Assessment report

Zoely

International Non proprietary Name: nomegestrol/estradiol

Procedure No. EMEA/H/C/001213

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Serono Europe Ltd. submitted on 29 July 2009 an application for Marketing Authorisation to the European Medicines Agency for Zoely, through the centralised procedure falling within the Article 3(2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the Agency/CHMP on 19 February 2009. The eligibility was revised from 3(2)a to 3(2)b because the CHMP became aware that the same combination has already been approved. The eligibility to the centralised procedure under Article 3(2)b of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The legal basis for this application refers to Article 10(b) of Directive 2001/83/EC – fixed combination application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

The applicant applied for the following indication:

> *Oral contraception. Zoely 2.5mg/1.5mg, film-coated tablet is indicated in fertile women including post-menarcheal adolescents from the age of 12 years.*

The approved indication by the CHMP was:

> *Oral contraception*

Information on Paediatric requirements

Pursuant to Article 8, of Regulation (EC) No 1901/2006 the application included an EMA Decision P/61/2010 for the following condition:

- Contraception

on the agreement of a paediatric investigation plan (PIP) and granting of a product specific waiver with deferral. The PIP is completed. The PDCO issued an opinion on compliance.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 28 April 2006 in procedure EMEA/H/SA/705/1/2006/II. The Scientific Advice pertained to clinical advice on the performance of haemostasis studies. Of note, specific requests/questions were asked by the applicant on the design of studies that investigate the effect of hormonal contraceptive on haemostasis parameters.

The applicant has also received Scientific Advice from National Competent Authorities. The Scientific Advice pertained to the non-clinical part of the dossier. Non clinical scientific advice on the need for carcinogenicity studies was discussed with the French Medical Agency (Afssaps) in a meeting held on July 1st, 2005. Written advice on the same topic was received from the Medical Products Agency (MPA, Sweden) on August 28th, 2005.

Licensing status

Zoely was not licensed in any country at the time of submission of the application. An application for the same product was filed in the USA on 30 June 2009. The NDA was considered by the FDA not completed for acceptance in 2009. The file was re-submitted on 5 January 2011.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Philippe Lechat** Co-Rapporteur: **János Borvendég**

- The application was received by the Agency on 29 July 2009.
- The procedure started on 19 August 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 November 2009.
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 09 November 2009.
- During the meeting on 17 December 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted a letter requesting a 3-month extension to submit the responses to the CHMP consolidated List of Questions on 12 February 2010.
- The applicant submitted a letter requesting an additional 2-month extension to submit the responses to the CHMP consolidated List of Questions on 10 June 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 September 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 02 November 2010.
- During the CHMP meeting on 18 November 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 11 January 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 17 February 2011.
- During the CHMP meeting on 17 February 2011, the CHMP agreed on the Second List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP Second List of Outstanding Issues on 23 February 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the Second List of Outstanding Issues to all CHMP members on 04 March 2011.
- During the meeting on 17 March 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zoely on 22 March 2011. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 14 March 2011 Annex 8.

2. Scientific discussion

2.1. Introduction

Hormonal contraception refers to birth control methods that act on the endocrine system. The vast majority of methods are composed of steroid hormones. There are two main types of hormonal contraceptive formulations: combined methods which contain both an estrogen and a progestin, and progestogen-only methods which contain only progesterone or one of its synthetic analogues (progestins). Traditionally the combined hormonal contraceptives contain two steroids: one with gestagenic and the other with estrogenic effects. The functions of progestagens are to inhibit ovulation, primarily by the central feedback mechanism resulting in decreased luteinizing hormone (LH) secretion by the pituitary gland. The estrogen component also contributes to contraceptive efficacy by inhibiting the effect on FSH secretion but the major function of estrogens in the contraceptive pill is to provide stability to the endometrium and consequently to provide acceptable cycle control and bleeding pattern. The progestagen components of combined hormonal contraceptive pills are nor-testosteron or progesterone derivatives. Combined hormonal contraceptives almost without exception contain 17-alpha-ethinylestradiol (EE) and some first generation combined hormonal contraceptives contain mestranol. 19-nor-testosteron derivatives have, besides their gestagenic effects, mild to moderate androgenic effects and might have negative impact on the lipid metabolism. They can also cause intrahepatic cholestasis.

Nomegestrol Acetate (NOMAC) is a highly selective progestin derived from the naturally occurring steroid hormone, progesterone. The 17β-estradiol (E2) compound is identical to the endogenous human E2 and is therefore classified as a natural estrogen. Zoely 2.5mg/1.5mg, film-coated tablet (NOMAC-E2) is a new novel monophasic oral preparation which contains 2.5mg of the progestagen nomegestrol acetate (NOMAC) and 1.5mg of the estrogen 17β-estradiol (E2). The two active components are already approved for marketing, either individually or as a combination: Estreva® tablets (1.5 mg E2), Lutenyl® tablets (3.75 mg and 5 mg NOMAC) or Naemis® tablets (E2 1.5 mg for 10- days and E2 1.5 mg + NOMAC 3.75 mg for the next 14 days).

The 17-alpha-ethinylestradiol compound has a very strong estrogenic activity; its bioavailability is very high (=90%). The 17-alpha-ethinyl side chain protects the molecule against the rapid metabolism (first pass metabolism) by the liver. Ethinylestradiol has a stronger effect on the metabolic activity of the liver compared to estradiol, and namely increases in a dose dependant way the production of several serum factors which facilitate coagulation. The main aim to develop this compound was to use more natural hormones in the hormonal combined contraception in contrast with those which are available. Nomegestrol acetate has strong affinity for the human progesterone receptor an antigonadotropic activity and has no androgenic or mineralocorticoid effects. In addition NOMAC shows moderate antiandrogenic effects as well.

NOMAC-E2 is classified under ATC code G03AA14, therapeutic/pharmacological group: "Genitorurinary system and sex hormones – sex hormones and modulators of the genital system – hormonal contraceptives for systemic use- progestagens and estrogens, fixed combinations".

The main mechanism by which the combination of NOMAC-E2 provides its contraceptive effect is ovulation inhibition. Additional mechanisms concern the induction of cervical mucus impenetrable to sperm and induction of an atrophic endometrium which is not suitable for nidation. The approved indication is oral contraception. One tablet is to be taken daily for 28 consecutive days.

2.2. Quality aspects

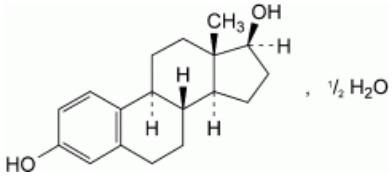
2.2.1. Introduction

Zoely is a novel oral contraceptive and is presented as film coated tablets, containing 2.5 mg nomegestrol acetate and 1.5 mg estradiol packed in blisters. Each blister contains 24 white active tablets with 4 placebo tablets.

2.2.2. Active Substance

Estradiol hemihydrate

The chemical name of the active substance is Estra-1,3,5(10)-triene-3,17β-diol hemihydrate. The molecular formula of active substance is $C_{18}H_{24}O_2$,½H_2O. Its relative molecular mass is 281.4 and its structural formula is shown below:



Estradiol hemihydrate is a white or almost white, crystalline powder, practically insoluble in water and sparingly soluble in ethanol. According to the presented results estradiol has several polymorphic forms and exhibits a strong tendency to form solvates. It has been demonstrated however that the proposed manufacturing process consistently yields the desired form.

Manufacture

A Certificate of Suitability (CEP) has been provided for the drug substance manufactured by the proposed supplier covering the manufacturing. The CEP also contains a declaration about the absence of use of material of human or animal origin in the manufacture of the substance.

Specification

Estradiol hemihydrate is described in the European Pharmacopoeia (Ph. Eur). The specification of the active substance as set up by the drug product manufacturer includes tests and limits for appearance and colour (visual), identification (IR, UV, melting range), impurities (HPLC), assay (Ph.Eur., HPLC), residual solvents (GC), optical rotation (Ph.Eur.), water (Ph.Eur.) and particle size (LDS).

A specific control of the polymorphic form is not included in the specification because the most stable polymorphic form is used, and polymorphism is not considered a critical quality attribute in the unit operations utilised in the drug product manufacturing process.

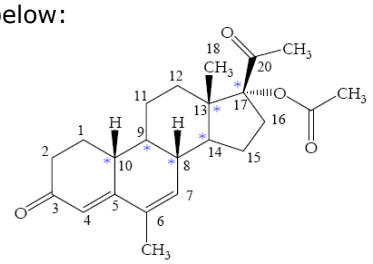
Stability

The retest period is covered by the CEP.
In accordance with EU GMP guidelines [1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

Active Substance

Nomegestrol acetate

The chemical name of the active substance is 17α-acetoxy-6-methyl-19-norpregna-4,6-dien-3,20-dione. The molecular formula of active substance is $C_{23}H_{30}O_4$ and the relative molecular mass 370.48 and its structural formula is shown below:



Nomegestrol acetate is a white to off-white non-hygroscopic crystalline powder. It is practically insoluble in water. The partition coefficient at 25°C: logP (octanol/purified water) was found 3.70.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

It has 6 asymmetric carbons: the isomers in C8, C9, C10, C13 and C14 are determined by the ring structure. Structural inversion is not possible without ring rupture for these isomers.
Nomegestrol acetate shows polymorphism. A number of different polymorphs were found. In the manufacturing process conditions however, it is only possible to obtain one form.

Manufacture

For nomegestrol acetate an ASMF has been provided. The route of synthesis as it is included in the submitted ASMF is adequately described. Specifications for starting material, reagents, and intermediates were given. In-process controls are described. Carry-over of potentially toxic reagents was discussed and justification for non-routine control was presented.

Specification

Nomegestrol acetate is described in the European Pharmacopoeia (Ph. Eur). The specification of the active substance as set up by the drug product manufacturer includes tests and limits for appearance and colour (visual), identification (Ph.Eur.), impurities (HPLC, ICP), assay (HPLC), residual solvents (GC), optical rotation (Ph.Eur.), loss on drying (Ph.Eur.), and particle size (LDS). In addition the active substance supplier includes the two following tests in the specification for nomegestrol acetate: appearance of solution (Ph.Eur.), heavy metals (Ph.Eur.) and sulphated ash (Ph.Eur.).

Analysis results from the ASMF holder were provided for three batches. All results comply with the proposed specifications. Analysis results from the applicant were provided for nomegestrol acetate batches used in clinical, development and stability studies. All results except particle size distribution comply with the proposed specifications which have been refined through development and revised during procedure.. Batch consistency was demonstrated.

Stability

The stability studies on nomegestrol acetate drug substance are performed under ICH storage conditions on three commercial batches. The samples for stability study were stored in similar containers to those used for industrial batches for up to 36 months under 25°C/60%RH and for six months at 40°C/75%RH.

The results showed that the substance remains within the specifications, moreover no significant changes in the data can be observed. Supportive stability data for four batches were attached, which indicate that the stability is not adversely affected by particle size reduction. One batch of drug substance was exposed to heat, light, acid, alkaline and neutral pH, oxidising medium and radical initiator medium. Results indicated that the drug substance is not sensitive to light in the solid state but it slightly degraded when exposed to heat in the solid state and, in solution, it is hydrolysed to nomegestrol. It is not sensitive to an oxidising medium but degraded in presence of the radical initiator medium which was subjected to. Based on the presented information the proposed retest period is accepted. In accordance with EU GMP guidelines, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Nomegestrol acetate and estradiol hemihydrate are commercially available in the EU in other products. These products were the starting products to establish the contraceptive efficacy of this combination. Based on these results a combination tablet has been developed. The drug product consists of a combination of 24 active, white film-coated tablets, each containing 2.5 mg of nomegestrol acetate and 1.5 mg of estradiol, and 4 placebo yellow film-coated tablets, packed together in a blister. The colour of the film-coat enables to distinguish between active and placebo tablets and also serves to reduce health, safety and environment (HSE) risks during packaging. The objective for the formulation development was obtaining comparable pharmacokinetic profiles as obtained in phase IIA and IIB studies. Both active substances are BCS class II compounds (low solubility and high permeability).

Initially, two formulations and two different manufacturing approaches have been tried. Since the dissolution profiles were similar for both developed products, the simplest formulation and

manufacturing process were preferred. The placebo tablets developed were directly derived from the formula and manufacturing process of the active tablet. To avoid the risk of any mix-up during the packaging it was decided to differentiate the placebo tablet from the active ones by the addition of a coloured film coat.

Excipients were selected based on their previously established compatibility with the same active substances in other products. Their amount has been optimized. The amount of the film-coat has been optimized with regard to disintegration time and dissolution. For comparability reasons with the uncoated drug product an extensive set of dissolution experiments were performed. No effect of the film coat layer was found.

After the production of the pivotal clinical batches, a Quality by Design (QbD) based approach was applied. The science- and risk- based pharmaceutical development studies performed and a reasonably wide range for the different (potentially) critical quality attributes and process parameters has been investigated during development of drug product. Critical Quality Attributes that impact safety, efficacy and/or manufacturability have been identified and risk management processes have been used to facilitate risk reduction. The applicant has carried out extensive development studies in order to better understand and control the manufacturing process. However, no multifactorial (design of experiments) or full interaction studies have been carried out to address the potential impact of interactions between attributes and/or parameters on drug product quality. Instead, the impact of attributes/parameters on drug product quality has been studied one factor at a time, leading to a satisfactory set of proven acceptable ranges. A NIR on-line PAT application has been developed for the control of blend uniformity of active tablets and the performance of the application has been satisfactorily optimised. Appropriate control strategy has been implemented based on the knowledge gained from the manufacture of the pivotal clinical batches, process development studies, the manufacture of the primary stability batches and the scale-up studies. Appropriate process controls and monitoring are described for both active and placebo tablets. Because the selected polymorphic forms are unambiguously being provided by the drug substance manufacturers and show very good stability, polymorphism is not considered a critical quality attribute. Studies were conducted varying the amount of excipients focusing on the effect on critical quality attributes. Results confirmed the robustness of the formulation and production process since relatively large intentional variations in the amounts of the excipients in the tested ranges did not affect the quality of the drug product.

The impact of the particle size distribution of the two active substances on the content uniformity and dissolution was evaluated and appropriate specifications have been set. The impact of moisture content on disintegration, dissolution, and processability was also evaluated. Results show that disintegration and dissolution were not significantly affected. The control of the environment parameters and the set specifications for moisture content of excipients assure adequate processability. The relationship between disintegration and dissolution has been investigated. Disintegration was always very fast for all these batches. Over the range of disintegration time observed, no impact was displayed on dissolution. The differences of the formulations studied and clinically tested during development of drug product and the intended for marketing can be considered minor having no impact on drug product bioavailability.

A commitment has been undertaken by the applicant that before application in routine, the performance with the final optimised settings will be validated on industrial scale batches. For these batches, the NIR application will be used to control the mixing time and it will be demonstrated by comparison with extended blend sampling and tablet stratified sampling that the NIR end-point criterion corresponds to a uniform blend. If needed, the applicant should submit appropriate variations to change the NIR method parameters or equipment.

Adventitious agents

Only lactose is of animal origin. Satisfactory documentation has been provided that lactose used in the manufacture is in compliance with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA 410/01 Rev. 2).

Manufacture of the product

Satisfactory description of the manufacturing process is provided for both the active and placebo tablets. Both the critical and the potentially critical process parameters and quality attributes, were

defined. IPCs and critical steps are specified. The process controls are derived from the risk and science based development approach.

Process validation scheme for the manufacturing scale batches was presented. As the estradiol active substance content of the tablet is below 2% the manufacturing process is not considered to be a standard one. Validation report should be submitted according to the guideline CPMP/QWP/848/96 Process validation. Manufacturing process of active and placebo tablets is considered validated at full scale at the claimed manufacturing site. A commitment is undertaken by the applicant to validate the manufacturing process on the three consecutive commercial batches of active and placebo tablets.

Product specification

The active tablets release and shelf life specifications include tests and limits for: appearance and colour (Ph.Eur.), identification (HPLC or UHPLC- at release only), assay (HPLC or UHPLC), impurities (HPLC or UHPLC), uniformity of dosage units (Ph.Eur. - at release only), dissolution (Ph.Eur.) and microbial tests (Ph.Eur.). The placebo tablets release and shelf life specifications include tests and limits for: appearance and colour (Ph.Eur.), identification (HPLC or UHPLC- at release only) and microbial tests (Ph.Eur.).

For the active tablets, results from six primary stability batches and two commercial size batches were presented. Supportive data from another 13 batches manufactured at different sites as well as historical batches (not film coated) were also provided.

The data provided on the batches described above include batch analysis data and data on stratified sampling. A comparison of the performance of the methods used over the course of development is provided. The results are comparable.

All active tablets batch data met the specifications and confirmed the suitability of the same. For the placebo tablets, results from one primary stability batch and one commercial size batch were presented. Supportive data from one pivotal clinical manufactured at a different site was also provided. The composition of the commercial scale batch is identical to the market formulation of placebo tablets. The composition of the other two batches is equivalent to the market formulation, with the exception of colour. All results comply with the proposed specifications.

Stability of the product

Six primary stability batches manufactured according to the commercial formulation were put on stability studies at ICH conditions. The container closure system is identical to that proposed for the commercial product except for the use of a coloured lidding foil.

Results have been provided for up to 24 months at 5°C/ambient RH, up to 24 months at 25 °C/60% RH, 30 °C/40% RH and 30 °C/75% RH and up to 6 months at 40 °C/75% RH.
No relevant changes in active substances content or individual impurities were observed. All other parameters remained within the specifications.

Stability data of seven supporting stability batches have also been provided. The compositions of the tablets are identical to the proposed marketing formulation, manufacturing site and process and the packaging is the same as for the primary stability batches. Results of three scale up batches are also provided. Stability results for the supportive batches are in line with the results of the primary stability batches. Two primary stability batches were involved into the photostability studies. There were no significant changes in the packed and unpacked product for the tested parameters.

Stability studies were also provided for three placebo batches; one primary stability batch, one supportive and one clinical batch. All batches were packed in the commercial blister.
Results have been provided for up to 24 months for the primary stability batch and up to 33 months for the other two batches at 5°C/ambient RH, 25 °C/60% RH, 30 °C/40% RH and 30 °C/75% RH and up to 6 months at 40 °C/75% RH. The yellow colour used for the intended commercial placebo tablet shows no change under the various temperature and humidity conditions.

The overall stability results support the proposed shelf-life and storage conditions.

In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Zoely film-coated tablets is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Information on development, manufacture and control of the drug substances has been presented in a satisfactory manner. The quality of the active substances is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug product has been presented.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life. At the time of the CHMP opinion, there was one quality issue that will be resolved as Follow-up Measure within an agreed timeframe. This issue relates to validation of commercial scale batches and the use of the NIR application as control of the mixing. However, this issue is not expected to have a negative impact on the Benefit Risk balance of the product.

2.3. Non-clinical aspects

2.3.1. Introduction

NOMAC-E2 is a monophasic combined oral contraceptive (COC) combining the natural estrogen, 17β-estradiol (E2) and nomegestrol acetate (NOMAC), a 19-norprogesterone progestin with a potent gonadotropin-inhibiting effect in females. NOMAC binds with a strong affinity to the progesterone receptor (PR) derived from hormone-sensitive cell lines and tissues from rat, rabbit, and human origin and has no activity on other steroid receptors with the exception of a weak in vitro and in vivo anti-androgenic activity. Non- clinical studies showed that NOMAC exhibits the profile of a full progestogen, which is intrinsically active by the oral route. NOMAC inhibits ovulation in the rat and monkey. Moreover, NOMAC displays anti-androgenic activity, anti-estrogenic activity, and pituitary inhibitory potency. The estrogen contained in Zoely is 17β-estradiol, a natural estrogen identical to the endogenous human 17β-estradiol. E2 is combined with NOMAC in order to compensate the decrease of the endogenous estrogen production (anti-gonadotropic effect of NOMAC). E2 may also reinforce the anti-gonadotropic effect of NOMAC, measured by FSH and LH blood levels.

2.3.2. Pharmacology

A full non-clinical testing program was performed for NOMAC. The estrogen in NOMAC-E2, being 17β-estradiol, is a well-established pharmaceutical product and concerning its effects and metabolism abundant literature data are available. Therefore, no non-clinical studies with E2 alone were performed during the development of NOMAC-E2. This was accepted by the CHMP.

Primary pharmacodynamic studies

Primary pharmacodynamics in vitro
Receptor binding studies have shown that NOMAC binds with a high affinity to the progesterone receptor (PR) in various hormone sensitive cell lines derived from rat, rabbit or human and transactivates human PR in HeLa and CHO cells transfected with progesterone receptor B (PRB). NOMAC showed anti-androgenic activity with an IC_{50} value of 92,1 nmol/L. NOMAC does not show (anti)-mineralocorticoid activity.

Primary pharmacodynamics in vivo

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

In vivo, NOMAC exhibited the profile of a full progestogen in classical progestagenic bioassays performed in rabbits (Mc Phail and Mc Ginty tests) and rats. NOMAC induced a high decidual proliferation/ differentiation in immature estrogen-primed female rabbits and induces a decidual reaction after trauma of the uterine horn of the rat. NOMAC had a strong anti-gonadotropic activity, which resulted in an inhibition of spontaneous ovulation in rats and monkeys. The oral ID_{50} (inhibition of ovulation in 50% of treated animals) was 0,5 mg/kg and 0,2 mg/kg in rats and monkeys respectively. Moreover, NOMAC displays anti-androgenic activity, anti-estrogenic activity and pituitary inhibitory potency. No in vivo pharmacodynamic studies were performed with the combination NOMAC-E2.

Secondary pharmacodynamic studies

NOMAC was tested in combination with E2 in studies using OVX animals in the context of the development of NOMAC in HRT. The main characteristic of NOMAC was its neutral effect on the beneficial action of estradiol in non-genital targets. Combined NOMAC did not interfere with the beneficial effects of E2. NOMAC had a strong progestational and anti-estrogenic effect on the uterus and significantly reduced the proliferation that occurs with estradiol alone. NOMAC alone had no functional impact on glucid and lipid metabolism at doses up to 10 times higher than the effective dose on bone in rats. In combination with E2, the functional impact was limited to amplification of the pharmacological.

Safety pharmacology programme

NOMAC was assessed for its effect on core battery safety pharmacology tests. Studies investigating the central nervous, respiratory and gastrointestinal systems and the hemodynamic study in anesthetized beagle dog were performed in the context of nomegestrol acetate development in Hormone Replacement Therapy. Additional cardiovascular safety studies (hERG tail current study in stably transfected HEK-293 cells and study in telemetered Cynomolgus monkeys) were recently completed and were included in the MAA dossier. NOMAC did not produce any unexpected or toxic effects.

Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies were not performed with NOMAC-E2. Two human drug interaction studies were performed in which the pharmacokinetic parameters for NOMAC were evaluated.

The lack of formal pharmacodynamic interaction studies has been considered acceptable by the CHMP taking into account that the interactions of progestogens are well known and NOMAC-E2 has been registered for HRT since 2003 in several European countries.

2.3.3. Pharmacokinetics

The absorption, distribution, metabolism and excretion (ADME) of NOMAC have been investigated in several species, especially in rats and monkeys at the time of the development of NOMAC in HRT. No specific pharmacokinetic animal studies were performed with the NOMAC-E2 combination. In addition, results of recent *in vitro* studies performed with NOMAC alone have been provided: *in vitro* metabolism in human hepatic microsomes, recombinant CYP450s, *in vitro* studies investigating the inhibition and induction of CYP450 enzymes and P-glycoprotein interaction study.

<u>Absorption</u>
NOMAC was rapidly absorbed after oral administration to mice, rats and monkeys. After a single oral dose, the T_{max} varied between 0.25 to 0.5 h (mouse), 1 to 2 h (rat and monkey). In dogs, the absorption was relatively slow with a T_{max} of 6.7 h. Elimination is slow in human and monkey as opposed to rodents.

Regarding E2, subject to a known substantial intestinal and/or liver first-pass effect, there is a large variability in humans in the rate of absorption with median Tmax of 48 h (min – max: 1.0 – 145 h) following single dose of 1.5 mg estradiol and mean Cmax of 253 ± 179 pg/ml. Following repeated dosing in humans, median Tmax is 6 h (min – max: 0.5 – 144 h) with mean Css, max of 86.0 ± 51.3 pg/ml. Thus, this pivotal study, conducted with the to-be-marketed coated tablet shows that NOMAC is

rapidly absorbed by oral route, with time independent kinetics. As expected for E2, endogenous secretion and large first-pass effect give rise to large variability in its rate of absorption.

Distribution
NOMAC has a high plasma protein binding: around 91% in rats and rabbit, 93% in mouse and monkey and 95-97% in human. In human, albumin binds NOMAC (98%), indicating a major role for albumin in plasma protein binding.

Following oral administration of [^{14}C]-NOMAC to rats and monkeys, radioactivity was widely distributed. Distribution was principally to the liver in rat and monkey, stomach and adrenals in rat and intestine in monkey. No significant residues of radioactivity were observed at 96h after dosing in both species.

Metabolism
The metabolism of NOMAC involves CYP450 enzymes. *In vitro* studies using hepatic microsomes and recombinant CYP450s have shown that several CYP are involved in the metabolism of NOMAC (CYP3A4/5, CYP2C8 and CYP2C19). NOMAC was extensively metabolized. The metabolism of NOMAC is characterized by hydroxylation reactions followed by conjugation. Moreover, in rabbit and rat plasma; monkey and human urine, a deacetylated metabolite (nomegestrol) was observed. Whereas the rat produced 2 major urinary metabolites, the pattern in monkey was significant different consisting of essentially highly polar metabolites.

Unchanged NOMAC accounted for 25-35% of total drug related material in circulation in human at 2h post dosage dropping to some 12-21% at 48h post dosage. By comparison, 9% of radioactivity represented NOMAC at 1.5h in rat plasma, decreasing to 5% at 12h and a steady 1% of radioactivity represented NOMAC at 1.5h and 6 h in monkey plasma. Part of the circulating (at Cmax) and excreted (0-24 h) metabolites appears to be conjugated (i.e. phase 2 metabolites), especially in monkey (55%, both in urine and plasma) and human (30%, urine) and to a lesser extent in rats (12% in plasma and 20% in urine). By enzymatic degradation the conjugates were shown to be mainly glucuronides and sulfates in all these species.

Excretion
In vivo excretion/mass balance studies with [^{14}C]-NOMAC were carried out in monkeys and humans. NOMAC drug related material was observed in both urine and feces. The percentage of total dose recovered in feces was 74, 40-57 and 55-67 of the dose for female rats, monkeys and humans respectively. The percent of total dose recovered in urine was 19% in rats, 13-41% in monkeys and 23-41% in human respectively.

Pharmacokinetic drug interactions
Pharmacokinetic interaction studies in vitro examined the potential of NOMAC to inhibit a range of CYP isoenzymes or to cause induction of cytochrome P450 activities. NOMAC did not inhibit or cause induction of any CYP450 activities tested. NOMAC was a weak inhibitor of P-gp-mediated transport, 50% inhibition occurred only above concentration of 3 μM. Therefore, significant P-gp inhibition would only occur at plasma concentrations of at least 100 fold the Cmax. In-vivo interaction studies were not carried out in animals.

2.3.4. Toxicology

In the context of the development of the combination of NOMAC and E2 for Hormone Replacement Therapy, single and repeat-dose toxicity studies bridging studies were performed with the combination of NOMAC and E2, using a 0,4 E2/ NOMAC ratio.

Single dose toxicity

NOMAC
Single dose toxicity was investigated in mice and rats following oral and intraperitoneal administration. The acute toxicity via the oral route is low, the maximum non-lethal dose being 2000 mg/kg or higher. Following intraperitoneal administration, the maximum non-lethal dose is 705 and 385 mg/kg for female mice and rats respectively.

NOMAC-E2 oral toxicity studies were conducted in mice and rats at maximum doses of 2000 mg/kg. Toxicity was low and appeared in form of mild hypoactivity and sedation.

Repeat dose toxicity

Repeated-dose toxicity studies conducted with the NOMAC-E2 combination (E2/NOMAC ratio of 0,4) have been performed in rats and Cynomolgus monkeys up to 13 weeks with respectively 4 and 6 weeks of recovery. In females of both species, an increase in body weight and in food consumption was observed, as well as decrease in the weight of the ovaries and uterus, mammary hyperplasia, blockade of ovarian activity, and in monkeys endometrial hyperplasia. In addition, two 13-week oral toxicity studies were performed with the NOMAC-E2 combination using the E2-NOMAC ratio of 0,6; this is the ratio selected for the claimed contraceptive indication. The studies were performed in mouse and rats by oral gavage up to 13 weeks.

Bridging repeated dose toxicity studies have shown toxic effects which were consistent with the amplification of the hormonal activity which is predominantly estrogenic. The estrogenic effect was apparent in biochemical signs such as anaemia and variations in coagulation parameters and plasma lipid levels, and was also shown by variations in the weight of certain organs, including decreased weight of the ovaries, thymus and spleen, and increased weight of the liver and pituitary and adrenal glands depending on the species. This was often related to pathological changes (inhibition of the ovarian function, endometrial hyperplasia, hyperactivity of the mammary glands). In terms of plasma level, the E2 highest exposure was observed in monkey and the NOMAC highest exposure was observed in rat.

The administration of the NOMAC-E2 combination to mice, rats and Cynomolgus monkeys exhibited a toxicological profile typical of an estrogen-progestin combination (with a predominance of estrogenic effects, particularly in the rat).

Genotoxicity

NOMAC had no mutagenic potential. A battery of in vitro and in vivo genotoxicity tests have been performed with NOMAC. None of the tests indicated any suspicion of genotoxicity. Therefore, no additional genotoxicity testing was performed with the NOMAC-E2 combination.

Carcinogenicity

Long-term carcinogenicity studies were not performed with the combination NOMAC-E2. This was accepted since NOMAC had no carcinogenic effect in the rat and only induced mammary and pituitary tumors in mice, findings which are known for this class of compounds in rodents. Because of this and as NOMAC is combined to an approved estrogen known for its carcinogenic potential in animals, the lack of carcinogenicity studies with the NOMAC-E2 combination is considered acceptable.

Reproduction Toxicity

Reproductive and developmental toxicity studies were conducted with NOMAC in order to comply with recent guidelines. Specific repro-toxicology studies have been carried out with the NOMAC-E2 combination. No reproductive and developmental toxicity studies were conducted with E2.
Teratology studies were performed in rat and rabbit with the NOMAC-E2 combination (E2/NOMAC ratio = 0,6). Maternal toxicity was observed in both species as well as developmental toxicity which were not observed with NOMAC alone. Developmental toxicity was evidenced by reduced fetal weights and embryo-fetal viability. In rats, development delays (reduced ossification) considered related to the treatment were observed at the highest doses (NOMAC/E2 doses of 4 /2,4 and 10/2,4).

The NOAEL was established at NOMAC/E2 1/0,6 mg/kg/day for maternal toxicity and fetus development. In rabbits, at the highest dose tested (NOMAC/E2 = 15/0,5) there were increases in the litter and/or fetal incidences of thoracic hemi-vertebrae and sternal alterations. However, because the increase in post-implantation loss at 0,83/0,5 and 1,7/1 mg/kg/day lowered the number to be examinated, it cannot be fully ascertained whatever the individual fetal alterations seen at 15/0,5 mg/kg/day would not have been occurred in these dosage groups. In rabbits, no NOAEL could be established for maternal toxicity and fetus development.

The maternal toxicity and fetal variations observed in the above studies appeared at systemic exposures similar to or slightly higher than that expected in the woman, indicating that changes observed with the combination were related to the presence of E2. In the return to fertility study

performed in female rats with the NOMAC-E2 combination up to 16/9,6 mg/kg/day for 2 weeks, females returned to normal fertility after a 2-week treatment withdrawal.

Toxicokinetic data

Local Tolerance

Local tolerance studies were not performed. This was considered acceptable by the CHMP.

Other toxicity studies

Metabolites
The metabolite 3 (or TX 219), which has been under development for a different pharmacological target, was investigated in 4-week toxicity studies in rat and dog using the subcutaneous route. There was no test substance related toxicity.

Impurities
The specification of TX071 and TX271, which are two potential impurities in NOMAC drug substance, were set at ≤ 0.1% and thus no further toxicological qualification was needed for these potential impurities.

2.3.5. Ecotoxicity/environmental risk assessment

The PEC $_{surface\ water}$ for the active ingredients of NOMAC-E2 is as follows:

- For NOMAC :
  PEC $_{surface\ water}$ (mg/L) = 2,5 x 0.01 / 200 x 10 = 0,0125 µg/L
- For E2 :
  PEC $_{surface\ water}$ (mg/L) = 1,5 x 0.01 / 200 x 10 = 0,0075 µg/L

The PEC $_{surface\ water}$ for NOMAC is above the guideline limit of 0.01 µg/L,.
Although the PEC $_{surface\ water}$ for estradiol is below the Guideline limit, this drug substance is regarded as endocrine disrupter. [NOEC 0.003 µg/L for reproduction in the fish, *Oryzias latipes*]. Since the estimated NOEC for estradiol is below the (reproduction) threshold of 0.01 µg/L, the PNEC is also < 0.01 µg/L.

Therefore a Phase II environmental effect analysis and risk assessment has been performed.
The ERA data provided a phase II assessment for each compound. These data include results of studies on aquatic organisms performed on nomegestrol acetate according to the principles of the guideline and an extensive review of bibliographical data on 17β-estradiol. (see summary results below)

Phase II Tier A. Results for NOMAC

Physical chemical properties :

Endpoint	Result	Reference
Water Solubility	5 mg/L at 25 °C	(Nomegestrol Acetate Drug Master File, 2006)
Solubility in Aqueous Test Solutions (OECD Guidance of Toxicity Testing of Difficult Substances and Mixtures)	Approx. 5 mg/L	(Meller and Goldberg, 2006)
Log K_{ow}	3.7 at 25 °C	(Nomegestrol Acetate Drug Master File, 2006)

Phase I I Tier A :

Environmental fate data:

Endpoint	Result	Method/ (Reference)
Aerobic Biodegradation in Water	Not readily biodegradable; There was essentially no degradation over the 28 day period.	OECD 301B/ (Kronenberger, 2006)
Sorption to Soil and Sewage Sludge	Log K_{oc} = 3.5 (sludge) Log K_{oc} = 3.3 (soil)	OECD 121 draft of August 1999/ (Brachet and Janssoone, 2006)
Sorption to 3 soils and 2 sludges	K_{oc} of 623 and 721 in sludges (Log K_{oc} 2.79-2.86); K_{oc} of 1176-2218 in soils (Log K_{oc} 3.07-3.35)	OECD 106/ (Simmonds and Burgess, 2009)

Effects on aquatic species:

Endpoint	Result	Method/(Reference)
Activated Sludge Respiration Inhibition	EC50 > 2.8 mg/L;	OECD 209 / (Meller and Goth, 2006; Meller and Egeler, 2006)
Toxicity to Algae	For both growth rate and yield: NOEC = 0.69 mg/L; LOEC – 3.07 mg/L;	OECD 201 / (Junker and Chambers, 2010)
Daphnia magna Reproduction	NOEC > 3.65 mcg/L;	OECD 211 / (Gilberg et al, 2010)
Zebrafish Reproduction	No effects different from control were noted. NOEC > 1.3 mcg/L (measured concentration)	Based on OECD screening paper 47 and US EPA 2002 / (Egeler et al, 2007)

PEC/PNEC assessments:

Compartment	PEC	PNEC	PEC/PNEC
Surface water	0.0125 mcg/L	0.13 mcg/L	0.096
Groundwater	0.0031 mcg /L	0.365 mcg/ L	0.0085
Wastewater treatment facility	0.0125 mcg/L	88 mcg/L	0.000142

The PEC/PNEC ratios with respect to surface water, groundwater and micro-organisms are all substantially less than 1 and/or 0.1 for NOMAC. Based on these data, the use of NOMAC is not considered to be a cause for concern relative to these environmental compartments. However, the log K_{ow} value suggests a potential for bioconcentration in aquatic species, so it is therefore necessary to conduct a fish bioconcentration study. Based on log K_{oc} values all below 4.0, the impact to terrestrial organisms was not assessed. An assessment of bioconcentration in zebrafish is included in the following Phase II Tier B.

Phase II Tier B: (extended environmental for NOMAC)
NOMAC was evaluated in a bioconcentration study in zebrafish aged 4-6 months, according to the guidelines of OECD 305 (Egeler et al., 2009). The results of the bioconcentration study in zebrafish indicate that only a small accumulation occurs in the uptake phase. BCF values expressed based on content of parent compound in water and fish were 14.8 and 15.0 for the low and high exposures, respectively. Two other radioactive peaks were identified in the fish and were considered to be polar metabolites of NOMAC. Depuration resulted in a rapid elimination of residues from the fish, with approximately 9.5% remaining after 10 days.

Estradiol (E2)
Phase II Tier A :

PEC/PNEC assessments:
The data from studies on aquatic species and sludge organisms were used to derive predicted no-effect concentrations (PNEC) for relevant environmental compartments.

Regarding $PNEC_{SURFACEWATER}$, numerous studies have been conducted with E2. The various fish species were typically much more sensitive to sub-chronic and chronic exposure to E2 vs. non-fish species. Therefore the repeat exposure and reproduction studies for fish species were reviewed to determine the most appropriate endpoint for deriving a $PNEC_{SURFACE\ WATER}$ for E2.

The full-life cycle study in Japanese medaka (Seki et al., 2005) was selected to derive the PNEC. This is a standard life cycle study that evaluated several aspects of general toxicity and reproductive function in the fish after exposure to E2. Of the life cycle and multigenerational studies, this study gave the lowest NOEC (2,6 ng/L) . The study of Lahnsteiner et al., (2006) provides supporting evidence for an effect of E2 on male fish as evidenced by decreased semen volume and semen fertility, but mating and reproduction were not evaluated as in a standard life cycle study.

The $PNEC_{GROUNDWATER}$, was derived from the NOEC in a full life-cycle toxicity study of daphnids using an assessment factor of 10. The NOEC for the reproduction study with Daphnia magna from (Brennan et al., 2006) was selected. The NOEC was >/= 200 mcg/L, based on survival.

Compartment	PEC (mcg/L)	PNEC (mcg/L)	PEC / PNEC
Surface water	0.000232	0.000286	0.81
Groundwater	0.000058	20	2.9×10^{-6}
Wastewater treatment facility	0.000232	10,000	2.32×10^{-8}

The PEC/PNEC ratios for surface water and groundwater are less than 1 and the PEC/PNEC ratio for the WTP is less than 0.1. Based on these results, the use of this product is not considered to pose a risk to the aquatic environment. As noted previously, however, the log Kow value suggests a potential for bioconcentration in aquatic species, so it is therefore required to conduct a fish bioconcentration study. Based on log Koc values all below 4.0, it is not required to assess the impact to terrestrial organisms. An assessment of bioconcentration in relation to fish and other species is included in the following Phase II Tier B. Also as E2 is likely to partition to sediment to some extent, a discussion of potential impact to sediment organisms is included in Phase II Tier B.

Phase II Tier B : extended environmental
The results of the bioconcentration studies in fish indicate that bioconcentration is not a significant environmental concern for these species. In most of the non-fish species a similar conclusion can be reached based on relatively low BCFs. The results from the studies in zebra mussels are interesting, but seem to indicate that E2 is taken up by these organisms and stored in an inactive form. There is less data available concerning the effect of E2 on sediment organisms. However, based on analogy to EE2, a much more potent estrogen, it is not expected to have significant effects on sediment species.

In conclusion, based on the above results, NOMAC-E2 does not appear to present a specific risk to the aquatic environment. However, given the hormonal activity of both components, nomegestrol acetate and estradiol, a warning has been included in the relevant section of the product SmPC and in the package leaflet as follows:

"*Zoely tablets no longer required should not be disposed via wastewater or the municipal drainage system. The hormonal active compounds in the tablet may have harmful effects if reaching the aquatic environment. Return them to a pharmacy or dispose them in another safe way according to local requirements. These measures will help to protect the environment*."

2.4. Clinical aspects

2.4.1. Introduction

Three dose finding clinical trials were initially performed with either NOMAC alone (2.5 mg) or subsequently with combination of 1.5 mg estradiol. Based on the results of these clinical trials the combination of 2.5 mg NOMAC + 1.5 mg E2 was selected for the further clinical studies. The applicant justified the choice of the 24/4 regimen, that is 24 active tablets followed by 4 placebo tablets by a better bleeding profile, lower overall number of days with vaginal bleeding than the 21/7 regimen. The final phase clinical program started in May 2006 in two adequate and well-controlled trials (292001 and 292002). The contraceptive effect of NOMAC-E2 was investigated and proved as compared to that of DRSP-EE 3.0 mg/30 µg reference product. These trials generated evidence of contraceptive efficacy and sufficient general safety data. In the clinical phase III program the metabolic safety of the product including effects on hemostasis, lipid metabolism, carbohydrate metabolism, adrenal and thyroid function and effects of androgens were also investigated (trial 292004) and compared to those of LNG-EE (levonorgestrel + ethinylestradiol). The PK of NOMAC-E2 was investigated in trial 292006 and 292007. The contraceptive mechanism of NOMAC-E2 vs. DRSP-EE was studied in trial 292003. The possible impact of NOMAC-E2 on QTc interval was studied in healthy women trial 292011. One study was in progress aiming to study the impact of NOMAC-E2 on bone mineral density. One study was planned to investigate the PK properties of NOMAC-E2 in adolescents (trial 292008).

The indication as claimed by the applicant was:

Oral contraception in fertile women including post-menarcheal adolescents from age of 12 years.

The approved indication by the CHMP was:

Oral contraception

GCP

The data submitted are derived from forty-one trials in the NOMAC-E2 clinical development program. Twenty trials were conducted in accordance with ICH-GCP, while twelve were conducted under EU-GCP. All trials were conducted with the approval of Ethics Committees or Institutional Review Boards. However, six trials (LUT 5-03-01, LUT 5-21-01, LUT 5-22-01, LUT 5-17-01, LUT 4-13 and LUT 4-12-01) did not comply with the principles of the ICH-GCP and for three other trials, GCP was not effective because these trials were performed in 1982-1983 prior to the implementation of GCP. This was accepted by the CHMP.

2.4.2. Pharmacokinetics

A large number of pharmacokinetic trials and BA/BE studies have been performed in women of childbearing potential, post-menopausal women or men with NOMAC alone or different doses of NOMAC combined with E2. However, a limited number of trials were conducted with NOMAC-E2 at the contraceptive dose of NOMAC 2.5mg – E2 1.5mg in the target population, i.e. women of childbearing potential. These latter trials are presented while the others are considered as supportive.

Table 1 summarises the main pharmacodynamic studies performed for the current application (Mechanism of action, in trials employing combinations of 1.5mg E2 and various doses of NOMAC). The pharmacodynamic properties of this new contraceptive pill have been established in different steps. Thus, a complete pharmacodynamic program to assess the contraceptive effect of this NOMAC-E2 has been performed by the applicant. Five dose ranging studies have been performed first to sustain the choice of the selected NOMAC optimal dose. Of note, four of these studies are non compliant with the European GCP guidelines and ICH-GCP as they were performed in the 1980s before there were guidelines applied. This is not of concern to our point of view as complementary/additional PD studies

have been performed to confirm and sustain the PD effects of NOMAC-E2 mainly on the inhibition of ovulation.

Thus, the main PD program comprises three Phase II and two Phase III studies that assessed successively the selection of the optimal NOMAC dose in combination with 17-beta estradiol (96-ESC/NOM-1-RD and 98-ESC/NOM-1-RD), the selection of the optimal therapeutic regimen (03-ESC/NOM-1-RD), and lastly the ovulation inhibitory properties that were assessed during 6 cycles of treatment in study 292003.

Table 1. Pharmacokinetic and pharmacodynamic studies

Study ID	Design	Study posology	Study objective	Subjs by arm entered / compl.	Duration of treatment	Diagnosis incl. criteria
INT00104097 BA Phase I during Phase III	See trial 292006 Trial 307001: Open-label, s ingle-center, explorative parallel group	See trial 292006 Trial 307001: 1.15mg NOMAC + 0.40mg E2; single infusion; intravenous	To establish the absolute bioavailability of NOMAC and E2 in an oral combination tablet compared to a combined intravenous infusion	Trial 292006: n=19 Age range: 21-47 yrs Trial 307001 n=23 Age range: 19-37 yrs	See trial 292006 Trial 307001: 30 minutes	Healthy women of childbearing potential
02-TX127066-1-RD BA Phase I	Open-label, single-center, randomized, three-way cross-over	2.5mg NOMAC + 1.5mg E2 tablet; single dose under fasting and fed conditions; oral dosing 2.5mg NOMAC + 1.5mg E2 capsule; single dose under fasting conditions; oral dosing	To compare the bioavailability in healthy female volunteers of a single dose of NOMAC-E2 as a tablet obtained by direct compression under fed and fasted conditions versus a capsule under fasted conditions	Subjects: 16 randomized, 16 treated and 13 completed Age range: 19-39 yrs:	3 days (one single dose during Day 1-5 of 3 consecutive cycles)	Healthy women of childbearing potential
02-TX133066-1-RD BA Phase I	Open-label, single-center, randomized, three-way cross-over	2.5mg NOMAC + 1.5mg E2 tablet; single dose under fasting and fed conditions; oral dosing 2.5mg NOMAC + 1.5mg E2 capsule; single dose under fasting conditions; oral dosing	To compare the bioavailability in healthy female volunteers of a single dose of NOMAC-E2 as a tablet obtained from a granulate under fed and fasted conditions versus a capsule under fasted conditions	Subjects: 16 randomized, 16 treated and 13 completed Age range: 20-34 yrs	3 days (one single dose during Day 1-5 of 3 consecutive cycles)	Healthy women of childbearing potential
292006 PK Phase I during Phase III	Open-label, s ingle-center, combined multiple dose, single dose (double-blind randomized)	MD part: 2.5mg NOMAC + 1.5mg E2; once daily; oral dosing SD part: 2.5mg NOMAC + 1.5 mg E2 or placebo; oral dosing	To assess the pharmacokinetic profile of NOMAC, E2 and E1 after oral administration of NOMAC-E2	Subjects in MD phase: 24 included and treated 23 completed Subjects in SD phase: 23 randomized, treated and completed 24 AST 24 ASPE Age range: 21-47 yrs	MD: 2 weeks (synchronization) and 24 days in-treatment SD: 1 day	Healthy women of childbearing potential

292007 PK Phase I during Phase III	Open-label, single-center	2.5mg NOMAC + 1.5mg E2 tablet in six NOMAC-E2 batches differing in NOMAC particle size; 2 single doses; oral dosing	To compare the PK profile of NOMAC after single oral dose administration of different NOMAC-E2 batches in order to assess the effect of particle size of the NOMAC drug substance on the PK parameters of NOMAC; secondary objective was to explore the in vitro – in vivo correlation between the in vitro release information of NOMAC and the in vivo PK of NOMAC	Subjects: 18 randomized, treated and completed Age range: 18-44 yrs	2 days (2x single dose with wash-out or at least 2 weeks)	Healthy women of childbearing potential
292011 S, PK Phase I during Phase III	Double-blind, single center, randomized, double dummy, placebo and positive controlled, parallel group	NOMAC-E2 (2.5mg – 1.5mg or 12.5mg – 7.5mg) and/or identical placebo tablet; once daily; oral dosing 400mg Moxifloxacin (Avelox) (positive control) capsule / placebo capsule; single dose; oral dosing	To investigate whether once daily multiple therapeutic and supra-therapeutic doses of NOMAC-E2 prolong the mean QTcF interval at steady state to the threshold of regulatory concern as compared to placebo. To establish assay sensitivity after a single oral dose of 400 mg moxifloxacin.	Subjects: 189 randomized 189 treated 182 completed 180 PP Age range: 18-50 yrs	14 days	Healthy women of childbearing potential
02-ESC/NOM-1-RD PK, PK/PD phase II	Double blind, single center, randomized comparative	2.5mg NOMAC + 1.5mg E2 / placebo tablet; 24/4 regimen; oral dosing 2.5mg NOMAC + 1.5mg E2 / placebo tablet; 21/7 regimen; oral dosing	To assess two regimens (21/7 and 24/4) of NOMAC and E2 on the follicle like structure maturation during the treatment free period (regimen validation trial)	Subjects: 80 randomized 77 treated 72 completed 76 ITT 65 PP Age range: 19-38 yrs	3 cycles of 28 days	Healthy women of childbearing potential
292008 PK Phase I	Open-label, single center, parallel group	2.5mg NOMAC + 1.5mg E2, single dose, oral dosing	To compare the pharmacokinetics of NOMAC between female adolescents (aged 14-17 years) and female adults (aged 18-50 years) after single dose administration of NOMAC-E2.	Subjects: 30 subjects (15 subjects aged 14-17 years and 15 subjects aged 18-50 years)	Single dose	Healthy women of childbearing potential
P06328 PK Phase I	Open-label, randomized, single-dose, four-way, replicate, crossover design, conducted in 2 parallel parts	Part 1: 2.5mg NOMAC + 1.5mg E2, batch CD078/ batch CA057, single dose, oral dosing Part 2: 2.5mg NOMAC + 1.5mg E2, batch CD078/ batch CZ189, single dose, oral dosing	To assess bioequivalence of NOMAC and E2 between drug product manufactured using the large scale commercial process (batch CD078) and the phase 3 pivotal clinical batch used in Trial 292006 (batch CA057) and Trial 292001 and 292002 (batch CA057 and CZ 189)	Subjects: 72 subjects in each study part	Single dose on four separate occasions with a wash-out period of at least 2 weeks	Healthy postmenopausal women

Absorption

During the formulation development program, two different tableting technologies were tested, and. BA/BE studies were conducted to finally select the direct compression technology. Later on, a film coating was added for environment reasons as well as to improve the appearance of the tablet and other manufacturing changes were operated.

The pivotal trial 292006 (with film-coated, direct compression tablet TX127066) was specifically designed to assess the PK profile of NOMAC-E2 (2.5mg/1.5mg) as administered via the film coated combined tablet formulation after multiple and single oral dosing in women of childbearing potential. Thus, this pivotal study, shows that NOMAC is rapidly absorbed by oral route, with time independent kinetics. As expected for E2, endogenous secretion and large first-pass effect give rise to large variability in its rate of absorption.

Oral absolute bioavailability. In the trial INT00104097 (combined analysis of trial 292006 and trial 307001), the absolute bioavailability of NOMAC from the combination tablet is 63.4%. For E2, the absolute bioavailability is very low (with or without baseline correction), about 1%. This is a known and expected information as a result of pre-systemic conjugation and first-pass metabolism.

Bioequivalence. Two bioavailability-bioequivalence studies with the same objectives and the same study design were performed to compare, the two different tableting technologies of the combination NOMAC 2.5 mg– E2 1.5 mg with a capsule containing the same combination in two separate tablets: i) Trial 02-TX133066-1-RD and ii) Trial 02-TX127066-1-RD. Both studies were open, randomised three-way cross-over study performed in healthy volunteers.

Based on the results of these two BA-BE studies, the Applicant selected the formulation that was most comparable to the capsule with respect to bioavailability for both components of the product. Therefore, all subsequent phase III trials and additional phase I trials were performed with this formulation. The change from an uncoated tablet to a film-coated tablet was supported by a comparative in vitro dissolution study in different appropriate media. Three other changes to the manufactured tablet were also reported by the Applicant: i) change in mixer type for the blending step; ii) site and scale changes as part of the technology transfer iii) introduction of a milling step for drug substance

To bridge between this new intended commercial NOMAC-E2 combination tablet and the to-be-marketed tablet an IVIVC trial (Trial 292007) was conducted to investigate the relationship between the in vitro dissolution curves and the in vivo exposure. In brief, six batches of NOMAC-E2 were investigated in eighteen female subjects of child bearing potential.

Subjects were randomly allocated to one of the six treatment sequences, each including two different batches. Blood samples were collected up to 144 hours post dose. The development of an IVIVC-A level model was undertaken, following the recommended procedures (computing resources: WinNonlin® ver 5.2, IVIVC Toolkit, IVIVC Wizard). Based on 4 selected batches the internal predictability of the model was good, with absolute percent prediction errors below the guidance criterion of 10% for Cmax and AUC. However, the external validation results with the two remaining batches were not acceptable since the prediction error was greater than the guidance criterion of 10%. This analysis was followed by a population pharmacokinetic study (not discussed here) aimed to characterize and quantify the influence of batch differences on the pharmacokinetics of NOMAC during simulated steady-state conditions. As main result, the difference in the in vitro dissolution rate of Cmax would tend to decrease from a single dose to a steady-state situation.

Regarding bioequivalence between the to-be-marketed formulation and subsequent manufacturing changes, a major issue was raised by the CHMP. Since study 292007 failed to establish a relevant IVIVC-A level model, the Applicant was asked to perform an additional bioequivalence study between the intended to-be-marketed formulation and the final commercial tablet**.** This study (study P06328) is based on two parallels parts conducted in two separate US clinical centers, each part including 72 healthy postmenopausal women in a replicate four-way crossover design. The first part was comparing the final commercial tablet batch CD078 versus the phase III batch CA057, while the second part was comparing this same final commercial tablet batch CD078 to the phase III batch CZ189.

In Study P06328, bioequivalence with NOMAC and E2 has been shown between batch CA057 and the final commercial batch CD078. However, a similar conclusion could not be drawn for batch CZ189, as the Cmax value for NOMAC is higher with the commercial batch CD078 compared to the reference Batch CZ189 (Ratio test/ref= 137.5 (131.0;144.4).

The updated Level A (and C) IVIVC analyses have confirmed the consistency and suitability of the established NOMAC relationship between in vitro dissolution and Cmax

Influence of food.

In trials 02-TX127066-1-RD and 02-TX133066-1-RD the effect of concomitant food on bioavailability of the combination NOMAC-E2 (2.5 mg – 1.5 mg) was also studied. The meal served was designated as "standard FDA meal", to be consumed within 30 minutes before the drug intake. There is a moderate food effect on the bioavailability of NOMAC from either tableting technology, with on average, a 27% increase in the extent of systemic exposure and a more variable impact of 27 to 66% for the peak of exposure. For E2, food effect is probably less with geometric mean ratios very close to 1 for Cmax and AUC, even if we observe very wide 90% confidence intervals, never contained within the regulatory interval of bioequivalence (0.80 – 1.25). The CHMP finally agreed that the food effect is actually not clinically relevant so that no recommendation with food should be mentioned in the SPC.

Distribution

NOMAC and E2

- In vitro

In vitro studies showed NOMAC to be highly bound (97-98%) in a non saturable way to plasma proteins across a wide concentration range, including therapeutic and supratherapeutic concentrations. Albumin displayed a high binding with NOMAC (98%) thus indicating a major role for albumin in plasma protein binding. SHBG and CBG on the other hand showed no detectable NOMAC binding. Estimation of red blood cell uptake gave low values in the range 14 – 22%. The distribution of exogenous natural estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. In plasma, Estradiol circulates bound to SHBG (37%) and to albumin (61%), while only approximately 1-2% is unbound.

- In vivo

A pooled population pharmacokinetic analysis (INT00101987), described the pharmacokinetics of NOMAC using a two-compartment model and resulted in a total apparent volume of distribution ([central + peripheral volume of distribution]/F) of 1246L. Using the estimate of absolute bioavailability (63.4%), the overall volume of distribution of this analysis was calculated to be 790 L. Another population pharmacokinetics analysis (Trial 292007) provided a total apparent volume of distribution ([central + peripheral volume of distribution]/F) of 946 L, which resulted in an overall volume of distribution of 600 L. Both population pharmacokinetic analyses were in line with the non-compartmental distribution volumes (979 and 662 L) following intravenous administration. The relatively large volume of distribution of NOMAC indicates extravascular distribution and is in line with the lipophilicity of NOMAC.

In conclusion, NOMAC is highly bound to plasma proteins (consistently over 97%) while displaying a very large volume of distribution (over 20 l/kg). Thus, there is no reason to believe that drug-drug interaction may occur because of drug protein displacement.

Elimination

Several studies were performed to study the excretion of NOMAC. Trials INT00104097 and 292006 were performed in women with childbearing potential. Trials LUT-4-06-01, LUT 4-12 and LUT 4.13 were performed in healthy post menopausal women. In summary, with NOMAC, the total amount of radioactivity recovered within the first 24 h post dose is high, at least 90%. Since the oral absolute bioavailability is estimated around 64%, the radioactivity recovered in faeces comes likely from unabsorbed drug and/or from enterohepatic recycling. In urine, unchanged NOMAC is low or undetectable which in turn means the presence of various conjugated or unconjugated polar metabolites. With exogenous E2, less information is available. However, the fate of the natural hormone is rather well established elsewhere so that no further requirement is needed from a pharmacokinetic point of view.

Dose proportionality and time dependencies

In post-menopausal women, dose proportionality was investigated at steady-state and established across a NOMAC dose range of 0.625 mg - 5 mg (NOMAC in combination with 2 mg estradiol valerate, Trial 96-LUT-1-RD). In another trial (Trial 98-ESC-NOM) dose linearity (0.625 mg – 2.5 mg NOMAC with 1.5 mg E2) was observed in women of childbearing potential.

In summary, no accumulation of NOMAC is observed following single administration of a dose ranging from 0.625 mg to 12.5 mg for 14 days. The range of linearity is probably much wider. Dose proportionality and time independency of NOMAC pharmacokinetics have been correctly demonstrated. Since NOMAC can interfere with endogenous E2 secretion in women of child-bearing potential, it is noted that methodological difficulties were overcome to reliably evaluate dose proportionality and time dependency with exogenous E2.

Regarding time dependency, NOMAC is considered a substrate for cytochrome P450 without inhibitory or inducer properties. The film coated tablet NOMAC-E2 (2.5–1.5 mg) gave similar data between infinite AUC after single dose (112 hxng/ml) and steady-state AUC0-24 (106 hxng/ml) in women of child bearing potential (Trial 292006), suggesting time-independent pharmacokinetics. Same results were observed in 24 post-menopausal women with the fixed combination NOMAC-E2 (3.75 – 1.5 mg) following single and repeated dosing for 14 days (Trial 95-TX323/NOM-2-RD) with mean AUC0-72h (first dose) of 180.7 hxng/ml and AUCss on day 14 of 209.8 hxng/ml.

Special populations

Impaired renal function
No study has been performed in patients with renal insufficiency and this population was excluded from pivotal trials 292001 and 292002 due to the known antimineralocorticoid activity of the comparator drospirenone. However, no specific issue is expected in the target population as nomegestrol acetate does not have any mineralocorticoid activity.

Impaired hepatic function
No study has been performed in patients with hepatic insufficiency and this population was excluded from pivotal trials 292001 and 292002 due to the known antimineralocorticoid activity of the comparator drospirenone. However, no specific issue is expected in the target population as nomegestrol acetate does not have any mineralocorticoid activity.

Gender
N/A

Race

Studies INT001016987 and INT00105057 showed the impact of race, age and BMI. In addition, a population PK model was developed to evaluate the effects of the covariates age, race and BMI on the pharmacokinetics of NOMAC.

The analysis was performed on data gathered from studies 292006 and 292002. The database is rather small with 1139 NOMAC plasma concentrations from 75 Caucasian (92.6%), 4 black/African American (4.9%) and 2 Asian (2.5%) women of child bearing potential. The average age was 29 y (range: 18 – 47), the average weight was 61.9 kg (range: 44.2 – 97.5) and the average BMI was 23.3 kg/m^2 (18.3 – 34). The statistical analysis was performed with NonMen ver. VI (method FOCEI). The technical management of this population PK analysis follows the recommended procedures. No external validation of the model was done but its reliability is evaluated by a bootstrap approach. This is acceptable for such a database.

Despite a rich data subpopulation, the structural PK model did not perform well for the absorption phase, leading to the incorporation in the final model of a separate first order absorption rate constant for single dose and multiple dose (assumed to be caused by food effect), as well as a single lag-time parameter. However, this "data-driven" model could be considered as poorly reflecting the true pharmacokinetic profile of NOMAC. At Day 150, the applicant satisfactorily answered this question. Indeed, from a strict clinical point of view, we could consider as not relevant the influence of food. However, from a strictly PK point of view, this latter effect should be incorporated in the modelling process to obtain a good estimate for Cmax. At fasting state, median Tmax for NOMAC is around 2h with food, we observe a further delay of at least 1h. The reasonable sized, the limited number of blood samples around delayed Tmax may explain the difficulty to estimate Ka with food, and so Cmax.

Finally, the results of this population approach are not adding a lot to the general knowledge of NOMAC-E2 pharmacokinetics in the target population. No effect of age (in the limited range 18 – 47 y) or race was identified but for this latter covariate, there is an obvious lack of data. The covariate BMI was the only covariate incorporated in the final model. However, its contribution is small since, compared to the typical median CL/F value of 26.8 l/h, we observed a 12%-increase in CL/F with low BMI and a 19.8%-decrease in CL/F with high BMI. So, no dose adjustment is to be done based on BMI.

Overall, the effects of age, weight, race, renal and/or liver insufficiency on NOMAC-E2 pharmacokinetics can be considered as correctly investigated, not forgetting the important study in younger adolescents.

Weight
NOMAC pharmacokinetics were modeled with a 2-compartment model with first order absorption, a lag time on absorption and first order elimination. The volume of distribution (V2) was estimated to be 252 L with a clearance (CL) of 26.8 L·h-1. Both clearance and relative bioavailability were found to decrease exponentially with BMI. Combined this resulted in a small decrease of CL/F with increasing BMI. Although no effect of BMI on the volume of distribution was identified in the covariate analysis, a distribution phenomenon could also be a reason for the modest decrease in CL/F given the lipophilicity and high protein binding of NOMAC. Furthermore, no effects of age or race were identified.

Elderly
In Trial LUT 4-28-01 it has been showed, that endogenous E2 has no influence on the pharmacokinetics of NOMAC. E2 status does not influence the kinetics of NOMAC but the opposite is not true. NOMAC via suppressing the endogenous E2 synthesis and/or by inducing 17-beta-hydroxysteroiddehydrogenase has significant effect on the kinetics of E2. Increase of SHBG (sex hormone binding globulin) level is a third contributing factor.

Children
An exploratory population pharmacokinetic analysis of NOMAC using physiology-based pharmacokinetic (PBPK) modelling with special emphasis on effects associated with age and BMI in post menarche females (Trial INT00105057) was submitted. This analysis showed that no significant differences in the plasma pharmacokinetics of NOMAC after repeated oral administration in post menarche females or adolescents are expected in comparison to the female adult reference population. Moreover, the PBPK simulations indicate that the pharmacokinetics of NOMAC in post-menarche females is depending on the BMI (i.e. (re)distribution) rather than the age. So the WB-PBPK modeling, confirms the expectation that no significant age dependence on the pharmacokinetics of NOMAC is expected in post-menarcheal adolescent females aged 12 to 17 years compared to adult females (18 to 50 years).

In the study report, PBPK models have been generally used to predict the pharmacokinetics of toxic chemicals. One can also understand their implementation in support of drug development. However, there is still a long way to go before considering them as a cornerstone for drug approval since their practice remains confidential. By definition, a PBPK model requires a realistic description of the human physiology so that the model structure is predetermined and almost independent of the drug of interest. Precisely, the main criticism of this approach remains the risk of inaccurate prediction if the underlying assumptions of the mechanistic equations are not met. As requested by the PDCO, in order to further support the expectation that pharmacokinetic data will be similar, a single dose pharmacokinetic trial with NOMAC-E2 in post-menarcheal adolescents and adults has been performed.

The primary objective of trial 292008 was to compare the pharmacokinetics of NOMAC between female adolescents (aged 14-17) and female adults (aged 18-50) after single dose administration of NOMAC-E2 while secondary objectives were to explore the pharmacokinetics of E2 and estrone, the safety and tolerability of NOMAC-E2 and, if possible, to identify the major metabolites of NOMAC in plasma and urine of the female adults.

Study 292008 shows that there is less than 30% difference in the pharmacokinetic profile of NOMAC following a single 2.5 mg dose between adolescent and adult populations, so the profiles are considered similar.

For E2, a substantial variability in E2 and E1 serum levels was observed. A lower total exposure to E2 is observed (AUCtlast until 129 h after dosing) in adolescents as compared to adults (- 36% for adolescents versus adults). This can be explained by the single dose design of the study, i.e. the women were not synchronized for their natural menstrual cycle, leading to fluctuating endogenous E2 and E1 levels. Beyond 24 hours, taking also the short half-life of E2 into consideration (3.6 ± 1.5 h), the relative larger endogenous contribution in adults might cause AUCtlast values to differ.

Therefore, no conclusion can be drawn from these results about the pharmacokinetics of E2 in both groups, in the absence of a repeated dose study, with synchronisation of the cycles and baseline correction for E2.

The CHMP therefore agreed that no extrapolation of efficacy and safety results as found in the phase III clinical program for adults can be made to the post-menarcheal adolescent population. Indeed, lower E2 levels were observed in the adolescent population aged 14-17 years compared to an adult population. It seems difficult in that context to also extrapolate pharmacokinetic, efficacy and safety data observed in the 14-17 years to the 12-13 years age group. Thus, the applicant' proposal to only accept the following indication "Oral contraception" (Section 4.1.) and deleting all reference to "fertile women including post menarcheal adolescents from the age of 12 years" has been endorsed by the CHMP. Information regarding the pediatric population in the respective sections of the SmPC has been agreed on by the SmPC.

Pharmacokinetic interaction studies

- **In vitro**

In vitro studies showed that NOMAC is unlikely to affect the metabolism of co-administered drugs, as it has no direct or indirect cytochrome P450 inducing or inhibitory properties on CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5.

- **In vivo**

Two drug interaction trials were performed with a higher dosed-NOMAC -E2 combination (3.75 mg-1.5 mg) in post-menopausal women (Naemis®): i) trial NOM-OEST 4-04 (Interaction with rifampicin); ii) trial NOM-OEST 4-05 (Interaction with ketoconazole)

Interaction studies with a metabolic inducer showed that rifampicin interacts with the NOMAC/E2 combination, as it is the case with other estrogen-progestin combinations. Rifampicin considerably accelerated NOMAC metabolism, causing a ten-fold decrease in the peak and a twenty-fold reduction of the AUC. Conversely, estradiol metabolism was slowed down and the peak, which occurs earlier, increased by 2.6 while the AUC increased by 20 %. These issues must be taken into account when a patient is under treatment with an enzymatic inducer such as rifampicin, anticonvulsants, or anti-infectives, known to be enzyme inducers, since increased NOMAC metabolism associated with delayed E2 metabolism could lead to an estrogen-progestin imbalance which would have clinical consequences. However, ketoconazole does not modify or only slightly modifies E2 metabolism. Its effect on NOMAC is more significant, in particular on Cmax. Nevertheless, the increase in the peak and AUC of NOMAC may not cause any clinical consequence on safety side since the safety margin is quite large.

2.4.3. Pharmacodynamics

Mechanism of action

Nomegestrol acetate (NOMAC) is a highly selective progestin derived from, and structurally similar to, the naturally occurring steroid hormone, progesterone. NOMAC is combined with 17-beta estradiol (E2). This estrogen is identical to the endogenous human E2 and is therefore classified as a natural estrogen. The co-administration of estrogen results in a more stable endometrium, which greatly reduces cycle irregularities, especially when a pill-free interval is cyclically scheduled to allow for a hormone withdrawal bleeding. In addition, estrogen adds to ovulation-inhibition. The main mechanism by which the combination of NOMAC-E2 provides contraceptive effect is ovulation inhibition. Additional mechanisms concern the induction of cervical mucus impenetrable to sperm and induction of an atrophic endometrium which is not suitable for nidation.

The progestagen nomegestrol acetate (NOMAC) and the estrogen 17 beta estradiol (E2) are well-known substances of which pharmacological properties are well known and have already been extensively studied. Both substances already exist on the market associated together or not. However, the combination of NOMAC and 17 beta estradiol has never been used for contraception in women of childbearing potential.

Primary and Secondary pharmacology

Five dose ranging studies have been performed first to sustain the choice of the selected NOMAC optimal dose. The pharmacodynamic program for NOMAC comprises three Phase II and two Phase III studies that assessed the selection of the optimal NOMAC dose in combination with 17-beta estradiol (96-ESC/NOM-1-RD and 98-ESC/NOM-1-RD), the selection of the optimal therapeutic regimen (03-ESC/NOM-1-RD), and lastly the ovulation inhibitory properties that were assessed during 6 cycles of treatment in study 292003.

Dose ranging studies showed that NOMAC inhibited ovulation at daily doses of 1.25 or more. Dose dependent effects of NOMAC on cervical mucus were also observed. NOMAC 2.5 mg was selected as compared to lower tested dosages as better results / effects were observed on ovulation inhibition. The incidence of bleeding and / or spotting was, however, higher with NOMAC 2.5mg. Lastly, the anti-gonadotropic effect measured by LH and E2 blood levels was also stronger with the NOMAC 2.5 mg dose Thus, NOMAC had a strong progestational and anti-estrogenic effect on the uterus and significantly reduced the proliferation that occurs with estradiol alone.

Effects of 17-beta estradiol. The estrogen contained in the combination tablet is E2. This estrogen is identified to the endogenous estragon E2 and therefore is classified as a «natural» estrogen. The applicant investigated whether the addition of 1.5mg E2 to NOMAC offers additional PD effects, especially antigonadotropic effects. Compared to NOMAC alone, the addition of 1.5 mg E2 leads to higher E2 plasma levels, reinforces the LH inhibition and also decreases FSH levels (elevated with NOMAC alone). Inhibition of ovulation is the major pharmacodynamic action of interest. NOMAC had an anti-gonadotropic activity, which resulted in an inhibition of spontaneous ovulation in humans. This effect seems to be dose dependent. An ovulation inhibition effect was observed with a 2.5mg NOMAC dose when combined with a 1.5 mg E2 dose. Thus, NOMAC 2.5mg seems to be the optimum combination dosage for ovulation inhibition. However, it remains unclear whether this estradiol dose is the optimal/adequate dose for contraception and bleeding control. A study evaluating the combination of NOMAC 2.5 mg with different E2 doses (1mg, 1.5mg and 2mg) should have been considered.

In animals the secondary pharmacological properties of NOMAC associated with E2 leads to an increase in the levels of blood glucose and insulin, a drop in plasma cholesterol levels (total and HDL) and an increase in plasma triglycerides and glucose clearance. No impact on glucose tolerance and insulin sensitivity was seen in humans during a 6-month trial evaluating the effects on carbohydrate metabolism compared to LNG-EE (292004). No impact of NOMAC associated with E2 on coagulation has been detected in animals and humans. NOMAC shows anti-androgenic activity but not glucocorticoid or anti-glucocorticoid activity nor mineralocorticoid or anti-mineralocorticoid activity. Finally, NOMAC was without any notable activity on bone parameters, whether given as single compound or in combination with E2.

2.4.4. Discussion on clinical pharmacology

Bioequivalence with the to-be-marketed formulation
The bioequivalence between the to-be-marketed formulation TX127066 and subsequent manufacturing changes was identified as an issue during the assessment of the product. In study 29007 assessing the influence of the granulometry of NOMAC on the dissolution process of the tablet, six different batches were used: CB105 (coarse particles), CB106 (fine particles), CB107 (fine particles), CB108 (fine particles), CB109 (micronized particles) and CZ189 (coarse particles). This study failed to establish a relevant IVIVC-A level model.

Missing information with respect to the effect of food on the bioavailability of the final commercial formulation was also a concern identified by the CHMP. Moreover, the influence of reduced particle size of NOMAC regarding the bioavailability of the tablet when administered with concomitant food was a specific issue.

It was demonstrated that NOMAC particle size is not a comprehensive predictor for pharmacokinetic performance. The impact of the particle size distribution of the two active substances on the content uniformity and dissolution was evaluated and appropriate specifications have been set.
Regarding the bioequivalence between the batches used in clinical trials and the final commercial batches, the Applicant has been requested to state how many participants in the pivotal efficacy studies 292001 (Europe) and 292002 (US) received tablets from batch CA057 and CZ189. If a relevant

number of patients in the two trials received tablets from batch CA057, it could be considered to calculate in this subgroup the PI for user failure and method failure in the population of women 18 to 35 years of age and to analyse the data also with respect to bleeding pattern and pattern and frequency of adverse events. The applicant should also state whether and how many participants in other clinical trials received tablets from batch CA057.

Since there is no accepted demonstration of predictive in vitro-in vivo correlation (cf. Study 292007), in vitro comparison between final commercial batch CD078 and previous clinical batches are not deemed sufficient. The recommendation of no restriction regarding drug dosing with food could be challenged when considering the marked bio-inequivalence on Cmax between batch CD078 and batch CZ189 following a single dose at fasting state. Regarding the influence of a reduced particle size of NOMAC on pharmacokinetic parameters when administered with food, no further clinical or in-vitro investigation have been performed by the Applicant. Therefore, as requested by the CHMP, the Applicant agrees to perform as a Follow-Up measure an in-vivo study to study the effect of concomitant food intake on bioavailability of NOMAC-E2, using both a commercial batch and the clinical batches (CA057 and CZ189).

Lack of E2 dose selection study
Regarding pharmacology the fact that no dose response has been performed for E2 was identified by the CHMP as an issue. Indeed, the efficacy of 1.5 mg/day has not been substantiated. The Applicant was asked to bring convincing arguments that 1.5mg E2 is well the optimal dose for the combination with 2.5mg NOMAC. Of note, whether the NOMAC dose has been investigated, no E2 dose selection study has been performed; the E2 dose was selected only on the fact that this is the dose used in the already HRT preparation Naemis. It remains unclear whether this estradiol dose in combination with NOMAC is the optimal/adequate dose for contraception and bleeding control. A study evaluating the combination of NOMAC 2.5 mg with different E2 doses (1mg, 1.5mg and 2mg) should have been considered by the applicant..

This issue regarding the choice of a 1.5 mg/day E2 dosage, provides adequate estrogen levels for estrogen replacement therapy and prevention of osteoporosis in post-menopausal women. But the target population of NOMAC-E2 is different, i.e. fertile women and the question whether 1.5 mg of E2 could compensate the antiestrogenic effect of NOMAC in fertile women was identified as a concern by the CHMP. The choice of the 1.5 mg E2 dose was mainly based on the dose used for HRT in post-menopausal women. In adult fertile women, the question whether 1.5 mg of E2 may compensate the anti-estrogenic effect of NOMAC remains to be answered, considering the strong suppression of endogenous production. Thus, since no study was performed to optimize the dose of E2, there is a theoretical inference where 1.5 mg exogenous E2 would generate circulating E2 levels close to what is observed either at the beginning of the follicular phase or the end of the luteal phase. However, the lack of dose response study for E2 in adult fertile women could be acceptable, provided that the SmPC adequately mentions the bleeding profile of NOMAC-E2 (i.e. occurrence of breakthrough bleeding/spotting and absence of withdrawal bleeding) that reflects the estrogenic stimulation.

2.4.5. Conclusions on clinical pharmacology

NOMAC-E2 (2,5 mg–1,5 mg) is able to inhibit ovulation. The inhibition appears consistent and seems to be reliable. Additional contraceptive mechanisms contribute to the contraceptive effect namely changing the viscosity of cervical mucus and thinning the endometrium. The first mechanism may hamper the penetration of sperm into the uterus cavity and the second one decreases the likelihood of implantation of the fertilized eggs. Ovulation after stopping NOMAC-E2 returns within at least 16 days after taking the last active tablet.

The CHMP noted that the selection of the daily dose of E_2 (1,5 mg) has not been justified neither in this nor in the dose finding studies, the question can be raised whether this quantity of E_2 given orally can compensate for the complex antiestrogenic effect of NOMAC when it is used for long-term periods, especially in adolescents. There are no PK/PD or clinical data available on this segment of the target population.

2.5. Clinical efficacy

The main documentation in support of the contraceptive efficacy includes 2 clinical phase III studies (292001 and 292002) and 2 supportive studies (292003 and 292004). Studies 292001 and 292002 are considered the pivotal studies with respect to the contraceptive effect of NOMAC/E2. Studies 292003

and 292004 are clinical supportive pharmacology studies as contraceptive efficacy was assessed in these studies as secondary but not primary objective.

Table 2: Overview of clinical trials relevant for evaluating the efficacy of NOMAC-E2

Study ID	Design	Study posology	Study objectives	Subjects/arm entered / completed	Duration of treatment	Diagnosis incl. criteria
PIVOTAL Phase III studies for the evaluation of contraceptive effect						
292001 Phase III	Open-label, multi-center, randomized, comparative	2.5mg NOMAC + 1.5mg E2 / placebo tablet; 24/4 regimen; oral dosing 3mg DRSP + 30 µg EE / placebo tablet; 21/7 regimen; oral dosing	To evaluate the contraceptive **efficacy**, cycle control, **safety** and acceptability of NOMAC-E2 compared to DRSP-EE Pharmacogenetics	Subjects: 2152 randomized 2126 treated 1552 completed 2124 ITT 1928 Restr. ITT c 2081 PP Age range: 18-49 yrs	13 cycles of 28 days	Healthy women of childbearing potential
292002 Phase III	Open-label, Multi-center, Randomized, comparative	2.5mg NOMAC + 1.5mg E2 / placebo tablet; 24/4 regimen; oral dosing 3mg DRSP + 30µg EE / placebo tablet; 21/7 regimen; oral dosing	To evaluate the contraceptive **efficacy**, cycle control, **safety** and acceptability of NOMAC-E2 compared to DRSP-EE Pharmacokinetics Pharmacogenetics	Subjects: 2281 randomized 2220 treated 1332 completed 2193 ITT 1814 Restr. ITT 2040 PP Age range: 18-50 yrs	13 cycles of 28 days	Healthy women of childbearing potential
SUPPORTIVE Phase III studies for the evaluation of contraceptive effect						
292003 PK, PK/PD Phase III	Open-label, single-center, Randomized, comparative	2.5mg NOMAC + 1.5mg E2 / placebo tablet;	To evaluate the effects on **ovarian function** of NOMAC-E2 compared to	Subjects: 48 randomized 48 treated 41 completed	6 cycles of 28 days	Healthy women of childbearing potential

		24/4 regimen; oral dosing 3mg DRSP + 30 µg EE / placebo tablet; 21/7 regimen; oral dosing	DRSP-EE Pharmacogenetics	48 ASR/AST/ITT 45 PP Age range: 18-36 yrs		
292004 Phase III	Open-label, multi-center, Randomized, comparative	2.5mg NOMAC + 1.5mg E2 / placebo tablet; 24/4 regimen; oral dosing 150µg LNG + 30 µg EE / placebo tablet; 21/7 regimen; oral dosing	To evaluate the effects on hemostasis, lipids and carbohydrate metabolism and adrenal and thyroid function of NOMAC-E2 compared to LNG-EE	Subjects: 121 randomized 118 treated 105 completed 118 AST/ITT 113 Restr ITT 115 PP Age range: 18-48 yrs	6 cycles of 28 days	Healthy women of childbearing potential

2.5.1. Dose response study(ies)

Dose-response studies and main clinical studies.

2.5.2. Main study(ies)

Studies 292001 and 292002 were multicenter, open, comparative studies to investigate the contraceptive efficacy of NOMAC 2.5mg / E2 1.5mg versus a COC containing 3mg DRSP and 30µg EE in healthy female volunteers at risk for pregnancy and in need for contraception. In both studies, the women were to be treated for 13 cycles of 28 days each. Of note, study 292001 was performed in European countries whereas study 292002 was performed in the USA.

Table 3. Summary of Efficacy for Trial 292001

Title: A randomized, open-label, comparative, multi-center trial to evaluate contraceptive efficacy, cycle control, safety and acceptability of a monophasic combined oral contraceptive (COC) containing 2.5 mg nomegestrol acetate (NOMAC) and 1.5 mg estradiol (E2), compared to a monophasic COC containing 3 mg drospirenone (DRSP) and 30 µg ethinylestradiol (EE)

Study identifier	292001		
Design	Randomized, open-label, group-comparative, multi-center		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	13 cycles of 28 days each not applicable 6 weeks follow-up	
Hypothesis	To fulfill – in conjunction with trial 292002 – the CHMP criterion on the precision of the two-sided 95% CI for the Pearl index estimate in the NOMAC-E2 group (age class 18-35 years) with probability of 80% such that the difference between the upper limit and the point estimate does not exceed 1		
Treatments groups	Nomegestrol acetate (NOMAC) and estradiol (E2)		One tablet per day orally for 13 consecutive 28-day cycles in a 24/4-day regimen. Each active tablet contains 2.5 mg NOMAC and 1.5 mg E2. Days 1-24: NOMAC-E2 tablets, Days 25-28: placebo tablets. 1613 randomized subjects
	Drospirenone (DRSP) and ethinylestradiol (EE)		One tablet per day orally for 13 consecutive 28-day cycles in a 21/7-day regimen. Each active tablet contains 3 mg DRSP and 30 µg EE. Days 1-21: DRSP-EE tablets, Days 22-28: placebo tablets. 539 randomized subjects
Endpoints and definitions	Primary endpoint	Pearl Index	Number of pregnancies per 100 woman years of exposure; Pearl index based on the Poisson distribution
	Secondary endpoint	Pearl Index Ratio	Ratio of Pearl Indices NOMAC-E2 vs. DRSP-EE
	Secondary endpoints	Kaplan-Meier estimates	Cumulative probability of in-treatment pregnancies at day 364
Database lock	05 MAY 2008		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Restricted ITT Analysis Set: All subjects from the ITT Group in the primary age class of 18-35 years with exclusion of cycles not expected to be at risk for pregnancy (cycles with recorded use of condoms or without confirmed intercourse); in-treatment period extended with +2 or +14 days			
Descriptive statistics and estimate variability	Treatment group	NOMAC-E2	DRSP-EE	
	Number of subjects	1193	402	
	Pearl index (+2 days extension)	0.57	1.26	
	Variability statistic (95% CI)	(0.16; 1.46)	(0.26; 3.68)	
	Pearl index (+14 days extension)	1.00	1.68	

	Variability statistic (95% CI)	(0.40; 2.06)	(0.46; 4.30)	
Effect estimate per comparison	<Co->Primary endpoint	NA	NA	
		NA	NA	
		NA	NA	
		NA	NA	
	Secondary endpoint	Comparison groups	NOMAC-E2 : DRSP-EE	
		Pearl Index ratio (+2 days extension)	0.45	
		Variability statistic (95% CI)	(0.08; 3.09)	
		P-value	0.502	
	Secondary endpoint	Comparison groups	NOMAC-E2 : DRSP-EE	
		Pearl Index ratio (+14 days extension)	0.59	
		Variability statistic (95% CI)	(0.15; 2.77)	
		P-value	0.592	
Notes	As sensitivity analyses, Kaplan-Meier estimates and 95% CIs were calculated and compared between the treatment groups.			
Analysis description	**Pregnancy analysis based on recommendations from EMA**			
Analysis population and time point description	ITT Group excluding cycles with backup methods: All subjects from the ITT Group in the primary age class of 18-35 years with exclusion of cycles not expected to be at risk for pregnancy (cycles with recorded use of condoms); in-treatment period extended with +2 days			
Descriptive statistics and estimate variability	Treatment group	NOMAC-E2	DRSP-EE	
	Number of subject	1315	442	
	Pearl index (+2 days extension)	0.38	0.81	
	Variability statistic (95% CI)	(0.10; 0.97)	(0.17; 2.35)	
Effect estimate per comparison	<Co->Primary endpoint	NA	NA	
		NA	NA	
		NA	NA	
		NA	NA	
	Secondary endpoint	Comparison groups	NOMAC-E2 : DRSP-EE	
		Pearl Index ratio (+2 days extension)	0.47	
		Variability statistic (95% CI)	(0.08; 3.21)	
		P-value	0.531	
Notes	As sensitivity analyses, Kaplan-Meier estimates and 95% CIs were calculated and compared between the treatment groups.			
Analysis description	**Secondary analyses:** The same analyses for 1) ITT group, 2) PP group (excluding exposure with protocol violations as well as cycles with recorded use of condoms or without confirmed intercourse), 3) PP group according to EMA (excluding exposure with protocol violations as well as cycles with recorded use of condoms). **Secondary analyses:** All analyses were also done for the upper age class (36-50 years) and for the overall age class (18-50 years).			

Table 4. Summary of Efficacy for Trial 292002

Title: A randomized, open-label, comparative, multi-center trial to evaluate contraceptive efficacy, cycle control, safety and acceptability of a monophasic combined oral contraceptive (COC) containing 2.5 mg nomegestrol acetate (NOMAC) and 1.5 mg estradiol (E2), compared to a monophasic COC containing 3 mg drospirenone (DRSP) and 30 µg ethinylestradiol (EE)

Study identifier	292002		
Design	Randomized, open-label, group-comparative, multi-center		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		13 cycles of 28 days each not applicable 6 weeks follow-up
Hypothesis	To fulfill – in conjunction with trial 292001 – the CHMP criterion on the precision of the two-sided 95% CI for the Pearl index estimate in the NOMAC-E2 group (age class 18-35 years) with probability of 80% such that the difference between the upper limit and the point estimate does not exceed 1		
Treatments groups	Nomegestrol acetate (NOMAC) and estradiol (E2)		One tablet per day orally for 13 consecutive 28-day cycles in a 24/4-day regimen. Each active tablet contains 2.5 mg NOMAC and 1.5 mg E2. Days 1-24: NOMAC-E2 tablets, Days 25-28: placebo tablets. 1613 randomized subjects
	Drospirenone (DRSP) and ethinylestradiol (EE)		One tablet per day orally for 13 consecutive 28-day cycles in a 21/7-day regimen. Each active tablet contains 3 mg DRSP and 30 µg EE. Days 1-21: DRSP-EE tablets, Days 22-28: placebo tablets. 539 randomized subjects
Endpoints and definitions	Primary endpoint	Pearl Index	Number of pregnancies per 100 woman years of exposure; Pearl index based on the Poisson distribution
	Secondary endpoint	Pearl Index Ratio	Ratio of Pearl Indices NOMAC-E2 vs. DRSP-EE
	Secondary endpoints	Kaplan-Meier estimates	Cumulative probability of in-treatment pregnancies at day 364
Database lock	22 AUG 2008		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Restricted ITT Analysis Set: All subjects from the ITT Group in the primary age class of 18-35 years with exclusion of cycles not expected to be at risk for pregnancy (cycles with recorded use of condoms or without confirmed intercourse); in-treatment period extended with +2 or +14 days			
Descriptive statistics and estimate variability	Treatment group	NOMAC-E2	DRSP-EE	
	Number of subject	1158	378	
	Pearl index (+2 days extension)	1.96	3.09	
	Variability statistic (95% CI)	(0.98; 3.51)	(1.13; 6.73)	
	Pearl index (+14 days extension)	2.50	4.64	

	Variability statistic (95% CI)	(1.37; 4.19)	(2.12; 8.80)	

Effect estimate per comparison	<Co->Primary endpoint	NA	NA
		NA	NA
		NA	NA
		NA	NA
	Secondary endpoint	Comparison groups	NOMAC-E2 : DRSP-EE
		Pearl Index ratio (+2 days extension)	0.63
		Variability statistic (95% CI)	(0.22; 2.09)
		P-value	0.514
	Secondary endpoint	Comparison groups	NOMAC-E2 : DRSP-EE
		Pearl Index ratio (+14 days extension)	0.54
		Variability statistic (95% CI)	(0.22; 1.41)
		P-value	0.223
Notes	As sensitivity analyses, Kaplan-Meier estimates and 95% CIs were calculated and compared between the treatment groups.		
Analysis description	**Pregnancy analysis based on recommendations from EMA**		
Analysis population and time point description	ITT Group excluding cycles with backup methods: All subjects from the ITT Group in the primary age class of 18-35 years with exclusion of cycles not expected to be at risk for pregnancy (cycles with recorded use of condoms); in-treatment period extended with +2 days		

Descriptive statistics and estimate variability	Treatment group	NOMAC-E2	DRSP-EE	
	Number of subject	1375	463	
	Pearl index (+2 days extension)	1.16	1.89	
	Variability statistic (95% CI)	(0.58; 2.08)	(0.69; 4.11)	

Effect estimate per comparison	<Co->Primary endpoint	NA	NA
		NA	NA
		NA	NA
		NA	NA
	Secondary endpoint	Comparison groups	NOMAC-E2 : DRSP-EE
		Pearl Index ratio (+2 days extension)	0.62
		Variability statistic (95% CI)	(0.21; 2.03)
		P-value	0.479
Notes	As sensitivity analyses, Kaplan-Meier estimates and 95% CIs were calculated and compared between the treatment groups.		
Analysis description	**Secondary analyses:** The same analyses for 1) ITT group, 2) PP group (excluding exposure with protocol violations as well as cycles with recorded use of condoms or without confirmed intercourse), 3) PP group according to EMA (excluding exposure with protocol violations as well as cycles with recorded use of condoms). **Secondary analyses:** All analyses were also done for the upper age class (36-50 years) and for the overall age class (18-50 years).		

Methods

The following major inclusion criteria had to be observed: sexually active women, at risk for pregnancy and not planning to use condoms; women in need for contraception and willing to use an oral contraceptive for 12 months (13 cycles); at least 18 but not older than 50 years of age at the time of screening; body mass index ≥ 17 and ≤ 35 kg/m²; good physical and mental health; willing to give informed consent in writing.

In general, inclusion/exclusion criteria were representative of the standard population used for evaluation of contraception in healthy women of childbearing potential. However, some women in the class age 45-50 could have completed the menopause transition and thus were not at risk of pregnancy. Otherwise, women with hypothalamic amenorrhoea due to a low body weight (17.1 kg/m² < BMI < 18.9 kg/m²) have a low probability of spontaneous ovulation. These two populations of women were not excluded from these trials.

Study Participants

Healthy female volunteers aged between 18 and 50 years, requesting contraception, without contraindications for combined OC use were screened. A total of 3233 subjects participated in the two pivotal clinical trials (292001 and 292002) providing 32781 cycles or 2522 women years. The combined exposure to NOMAC-E2 for the restricted ITT group 18-35 years (main analysis population) was 2351 subjects generating 16396 cycles which is equivalent to 1261 women years.

Treatments

Subjects received either a COC containing 2.5 mg NOMAC and 1.5 mg E2 or a COC containing 3mg DRSP and 30µg EE. From day 1 up to and including day 28 one tablet was taken orally at approximately the same time every day. This was done for 13 consecutive 28-day cycles.

In PD studies, NOMAC-E2 sufficiently inhibited ovulation. The comparator DRSP-EE (3mg/30µg) was chosen by the applicant as it has already been approved in numerous countries and is used worldwide. Similar mechanism of action (PD properties on ovulation inhibition) compared to NOMAC/E2.

Objectives

The primary objective was to assess contraceptive efficacy, vaginal bleeding patterns (cycle control), general safety and acceptability of the NOMAC-E2 COC in a large group of women aged 18-50 years. The secondary objectives of these studies were to evaluate the effect of the NOMAC-E2 COC on satisfaction and health related quality of life, libido, acne, menstrual symptoms, and body weight and to explore the aforementioned characteristics of the NOMAC-E2 COC in comparison with the DRSP-EE COC. As optional pharmacogenetic component the study objectives included collection and store of blood samples for further anonymized pharmacogenetic assessment.

Outcomes/endpoints

Primary and secondary efficacy parameters and safety parameters are in line with what is required in the CHMP Note for Guidance on the clinical investigation for hormonal contraception. Four parameters were taken into account in the assessment of the efficacy of NOMAC-E2:

1.- Contraceptive efficacy (Primary efficacy parameter)

The primary efficacy analysis of this trial was the Pearl Index i.e., the number of in-treatment pregnancies per 100 woman years of exposure for the restricted ITT Analysis Set (excluding cycles expected not to be at risk for pregnancy) in the age class of ≤ 35 years. Two definitions for in treatment pregnancies were used to analyze contraceptive efficacy, in order to comply with requests from regulatory authorities:

- In-treatment pregnancies were pregnancies with an estimated date of conception from the day of first intake of trial medication up to and including the day of last (active or placebo) intake of trial medication extended with a maximum of 2 days => definition used in Europe.

- In-treatment pregnancies were pregnancies with an estimated date of conception from the day of first intake of trial medication up to and including the day of last (active or placebo) intake of trial medication extended with a period of 14 days => definition used in the USA.

Secondary efficacy analyses were performed for the upper age class (> 35 years) and for the overall age class. Additional analyses were performed for the ITT group and PP group for both age classes separately and overall.

Differences between the treatment groups were explored for the ITT, restricted ITT and PP analysis (and separately per age class) using an exact 95% CI for the ratio of the two Pearl Indices based on the Poisson distribution with associated exact test for equality of the two Pearl Indices. For all subjects in the ITT group, a time to pregnancy analysis was performed secondary to the Pearl Index analysis. This analysis was also performed for each age class separately.

2.- Vaginal bleeding pattern (secondary efficacy parameters)

Women daily recorded bleeding (including bleeding intensity) throughout the treatment phase using electronic diaries. Electronic diaries were used for daily recording of vaginal bleeding events. Each subject was asked to record on a daily basis whether vaginal bleeding was present, and if vaginal bleeding was present, indicate whether it was considered spotting, or bleeding. The subject was asked to document her vaginal bleeding up to and including one week after stopping treatment.

3.- Cycle analysis

Primary vaginal bleeding pattern included: occurrence of breakthrough bleeding/spotting; absence of withdrawal bleeding.

Secondary vaginal bleeding parameters included: Occurrence of breakthrough bleeding; Occurrence of breakthrough spotting; Occurrence of early withdrawal bleeding; Occurrence of continued withdrawal bleeding; Number of breakthrough bleeding/spotting days; Number of withdrawal bleeding/spotting days.

4.- Cumulative amenorrhoea

Cumulative amenorrhoea is summarized as the percentage of women who were amenorrheic in a given cycle and remained so throughout the end of the trial (Cycle 13). Amenorrhoea was defined as the absence of bleeding and/or spotting within a cycle, which is in line with the definition used in the reference period analysis.

Sample size

These two trials were designed to obtain a sufficient number of evaluable cycles of exposure to the NOMAC-E2 COC in fertile women to fulfill the Committee for medicinal Products for Human Use (CHMP) criterion on the precision of the two-sided 95% confidence interval for the Pearl Index estimate with a power of at least 80%. Each trial was designed to contribute half of the required exposure. In Study 292001, a total of 1591 subjects were randomised and treated with NOMAC-E2 for a period of 13 cycles whereas there were 1666 subjects included in Study 292002.

Randomisation

Randomization was performed with an allocation ratio of 3:1 (NOMAC-E2: DRSP-EE) and was stratified by age class (up to 35 years, more than 35 years). For statistical analysis Pearl Index (CV), Kaplan Meier estimates, CV (including Log-rank and Wilcoxon test) were used.

The clinical trial population at baseline were well balanced between the two treatment groups in all clinical trials.

Blinding (masking)

These two clinical trials were conducted in an open-label fashion, as the differences in regimen between NOMAC-E2 and DRSP-EE (24/4 versus 21/7) would lead to obvious differences in the timing of withdrawal bleeding. Even if an open design has already been previously used in the development of other OCs.

Statistical methods

The statistical methods include Pearl Index and confidence interval (Poisson distribution); confidence interval (Poisson distribution) for the ratio of Pearl Indices with associated exact test for equality; time-to-pregnancy analysis with Kaplan-Meier estimates and confidence intervals (including Log-rank and Wilcoxon test); Cycle analysis incidence rates: confidence intervals (binomial method) per group and confidence intervals (normal approximation) for the difference between the groups; frequency tables, descriptive statistics; reference period analysis: frequency tables, descriptive statistics.

Other analyses related to efficacy:
Patient reported outcome questionnaires (summary scores) by two-way analysis of variance methods; comparison of acne rating scales by Wilcoxon-type test stratified by age class and baseline values; frequency tables, and descriptive statistics.

Results

Recruitment

For the clinical trial 292001 the study duration was 13 consecutive 28-day cycles for each subject, (May 2006 until April 2008). The clinical trial 292002 had the same study duration as Trial 292001 (from June 2006 until July 2008).

Conduct of the study

Two amendments were adopted for studies 292001 and 292002.
Amendment 1 concerned several sections of the protocol such as exclusion criteria, assignment to treatment, concomitant medications, contraceptive efficacy, post-treatment evaluation, secondary efficacy parameter. In particular, the definitions of pre- in and post treatment pregnancies used at the time of the redaction of the initial protocol were different from those used for other OCs. In order to adequately compare the Pearl Index with other OCs, similar definitions were used. Results are given/analysed with these modified definitions. Of note, amendment 1 was adopted in May 2006 at the beginning of patient enrollment in Study 292001 (after one month). This amendment was adopted in November 2006, 5 months after the beginning of Study 292002enrollment.

Amendment 2 consisted in adding an optional pharmacogenetic assessment in both trials 292001 and 292002 and a population pharmacokinetic assessment in trial 292002. This protocol amendment is considered to have no impact on already included subjects and on efficacy and safety results of the two trials. This pharmacogenetic assessment initially planned has not been performed.

Baseline data

An analysis of demographic and baseline characteristics (including gynaecological and contraceptive history and socioeconomic background) revealed that subjects were mostly comparable between groups in each trial individually (282001 and 292002). Of note, no statistical test was performed to compare results between groups which is usual for demographic characteristics.

Baseline characteristics differ between Study 292001 and 292002 with regards to race, ethnicity, weight, gynaecological and contraceptive history and socioeconomic background. Women included in both studies belonged to the age class 18-50. No post-menarche adolescents of the age class 12-18, which is also a target population claimed for this new contraceptive pill have been included in both pivotal clinical studies. Population characteristics are also discussed in section Clinical Safety.

Numbers analysed

Table 5 shows the number of participants in each of the defined study population per treatment group and age class for the individual trials (Trials 292001, 292002, 292003, 292004) and the combined data of the two well-controlled trials (Trials 292001 and 292002) (Table 5).

The data sets presented are as follows:
All-Subjects-Randomized (ASR), All-Subjects-Treated (AST), Intent-to-Treat (ITT), restricted ITT and Per-Protocol (PP) (**Table 5).**

Subject data sets

Number of subjects per trial, analysis data set and age class

Trials 292001, 292002, 292001+292002 combined, 292003, and 292004

Subject data set		292001		292002		292001+292002		292003		292004	
		NOMAC-E2	DRSP-EE	NOMAC-E2	DRSP-EE	NOMAC-E2	DRSP-EE	NOMAC-E2	DRSP-EE	NOMAC-E2	LNG-EE
		(N=1613)	(N=539)	(N=1710)	(N=571)	(N=3323)	(N=1110)	(N=32)	(N=16)	(N=60)	(N=61)
18-35 years	All-Subjects-Randomized (ASR)	1336	446	1444	483	2780	929	32	15	46	46
	All-Subjects-Treated (AST)	1319	443	1406	469	2725	912	32	15	46	44
	Intent-to-Treat (ITT)	1317	443	1385	466	2702	909	32	15	46	44
	Restricted ITT[a]	1193	402	1156	378	2351	780	24	11	43	42
	Per-Protocol group (PP)[b]	1292	430	1291	423	2583	853	31	13	44	43
36-50 years	All-Subjects-Randomized (ASR)	277	93	266	88	543	181	0	1	14	15
	All-Subjects-Treated (AST)	272	92	260	85	532	177	0	1	14	14
	Intent-to-Treat (ITT)	272	92	259	83	531	175	0	1	14	14
	Restricted ITT[a]	249	84	212	66	461	150	0	1	14	14
	Per-Protocol group (PP)[b]	268	91	248	78	516	169	0	1	14	14
Overall (18-50 years)	All-Subjects-Randomized (ASR)	1613	539	1710	571	3323	1110	32	16	60	61
	All-Subjects-Treated (AST)	1591	535	1666	554	3257	1089	32	16	60	58
	Intent-to-Treat (ITT)	1589	535	1644	549	3233	1084	32	16	60	58
	Restricted ITT[a]	1442	486	1370	444	2812	930	24	12	57	56
	Per-Protocol group (PP)[b]	1560	521	1539	501	3099	1022	31	14	58	57

Data were taken from Table 3.1.1-1 in Appendix B.

[a] All subjects in the ITT Group with at least one cycle at risk for pregnancy

[b] All subjects in the ITT Group without major protocol violations

Outcomes and estimation

Subject discontinuations

In each trial, discontinuations due to AE/SAE are more frequent in NOMAC-E2 groups than DRSP-EE groups. In the NOMAC-E2 group, the most frequent reported SOC that led to premature discontinuation was "psychiatric disorders" (5.9%), followed by "reproductive system and breast disorders" (5.2%). The incidences of discontinuations due to AEs in these two SOCs are lower for DRSP-EE subjects (2.9% and 2.2%, respectively).

When comparing trials 292001 and 292002, the total number of subjects who discontinued prematurely from treatment was higher in Study 292002 compared to study 292001 (28.2% of the NOMAC-E2 subjects versus 23.4% of the DRSP-EE subjects for Study 292001; 41.1% of the NOMAC-E2 subjects versus 38.3% of the DRSP-EE subjects for Study 292002). These percentages are rather high although lower than the discontinuation rates planned/assumed in the sample size calculations.

This discrepancy is due to a higher percentage of "withdrawal of informed consent" and "lost to follow up" in trial 292002 as compared to trial 292001. It seems that women in trial 292002 were less compliant than women in trial 292001. This is confirmed by the exclusion from the ITT group in Study 292002 of 27 subjects due to the limited credibility of their electronic data while only 2 subjects were excluded in trial 292001.

Contraceptive efficacy

The table 6 below presents the efficacy analysis, i.e., the estimated Pearl Index (and 95% CI) for both Restricted ITT analysis and ITT analysis (trials 292001 and 292002 individually, using the in-treatment definition + 2 days).

Table 6. Contraceptive efficacy: Pearl Index with 95% confidence interval – Primary efficacy analysis

– **Restricted-ITT and ITT analysis (using the in-treatment definition + 2 days)**

	18 – 35 years	> 35 years	overall

Restricted-ITT analysis Set (using the in-treatment definition + 2 days)			
Trial 292001 NOMAC-E2 DRSP-EE	**0.571 [0.1555, 1.4614]** N=1193 1.261 [0.2601, 3.6858] N=402	0 [0, 2.3594] N=249 0 [0, 6.4466] N=84	**0.467 [0.1271, 1.1948]** N=1442 1.017 [0.2097, 2.971] N=486
Trial 292002 NOMAC-E2 DRSP-EE	1.963 [0.9798, 3.5119] N=1158 3.092 [1.1347, 6.7299] N=378	0.807 [0.0204, 4.4977] N=212 2.572 [0.0651, 14.33] N=66	1.754 [0.9061, 3.0632] N=1370 3.005 [1.2082, 6.1917] N=444
ITT-analysis Set (using the in-treatment definition + 2 days)			
Trial 292001 NOMAC-E2 DRSP-EE	**0.367 [0.1, 0.9399]** N= 1317 0.783 [0.1615, 2.2892] N=443	0 [0, 1.5555] N=272 0 [0, 4.4364] N=92	**0.301 [0.0821, 0.7719]** N=1589 0.644 [0.1327, 1.8808] N=535
Trial 292002 NOMAC-E2 DRSP-EE	**1.117 [0.5574, 1.9981]** N=1385 1.796 [0.6593, 3.9102] N=466	0.477 [0.0121, 2.6567] N=259 1.452 [0.0368, 8.0926] N=83	**1.004 [0.519, 1.7544]** N=1644 1.738 [0.6986, 3.5803] N=549

In the clinical trial performed with NOMAC-E2 in the European Union the following Pearl Indices for the age class 18-35 years were calculated:

Method failure: 0.40 (upper limit 95 % confidence interval 1.03)
Method and user failure: 0.38 (upper limit 95 % confidence interval 0.97)

In the clinical trial performed with NOMAC-E2 in the United States the following Pearl Indices for the age class 18-35 years were calculated:

Method failure: 1.22 (upper limit 95 % confidence interval 2.18)
Method and user failure: 1.16 (upper limit 95 % confidence interval 2.08)

In the controlled comparative studies, NOMAC-E2 shows less withdrawal bleeding than the comparator and is in general of less intensity. Cumulative amenorrhea was observed in 25.7% of women at cycle 13 compared to 1 % for the comparator. The "occurrence of the absence of withdrawal bleeding" was statistically significantly higher with NOMAC-E2 compared to DRSP-EE for all cycles and tended to increase over cycles while it was not the case in the DRSP-EE group.

Regarding intracyclic bleeding, breakthrough bleeding and spotting decreased over time in the NOMAC-E2 group and breakthrough spotting occurred more frequently than breakthrough bleeding in both treatment groups. However, the number of breakthrough bleeding/spotting days was similar between the two treatment groups. Lastly, the number of withdrawal bleeding/spotting days was slightly lower in the NOMAC-E2 group as compared to the DRSP-EE group. Overall, the total number of days with bleeding/spotting is less with NOMAC-E2.

For the NOMAC-E2 group, the incidence of cumulative amenorrhoea increased steadily over time, from 2.0% in Cycle 1 (i.e., amenorrheic from Cycle 1 through Cycle 13) up to 9.0% in Cycle 9 (i.e., amenorrheic from Cycle 9 through Cycle 13) and 25.7% in Cycle 13. For the DRSP-EE group, the incidence of cumulative amenorrhoea was low ≤1.0%). The occurrences of the absence of withdrawal bleeding were statistically significantly higher in the NOMAC-E2 group as compared to the DRSP-EE group for all cycles.

Ancillary analyses

Clinical studies in special populations

No special population studies have been conducted. Patients with renal insufficiency, hepatic dysfunction and adrenal insufficiency were excluded from trials 292001 and 292002 due to the known antimineralocorticoid activity of the comparator Drospirenone (in accordance with the SmPC/Package insert of DRSP-EE). Therefore the information in these groups is limited.

NOMAC-E2 is contra indicated in patients with severe renal insufficiency or acute renal failure like drospirenone-containing products. For patients with hepatic insufficiency, the statement in section 4.3 "*presence or history of severe hepatic disease as long as liver function values have not returned to normal*" is considered appropriate.

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

Efficacy results of both trials 292001 and 292002 have been combined and presented. The extent of heterogeneity has not been determined with a statistical test.

Supportive study(ies)

Study 292003. This was a randomized, open label, comparative, six-cycle, single center trial to evaluate the effects on ovarian function of NOMAC-E2 (2.5mg NOMAC / 1.5mg E2; 24/4 regimen) in comparison to DRSP-EE (3mg DRSP / 20µg EE; 21/7 regimen) in healthy female volunteers aged 18 to 35 years. A total of 48 subjects were randomized, 32 subjects in the NOMAC-E2 group and 16 subjects in the DRSP-EE group. In trial 292003 the subjects were allocated randomly in 2:1 to either the NOMAC-E2 or DRSP-EL

Study 292004. This was a randomized, open-label, comparative, six-cycle, multi-center trial to evaluate the effects on haemostasis, lipid and carbohydrate metabolism and on adrenal and thyroid function of NOMAC-E2 (24/4 regimen) in comparison to 150µg Levonorgestrel – 30µg ethinylestradiol (21/7 regimen) in healthy female volunteers aged 18 to 50 years. The duration of treatment was six cycles of 28 days.

A total of 121 subjects were randomized, 60 subjects in the NOMAC-E2 group and 61 subjects in the LNG-EE group. The primary objective of this trial was to assess secondary pharmacological properties (effects on haemostasis, lipid, carbohydrate metabolism and adrenal and thyroid function) of NOMAC-E2. As contraceptive efficacy was only a secondary objective, this trial is considered supportive for the evaluation of the contraceptive effect of NOMAC-E2. In trial 292004 the allocation ratio was 1:1 (randomly to NOMAC-E2 or to LNG-EE).

2.5.3. Discussion on clinical efficacy

The following considerations have been evaluated during the assessment:

Pearl Index calculation
Several issues regarding the calculation of the Pearl Indexes were raised during the procedure, among them, the MAH was requested to further justify the difference of Pearl Index between the EU and the US studies particular, recalculate the Overall Pearl Index excluding only cycles where condoms were used; provide justification for pooling Pearl Indexes from both clinical studies and finally to calculate Pearl Indexes for method failure. Values of Overall Pearl Indexes for NOMAC-E2 in the European study were in the range of PI that were already accepted for other OCs, i.e. below 1 (0.378 for age group 18-35 years and 0.309 for age group 18-50 years). In the US Study, overall Pearl Indexes were however much higher, above 1. All Overall Pearl Indexes for NOMAC-E2 fulfill the criteria of the NfG, as the difference between the estimated PI and the upper limit of the CI does not exceed 1. Baseline characteristics differ between Study 292001 and 292002 with regards to race, ethnicity, weight, gynaecological and contraceptive history and socioeconomic background. The impact of the differences in baseline in demographics and baseline characteristics on estimated Pearl Index between both clinical studies 292001 and 292002 has been addressed by the CHMP during the assessment of the procedure.

In the NOMAC-E2 project, compliance to trial medication intake was primarily based on the response values entered by the subjects in the electronic diaries on a daily basis. The Drug Accountability (DACC)

form was only an additional limited source of information for the determination of compliance. On the DACC form, the number of strips dispensed and returned was recorded at each visit. Strips were handed out for 3 or 4 cycles to the women. The women returned to the clinic after three or four cycles of use and the total number of tablets returned over this period (three or four cycles) was recorded on the DACC form at each visit. Therefore, compliance can also be determined from the DACC form, but this is less specific as compared to the diary data and in general mostly not cycle specific. Therefore, the DACC form was only used to determine the overall subject compliance over the whole treatment period.

The most conservative approach for the Pearl Index calculation of method failures has been used for the exclusion of pregnancies from the numerator and the inclusion of exposure in the denominator. This approach may lead to a potential overestimation of pregnancies in the numerator and an underestimation of exposure in the denominator and thus results in the most conservative estimation of the Pearl Index for method failure. Regarding the determination of the number of pregnancies due to method failure, it was investigated whether the date of conception fell into a period that the subject was non-compliant to tablet intake. As explained above, non-compliance was based on the response values entered by the women in the electronic diary. Non-compliance to tablet intake during the scheduled active cycle period (days 1-24 for NOMAC-E2 and days 1-21 for DRSP-EE) was defined as 4 or more days with forgotten tablets, or two or more consecutive days with forgotten tablets. According to the protocol, in case the date of conception fell into a non-compliant cycle based on the data from the diary with the definition as described above, pregnancies are only excluded if non-compliance is confirmed by the data on the DACC form. If no tablets were returned in the period in which the estimated date of conception fell, the pregnancy was kept in the numerator. Since the data of the DACC form is less specific as compared to the diary data, the addition of this check on the DACC form is a very conservative approach. By using this very conservative approach, several in-treatment pregnancies with an estimated date of conception that fell into a period that the subject was non-compliant according to the diary, were still included in the calculation of Pearl Index for method failure because the noncompliance could not be confirmed by the data on the DACC form.

The denominator of the method failure Pearl Index, non-compliance was only based on the response values entered by the women in the electronic diary. The additional check on the DACC form was not performed for the denominator. In fact, excluding cycles (already known as non-compliant based on the diary data) only if this was confirmed by the DACC form, would lead to a substantial number of cycles for which non-compliance could not be confirmed. (It is also known for clinical trials that the number of returned tablets is usually underestimated.) This would lead to a bias towards higher exposure and thus an underestimation of the Pearl Index for method failure.

The methodology used for method failure can be considered to be the most conservative approach, i.e. increasing the Pearl Index estimation. In conclusion, this method tends to increase the numerator and to decrease the denominator, and therefore may only have increased the ratio.

Vaginal bleeding pattern
In the two clinical comparative studies, NOMAC-E2 shows less "withdrawal bleeding" than the comparator with in general less intensity. Cumulative amenorrhea was observed in 25.7% of women at cycle 13 compared to 1 % for the comparator. The "occurrence of the absence of withdrawal bleeding" was statistically significantly higher with NOMAC-E2 compared to DRSP-EE for all cycles and tended to increase over cycles while it was not the case in the DRSP-EE group.

Regarding intracyclic bleeding, breakthrough bleeding and spotting decreased over time in the NOMAC-E2 group and breakthrough spotting occurred more frequently than breakthrough bleeding in both treatment groups. However, the number of breakthrough bleeding/spotting days was similar between the two treatment groups. Lastly, the number of withdrawal bleeding/spotting days was slightly lower in the NOMAC-E2 group as compared to the DRSP-EE group. Overall, the total number of days with bleeding/spotting is less with NOMAC-E2 and subjects with regular withdrawal bleedings in the early cycles are likely to have also regular withdrawal bleedings in the later cycles, whereas the incidence of breakthrough bleeding/spotting tends to decrease over the cycles. As requested by the CHMP, additional analyses have been performed to investigate the occurrence of breakthrough bleeding/spotting and absence of withdrawal bleeding (primary vaginal bleeding parameters in cycle analysis) in the subgroup of women with a regular withdrawal bleeding. In total, 1055 subjects (56.8%) did have a regular withdrawal bleeding, i.e. withdrawal bleeding in Cycles 2, 3 and 4.

For the subgroup of women with a regular withdrawal bleeding during Cycles 2, 3 and 4, the occurrence of breakthrough bleeding/spotting in Cycles 5 to 13 was very similar to the remainder population, decreasing over Cycles 5 to 13 from 19.0% to 14.0% in this subgroup versus 21.4% to

15.7% in the remainder group. For the subgroup of women with a regular withdrawal bleeding during Cycles 2, 3 and 4, the occurrence of absence of withdrawal bleeding in Cycles 5 to 12 was lower as compared to the remainder population increasing from 7.6% to 14.6% in this subgroup versus 51.2% to 61.9% in the remainder group.

The high occurrence of absence of withdrawal bleeding indicates that the estrogenic stimulation is less than that of other COCs, e.g. LNG-EE product (in Study 292005, the occurrence of absence of withdrawal bleeding was statistically significantly higher in NOMAC-E2 group compared to LNG-EE group for all cycles).

In conclusion, this phenomenon clearly shows the dominance of the gestagenic effect of NOMAC-E2 in a high percentage of the users. Indeed, the bioavailability of E2 is only about 1% from NOMAC-E2. Therefore, for the NOMAC-E2 users whose endometrium is adequately stimulated with E2, no (or less) breakthrough bleeding/spotting occurred and they had regular withdrawal bleeding. However for the remainder group the absence of withdrawal bleeding in cycles 5 to 12 were 51.2 % to 61.9 %.
Clinicians should be aware of the bleeding profile with NOMAC-E2 as this should be taken into consideration when choosing an OC.

Return to ovulation
Return of ovulation was considered as an important secondary efficacy parameter to be assessed for OCs. Overall, return to ovulation was considered adequate: detected in the first cycle after the last tablet intake in 78.6% (22/28) of NOMAC-E2 subjects and 75.0% (12/16) of DRSP-EE subjects.

In conclusion applicant has appropriately addressed efficacy issues of NOMAC-E2 in the clinical part of dossier.

2.5.4. Conclusions on the clinical efficacy

Conclusions on clinical efficacy

The efficacy of NOMAC-E2 (in daily dose of 2.5mg NOMAC + 1.5mg E2) in respect of ovulation inhibition has been shown in the two pivotal studies. The exposure of the patients and also taking into account the exposure of cycles and woman years is acceptable for calculating the Pearl Index. For NOMAC-E2 the values are 0.38 (EU) and 1.16 (USA) and higher for DRSP-EE 1.16 (EU) and 1.89 (USA).. Breakthrough bleeding and spotting occurred more frequently in NOMAC-E2 group in the first cycles of the treatment but the incidence of these events slowly decreased in time. Less frequent and less intense withdrawal bleeding occurred in this group and finally a significant proportion of the subjects had permanent amenorrhea. Amenorrhea developed only in 0.1% of the participant in the DRSP-EE group.

In conclusion it can be established that the contraceptive effect (ovulation inhibition) of NOMAC-E2 is at least equal to that of DRSP-EE, but the bleeding pattern and cycle control of NOMAC-E2 product is different. No clinical efficacy and safety data are available in adolescents under 18 years of age.

2.6. Clinical safety

Patient exposure

Data related to safety of NOMAC-E2 have been collected from 8 clinical trials in which NOMAC-E2 was used and administered in a 24/4 regimen. The trials were as follows: 292001, 292002, (13 cycle trials), 292003, 292004 (6 cycle trials) and 02-ESC/NOM-1RD and 2RD (3 cycle trials). The data from these 6 trials were pooled for a main integrated analysis for general safety. Two pivotal phase III trials contribute about 95 % of the total number of NOMAC-E2 treated subjects which were included in the integrated safety data analysis. General safety was assessed as reported as adverse events or serious adverse events and also using the data of routine laboratory parameters and vital signs. In addition specific safety data were collected which were related to the uterine cervix (cervical mucus), endometrium (wall thickness and biopsy results), cardiac safety (effects on QTc), haemostasis, lipid and carbohydrate metabolism, androgens, SHBG, adrenal and thyroid function and data on folic acid plasma level. 3434 subjects were exposed to NOMAC-E2 for a total of 33838 cycles (2602 women years). 1105 subjects were exposed to the comparator drug DRSP-EE (3 mg – 30 μg). Data of Trials 292001, 292002 (13-cycle trials), 292003, 292004 (6-cycle trials), 02-ESC/NOM-1-RD and 02-ESC/NOM-2-RD (3-cycle trials) were pooled to provide the integrated safety data set (ISDS).

Table 7

Disposition (number of subjects) by trial
Integrated Safety Data Set
All-Subjects-Treated Group

Trial	NOMAC-E2 (2.5 mg-1.5 mg) (24/4 regimen)	DRSP-EE (3 mg-30 µg) (21/7 regimen)	LNG-EE (150 µg-30 µg) (21/7 regimen	LNG-EE (100 µg-20 µg) (21/7 regimen)
	(N=3434)	(N=1105)	(N=58)	(N=45)
	n (%)	n (%)	n (%)	n (%)
292001	1591 (46.3)	535 (48.4)	NA	NA
292002	1666 (48.5)	554 (50.1)	NA	NA
292003	32 (0.9)	16 (1.4)	NA	NA
292004	60 (1.7)	NA	58 (100.0)	NA
02-ESC/NOM-1-RD	40 (1.2)	NA	NA	NA
02-ESC/NOM-2-RD	45 (1.3)	NA	NA	45 (100.0)
Total	3434 (100.0)	1105 (100.0)	58 (100.0)	45 (100.0)

Data were taken from Table 1.2.1-6.A in Appendix B.
NA = Not applicable.
Note: ISDS includes Trials 292001, 292002, 292003, 292004, 02-ESC/NOM-1-RD (24/4 data only), and 02-ESC/NOM-2-RD.

Adverse events

Clinical safety of NOMAC-E2 was adequately documented. The adverse events reported are known to be associated with the use of oestrogens and progestogens. However, the incidence of adverse events is higher with NOMAC-E2 than in the comparator group DRSP-EE, with special higher incidence of acne, weight increase, lack of withdrawal bleeding, breakthrough bleeding/spotting and psychiatric AEs. In particular, new cases of acne and worsening of acne developed more frequently in the NOMAC-E2 subjects that could preclude an extensive use in adolescents or young adults.

Evaluation of endometrial effects in general showed a pattern known for COCs. Histopathology of endometrial biopsies does not indicate an untoward effect of NOMAC-E2 on the endometrium. Other side effects such as breast cancer, cervical dysplasia should be followed throughout the Pharmacovigilance surveillance and the RMPs as they are considered as class effect. Adequate information as for other OCs has been proposed to be included in the SPC.

”The mean exposure to NOMAC-E2 and DRSP-EE was slightly higher in Trial 292001 as compared to Trial 292002 which could be explained by a lower premature discontinuation rate in Trial 292001. The percentage of subjects with an AE was slightly higher in the NOMAC-E2 group (75.3%) as compared to DRSP-EE (69.0%). See table 8 for details. Two subjects in the NOMAC-E2 group died (0.1%), both deaths were unrelated to trial medication, none of the subjects died in any of the other treatment groups. The percentage of subjects that experienced an SAE was low in the NOMAC-E2 group (1.8%) and the DRSP-EE group (1.4%). The overall incidence of subjects who discontinued NOMAC-E2 treatment due to an AE (17.1%) was higher as compared to the incidence in the DRSP-EE group (10.1%). The percentage of subjects who reported an AE related to trial medication was higher in the NOMAC-E2 group (49.1%) as compared to the DRSP-EE group (37.3%). In total 387 subjects (11.3%) in the NOMAC-E2 group reported at least one AE with a severe intensity, and 112 subjects (10.1%) in the DRSP-EE group.

Most frequently reported AEs
In the NOMAC-E2 group, four AEs were reported with an incidence higher than or equal to 10% (acne, weight increased, headache and withdrawal bleeding irregular). Two other AEs were reported with an incidence between 5 and 10% in the NOMAC-E2 group (vs. DRSP-EE), i.e., ‘nasopharyngitis’ (6.7% vs. 7.2%), and ‘cervical dysplasia’ (5.5% vs. 6.6%).

Table 8

Number (%) of subjects with various types of adverse events occurring during the in-treatment period
Integrated Safety Data Set
All-Subjects-Treated Group

Event type	NOMAC-E2 (2.5 mg-1.5 mg) (24/4 regimen)		DRSP-EE (3 mg-30 µg) (21/7 regimen)		LNG-EE (150 µg-30 µg) (21/7 regimen)		LNG-EE (100 µg-20 µg) (21/7 regimen)	
	(N=3434)		(N=1105)		(N=58)		(N=45)	
	n	%	n	%	n	%	n	%
Subjects with AEs	2586	75.3	762	69.0	40	69.0	32	71.1
Deaths [a]	2	0.1	0	0.0	0	0.0	0	0.0
Subjects with SAEs	63	1.8	16	1.4	0	0.0	0	0.0
Subjects who discontinued due to AEs (according to EoT-Form)	588	17.1	112	10.1	4	6.9	0	0.0
Subjects with drug-related AEs [b]	1686	49.1	412	37.3	18	31.0	15	33.3
Subjects with AEs of known severe intensity	387	11.3	112	10.1	0	0.0	0	0.0

Data were taken from Table 2.1-7.A in Appendix B.
[a] Irrespective of time point of death.
[b] Relationship to trial medication according to investigator: 'definitely', 'probably', 'possibly'. Category 'Definite' was not used in Trials 02-ESC/NOM-1-RD and 02-ESC/NOM-2-RD.
Note: ISDS includes Trials 292001, 292002, 292003, 292004, 02-ESC/NOM-1-RD (24/4 data only), and 02-ESC/NOM-2-RD.
Note: The in-treatment period is defined as the period from first tablet intake up to last tablet intake plus 28 days.

Serious adverse event/deaths/other significant events

Carbohydrate metabolism.
NOMAC-E2 did not induce changes in glucose tolerance and insulin sensitivity (trial 292004).

Adrenal and thyroid function.
Trial 292004 (NOMAC-E2 slightly increased the plasma total cortisol, cortisol binding globulin and thyroxine binding globulin) but the extent of the increase was less in the NOMAC-E2 group as compared to LNG-EE group.

Androgens
Trial 292003 and trial 292004. The following androgen parameters were evaluated: free testosterone, total testosterone, DHT (dihydrotestosterone), androstenedione, and dehydroepiandrosterone. The level of all androgens decreased from baseline in mean values at cycle 6 and it was somewhat smaller in the NOMAC-E2 group as compared to the DRSP-EE and LNG-EE groups.

SHBG (Sex Hormone Binding globulin).
SHBG was increased in all three treatment groups (288% median increase from baseline in DRSP-EE, 44% in NOMAC-E2 and 22% in LNG-EE group). No relevant changes were found in folic acid level during NOMAC-E2 treatment. In summary NOMAC-E2 significantly reduced the plasma level of various androgenic hormones measured in the clinical trials, but less than with DRSP-EE and LNG-EE, and induced small increase in SHBG.

Vital signs, physical findings and other observations related to safety
The incidence of abnormal vital signs was low. NOMAC-E2 was associated with an increase in the body weight from baseline to the last measurement with median changes of 1kg and DRSP-EE 0.2kg. The relative increase of least 7% in body weight was observed for 15.8% of the subjects in the NOMAC-E2 group and 11.0% of the subjects in the DRSP-EE group. A trend for body weight gain was observed over one year of treatment.

Cervical smears
Cervical smears were taken in trials 292001 and 292002. Clinically relevant shifts could be detected from normal cervical smear result at screening to an abnormal cervical smear result, which considered to be mild, moderate or severe dysplasia.

Measurement was observed in 106 subjects, 4.6% in NOMAC-E2 group and 37 subjects (4.8%) in DRSP-EE group. Severe dysplasia was found only for two subjects, 1 subject (1%) 0.1% in the NOMAC-E2 group and also 1 subject in DRSP-EE group (0.1%). It should be noted that a background incidence for cervical dysplasia was found to be 6.1% in this trial population. Dysplasia was an exclusion criterion. It means that all subjects had a normal cervical smear at the start of the treatment. Cervical smears were taken only in two clinical trials (292001 and 292002) at the screening and at the end of the cycle 13.

Results of the cervical smear assessment are presented by assessment at baseline, after cycle 13 and last measurement during the in-treatment period along with the corresponding shifts. Here it should be mentioned that dysplasia was an exclusion criterion or these subjects were excluded later from the trial. Clinically relevant shift to mild dysplasia were observed for 95 subjects (4.1%) in the NOMAC-E2 group and 31 subjects (4.0%) in the DRSP-EE group. Clinically relevant shifts to moderate dysplasia was observed for 9 subjects (0.4%) in the NOMAC-E2 group and 5 subjects (0.6%) in the DRSP-EE group and shift to severe dysplasia was found for two subjects (0.1%) in the NOMAC-E2 group and one subject (0.1%) in DRSP-EE group. The incidence of cervical dysplasia as an adverse event was reported for NOMAC-E2 and DRSP-EE groups as 5.8% and 6.7% respectively. According to the Applicant the cervical dysplasia was evenly reported in both treatment groups. The Applicant mentioned some confounding factors which might have impact on the cervical smear findings and concluded that the incidence of cervical dysplasia does not give reason for concern in view of the background incidence in this population and regression to mean phenomenon was induced by the exclusion of the cervical dysplasia at screening.

Effects on endometrium
107 subjects participated in the endometrial biopsy substudy (85 in the NOMAC-E2 group and 22 in DRSP-EE group) but only 42 subjects provided both baseline and cycle 13 samples. The majority of the endometrial samples were classified as secretory at baseline of which 12 were classified as other, 5 as secretory and 2 as normally proliferative at the cycle 13 assessment. 13 samples were classified as other both at baseline and cycle 13. 2 samples were classified as normal proliferative at baseline of which 1 was classified as normally proliferative and 1 as other at cycle 13. The results of the cycle 13 biopsies were classified as other in 31 out of 42 samples. 11 samples were reported normally proliferative or secretory at the cycle 13 assessment. Histopatology of endometrial biopsies and ultrasound measurements of the endometrial thickness did not indicate an untoward effect of NOMAC-E2 on the endometrium.

Bone mineral density
When considering the impact the NOMAC-E2 prolonged use on the bone mineral density, it should be taken into account that nomegestrol acetate has definite progesterone-receptor mediated antiestrogenic effect. This consists of different factors – suppressing the FSH secretion, suppressing the follicular sensitivity to FSH stimulation and a consequence– decrease estrogenic endogenous estradiol production and nomegestrol acetate may also decrease the number of estrogenic receptors in the target organs. The issue to which extent can the exogenous estradiol compensate for the loss of endogenous E2 production was discussed by the CHMP during the assessment of this procedure. No clinically relevant effect on bone mineral density and no statistically significant difference in the effect on bone mineral density between NOMAC-E2 and the LNG-EE was observed in women aged 21-35 years and treated for 26 cycles (study 292005). These results cannot be referred directly to adolescents.

QTc elevations
Trial 292011 showed that therapeutic doses of NOMAC-E2 are not associated with QTc prolongation. It was randomised, double blind treatment with moxifloxacine as a reference product to demonstrate the sensitivity of the trial.

Use in pregnancy and lactation
Data related to use of NOMAC-E2 during pregnancy are limited but they are indicating that there are no adverse effects of NOMAC-E2 on the foetus or neonate. NOMAC-E2 is not recommended during lactation because it may reduce the quantity and the composition of breast milk. Small amounts of contraceptive steroids can be excreted with milk.

Overdose
There are no reports on serious effects of overdose.

Vital signs, physical findings
Vital signs (body weight, diastolic and systolic blood pressure) were determined throughout the clinical trials. The percentage of participants who have abnormal systolic or diastolic blood pressure was small in both groups (less than 2.4% for increases and decreases).
A small increase in body weight from baseline to last measurement could be observed in both NOMAC-E2 (1kg) and DRSP-EE group (0.2kg). A relative increase (at least 7% in body weight) was estimated during the treatment period for 16% of the subjects in the NOMAC-E2 group and for 11% of the subjects in DRSP-EE group.

Physical gynaecological breast examinations
In the well-controlled trials 292001 and 292002 and in the clinical pharmacology and PK trials did not find clinically relevant alterations.

Acne
Shift analyses on acne severity performed at baseline and at each visit suggests an overall neutral effect on acne. Doctors were obliged to report a worsening or new occurrence of acne as an AE.

Safety in special populations

Paediatric population
In order to further support the expectation that pharmacokinetic data will be similar, a single dose pharmacokinetic trial with NOMAC-E2 in post-menarcheal adolescents and adults was performed. The pharmacokinetics of nomegestrol acetate (primary objective) after single oral dosing of Zoely in healthy postmenarcheal female adolescents and adult subjects were similar. However after single oral dosing, for estradiol component (secondary objective), the exposure was 36% lower in adolescents versus adult subjects. The clinical relevance of these results is unknown in the absence of repeated dose data. Bone mineral density is a major problem in young female, especially in adolescent girls aged 12 to 14 or 15 years old.

Age 18-50 Subjects
The incidence of 'acne' was higher in subjects of the younger and middle age subgroups (n=280 [20.0%], and n=269 [18.1%]), respectively) as compared to the subjects in the older age subgroup (n=71 [12.9%]).

Safety related to drug-drug interactions and other interactions

Association between age and lipid and haemostasis parameters
In study 292004 the very low correlation coefficients and the spurious significant findings did not suggest any relevant associations of neither lipid nor haemostasis parameter changes within the NOMAC-E2 group with factor age. However this study is too short (only 6 Cycles) to give definitive conclusion.

Association between adverse events and body weight/BMI
The results showed that the incidences of 'acne' (16.3 to 19.6%), 'weight increased' (10.0 to 13.6%), and 'withdrawal bleeding irregular' (9.3 to 13.6%) tended to increase slightly with body weight category.

Association between adverse experiences and race
The results indicated that the incidences of 'acne', 'weight increase' and 'withdrawal bleeding irregular' were higher in Asian subjects as compared to white and Black/African Americans. The incidences of 'headache' and 'nasopharyngitis' were less frequently reported by Black/African Americans as compared to white and Asian subjects. The median extent of exposure of subjects categorized as Asian, white and 'Other' was similar (13.0 cycles), but the median exposure of Black/African Americans was markedly less (5.5 cycles).The number of Asian subjects is low.

Discontinuation due to adverse events

Of the 3434 NOMAC-E2 treated subjects and 1105 DRSP-EE treated subjects, 1143 subjects (33.3%) and 336 subjects (30.4%), respectively, discontinued treatment prematurely. The percentage of subjects who discontinued treatment prematurely was higher in Trial 292002 (40.7% in NOMAC-E2 group and 37.9% in DRSP-EE group) as compared to Trial 292001 (28.2% in the NOMAC-E2 group and 23.4% in the DRSP-EE group).

The percentage of premature discontinuations due to (S)AE in the NOMAC-E2 group (17.1%) was higher as compared to the DRSP-EE group (10.1%). The percentage of premature discontinuations due to 'unacceptable vaginal bleeding' in the NOMAC-E2 group was 3.7 % and 1.3 % in the DRSP-EE group. (127 subjects in the NOMAC-E2 and 14 subjects in the DRSP-EE group of studies 292001 and 292002). 'Unacceptable vaginal bleeding' is not a preferred term.

Discontinuation by SOC and PT

Psychiatric disorders was the most frequent reported SOC in the NOMAC-E2 group in which AEs were reported that resulted in premature discontinuation was. A total of 5.9% of the subjects reported AEs in this SOC as a reason for discontinuation from NOMAC-E2.
In the SOC 'Psychiatric disorders', the most frequent reported AEs leading to discontinuation (NOMAC-E2 vs. DRSP-EE, all causalities) were 'libido decreased' (2.0% vs. 1.0%), 'mood altered' (0.8% vs. 0.4%), 'depression' (0.8% vs. 0.4%), 'depressed mood' (0.7% vs. 0.2%), and 'loss of libido' (0.7% vs. 0.1%).

Reproductive system and breast disorder was the second most frequent reported SOC in which AEs were reported that resulted in premature discontinuation for the NOMAC-E2 group was. In total 178 subjects (5.2%) reported AEs in this SOC as a reason for discontinuation.
In SOC 'Reproductive system and breast disorders', the most frequent reported AEs (NOMAC-E2 vs. DRSP-EE, all causalities) were 'metrorrhagia' (1.4% vs. 0.8%), and 'withdrawal bleeding irregular' (1.3% vs. 0%).

Skin and subcutaneous tissue disorders (3.0% vs. 0.7%) In the SOC 'Skin and subcutaneous tissue disorders' the most frequent reported AE (NOMAC-E2 vs. DRSP-EE) was 'acne' (2.5% vs. 0.2%)
Nervous system disorders' (1.9% vs. 2.1%) In the SOC 'Nervous system disorders' the most frequent reported AE (NOMAC-E2 vs. DRSP-EE) was 'headache' (1.0% vs. 1.2%).
Investigations' (1.9% vs. 1.1%) In the SOC 'Investigations' the most frequent reported AE (NOMAC-E2 vs. DRSP-EE) was 'weight increased' (1.6% vs. 0.9%).

Post marketing experience

Available postmarketing data for NOMAC-E2 is not applicable to the indication prevention of pregnancy.
NOMAC alone (5 mg tablets; Lutenyl®) has been studied for use in menstrual disorders.
NOMAC-E2 (3.75 mg-1.5 mg tablets; Naemis®) has been studied for hormone replacement therapy in post-menopausal women and has been marketed in Europe since 2003.

In conclusion population in the two pivotal studies is different. The safety profile defined in these populations is not exactly the same. However it is possible to have a synthetic approach and it is possible to define for NOMAC-E2 a safety profile. In many specific points (more frequently AEs reported, discontinuations) the safety profile is less favourable than the safety profile of comparator drug. This fact is being reflected in SmPC and also be included in RMP. In contrast biological parameters suggest interesting pharmacological properties. However the small number of patients and the duration of exposure are too limited to adequately quantify the risk of rare events such as venous thromboembolism in particular.

2.6.1. Discussion on clinical safety

The adverse event profile of NOMAC/E2 appears worse compared with the comparator used in Phase III trials with more discontinuations due to AEs and higher frequencies of several AEs e.g. acne, weight increase, lack of withdrawal bleeding, irregular bleeding and also psychiatric AEs. Furthermore, signs of adverse liver effects have been noted both in nonclinical repeated dose toxicity and in clinical studies (requiring hospitalization in a number of cases).

Based on the provided data, acne, weight gain, lack of withdrawal bleeding, irregular bleeding and psychiatric AEs cannot be considered as emergent safety concerns for this new contraceptive pill even if higher rates were observed compared to DRSP-EE. However, the safety profile of NOMAC-E2 is adequately reflected in sections of the SmPC (sections 4.8. and 5.1). The differences observed between NOMAC-E2 and comparative pill containing DRSP-EE for acne, weight gain, and bleeding profile have been added in section 5.1.

Regarding Liver function, nonclinical data do not contain any signals that NOMAC-E2 may be associated with drug-induced liver injury. Bridging repeated dose toxicity studies have shown toxic effects which were consistent with the amplification of the hormonal activity which is predominantly estrogenic. No additional pre-clinical studies were necessary. In addition, cholelithiasis with or without cholecystis, considered as a class effect, is mentioned in section 4.4.; it has also been included in section 4.8. (Undesirable effects).

Bone Mineral Density (BMD) constitutes a specific point of interest in younger subjects, in the age class 12-17 years. The results of Trial 292005 were submitted by the applicant during the assessment of the procedure. The primary objective of this trial was to compare the effects of NOMAC-E2 on BMD with the effects of a monophasic COC containing LNG-EE. NOMAC-E2 (2/5 mg/1.5 mg) had no clinically relevant effect on bone mineral density and there was no statistically significant difference in the effect on bone mineral density between NOMAC-E2 and the LNG-EE in women aged 21-35 years and treated for 26 cycles. However, the population of women aged 21-35 years cannot be compared to the post-menarcheal adolescent. Indeed, for women aged 21-35 years the peak bone mass is already reached and the bone turnover is limited. Therefore, it is not surprising to find no differences in BMD between NOMAC-E2 users and LNG-EE users. On the contrary, in adolescents, the peak bone mass is not reached and bone turnover is maximum. Moreover, based on the data from literature, the association between the use of hormonal contraception and bone mineral density is still controversial. Therefore, the question remains open whether NOMAC-E2 prevents or not young women from obtaining peak bone mass and whether to reach peak bone mass is related to increase risk of osteoporosis later in life. This issue will be closely monitored by routine pharmacovigilance activities. It is acknowledged that the collection of bone mineral density will not be possible within a PASS study given the observational nature of this study.

2.6.2. Conclusions on the clinical safety

It can be established that the participants generally tolerated well the daily use of NOMAC-E2.
Its AE profile is similar to that of DRSP with some exception. Higher incidences were observed in acne, "weight increased" and "abnormal withdrawal bleeding" and in the incidence of hepatobiliary disorders in NOMAC group as compared to DRSP-EE.

The incidence of AE-s in %, and also the frequency of premature discontinuation due to primarily to AE-s was higher in NOMAC-E2 groups than in the DRSP-EE groups. It can probably explained by the higher incidence of acne, libido decrease, with increased abnormal withdrawal bleeding and amenorrhea. metrorrhagia. The number of SAE was small in both the NOMAC-E2 and in the DRSP-EE groups.
No DVT occurred in the NOMAC-E2 group and only one case in the DRSP-EE group. However, all women considered to be at risk of thromboembolic events were excluded from the trials.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan. **Table 9**

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks		
Migraine	Routine pharmacovigilance	Routine activities: • Inclusion in the SmPC as Adverse Drug Reaction.

		• Inclusion of a history of migraine with focal neurological symptoms in the SmPC as Contraindications.
Depression/depressed mood	• Routine pharmacovigilance • PASS (Depression is added as secondary outcome)	Routine activities: Inclusion in the SmPC as Adverse Drug Reaction.
Venous thromboembolic events	• Routine pharmacovigilance, including Specific Venous Thromboembolism Addendum for post marketing cases PASS (objective: To compare VTE incidence rate in Zoely users with the incidence rate in users of marketed COCs)	Routine activities: As with any combined hormonal contraceptive, Zoely should be used with caution in patients with an enhanced risk to thromboembolic disease. To prevent or minimise the risk of VTE, the risk of VTE is included in the SmPC under: • Contraindications. Zoely is contraindicated for women with the presence or a history of thrombosis. In addition, the presence of severe (e.g., hypercoagulopathies) or multiple risk factors may also constitute a contraindication. • Warning and Precautions • Undesirable effects. An additional sentence in Section 4.8 refers to the warnings and precautions of COCs (containing EE) in the SmPC, including the risk of VTE.
Acne	• Routine pharmacovigilance	Routine activities: Inclusion in the SmPC as Adverse Drug Reaction.
Important Potential Risks		
Cholelithiasis/cholecystitis/elevated hepatic enzymes	• Routine pharmacovigilance • PASS (Cholelithiasis is added as secondary outcome)	Routine activities: To prevent or minimize the risk of cholelithiasis and cholecystitis to occur or deteriorate with combined hormonal contraceptive use, the risk of cholelithiasis and cholecystitis is included in the SmPC under: • Warnings and Precautions. • Undesirable effects. Inclusion of cholelithiasis, cholecystitis, and elevated hepatic enzymes in the SmPC as Adverse Drug Reaction.
Inflammatory bowel disease	• Routine pharmacovigilance • PASS (Inflammatory bowel disease as secondary outcome)	Routine activities: In addition to the SmPC in the Warnings and Precautions, no further actions are deemed necessary.
Breast cancer	• Routine pharmacovigilance	Routine activities: In addition to the SmPC in the Warnings and Precautions, no further actions are deemed necessary.
Cervical dysplasia (class effect, see Section 1.8)	• Routine pharmacovigilance	Routine activities: In addition to the SmPC in the Warnings and Precautions, no further actions are deemed necessary.
Important Missing Information		
Safety in postmenarcheal adolescents	• Routine pharmacovigilance • PASS (objective: To compare VTE incidence rate in Zoely users with the incidence rate in users of marketed COCs)	Routine activities: In the SmPC a statement is included that the safety in adolescents below 18 years has not been established.

Safety in women aged over 50 years	Routine pharmacovigilance	Not applicable. The use in women aged over 50 years is considered to be low due to the proposed therapeutic indication.
Safety in women during pregnancy	• Routine pharmacovigilance • PASS (objective: To follow up pregnancies to neonatal outcome)	Routine activities: In addition to the SmPC in the Warnings and Precautions and in Section 4.6, no further actions are deemed necessary.
Safety in women during lactation	• Routine pharmacovigilance	Routine activities: In addition to the SmPC in Section 4.6, no further actions are deemed necessary.
Safety in women with metabolic dysfunctions	• Routine pharmacovigilance	Routine activities: In addition to the SmPC in the Warnings and Precautions, no further actions are deemed necessary.
Safety in women with a history of or risk factors for VTE and ATE	• Routine pharmacovigilance • PASS (objective: To compare VTE incidence rate in Zoely users with the incidence rate in users of marketed COCs)	Routine activities: The risk of VTE is included in the SmPC under Warnings and Precautions. The presence or a history of thrombosis is included in the Contraindications. In addition, the presence of severe (e.g., hypercoagulopathies) or multiple risk factors may also constitute a contraindication. An additional sentence in Section 4.8 refers to the Warnings and Precautions of COCs (containing EE) in the SmPC, including the risk of VTE.

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.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The readability test of the package leaflet of nomegestrol acetate and estradiol (2.5 mg/1.5mg) consisted of two parts; the first test round consisted of ten face-to-face interviews. Based on the results gathered, a small number of amendments were made to the leaflet. Subsequently, another series of ten face-to-face interviews was carried out (second test round). In total, 16 questions were used to assess the readability of the leaflet: 15 questions relating to traceability and comprehensibility and one additional question assessing traceability and applicability. Taking into account the results, the leaflet was written in a way that most potential users were able to trace, comprehend and apply the information given in the resulting leaflet.

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

The contraceptive effect of new contraceptive pill NOMAC-E2 can be considered demonstrated in an adult population. Sufficient inhibition of ovulation has been shown with NOMAC-E2, as documented in a sufficient number of volunteers. Effects on other efficacy parameters such as endometrial, cervix and vaginal epithelium, and antigonadotropic effect have also been adequately addressed. Two open, randomised, comparative, long term Phase III clinical studies (Study 292001 performed in Europe and Study 292002 performed in the USA) have been conducted to support the evaluation of the contraceptive effect of NOMAC-E2 in adults. Values of Overall Pearl Indexes for NOMAC-E2 in the European study were in the range of PI that were already accepted for other oral contraceptives, i.e. below 1 (0.378 for age group 18-35 years and 0.309 for age group 18-50 years). In the US Study, Overall Pearl Indexes were however significantly higher, above 1.

The CHMP was of the opinion that Pearl Indexes obtained in the EU 292001 study and in the US study 292002 is mentioned separately in the SmPC.

- Uncertainty in the knowledge about the beneficial effects.

Uncertainties on Pearl Index for method Failure
The values of overall Pearl Indexes for NOMAC-E2 in the European study were in the range below 1 (0.378 for age group 18-35 years and 0.309 for age group 18-50 years) however in the US Study, overall Pearl Indexes were above 1. The Applicant clarified why non-compliance to tablet intake was based on days with diary entry 'tablet not taken' and not on the Drug Accountability form. Indeed, the same method for determination of non-compliance should have been used at the numerator and at the denominator.

Uncertainties of the use of NOMAC-E2 in the age class 12-18 years
A single dose PK study was submitted to sustain the use of NOMAC-E2 in this age class, as requested by the PDCO. However, in this study, lower E2 levels were observed in the adolescent population aged 14-17 years compared to an adult population. The estradiol level is an important parameter to be considered in adolescents, as many physiological processes depend on proper estrogens supply (development of bones, sexual organs, sexual appearance). Therefore, no extrapolation of efficacy and safety results as found in the phase III clinical program for adults can be made to the post-menarcheal adolescent population. Thus, an extension of use in this age class cannot be endorsed by the CHMP. Uncertainties have been included in Section 4.4: it is unknown whether the amount of estradiol in NOMAC-E2 is sufficient to maintain adequate levels of estradiol in adolescents, especially for bone mass accrual (with cross reference to section 5.2). The age range is not be included in the claimed indication. Sections 5.1 and 5.2 of the SmPC reflect the available data in adolescents.

Risks

- Unfavourable effects

The safety profile of NOMAC-E2 was sufficiently documented. Both phase III studies included a sufficient number of women with sufficient duration of exposure. No unexpected adverse events emerged with the use of NOMAC-E2. The adverse events reported are known to be associated with the use of oestrogens and progestagens. However, higher incidence of some side effects such as acne, weight increase, lack of withdrawal bleeding, breakthrough bleeding/spotting and psychiatric AEs were observed with NOMC-E2 compared to DRSP-EE. These adverse events have been adequately addressed in the Product information (SmPC and PIL). In addition, the side effects will be adequately followed up in the RMP, either throughout routine pharmacovigilance or specific follow up in the PASS study.

- Uncertainty in the knowledge about the unfavourable effects

Bone Mineral Density
Based on the data from literature, the association between the use of hormonal contraception and BMD is still controversial. Results of clinical Trial 292005 show that NOMAC-E2 (2/5 mg/1.5 mg) had no clinically relevant effect on BMD and there was no statistically significant difference in the effect on BMD between NOMAC-E2 and the LNG-EE in women aged 21-35 years and treated for 26 cycles. For NOMAC-E2, the PK study failed to demonstrate similar AUC 0-tlast for estradiol in adolescents versus adults. The estradiol level is an important parameter to be considered in adolescents, as many physiological processes depend on proper estrogens supply. In particular, it is still controversial how combined contraceptive pills influence the bone mass accrual.

As for all OCs, uncertainties remain of the effect of NOMAC-E2 on bone formation in the youngest population (adolescents). Section 4.4 of the SmPC has been modified to reflect this uncertainty. This issue is part of the important missing information "safety in post-menarcheal adolescents" and will be monitored by routine pharmacovigilance.

- Uncertainties regarding additional claimed Pharmacodynamic properties

The PD properties concerning hepatic effects, and lower impact on SHBG levels and haemostasis parameters due to the use of 17ß-estradiol instead of ethinylestradiol have been identified as issues. A

planned large comparative post-marketing safety surveillance study that will be conducted to assess the VTE risk of NOMAC-E2 compared to other COCs in a non-selected target population is the only way to reliably assess the impact of 17ß-estradiol instead of ethinylestradiol on VTE risk. This is addressed as a specific measure in the Risk Management Plan.

Benefit-risk balance

NOMAC is a highly selective progestin derived from the naturally occurring steroid hormone, progesterone. E2 is identical to the endogenous human E2 and is therefore classified as a natural estrogen. Based on the data, there are no unresolved safety issues; missing information will be addressed by post marketing studies. Clarifications regarding pearl index calculations diagnostic value have been adequately addressed by the applicant and overall safety reports including the EU-RMP and Pharmacovigilance systems have been updated. The benefit-risk balance is favourable for NOMAC-E2.

2.8.1. Discussion on the benefit-risk balance

In summary the benefit-risk balance of Zoely for the claimed indication is considered positive. Questions remain regarding its safety in adolescent population, but these issues are addressed by appropriate labelling. For all identified and potential risks a Post-authorisation Registry study is requested. The aim of this PASS is to better characterise and compare the risk of (short and long term) use of NOMAC-E2 with marketed combined oral contraceptives.

2.8.2. Risk management plan

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, but that no additional risk minimisation activities were required beyond those included in the product information.

2.8.3. Significance of paediatric studies

The CHMP is of the opinion that study, which is contained in the agreed Paediatric Investigation Plan and has been completed after 26 January 2007, is considered significant.

2.9. Recommendation

Normal opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance of Zoely in the following indication:

"*oral contraception*"

was favourable and therefore recommended the granting of the marketing authorisation.

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.