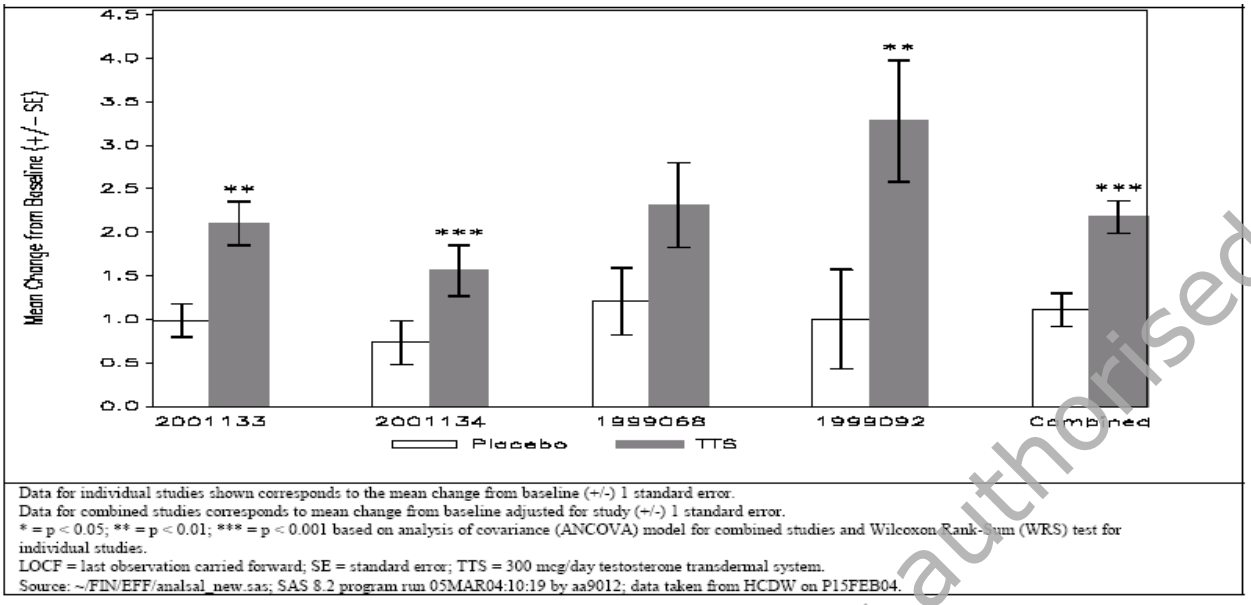


- **Analysis performed across trials (pooled analyses and meta-analysis)**

Analysis of the primary endpoint and main secondary endpoints were performed from the combined 24-weeks data from the two Phase III studies (2001133 and 2001134) and two Phase II studies (1999068 and 1999092). Treatment: INTRINSA with 300 µg testosterone release/day.

There was a significant increase with INTRINSA vs. placebo in the primary endpoint Change from baseline in 4-week frequency of Total Satisfying Episodes at Week 24 (ANCOVA).

Figure 5. Change from baseline in 4-week Frequency of Total Satisfying Episodes at Week 24(LOCF): Individual and Combined Studies 2001133, 2001134, 1999068, 1999992 (Intent-to-treat Patients)



Data for individual studies shown corresponds to the mean change from baseline (+/-) 1 standard error.
Data for combined studies corresponds to mean change from baseline adjusted for study (+/-) 1 standard error.
* = p < 0.05; ** = p < 0.01; *** = p < 0.001 based on analysis of covariance (ANCOVA) model for combined studies and Wilcoxon Rank-Sum (WRS) test for individual studies.
LOCF = last observation carried forward; SE = standard error; TTS = 300 mcg/day testosterone transdermal system.
Source: ~/FIN/EFF/analsal_new.sas; SAS 8.2 program run 05MAR04:10:19 by aa9012; data taken from HCDW on P15FEB04.

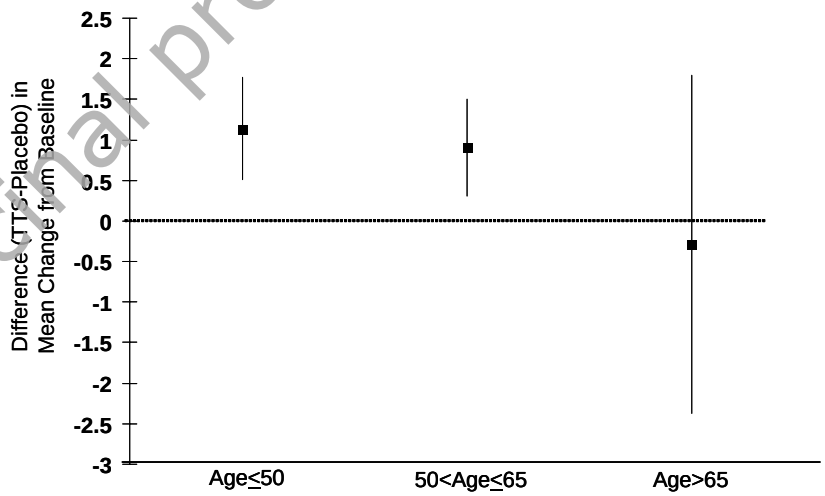
Consistent results were found for both secondary endpoints PFSF Sexual Desire and PDS Personal Distress Scale, at Week 24 (LOCF).

Subgroup analyses of the combined studies

In the combined subgroup analyses of primary endpoint outcome (SAL), mean improvement with INTRINSA treatment was greater than with placebo regardless of route of oestrogen, although the mean improvement was greater in the subgroup on transdermal oestrogen therapy

With regard to age, there was no difference in the combined analysis between those on INTRINSA and those on placebo among women over 65.

Figure 6. Change across trials in Total Satisfying Episodes at week 24 in the Intrinsa group compared to placebo



- Supportive studies: Qualitative and Quantitative Follow-Up (Study CMK US030993)

. The results were subsequently used to define a responder in the analyses of studies 2001033 and 2001034.

Baseline demographics and disease severity were representative of the entire group of women in the phase 3 studies. The primary assessment in the clinical relevance study was based on the subjects' answers (yes or no) to the following question, which was asked with reference to their experiences during the double-blind part of the studies: Patients were asked specifically if they experienced a meaningful benefit

. The questions and results are seen in Table 9.

Table 9. Overall treatment experience as expressed by patients on INTRINSA or placebo

Patients who Experienced Overall Meaningful Benefit from Study Patch by Treatment Group			
Question	Treatment Group	n/N (%)	p-value
Overall Meaningful Benefit	Placebo	21/68 (30.9%)	0.0254
	TTS	33/64 (51.6%)	
Meaningful Increase in Satisfying Activity	Placebo	21/68 (30.9%)	0.0108
	TTS	35/64 (54.7%)	
Meaningful Increase in Sexual Desire	Placebo	23/68 (33.8%)	0.0409
	TTS	34/64 (53.1%)	

Patient responses in this study were used to define minimally important clinical differences. Using Receiver Operating Characteristics (ROC) analysis, the differences were predefined as the values that best dichotomized subjects on the basis of reported meaningful benefit

- an increase of > 1.0 in SAL per 4 weeks
- an increase of ≥8.9 in PSFS
- a decrease of at least 20 points in PDS

These responder definitions were applied to the Phase 3 results to examine the differences between the percentages of responders on INTRINSA treatment and placebo (see above).

- **Discussion on clinical efficacy**

While clinical studies were well conducted and generally demonstrated that INTRINSA was superior to placebo, the CHMP was concerned about the effect size of the response, an average increase by 1 satisfactory sexual encounter per 4 week period, an increase in PSFS desire score by 6-7 on a 100 degree scale and a reduction of personal distress by 7 on a 100 degree scale. Therefore, the clinical relevance of the observed improvement, although statistically significant, was questioned.

The Applicant responded that there is an overall statistically significant change in favour of INTRINSA. The primary endpoint, SAL, consists of number of satisfying episodes per 4 weeks, i.e. is a simple numeric measure whereas the desire endpoint, PSFS, consists of several domains (arousal, orgasm, pleasure, reduced concerns, responsiveness and self image). The CHMP agreed that the meaningfulness of the change is supported by the fact that there is an improvement across all those domains.

In response to the major objection on the clinical meaningfulness of the effect, the Applicant also argued that the clinical relevance study (CMK#US030993) demonstrated that the patients´ perception of a meaningful effect corresponded to the measured endpoint results in SAL, PSFS and PDS. Patients who did not consider their own effect as meaningful, revealed low scores in all those endpoint parameters. Where this study only comprised 12% of the total study population, it is agreed that the results support that some patients perceive that INTRINSA treatment is clinically meaningful and, also, that others do not. The results indicate that patients are likely to be able to assess their own benefit of treatment and, therefore, also are able to identify themselves as responders or non-responders and discontinue treatment in case of no effect.

The responder rates in the pivotal clinical trials showed that many patients do not respond to INTRINSA treatment (46% of patients were responders using the lowest cut-off).

A responder regarding the primary endpoint (SAL), using cut-off scores that were predefined the clinical relevance study, was defined as an increase in the 4-week frequency of satisfying activities >1. In the combined data (4 studies), the difference in responder rates between INTRINSA and placebo was 14.8%, which demonstrates that the difference in responder rates in the active treatment group compared to placebo is small. The explanation presented by the Applicant, that sexual dysfunction is multifactorial, is accepted and therefore a substantial placebo effect is not unexpected.

With regard to maintenance of study effects, the data provided support that the effects *of INTRINSA are maintained for up to 1 year.*

There was an age-related difference in response, however all the women in the studies, regardless of age, were carefully selected for HSDD and met all the inclusion criteria. The Applicant has, in the response, agreed to limit use to women below the age of 60 years, as there are limited data to support use in women over 60.

The finding that the clinical effect of the INTRINSA depended on the route and dose of concomitant oestrogen with markedly greater effects in patients on transdermal compared to oral oestrogen seems not to have been entirely unexpected as patients were stratified by route of oestrogen administration at inclusion. However, the magnitude of this difference and the fact that oral oestrogen with CEE differed from oral oestrogen with non-CEE, appears not to have been anticipated.

The dominance of CEE in the studies negatively influenced the results in the pooled analyses as shown in the subgroup analyses, in which the efficacy data in women on non-CEE or transdermal oestrogens were consistently superior to those found in women on placebo or CEE. With regard to the primary endpoint SAL, the overall difference in responder rate between INTRINSA and placebo increased from 14.4% in the total study population of the pivotal studies to 21.3% when patients on CEE were excluded. Thus, in women on non-CEE oestrogens, a larger difference between INTRINSA and placebo was reported, and consequently a better efficacy was seen in that patient subgroup than in the pooled analyses.

The difference in INTRINSA treatment effects appears to correspond with the effect of the oestrogen on SHBG, which affects protein binding of testosterone and hence free testosterone. Markedly greater treatment effects were associated with lower SHBG and higher free testosterone levels as seen in the transdermal as compared to the oral oestrogen group.

The influence of route, type and dose of oestrogen on the efficacy of INTRINSA has been outlined in the SmPC.

The subgroup analyses revealed both ethnical and geographical differences in response to treatment. The Applicant argues that the studies were not designed and sized to provide sufficient power to examine treatment effects in various subgroups, which is acceptable.

Clinical safety

Introduction

The safety profile of the 300µg INTRINSA was evaluated primarily using the combined data from studies 2001133 and 2001134, which had open-label safety extensions following the 6-month, double-blind, placebo-controlled period. Furthermore, data from studies 1999068 and 19999062 were included in the safety analysis. All of the combined studies were placebo-controlled for the first 24 weeks. Study 1999092 ended at 24 weeks, study 1999068 continued as a double-blind, placebo-controlled study for an additional 28 weeks, and studies 2001133 and 2001134 continued with all remaining patients on open-label active treatment for an additional 28 weeks.

- Patient exposure

In total, 882 patients were exposed to the 300µg dose for more than 20 weeks and 348 patients for more than 48 weeks. In studies 2001133 and 2001134, 418 patients who had received placebo and 419 patients who had received INTRINSA during weeks 0 to 24 all received open-label INTRINSA in weeks 25 to 52. To assess whether there was an increased risk associated with longer INTRINSA exposure, the rates of adverse events during the 28-week open-label period in the patients continuing on INTRINSA (INTRINSA - INTRINSA group, second 6 months of exposure) were compared with the rates in the patients newly initiating INTRINSA treatment (placebo - INTRINSA group, first 6 months of exposure).

Seventy-eight percent of patients in the placebo and 300 µg/day treatment groups completed the 24-week, double-blind period in the combined studies (1999068, 1999092, 2001133, 2001134). There were no important differences between treatment groups in the time to or reasons for patient withdrawal from treatment during weeks 0-24; 8% of patients in both treatment groups withdrew due to adverse events.

Data from the natural menopause study (2002006) were taken into account for serious adverse events. This was a multicenter, randomized, 24-week, double-blind, placebo-controlled, parallel-group design study conducted in naturally menopausal women with HSDD on concomitant oral continuous oestrogen and progestogen therapy (HRT). The design was similar to studies 20001133 and 2001134. A total of 549 patients were enrolled in the US , Canada and Australia. A total of 433 (79%) patients completed the 24-week study.

- Adverse events

Common adverse events

The overall incidence of adverse events, serious adverse events, and withdrawals due to adverse events was similar in the INTRINSA and placebo groups in the combined studies during the double-blind period. A higher percentage of adverse events in the INTRINSA group were considered possibly or probably related to study drug compared with placebo (26.8% vs. 23.4%). This was mainly due to an increase in the incidence of androgenic adverse events seen in the INTRINSA group.

In the open-label period (weeks 25-52 of studies 2001133 and 2001134), the percentage of patients who reported any adverse events and serious adverse events, regardless of whether they reported such events in the double-blind period, was similar between the placebo - INTRINSA and the INTRINSA - INTRINSA groups.

The incidence of withdrawal due to adverse events was higher in the INTRINSA - INTRINSA group than in the placebo - INTRINSA group. This difference was largely a result of more patients withdrawing due to increased hair growth (hirsutism) and weight gain in the INTRINSA - INTRINSA group: n=10 (2.4%) and n=6 (1.4%), respectively, compared with the placebo – INTRINSA group: n=4 (1.0%) and n=0. More adverse events reported in the open-label period were assessed as severe in the INTRINSA - INTRINSA group: n=29 (5.8%) than in the placebo - INTRINSA group: n=16 (3.5%).

Table 10. Adverse event High Level Terms (HLT) and Preferred Terms (PT) reported by >=2% of patients in either treatment group in which the incidence for INTRINSA was higher than placebo.

	Placebo (N=703)		TTS (N=696)		
MedDRA SOC/ HLT/ PT	n (%)	Rate	n (%)	Rate	p-value
Endocrine disorders					
Female gonadal function disorders					
Hirsutism	35 (5.0%)	0.056	49 (7.0%)	0.079	0.1154
Overall HLT	35 (5.0%)	0.056	49 (7.0%)	0.079	0.1154
Gastrointestinal disorders					
Gastrointestinal and abdominal pains (excl oral and throat)					
Overall HLT	9 (1.3%)	0.014	19 (2.7%)	0.031	0.0578
General disorders and administration site conditions					
General signs and symptoms NEC					
Influenza like illness	8 (1.1%)	0.013	14 (2.0%)	0.022	0.2944
Overall HLT	10 (1.4%)	0.016	22 (3.2%)	0.036	0.0323
Infections and infestations					
Influenza viral infections					
Influenza	20 (2.8%)	0.032	20 (2.9%)	0.032	1.0000
Overall HLT	20 (2.8%)	0.032	20 (2.9%)	0.032	1.0000
Infections and infestations					
Upper respiratory tract infections - pathogen class unspecified					
Upper respiratory tract infection NOS	51 (7.3%)	0.084	57 (8.2%)	0.095	0.5484
Urinary tract infections					
Urinary tract infection NOS	19 (2.7%)	0.030	20 (2.9%)	0.032	0.8723
Overall HLT	22 (3.1%)	0.035	26 (3.7%)	0.042	0.5597
Viral infections NEC					
Gastroenteritis viral NOS	13 (1.8%)	0.021	15 (2.2%)	0.024	0.7070
Overall HLT	21 (3.0%)	0.034	25 (3.6%)	0.040	0.5517
Nervous system disorders					
Headaches NEC					
Headache	44 (6.3%)	0.072	48 (6.9%)	0.079	0.6669
Overall HLT	50 (7.1%)	0.083	57 (8.2%)	0.095	0.4819
Migraine headaches					
Migraine NOS	12 (1.7%)	0.019	16 (2.3%)	0.026	0.4517
Overall HLT	13 (1.8%)	0.021	16 (2.3%)	0.026	0.5790
Vascular disorders					
Peripheral vascular disorders NEC					
Flushing	13 (1.8%)	0.021	15 (2.2%)	0.024	0.7070
Overall HLT	13 (1.8%)	0.021	15 (2.2%)	0.024	0.7070
Vascular hypertensive disorders NEC					
Hypertension NOS	9 (1.3%)	0.014	14 (2.0%)	0.022	0.3013
Overall HLT	9 (1.3%)	0.014	14 (2.0%)	0.022	0.3013
Psychiatric disorders					
Anxiety symptoms					
Overall HLT	16 (2.3%)	0.026	16 (2.3%)	0.026	1.0000
Respiratory, thoracic and mediastinal disorders					
Coughing and associated symptoms					
Cough	15 (2.1%)	0.024	16 (2.3%)	0.026	0.8579
Overall HLT	15 (2.1%)	0.024	16 (2.3%)	0.026	0.8579
Skin and subcutaneous tissue disorders					
Acnes					
Acne NOS	46 (6.5%)	0.075	61 (8.8%)	0.101	0.1314
Overall HLT	46 (6.5%)	0.075	62 (8.9%)	0.103	0.1090
Alopecias					
Alopecia	15 (2.1%)	0.024	20 (2.9%)	0.032	0.3970
Overall HLT	19 (2.7%)	0.030	24 (3.4%)	0.039	0.4423

Androgenic adverse events

The overall incidence of androgenic adverse events (acne, alopecia, hirsutism and voice deepening) was higher in the INTRINSA group than in the placebo group in the combined studies (INTRINSA, 123 patients, 17.7%; placebo, 101 patients, 14.4%). This difference between treatment groups was more pronounced in study 2001134. The specific events that accounted for most of this difference were acne and hirsutism. The incidence of androgenic adverse events (acne, alopecia, hirsutism, and voice deepening) in the 24-week, double-blind period of the studies is summarized in Table 11.

In both treatment groups, more than 90% of the androgenic adverse events were assessed by the investigator as mild in severity, and less than 2% resulted in patient discontinuation from the study. Most patients in both treatment groups who had androgenic adverse events experienced only one such event. The risk of experiencing two androgenic adverse events or withdrawing from the study due to an androgenic adverse event was higher in the INTRINSA group than in the placebo group.

The objective assessment of acne, chin and upper lip hair growth and patient-reported depilation showed a slight increase in the INTRINSA group compared with the placebo group during the double-blind study period. This increase is consistent with the increase in androgenic adverse events reported during this period in the INTRINSA group. In the open-label period, the rate of individual androgenic adverse events was similar in the INTRINSA - INTRINSA and placebo - INTRINSA groups. The severity of the adverse events was also similar between the 2 groups. More patients withdrew due to hirsutism in the INTRINSA - INTRINSA group than in the placebo - INTRINSA group: N=10 (2.4%) and n=4 (1.0%), respectively.

Table 11. Summary of androgenic adverse events during the 24 week double-blind period

S-Table 6
Summary of Androgenic Adverse Events:
24-week Double-blind Period of Combined Studies
(Intent-to-treat Patients)

Parameter	Placebo (N=703)		TTS (N=696)		p-value
Number of adverse events (AEs)	123		165		
Mean number of AEs/patient	0.2		0.2		
Mean number of AEs/patients with AEs	1.2		1.4		
Patients[a]					
With Any AEs	101	(14.4%)	123	(17.7%)	0.0941
Acne	49	(7.0%)	63	(9.1%)	0.1680
Alopecia	19	(2.7%)	24	(3.4%)	0.4423
Hirsutism	35	(5.0%)	49	(7.0%)	0.1154
Voice Deepening	12	(1.7%)	16	(2.3%)	0.4517
With One Type of AE	88	(87.1%)	98	(79.7%)	
Acne Only	41	(40.6%)	48	(39.0%)	
Alopecia Only	14	(13.9%)	10	(8.1%)	
Hirsutism Only	28	(27.7%)	33	(26.8%)	
Voice Deepening Only	5	(5.0%)	7	(5.7%)	
With Two Types of AEs	12	(11.9%)	23	(18.7%)	
Acne and Alopecia	1	(1.0%)	5	(4.1%)	
Acne and Hirsutism	3	(3.0%)	7	(5.7%)	
Acne and Voice Deepening	3	(3.0%)	1	(0.8%)	
Alopecia and Hirsutism	2	(2.0%)	4	(3.3%)	
Hirsutism and Voice Deepening	1	(1.0%)	3	(2.4%)	
Alopecia and Voice Deepening	2	(2.0%)	3	(2.4%)	
With Three Types of AEs	1	(1.0%)	0	(0.0%)	
Acne, Alopecia and Hirsutism	0	(0.0%)	0	(0.0%)	
Acne, Hirsutism and Voice Deepening	1	(1.0%)	0	(0.0%)	
Alopecia, Hirsutism and Voice Deepening	0	(0.0%)	0	(0.0%)	
With Four Types of AEs	0	(0.0%)	2	(1.6%)	
Who Withdrew due to AEs	4	(0.6%)	11	(1.6%)	
AE Severity[a]					
Mild	116	(94.3%)	152	(93.3%)	
Moderate	7	(5.7%)	10	(6.1%)	
Severe	0	(0.0%)	1	(0.6%)	
Overall	123	(100.0%)	163	(100.0%)	

Weight gain

In the double-blind period, 11 patients in the placebo group (1.6%) and 11 patients in the INTRINSA group (1.6%) reported weight gain. One patient (INTRINSA group) discontinued treatment due to weight gain in this period. During the open-label period, weight gain adverse events were increased in the INTRINSA – INTRINSA group (11 new cases) as compared with the placebo- INTRINSA group (4 new cases). Six patients (1.4%) in the INTRINSA - INTRINSA group discontinued treatment due to weight gain, compared with 0 patients in the placebo - INTRINSA group.

The mean change from baseline in body weight in the double-blind period at week 24/exit in the placebo group was -0.22 kg, compared with a mean increase in the INTRINSA group of 0.33 kg. No net gain from baseline was observed in patients who continued INTRINSA therapy from 6-12 months.

The effect of treatment on the proportion of patients who experienced a weight gain of ≥7% of their baseline weight was analyzed. Thirty patients in the INTRINSA group (4.7%) and 10 patients in the placebo group (1.6%) gained ≥7% of baseline body weight by the week 24/exit visit. Examination of the cases with weight gain ≥ 7% from baseline indicated that the risk of having this increase did not appear to be associated with BMI, age, or use of concomitant medications. A higher percentage of patients in the group who gained weight reported smoking at baseline (36% vs. 17% in the overall population). Weight gain was not associated with changes in fasting glucose, insulin, lipid profiles, or blood pressure.

- **Psychiatric adverse events**

There was no increase in psychiatric adverse events (MedDRA Preferred Terms: agitation, aggression, or irritability) in the INTRINSA group compared with the placebo group in the combined studies during the 6-month, double-blind period. In the open-label period, there was no increase in the incidence rate or severity of psychiatric adverse events between the INTRINSA - INTRINSA group and the placebo - INTRINSA group.

- **Testosterone levels and androgenic adverse events**

Androgenic adverse events were also investigated by evaluating serum hormone levels (free testosterone, total testosterone and total DHT), in patients with these effects. There was a statistically significant association between the probability of having hirsutism and maximum serum free testosterone level (p=0.014). Hirsutism was more likely with increasing maximum free testosterone level. Although there was an association, a threshold maximum free testosterone level that acceptably predicted hirsutism could not be identified.

Approximately 20% of subjects in the INTRINSA group exhibited free testosterone levels above the normal range for women of reproductive age (normal range: 0.9-7.3pg/mL) as compared to 0.2% of women on placebo and occasional patients exhibited free testosterone levels above 20 pg/mL. There was, however, no clear evidence of a relationship between the probability of having other androgenic adverse events (acne, alopecia, voice deepening, each considered separately) and maximum serum hormone level.

Application-site reactions
The severity criteria for application-site reaction adverse events were different in the Phase II and Phase III studies. Because of these differences between studies, only the application-site reaction adverse events from studies 2001033 and 2001034 were combined in the safety summary.

Application-site reactions reported as adverse events were very common (reported by 30.4% of the patients) and occurred at a similar incidence in both the placebo and INTRINSA groups. The percentage of patients who withdrew from the studies due to adverse events of application-site reaction was low and similar between the treatment groups. The percent of patients experiencing a severe application-site reaction was also low. The majority of application-site reactions were assessed as mild by the investigators. Four patients during the double-blind study period (2 in the INTRINSA group and 2 in the placebo group) were identified by the investigator as cases of potential sensitization to the patch. Three of these patients withdrew from the study, and one patient continued.

- **Serious adverse event/deaths/other significant events**

Deaths
One patient, receiving placebo in study 2001134, died during the study due to a basal ganglia haemorrhage. Two patients who were receiving INTRINSA in the natural menopause study (2002006) died, both deaths were associated with motor vehicle accidents.

Serious Adverse Events
In the 6-month, double-blind study periods, 15 patients reported serious adverse events in each treatment group: INTRINSA n=15 (2.2%) and placebo n=15 (2.1%)]. In the open-label period, 7 patients reported serious adverse events in the placebo-INTRINSA group (1.7%) and 7 patients reported serious adverse events in the INTRINSA-INTRINSA group (1.7%). No patients in the extension of study 1999068 reported serious adverse events.

Two patients in the INTRINSA group reported serious adverse events assessed as possibly related to treatment by the investigators. These adverse events were a transient ischemic attack in one patient and one patient who reported an episode with the following symptoms: tightness in chest, diarrhoea, flushing, increased heart rate, nausea, tingling in the roof of mouth, and diaphoresis. In both cases, the adverse events resolved while the patient was on study drug.

Breast
In the double-blind period, one patient in the INTRINSA group reported a breast mass that resolved on its own. Another patient in the INTRINSA group was found to have "thickening of the left breast around the nipple" coded to breast dysplasia on physical exam. The patient withdrew due to migraines 8 months after the finding and refused to return to the site for any exit procedures including a mammogram. Fifteen patients had a reported breast mass or microcalcification in the open-label period (6 in the placebo-INTRINSA group and 9 in the INTRINSA-INTRINSA group). Five of these patients' masses resolved, 7 were diagnosed as benign or probably benign, 2 patients discontinued the study and refused further follow-up by the investigators, and 1 patient had a palpable mass that was not evident on mammogram.

One patient had an abnormal mammogram after approximately 29 weeks of INTRINSA therapy that was found to be a ductal carcinoma in situ (DCIS). One patient was diagnosed with metastatic adenocarcinoma of the breast approximately 5 weeks after initiation of INTRINSA treatment. Both of these adverse events were assessed as doubtfully related to therapy by the investigators.

- **Study on breast density and breast epithelial cell proliferation**

To explore the effects of testosterone on the breast, a 6-month randomised, double-blind, placebo-controlled study was conducted to assess the effects of the 300µg/day INTRINSA on breast density and breast epithelial proliferation, compared to the effects of continuous HRT alone in naturally menopausal women. Of the 99 patients randomly assigned to treatment, 88 (89%) completed the study. The treatment difference at 6 months in the mean change from baseline in epithelial cells proliferation showed reduced breast cell proliferation in the testosterone group. The difference was not statistically significant when adjusting for baseline. A total of 87 mammograms were evaluable, showing no statistically significant difference in breast density at month 6 between the two treatment groups, whether using the Wolfe classification, the percentage of dense parenchyma or the digitised assessment of breast density, even after adjusting on baseline values. Thus, overall, no negative effects on the breast were seen by testosterone addition during concomitant HRT.

Table 12. Breast epithelial cell proliferation, percent Ki67 positive cells

	Placebo (N=41)	Testosterone (N=47)	Overall (N=88)
Baseline	(n=27)	(n=30)	(n=57)
Mean (SEM)	1.20 ± 0.35	1.56 ± 0.37	1.39 ± 0.26
Median	0	0.81	0.46
Month 6	(n=35)	(n=33)	(n=68)
Mean (SEM)	3.10 ± 0.45	3.03 ± 0.70	3.07 ± 0.41
Median	2.50	2.05	2.20

N = number of patients with evaluable biopsies; n = number of patients with data at visit.

Table 13. Mammographic breast density after 6 months of treatment: Change from baseline

	Placebo (N=41)	Testosterone (N=46)	Overall (N=87)
	n (%)	n (%)	n (%)
Increase in breast density according to Wolfe Classification	7 (18%)	10 (22%)	17 (20%)
Decrease in breast density According to Wolfe Classification	0 (0%)	0 (0%)	0 (0%)
Increase in breast density according to the percentage scale	12 (29%)	14 (30%)	26 (30%)
Decrease in breast density according to the percentage scale	0 (0%)	0 (0%)	0 (0%)

The CHMP considered that while these experimental data on proliferation are reassuring, they cannot be used to predict actual breast cancer risk (see discussion on safety).

Cardiovascular System

There was a difference between the INTRINSA and placebo group when all adverse events within the MedDRA Cardiac Disorders System Organ Class (SOC) were compared in the double-blind study period: placebo, n=5 (0.7%) and INTRINSA n=10 (1.4%; Table 14). When the adverse events were assessed at the MedDRA Preferred Term (PT) level, no difference between groups was noted. In the open-label period of the study, there was no difference in the rates of cardiovascular adverse events between the INTRINSA–INTRINSA group and the placebo-INTRINSA group.

Table 14. Cardiac disorders reported as AEs in the combined studies during 24 weeks double-blind period

MedDRA SOC/ HLT/ PT	Placebo (N=703)			TTS (N=696)			p-value
	n (%)	Rate	nAE	n (%)	Rate	nAE	
Cardiac disorders							
Cardiac signs and symptoms NEC							
Palpitations	3 (0.4%)	0.005	3	5 (0.7%)	0.008	5	0.5046
Overall HLT	3 (0.4%)	0.005	3	5 (0.7%)	0.008	5	0.5046
Coronary artery disorders NEC							
Coronary artery disease NOS	1 (0.1%)	0.002	1	0 (0.0%)	0.000	0	1.0000
Overall HLT	1 (0.1%)	0.002	1	0 (0.0%)	0.000	0	1.0000
Ischaemic coronary artery disorders							
Angina pectoris	0 (0.0%)	0.000	0	2 (0.3%)	0.003	2	0.2473
Overall HLT	0 (0.0%)	0.000	0	2 (0.3%)	0.003	2	0.2473

- **Systolic and diastolic blood pressure**

No general difference in systolic or diastolic blood pressure between INTRINSA and placebo was seen. The open label phase permitted assessment of changes from baseline or differences in blood pressure based upon duration of testosterone exposure. Those subjects who had been exposed to placebo in the first six months (double blind phase) of the clinical trials, had baseline values at the visit just prior to their initiation of testosterone therapy. The changes from baseline in mean systolic blood pressure was 1.6 (SD 12.3) and in median systolic blood pressure 2.0 mm Hg in the placebo->INTRINSA group. In the INTRINSA->INTRINSA group, the corresponding changes from baseline were 1.5 (mean; SD 14.0) and 0 (median) mm Hg. For diastolic blood pressure, the mean (SD) and median changes from baseline were 0.9 (9.0) and 0 mm Hg in the placebo->INTRINSA group, and 0.5 (9.7) and 0 mm Hg in the INTRINSA->INTRINSA group.

- **Laboratory findings**

Lipids, liver function tests, measures of carbohydrate metabolism, and haematology were reported. There were no clinically significant changes in any of these laboratory parameters in any treatment group in any of the clinical studies.

Lipids
No differences were noted in total cholesterol or triglyceride levels between INTRINSA-treated patients and the placebo-treated patients during the 24-week double-blind period in either the phase II or phase III studies or with additional therapy up to 52 weeks.

Liver, renal and carbohydrate function
No clinical cases of hepatic injury or hepatic malignancy were reported in any of the studies. Abnormal liver function test (HLT of "liver function analyses" including increased ALT and/or AST, or bilirubin) as an adverse event was reported at a higher incidence in the INTRINSA group (6 patients, 0.9%) compared with the placebo group (1 patient, 0.1%) during the 6-month, double-blind study period. In the open-label period of the studies, 3 patients in the INTRINSA–INTRINSA group and none in the placebo-INTRINSA group experienced increased liver enzymes (2 ALT and 1 AST) reported as adverse events. One patient withdrew due to an elevated ALT level.

- Safety in special populations

N/A

- Safety related to drug-drug interactions and other interactions

N/A

- Discontinuation due to adverse events

N/A

- Post marketing experience

- Discussion on clinical safety

In the short-term perspective up to 12 months of exposure, there was little safety concern emerging from the clinical trials programme. The lack of difference between INTRINSA and placebo may, however, be due to the relatively limited number of mostly healthy women exposed in the trials for a comparatively short time. However, as duration of treatment could be assumed to continue over several years, provided a positive effect is perceived by the patient, long-term safety data are unavailable but will be addressed via the agreed follow up measures

As expected, women treated with INTRINSA had a slightly higher rate of androgenic adverse effects, most often mild to moderate. The relative rates of acne, alopecia, hirsutism and voice deepening were less than 1.5, and the increase versus placebo was statistically significant for hirsutism and acne only. It should be noted however, that androgenic events such as acne, hirsutism and voice deepening may not be reversible and are likely to increase with long-term use and therefore will remain a concern of importance. In the resolution of androgenic adverse events study (from studies 2000133 and 200134) subsequently presented by the Applicant, it was reported that in 27% of patients with acne, 57.5% of hirsutism, 39% of alopecia and 40% of women with voice deepening, androgenic events had not resolved, indicating the importance of appropriate observation and follow-up measures. Resolution rates were similar in INTRINSA and placebo groups.

It is agreed that androgenic adverse events are uncommon and, if they occur, they should lead to discontinuation of INTRINSA use. This is taken into account in section 4.4 of the SmPC.

The CHMP was mainly concerned about long-term safety. Long-term safety of the INTRINSA is little studied and creates concerns which relate to cardiovascular and breast, but also to endometrial safety, should the INTRINSA be inadvertently used in non-hysterectomised women. The Applicant has submitted a comprehensive review of the literature on testosterone and the risk of breast and endometrial cancer and cardiovascular events. The analysis of the General Practitioner Research Database (GPRD) /Health Improvement Network (THIN) database from the UK comprises

2103 women treated with testosterone, followed for an average of 8.6 years. The Ingenix US-based medical claims database comprises around 20,000 oestrogen-testosterone users followed for a mean time of 1,6 years. The results from these two studies show no obvious safety concerns but do have limitations, particularly with regard to limited follow-up and relatively short duration of exposure, so that it is unlikely that risks associated with long-term use would have been detected.

Finally, the Applicant has submitted a Risk Management Plan, in which a number of safety actions are proposed.

The Applicant has presented a review of the literature of data on testosterone and the risk of breast cancer both with regard to endogenous testosterone levels in women with breast cancer and with regard to women treated with exogenous testosterone. Some studies showed a statistically significant correlation between endogenous testosterone levels and breast cancer risk whereas other studies found that a correlation was no longer present after adjusting for oestrogen levels. One case cohort study showed that, in women at high risk for breast cancer, high endogenous testosterone levels were not associated with increased risk for breast cancer and that there was a trend toward lower risk with higher levels of testosterone. However, a prospective study in post-menopausal women who were operated on for breast cancer showed that serum levels of testosterone were significantly higher in patients who had recurring breast cancer than in patients who did not.

A review of the literature on testosterone effects on the breast found that *in vitro* studies of the effects of androgens in various breast cancer cell lines predominantly support apoptotic and antiproliferative effects of androgens on the mitogenic effects of oestrogens. On the other hand, animal studies exist that show a proliferative effect of testosterone on breast tissue. An *in vivo* randomised, placebo-controlled, 6-month study to assess the potential effect of INTRINSA on breast epithelial cell proliferation in naturally menopausal women on oestrogen norethindrone acetate (Study 2003082) was included in the original market authorization application. Additional data from that study indicate that testosterone reduced epithelial and stromal breast cell proliferation compared with placebo in this population.

Observational studies with longer term follow-up of women treated with testosterone revealed conflicting results. Two studies suggested an increased risk of breast cancer (Ewertz M: Int J Cancer 1988; 42: 832-838; Colditz GA et al.: New Engl J Med 1995; 332; 1589-1593) while others did not support this finding (Dimitrakakis et al, 2004; GPRD/THIN & Ingenix).

- In summary, data in the literature regarding the influence of testosterone on the risk of breast cancer in women are limited, inconclusive and conflicting. The long-term effect of testosterone treatment on the breast is currently unknown, therefore patients should be carefully monitored with regard to breast cancer. Breast safety, , needs to be monitored and investigated further, as suggested in the pharmacovigilance plan.
- In section 4.2 of the SPC, breast cancer is listed as a contraindication for use of INTRINSA.

Since the current MAA relates to bilaterally oophorectomised and hysterectomised (surgically menopausal women), no endometrial data exist from pivotal trials. Limited data have been generated during INTRINSA use in naturally menopausal women over a two-year period. Endometrial biopsies showed 2 cases of hyperplasia among 226 non-hysterectomized patients on testosterone.

Data on endometrial effects are available from two epidemiological databases, GPRD/THIN and Ingenix, where patients who received testosterone other than INTRINSA as part of their HRT have been evaluated for the occurrence of endometrial cancer. In the GPRD/THIN study no testosterone user was diagnosed with endometrial cancer compared with 5 control patients. In the Ingenix database, the risk of endometrial cancer was similar in users and non-users of testosterone.

- In summary, limited data evaluating the effect of low-dose testosterone on the endometrium does neither allow conclusions nor reassurance. In the event of misuse of INTRINSA in non-hysterectomised and non-oophorectomized women, endometrial safety will be investigated further as part of the pharmacovigilance plan.

With respect to cardiovascular events, the clinical trials on INTRINSA did not reveal overall alterations versus placebo of lipids, carbohydrate metabolism, coagulation factors or blood pressure. Weight gain which increased with time was, however, more frequent in patients INTRINSA. The weight gain observed was not accompanied by effects in other markers of cardiovascular safety.

Nevertheless, literature data recently confirmed possible long-term effects of testosterone in women on insulin resistance and lipid profile (see N Engl J Med April 2006).

The Applicant presents an analysis of a subset of patients, comprising around 15% of all patients in the clinical INTRINSA trials, with cardiovascular risk factors at baseline (BMI>30, on antihypertensive treatment or systolic/diastolic BP $\geq$130/85, on lipid lowering medication or triglycerides$\geq$150mg/dL or HDL$\leq$50mg/dL, fasting glucose>110mg/dL). A mean increase of around 4 mm in systolic and diastolic blood pressure was found among INTRINSA patients also taking HRT whereas no such increase in blood pressure was seen in patients with CV risk factors not taking concomitant HRT. It cannot be excluded that this finding for the risk of cardiovascular disease is clinically relevant.

Analyses from the observational databases (GPRD/THIN; Ingenix) did not reveal statistically significant differences between women treated and not treated with testosterone in the rates of cerebrovascular disease, ischemic heart disease, deep venous thrombosis/pulmonary embolism, and diabetes mellitus. The rate of ischemic heart disease and myocardial infarction was comparable between testosterone users and control patients both in those with and without a baseline history of diabetes, cardiovascular disease, smoking and high BMI. There was, however, an increasing RR of deep vein thrombosis (DVT) in the testosterone group with increasing age. The finding in GPRD/THIN of a statistically significantly increased risk of ischemic heart disease after 350 weeks (6.7 years), is of concern and underlines the need for continued monitoring as well as limitation of the duration of treatment.

- In summary, data evaluating cardiovascular and associated risks in relation to testosterone use in women are still limited. The data are mostly reassuring but cannot exclude that long-term use may carry an increased risk of cardiovascular events.
- Information on a possible risk increase in women with own cardiovascular risk factors and after long-term use is included in the SPC.

The Risk Management Plan contains various approaches to post-marketing surveillance, including stimulated reporting, active surveillance through prescription event monitoring, review of ongoing studies and observational studies using existing databases. A non-interventional prospective observational study (EMPOWER) will be set up by the Applicant. In general, those activities are endorsed. Review of ongoing studies will be able to pick-up more data on androgenic adverse events, but, due to small sizes, those studies will have limited potential to study cardiovascular and cancer risks. The studies originating from existing databases will have a reasonable potential to discover long-term safety effects (cardiovascular, cancer) as they already contain women treated with other testosterone products. It is likely that the NIPOS will take considerable time before interpretable results are available. It is also of particular importance that risk minimization measures, i.e. adherence to the SPC and PL information be evaluated by the Applicant and that off-label use, i.e. use by naturally menopausal patients and use without additional HRT, be discouraged and monitored.

In conclusion, the safety data as presented by the Applicant does not reveal any apparent safety problem but data are limited. Although none of the studies presented, neither experimental nor observational, provides conclusive data on the effect of testosterone on breast cells or breast cancer risk, the available data do not suggest an increased risk of breast cancer and may even suggest that androgens have an antiproliferative effect on breast cells when given in combination with oestrogen therapy. Breast safety, however, needs to be monitored and investigated further within the Risk Management Plan activities.

Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan, to address identified (androgenic) and.potential safety concerns (breast cancer, endometrial cancer and cardiovascular effects.

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The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

5 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

The effects of endogenous and administered testosterone in both men and women have been evaluated and reported in the literature. Overall this information establishes that adverse effects reported are due to the pharmacological profile of the hormone.

Published data provide an adequate basis for the assessment of the end-points not deliberately tested for in the clinic, *i.e.* acute toxicity, genotoxicity, carcinogenicity and reproductive toxicity.

Testosterone is not genotoxic, yet produces tumours in a range of organs, including endometrium, mammary gland, and liver, in rodents when administered at high doses.
Consistent with other marketed testosterone products, statements about rodent carcinogenic data are included in the 5.3 section of the SPC.

In addition it is also clear that testosterone can have adverse effects on the developing foetus and should not be used by women who are, or who are likely to become, pregnant. This is taken into account in Sections 4.6 and 5.3 of the SmPC.

Efficacy

The efficacy of the INTRINSA transdermal system to relieve symptoms of HSDD in surgically induced menopausal women with HSDD on concomitant oestrogen treatment has been adequately and consistently demonstrated for all three endpoints and in responder rates across placebo-controlled studies. Greater effects versus placebo have been demonstrated on satisfying sexual activity (SAL; primary endpoint), sexual desire and personal distress (PSFS, PDS; secondary endpoints).

There has been some concern regarding the magnitude of the efficacy and whether the effects over placebo could be considered clinically meaningful.

In the pivotal clinical trials, around 25% of women were on transdermal and 75% of the women took oral oestrogens and of those, 60% took conjugated equine oestrogens (CEE) and around 40% took non-CEE. All data suggest that the efficacy of INTRINSA was affected by the type of oestrogen used with a clearly poorer effect in women on CEE. The dominance of CEE in the studies has negatively influenced the results in the pooled analyses as shown in the subgroup analyses, in which the efficacy data in women on non-CEE or transdermal oestrogens were consistently superior to those found in women on placebo or CEE. With regard to the primary endpoint SAL, the overall difference in responder rate between INTRINSA and placebo increased from 14.4% in the total study population (including patients on concomitant CEE treatment) of the pivotal studies to 21.3% when patients on CEE were excluded. Thus, in women on non-CEE oestrogens, a larger difference between INTRINSA and placebo was reported, which should affect the final judgement with regard to clinical meaningfulness.
The limited data from surgically menopausal women without oestrogen replacement suggest that the magnitude of efficacy was similar to that seen in women on non-CEE ERT but the results are not conclusive.

In conclusion, INTRINSA has been adequately and consistently shown to relieve symptoms of HSDD in surgically induced menopausal women with HSDD on concomitant non-CEE oestrogen treatment. The recommendation against concomitant use of CEE with INTRINSA, is included in the SmPC.

Safety

The safety data as presented by the Applicant does not reveal any apparent safety problem, nevertheless are limited. Long-term safety of the INTRINSA is little studied and creates concerns which relate to cardiovascular and breast, but also to endometrial safety, should the INTRINSA be inadvertently used in non-surgically menopausal women.

Available data regarding the influence of testosterone on the risk of breast cancer in women are limited, inconclusive and conflicting. The long-term effect of testosterone treatment on the breast is currently unknown. Breast safetywill be monitored and investigated further, as suggested in the pharmacovigilance plan.

The present indication does not include non-hysterectomized women; nevertheless limited data evaluating the effect of low-dose testosterone on the endometrium do not allow conclusions nor reassurance. Therefore endometrial safety will be investigated further as part of the pharmacovigilance plan.

Data evaluating cardiovascular and associated risks in relation to testosterone use in women are still limited. The data are mostly reassuring but cannot exclude that long-term use may carry an increased risk of cardiovascular events.

The activities proposed in the Risk Management Plan are endorsed.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

Risk-benefit assessment

The efficacy of INTRINSA transdermal system to relieve symptoms of HSDD in oophorectomized hysterectomized (surgically induced menopausal) women with HSDD on concomitant oestrogen treatment, has been adequately and consistently demonstrated across placebo-controlled clinical studies.

The benefit was based on the increase of number of satisfying sexual episodes (SAL, primary endpoint), as well as improvement on sexual desire and personal distress evaluation (PSFS, PDS; secondary endpoints).

The rate and severity of androgenic adverse event is low and does not appear to increase with prolonged treatment up to one year. Furthermore, no apparent risk has been identified.

Nevertheless potential long-term risks, such as breast cancer, cardiovascular events, and endometrial effects have been identified as issues that should be carefully monitored according to the Risk Management Plan.

Overall, after review of the Applicant´s response to the efficacy and safety issues raised, the risk/benefit ratio is considered positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Intrinsa in the treatment of hypoactive sexual desire disorder (HSDD) in bilaterally oophorectomized and hysterectomized (surgically induced menopausal) women receiving concomitant estrogen therapy was favourable and therefore recommended the granting of the marketing authorisation.