Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Nomegestrol acetate/oestradiol

Proprietary Product Name: Zoely

Sponsor: Merck Sharp & Dohme (Australia) Pty Limited

October 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission:	New Chemical Entity
Decision:	Approved
Date of Decision:	10 August 2011
Active ingredient(s):	Nomegestrol acetate Oestradiol (as hemihydrate)
Product Name(s):	Zoely
Sponsor's Name and Address:	Merck Sharp & Dohme (Australia) Pty Limited 54-68 Ferndell Street South Granville NSW 2142
Dose form(s):	Film coated tablet
Strength(s):	2.5 mg nomegestrol acetate and 1.5 mg oestradiol (as hemihydrate)
Container(s):	Blister pack
Pack size(s):	Pack containing 24 active tablets and 4 placebo tablets
Approved Therapeutic use:	Oral contraception
Route(s) of administration:	Oral
Dosage:	One tablet daily
ARTG Number:	168332

Product Background

This AusPAR describes the evaluation of a submission by Schering-Plough Pty Limited (the sponsor) to register Zoely. Zoely is a novel monophasic oral contraceptive containing 2.5 mg nomegestrol acetate (NOMAC) and 1.5 mg of 17β-estradiol (E2).

NOMAC is a progestogen derived from the naturally occurring steroid hormone progesterone and has strong anti-gonadotropic activity, moderate anti-androgenic activity and anti-oestrogenic effect on the uterus, and is devoid of any estrogenic, glucocorticoid or mineralocorticoid activity. E2 is the natural oestrogen produced endogenously by a woman's ovaries.

The contraceptive effect of NOMAC-E2 is primarily achieved by inhibition of ovulation, an effect which is already achieved by NOMAC (2.5 mg) alone, and increased viscosity of cervical mucus (which hampers sperm entry into the uterus). E2 has been added to restore suppressed oestradiol levels. NOMAC-E2 is given as 24 active tablets followed by 4 placebo tablets (24/4 day regimen). The 24/4 regimen was chosen to provide users with a robust contraceptive method and a better vaginal bleeding pattern (lighter and of shorter duration) as compared to a classical 21/7 regimen. The effect on vaginal bleeding is considered to be the result of the combination of NOMAC and E2.

The primary indication for NOMAC-E2 is oral contraception.

Regulatory Status

The progestogen nomegestrol (NOMAC) is a new product on the Australian market but this progestogen has been available for many years in the European Union (EU).

The two active components have been approved for marketing, either individually or as a combination, in the EU. These products are:

- Estreva tablets (1.5 mg E2); used for oestrogen replacement therapy in menopausal women and for the prevention of osteoporosis;
- Lutenyl tablets (3.75 mg and 5 mg NOMAC); used for menstrual disorders associated with deficient or absent progesterone secretion in premenopausal women, and, in combination with an oestrogen, for the induction of artificial menstrual cycles in postmenopausal women; and
- Naemis tablets (E2 1.5 mg for 10 days and E2 1.5 mg + NOMAC 3.75 mg for the next 14 days); used as a sequential combination for HRT in postmenopausal women with oestrogen deficiency symptoms.

NOMAC-E2 was approved in the EU on July 27 2011. The application submitted to the TGA is identical to that submitted in the EU. It was withdrawn from the USA on 25 August 2009 because the FDA required an additional pharmacokinetic study to be performed to finalise the new drug application (NDA). An application for this product has not been made in Canada.

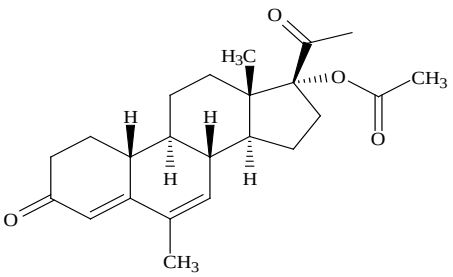
Product Information

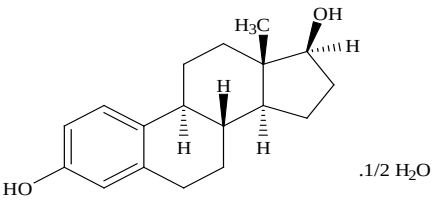
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Nomegestrol acetate is a derived progestogen and a new chemical entity.
Oestradiol is a naturally occurring (endogenous) oestrogen which has been used for many years. Structures are shown below.





nomegestrol acetate
$C_{23}H_{30}O_4$ MW = 370.48
CAS # = [58652-20-3]
aqueous solubility ~0.005 mg/mL (0.0005 %) {practically insoluble}

oestradiol hemihydrate
$C_{18}H_{24}O_2.1/2\ H_2O$ MW = 272.38 (without water)
CAS # = [50-28-2] (without water)
aqueous solubility <0.1 mg/mL (<0.01 %) {practically insoluble}

The nomegestrol acetate is manufactured by Monachem in Monaco. Different polymorphs were found. However, with the synthesis conditions used, only one form is obtained. It is

prepared in a purely synthetic multiple-step process. It has 6 chiral centres but these are very unlikely to invert. It is BCS class II.[1]

The specifications are consistent with the European Pharmacopoeia (EP)/British Pharmacopoeia (BP) monograph for NOMAC and include satisfactory limits for assay and related substances.

The particle size distribution is controlled with limits. However questions were raised about the stability of the polymorphic form and in relation to the particle size distribution limits.

The final solvent used in the synthesis is methanol and this is controlled in line with International Council on Harmonisation (ICH) guidance.

The oestradiol hemihydrate is manufactured by NV Organon at two sites in Oss, Netherlands. It is prepared in a purely synthetic multi-step process. It has 5 chiral centres but these are very unlikely to invert. It is BCS class II.

A European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability was provided indicating compliance with the EP/BP monograph for oestradiol hemihydrate. Even tighter limits were set for known related substances. The control of the particle size distribution was considered adequate.

The final solvent used in the synthesis is ethanol and this is controlled in line with ICH guidance.

Drug Product

The active tablets are manufacture by Organon (Ireland) Ltd. The process (which involves dry blending, compression and film coating) was adequately validated and included appropriate in-process controls.

The tablets are well controlled with expiry limits for both assays and degradants of NOMAC and oestradiol (E2) meeting regulatory requirements.

The proposed product appears stable and no changes were observed on storage. Stability data was provided that supported a shelf life of 3 years when stored below 30ºC in PVC/Al blister packs.

The placebo tablets are very similar to the active tablets except that the active drug substances are replaced with additional lactose, the film coat is yellow instead of white and they are marked ‘p’ instead of ‘ne’.

Biopharmaceutics

Introduction

The Phase III clinical efficacy studies were performed using batch CZ189 (study 292001) and batch CA057 (study 292002).

The proposed tablets for registration differ from the above tablets in a number of ways:

- Most importantly the particle size distribution of the NOMAC will be smaller in the registered tablets (*fine*) compared to the Phase III clinical efficacy study tablets (*coarse*).

[1] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

- The registered tablets will be manufactured using a convection mixer, whereas the Phase III clinical efficacy study tablets were manufactured using a diffusion mixer.
- The film coats of the tablets are slightly different (*registered white active and yellow placebo, clinical white*) but core formulations are the same.

Data Provided

To support registration, two bioavailability studies were provided together with a cross study comparison to determine the absolute bioavailability of nomegestrol acetate (NOMAC) and E2 and a study to investigate the presence of an *in vivo*, *in vitro* correlation (IVIVC) between the dissolution and bioavailability of NOMAC.

Results

Study 02-TX-127066-1-RD compared the bioavailability of a tablet with and without food (high fat meal) and also to a capsule formulation (used in Phase II). The tablets were as per the Phase III clinical efficacy studies but uncoated. However given the results of study P06328 it was accepted that the study is relevant to the proposed tablets. The results indicated that food increased the bioavailability of NOMAC by 25-30% and may or may not have changed the bioavailability of E2 as, although the point estimates are close to 1, the confidence intervals are outside of 0.80-1.25. The bioavailability of oestrone, the primary metabolite of E2 was increased by 20%.

Study P06328 compared a tablet for registration (batch CD078) to batches CZ189 and CA057 used in the Phase III clinical efficacy studies 292001 and 292002 (respectively) in a two part design (Part I was comparing batch CZ189 with CD078 and Part 2 was the comparison between batch CA057 and batch CD078). The results indicated that:

- With respect to the pharmacokinetic profiles of E2, the commercial tablet was bioequivalent to the tablets used in the Phase III efficacy studies and there were no statistical difference in the maximum plasma concentration (C_{max}) and the area under the plasma concentration time curve (AUC) responses from the commercial tablet and the tablets used in the Phase III clinical efficacy studies.
- With respect to the pharmacokinetic profiles of NOMAC, there were statistical differences in the C_{max} and AUC responses from the commercial tablet compared to the tablets used in the Phase III clinical efficacy studies but this did not lead to the AUC responses being outside the range for bioequivalence (106.4-113.7 compared to batch CZ189 and 100.9-105.7 compared to batch CA057).
- However this did lead to the C_{max} responses being outside this range for Part 1, but not Part 2 (131.0-144.4 compared to batch CZ189 from study 292001 and 107.5-116.4 compared to batch CA057 from study 292001). The sponsor stated that this increase in C_{max} has no clinical relevance.
- If follows from the above that batch CA057 of tablets will have a higher C_{max} than batch CZ189 of tablets (ratio calculated to be 1.23). Hence, if the safety profile observed in the clinical efficacy study 292002 performed with batch CA057 of tablets (where C_{max} was bioequivalent to the proposed tablets) was similar to that observed in the clinical efficacy study 292001 performed with batch CZ189 of tablets (where C_{max} was not bioequivalent), the proposed particle size distribution limits for the 'fine' NOMAC used in the commercial tablets will be acceptable (see above).
- It was noted that some subjects in this study returned high pre-dose E2 levels most likely related to fluctuations in endogenous E2 levels in one of the four treatment periods. Though this observation does not affect the conclusions to the

study, the sponsor put forward untested hypotheses for these results which were brought to the attention of the Delegate.

Absolute Bioavailability

The sponsor provided a cross study comparison to estimate the absolute bioavailabilities of NOMAC and E2 from the tablets. The absolute bioavailability of NOMAC was estimated to be 63% and that of E2 5% prior to base line correction and 0.8% after baseline correction. However it was argued that the result for E2 was not accurate and an estimate of 1-5% was a better conclusion. This is reasonable and the Draft PI cites a figure of 5%.

In Vivo, In Vitro Correlation (IVIVC)

The sponsor attempted to determine if there was any *in vivo*, *in vitro* correlation (IVIVC) between the dissolution and bioavailability of NOMAC.

- In study 292007 subjects were administered tablets manufactured with 'coarse', 'fine' and 'micronised' NOMAC. The study design was underpowered to determine bioequivalence in that only 6 subjects received each treatment (3 received treatments A and B, 3 received B and C, etc). There was no correlation between AUC results and the dissolution of NOMAC using the proposed dissolution test method. Further, although there was an increase in C_{max} with increasing dissolution, there was no correlation between the C_{max} results and the dissolution of NOMAC using the proposed dissolution test method.
- Following, the outcome of Study P06328, this was again investigated against a different dissolution test method (which slowed the dissolution rates). It was then concluded that there was a multiple Level C correlation of C_{max} with the dissolution at 15, 60 and 120 minutes and that a Level A correlation was likely though all requirements of FDA guidance (and EU guidance) were not met. Further, as the dissolution method used was different to that proposed for routine control, the correlation cannot be used to support future changes and there was no correlation of dissolution to AUC.

Bioavailability in Relation to the Product Information Document (PI)

The results of study 02-TX-127066-1-RD are at odds with statement that the tablets can be taken 'without regard to meals'. The sponsor stated that observed and possible food effects are not clinically relevant.

The absolute bioavailabilities cited in the PI are supported by the results of the cross study comparison.

Advisory Committee Consideration

This application was initially presented to the 135th meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) in November 2010. The PSC was unable to recommend approval for registration due to the deficiencies in the data provided. In particular the Committee had concerns regarding:

- The particle size distribution of NOMAC (partially resolved by study P06328, but dependant on the safety profiles of studies 2929001 and 292002).
- Whether the proposed tablet was bioequivalent to those used in the clinical efficacy studies (study P06328 was provided).
- The stability of the polymorphic forms of the drug substances within the tablets (appropriate data was provided).

- The stability of the tablet as proposed for registration (appropriate data was provided).

The PSC also had concerns on the use of a cross study comparison for the estimation of the absolute bioavailabilities (but accepted the sponsor's estimates) and noted that while the population pharmacokinetic analyses were acceptable, it would have been helpful if the "covariate" for dissolution rate was also explored.

Following the receipt and evaluation of Study P06328 (and responses to other issues), the application was re-presented at the 137th meeting of PSC in March 2011. The Committee agreed that the attention of the Delegate should be drawn to the increased C_{max} observed in Study P06328 for the tablet proposed for registration compared to the tablets used in clinical efficacy studies.

Quality Summary and Conclusions

Approval of this submission was recommended with respect to chemistry and manufacturing control but only if the safety profile observed in the clinical efficacy study performed with batch CA057 of tablets was similar to that observed in the clinical efficacy study performed with batch CZ189 of tablets. Specifically, if the safety profiles are worse in study 292001 than study 292002, the proposed particle size distribution limits of NOMAC will not be acceptable.

With respect to bioavailability:

The results of study P06328 indicate that the proposed tablets for registration CD078 are:

- bioequivalent to the tablets used in the clinical efficacy studies (batch CZ189 from study 292001 and batch CA057 from study 292002) with respect to the rate and extent of E2,
- bioequivalent to the tablets used in the clinical efficacy studies with respect to the extent of NOMAC,
- bioequivalent to tablet CA057 used in the clinical efficacy study 292002 with respect to the rate of NOMAC,
- not bioequivalent to tablet CZ187 used in the clinical efficacy study 292001 with respect to the rate of NOMAC.
    - This is due to the different particle size distributions of the drug substance used in the batches and leads to the qualified recommendation for approval with respect to chemistry and manufacturing control.

The results of study 02-TX-127066-1-RD are at odds with statement that the tablets can be taken 'without regard to meals'. The sponsor stated that observed and possible food effects are not clinically relevant.

III. Nonclinical Findings

Introduction

The general quality of the submitted studies was high. All of the pivotal safety related studies were compliant with Good Laboratory Practice (GLP) except for the chronic (12 month) repeat dose toxicity study in monkeys. This study was, however, conducted in an established laboratory and adequately documented. Reflecting NOMAC's initial development as a single agent to treat menstrual disorders (registered overseas), in consideration of oestradiol's long history of clinical use and consistent with the TGA-adopted EU guideline on fixed combinations, the submitted nonclinical studies were

mostly performed with NOMAC alone.[2] Studies with NOMAC and oestradiol (E2) in combination dealt with single dose toxicity, repeat dose toxicity (up to 3 months duration in mice, rats and monkeys) and reproductive toxicity. These involved administrations at either the proposed 0.6:1 E2: NOMAC dose ratio or a 0.4:1 ratio.

Pharmacology

Primary pharmacodynamics

An extensive set of *in vitro* and *in vivo* pharmacology studies was submitted; most of the studies were at least 20 years old. NOMAC was characterised as a full agonist at the progesterone receptor. Nanomolar affinity was demonstrated in radioligand binding assays with human, rat and rabbit isoforms of the receptor. In *in vitro* functional assays with Chinese hamster ovary (CHO) cells transfected with human progesterone receptors, the potency of NOMAC was comparable to levonorgestrel and 20 times greater than dienogest. Of relevance to the proposed clinical use (contraception), inhibition of ovulation following treatment with orally administered NOMAC was shown in the rat and monkey and in reproductive toxicity studies in rats, treatment with NOMAC combined with E2 (in the dose ratio proposed for Zoely) abolished fertility, with full reproductive capacity restored after a 1 to 2 week treatment free period. Progestogenic activity was also evident in other *in vivo* experiments (conducted in the rat or rabbit) as maintenance of gestation, stimulation of uterine decidualisation and endometrial development and apparent (but seemingly weak) pituitary suppression.

Four of the seven NOMAC metabolites identified in humans were assayed for progesterone receptor binding, with no or low (14 to 29 times weaker compared with NOMAC) affinity found.

Secondary pharmacodynamics

In vitro functional studies in HeLa cells (a human cervical carcinoma cell line) or CHO cells transfected with human steroid receptors showed NOMAC (concentrations up to 0.1 µM or more) had no agonist or antagonist activity at alpha or beta oestrogen or mineralocorticoid receptors; no or weak antagonist activity at glucocorticoid receptors; weak antagonist activity at androgen receptors (1.8 times less potent than cyproterone acetate in this case) and even weaker agonist activity at androgen receptors. Consistent with this, NOMAC (at progestogenic doses) had no or negligible direct oestrogenic, androgenic, mineralocorticoid or anti-mineralocorticoid activity in other *in vitro* or short term *in vivo* assays.

NOMAC inhibited the oestrogen induced stimulation of progesterone receptor expression in T47-D human breast cancer cells *in vitro* and in the rabbit uterus *in vivo*. Anti-oestrogenic activity was also evident as inhibition of E2 induced vaginal cell cornification in rats and of E2 induced uterine hypertrophy in mice and monkeys. Given the *in vitro* finding of no direct interaction of the drug with the oestrogen receptor, the anti-oestrogenic activity seen presumably reflects down regulation of the oestrogen receptor mediated by progesterone receptor activation. The drug did not interfere with the beneficial effects of E2 on bone density in ovariectomised rats or on vascular reactivity in ovariectomised monkeys.

Anti-androgenic activity was demonstrated in several studies in castrated rats where NOMAC inhibited testosterone induced proliferation of male reproductive tissues (cyproterone acetate was about 20 times more potent in this respect). NOMAC also showed some potential to disrupt lipid and glucose metabolism or cause insulin resistance

[2] EMEA, Committee for Medicinal products for Human Use (CHMP), 24 January 2008. Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products, CHMP/SWP/258498/2005.

in rats or rabbits (medroxyprogesterone acetate or progesterone were more potent in this respect). NOMAC did not affect blood clotting factors in ovariectomised rats.

Safety pharmacology

An adequate set of safety pharmacology studies was conducted. NOMAC showed no effects on the cardiovascular system in dogs (≤2.5 mg/kg intramuscular [IM]) or monkeys (≤80 mg/kg oral [PO]) and no significant effect on the respiratory system in guinea pigs (≤20 mg/kg/day PO). Slight acceleration of gastrointestinal transit was observed in rats with NOMAC at 50 mg/kg PO (and with progesterone at the same dose), but not at 2 or 10 mg/kg. A weak anticonvulsant effect (as reported with other progestogens) was seen in mice at 1000 mg/kg PO. Inhibition of the hERG K^+ channel by NOMAC was observed but was weak, with 36% inhibition observed at 10 μM (~300-times the clinical C_{max}). The electrocardiogram (ECG) was unaffected in monkeys at NOMAC doses up to 80 mg/kg PO (yielding peak plasma levels >40 times higher than the clinical C_{max}).

Pharmacokinetics

Absorption of NOMAC after oral dosing was rapid in mice, rats and cynomolgus monkeys, with peak plasma concentrations reached within 0.25–2 hours (h). Absorption was similarly rapid in humans, with the C_{max} for NOMAC observed at 1.5–2 h post dose in women given the recommended clinical dose of the NOMAC/E2 combination. Much slower absorption was evident in dogs (time to maximum plasma concentration [T_{max}], almost 7 h). Absolute oral bioavailability was not assessed in animals. Plasma AUC was dose proportional (mice, rats, monkeys) and consistently higher in female animals compared with males. Coadministration of E2 did not appear to have a significant effect on exposure to NOMAC (assessed in mice and rats). Clearance of NOMAC was considerably faster in the laboratory animal species, particularly rodents, compared with humans.

Plasma protein binding by NOMAC was high in all species (mouse, rat, rabbit, monkey and human). Binding to human serum albumin was very high (97%); no binding to sex hormone binding globulin or corticosteroid binding globulin was found. Widespread tissue distribution of radioactivity was observed in rats and monkeys following PO administration of ^{14}C-NOMAC; transfer across the blood brain barrier and the placenta was seen. There was no evidence for particular target organs for accumulation or retention of drug associated material. NOMAC was identified as a weak substrate and inhibitor of P-glycoprotein in experiments with Caco-2 cells; the median inhibitory concentration (IC_{50}) was 3.42 μM (>100 times the clinical C_{max}).

Metabolism of NOMAC involved hydroxylation at various sites and subsequent conjugation (glucuronide or sulphate) and was faster and more extensive in animals compared with humans. Seven phase I metabolites were identified in total and all of those found in human plasma were also identified as circulating metabolites in rats except for 2β-hydroxy-NOMAC (Metabolite 5'; TX 256). This is a relatively minor metabolite though (present at 5% of the level of the parent compound), detected *in vitro* in incubations with rat liver microsomes and is structurally related to another circulating metabolite that was formed in both species (that is, it is a spatial isomer of Metabolite 5 [TX 255; 2α-hydroxy-NOMAC]). No data on the potential progestogenic activity of the 2β-hydroxy metabolite was submitted. It should be noted, though, that a 14 fold reduction in progesterone receptor affinity was found for 2α-hydroxy NOMAC and while major differences in activity profile between stereoisomers are known to occur, this is not necessarily always the case. Other hydroxylated metabolites were also significantly less active than the parent. Metabolites (apart from nomegestrol [deacetylated derivative]) were not identified in monkeys, although metabolite profiles following incubation with monkey and human liver microsomes were seen to be qualitatively similar *in vitro*. Roles for human cytochromes

P450 (CYPs) 2C19, 3A4 (and possibly 3A5) and 2C8 in the metabolism of NOMAC were identified in *in vitro* studies. No or negligible inhibition of human CYPs 1A2, 2A6, 2C8, 2C9, 2D6, 3A4, 3A4/5, 2B6, 2C19 and 2E1, and no induction of CYP1A2 or CYP3A4, were seen with NOMAC at concentrations up to 120 ng/mL (almost 10 times the clinical C_{max}). Urine and faeces were both major routes of excretion (with faeces modestly greater) in rats, monkeys and humans, with little NOMAC excreted unchanged. Biliary excretion was shown in monkeys.

Based on comparisons of the pharmacokinetic profile of NOMAC across species, sufficient similarities exist to allow the laboratory animal species used in the pivotal repeat dose toxicity studied (rats and monkeys) to serve as appropriate models for the assessment of NOMAC toxicity in humans, noting, though, their limitation with respect to revealing any toxicity attributable to the unique circulating human metabolite 2β-hydroxy-NOMAC.

Toxicology

Acute toxicity

Single dose toxicity studies were conducted with NOMAC alone (PO and intraperitoneal [IP] routes) and in combination with E2 (PO only) in mice and rats. The observation period was 14 days, in accordance with the relevant TGA-approved EU guideline. Findings following oral administration at a total dose of 2000 mg/kg were largely unremarkable, limited to transient hypoactivity/sedation. IP doses of up to 705 mg/kg in mice and 385 mg/kg in rats were non-lethal. The studies indicate low potential for adverse effects in overdose.

Repeat dose toxicity

Repeat dose toxicity studies by the PO route were conducted with NOMAC alone in mice (13 weeks duration), rats and monkeys (up to 12 months in each species) and with NOMAC in combination with E2 in mice, rats and monkeys (up to 13 weeks in each species). The definitive studies were of adequate quality and appropriate design. These involved animals of both sexes for testing of single agent NOMAC and females only for the combination (acceptable given the indication).

Relative exposure

Exposure ratios have been calculated for the repeat dose oral toxicity studies based on animal:human area under the plasma concentration time curves from time zero to 24 hours (AUC_{0-24h}) values for NOMAC (Table 1). Quantitation of NOMAC in animal plasma was by a specific assay or (more often) a non-specific assay that cross reacted with the NOMAC metabolites. The use of the non-specific assay meant that substantial extrapolation and assumptions about the relative amounts of NOMAC and metabolites were required and therefore many of the NOMAC exposure data provide a rough indication of the general order of magnitude of exposure rather that an actual measure. Significant multiples of the clinical exposure to NOMAC were achieved in animals. Given the greater metabolism of NOMAC in animals, exposure ratios for the drug's metabolites (except for 2β-hydroxy-NOMAC [Metabolite 5']) are likely to be higher than for NOMAC.

Table 1: Relative exposure ratios for NOMAC

Species	Study	Treatment duration	Dose [NOMAC or oestradiol/NOMAC] (mg/kg/day); PO	NOMAC			
				AUC_{0-24h} (ng·h/mL)		Exposure ratio*	
				Males	Females	Males	Females
Mouse (CD-1)	LUT 3-29 [a]	13 weeks#	5	50	108	0.5	1.0
			10	110	256	1.0	2.4
			20	237	434	2.2	4
Mouse (Swiss)	801110	13 weeks	0.3 / 0.5	–	4.7	–	0.04
			2.4 / 4	–	44	–	0.4
			19.2 / 32	–	609	–	6
			0 / 32	–	728	–	7
Mouse (CD-1)	LUT 3-56-A (a) [carcinogenicity]	85–87 weeks#	3.2	29	56	0.3	0.5
			8	88	205	0.8	1.9
			20	237	434	2.2	4
			50	821	1615	8	15
Rat (OFA)	LUT 3-13-01 (b)	2 months#	0.2	–	55	–	0.5
			1	–	223	–	2.1
			5	969	1183	9	11
Rat (F344)	LUT 3-22 (c)	12 months#	0.5	39	68	0.4	0.6
			3	208	322	2.0	3.0
			20	1212	1578	11	15
Rat (Sprague Dawley)	NOM OEST 3-05	4 weeks	0.15 / 0.375	–	14	–	0.1
			1.2 / 3	–	284	–	2.7
			9.6 / 24	–	2243	–	21
	NOM OEST 3-07	13 weeks	0.15 / 0.375	–	18	–	0.2
			1.2 / 3	–	356	–	3.4
			9.6 / 24	–	2776	–	26
	801111	13 weeks	0.15 / 0.25	–	38	–	0.4
			1.2 / 2	–	206	–	1.9
			9.6 / 16	–	1536	–	14
			0 / 16	–	2958	–	28
	LUT 3-28-01 (b) [carcinogenicity]	2 years#	0.2	23	55	0.2	0.5
			1.5	278	335	2.6	3.2
			10	1938	2366	18	22
Monkey (Cynomolgus)	LUT 3-17-01 (d)	12 months	0.5	16	21	0.2	0.2
			3	60	95	0.6	0.9
			20	303	371	2.9	3.5
	NOM OEST 3-04	4 weeks	0.12 / 0.3	–	0.8	–	0.01
			0.72 / 1.8	–	3	–	0.03
			4.32 / 10.8	–	53	–	0.5
	NOM OEST 3-06	13 weeks	0.72 / 1.8	–	18	–	0.2
			2.16 / 5.4	–	257	–	2.4
			6.48 / 16.2	–	1144	–	11
Human	292006	steady state	[2.5 mg NOMAC + 1.5 mg oestradiol]	–	106	–	–

* = calculated as animal:human plasma AUC_{0-24h}; # = dietary administration; – = not applicable; a = based on Day 26–27 data, assuming NOMAC accounted for 50% of total immunoreactivity; b = based on Day 26–27 data, assuming NOMAC accounted for 40% of total immunoreactivity; c = based on Day 26–27 data, assuming NOMAC accounted for 40% of total immunoreactivity; d = data extrapolated from Day 28 data, assuming NOMAC accounted for 15% of total immunoreactivity.

In the 13 week studies with the combination, plasma AUC_{0-24h} values for E2 measured at the end of the treatment period were up to 2.2 times (mice), 6 to 10 times (rats) and 72 times (monkeys) that of women receiving the clinical dose. Considerable variation was observed in E2 measurements, which were confounded by endogenous oestrogen in some cases, making them of little quantitative value. In any case, significant exposure to the hormone was evident based on findings of clear oestrogenic effects in the animal studies.

Higher maximum doses of NOMAC could have been used in the pivotal (12 month) studies in both rats and monkeys. This is not a major pitfall of the studies, though, as the target organs have been clearly identified.

Major findings

A summary of the major changes is shown in Table 2.

Table 2: Summary of major changes observed in toxicity studies

Target	NOMAC alone	NOMAC + Oestradiol
Clinical signs (general condition)	None or obesity	Alopecia
Body weight gain	Increased consistently	Decreased (lower combination doses) or increased (higher doses)
Female reproductive tissues	Atrophic changes, reduced corpora lutea, oestrus cycles stopped/reduced menstrual bleeding, decreased ovary and uterus weights and endometrial hyperplasia	Atrophic or, at higher oestradiol doses, hyperplastic changes; vaginal mucification; inhibition of ovulation
Male reproductive tissues	↑ secretory activity in prostate; prostatitis or atrophy of prostate and seminal vesicles; ↓ cellularity in testes; ↓ spermatozoa in epididymides	Not assessed
Mammary gland	Hyperplasia (acinar cell), increased secretions	Hyperplasia, increased secretions
Adrenal gland	Hypertrophy (Δ cortical cell vacuolation), increased organ weight.	Hypertrophy (cortical cell vacuolation); ↑ or ↓ increased organ weight
Thyroid gland	Follicular atrophy	Cell hypertrophy
Pituitary	No changes reported in repeat-dose toxicity studies (but limited investigation); ↓ activity and number of gonadotrophic cells reported in rat carcinogenicity study	Hypertrophy/hyperplasia; ↑ prolactin, ↑ adrenocorticotrope and ↓ gonadotropin secretion/cells
Thymus	Atrophy, ↓ weight	Atrophy, ↓ weight
Spleen	↓ weight	↓ weight and cellular changes (lymphoid depletion, extramedullary haematopoiesis)
Liver	Hypertrophy; bile duct hyperplasia, pericholangitis, "tension lipidosis"	Hypertrophy; bile duct hyperplasia, pericholangitis
Kidney	↓ or ↑ weight, papillary nephrocalcinosis, pyelonephritis/pyelitis.	Lipofuscines present, pyelonephritis/pyelitis.
Clinical chemistry	No consistent or toxicologically significant effects	Shifts in ALP, ALT, AST, GGT, albumin, phosphorus, triglycerides, glucose, total lipids and/or cholesterol levels
Haematology	No consistent or toxicologically significant effects	↓ red and white blood cell counts and/or volume, ↑ platelets and coagulation elements
Other parameters	No notable changes observed for urinalysis, ophthalmology or cardiovascular parameters in studies where these were investigated	

Effects observed with NOMAC or with the combination were broadly similar across species. Pharmacological activity, as indicated by cyclic arrest and progestogenic changes in reproductive tissues, was evident at virtually all doses in the various studies. All of the above effects have been observed previously in animal studies with progestogens and progestogen/oestrogen combinations. Alopecia, decreases in body weight, and haematological and biochemical changes observed with the combination are attributable to oestrogenic activity.

Mammary gland stimulation, while not a novel finding, was more strikingly apparent in the studies with NOMAC than is typically found in nonclinical studies with progestogens, particularly those thought to have no oestrogenic activity. This was characterised by hyperplasia in rats and increased secretory activity (but not hyperplasia) in monkeys. These effects were seen at all dose levels in the pivotal 12 month studies (that is, at ≥0.5 mg/kg/day in rats and monkeys [relative exposure in the respective species, 0.6–15 and 0.2–3.5]) and were only partly reversed (rats) or persistent (monkeys) at the high dose levels following treatment free periods of 9–12 weeks. Increased body weight gain, observed in rodents (but not clearly in monkeys), also appeared to be more prominent in the studies with NOMAC. While accompanying pituitary changes were not observed in the pivotal 12 month studies, investigations were limited (and cellular changes were observed in the pituitary in the rat carcinogenicity study with NOMAC using specialised staining). Hormone levels were not monitored in any of the studies. In studies with the combination, lactating mammary glands (4 week study; 9.6/24 mg/kg/day E2/NOMAC), increased mammary gland development (13 week study; ≥0.15/0.375 mg/kg/day; reversible within 4 weeks) and mammary gland hyperplasia (13 week study; ≥1.2/2 mg/kg/day and with NOMAC alone at 16 mg/kg/day) were observed in rats and increased mammary gland development was observed in monkeys (13 week study; ≥0.72/1.8 mg/kg/day; reversible within 6 weeks). In the 13 week rat study using a 0.4:1 dose ratio, specific investigations showed an increase in prolactin and adrenocorticotropin cells and a decrease in gonadotrophin cells in the pituitary. Pituitary gland changes (increased prolactin cells and secretion and decreased somatrope cell activity) were also seen in the 13 week monkey study with the combination. In mouse studies, mammary gland atrophy was found in a 13 week dietary study with NOMAC alone at 20 mg/kg/day (relative exposure, 4), while no effects on the mammary gland were found in a 13 week study using gavage administration where NOMAC was given at a higher dose (32 mg/kg/day) alone or in combination with E2 (relative exposure to NOMAC, 6–7). Mammary gland findings are further discussed under *Carcinogenicity* below.

Genotoxicity

NOMAC was negative in a full set of adequately conducted genotoxicity assays, comprising tests for bacterial and mammalian mutagenicity, yeast mitotic gene conversion, chromosomal aberrations and unscheduled DNA synthesis *in vitro* and clastogenicity *in vivo* (mouse and rat bone marrow micronucleus tests). No new studies with E2 or studies with NOMAC and E2 in combination were submitted but these are not required.

Carcinogenicity

Studies were conducted for carcinogenicity with NOMAC alone (administered via the diet) in mice and rats. These were appropriately designed and adequately conducted. Treatment duration was 2 years in rats and 86 (males) or 88 weeks (females) in mice. The mouse study was scheduled to continue for 104 weeks but was terminated early due to poor survival; the duration still exceeds the minimum recommended under the relevant TGA-adopted EU guideline (18 months) and the validity of the study was not affected.

There was no evidence for an association between treatment with NOMAC and tumour development or rate of tumour development in rats (≤10 mg/kg/day; relative exposure, ≤18 in males and ≤22 in females). All doses were pharmacologically active in both sexes. Higher doses could have been used in the study as treatment was well tolerated but the selected high dose level did yield an exposure ratio close to the figure of 25 recommended under ICH guidance. Interestingly, mammary gland stimulation was not found in this study at exposure levels higher than those associated with hyperplasia in the shorter term studies.

Treatment with NOMAC increased the incidence of mammary gland carcinomas in female mice at doses ≥20 mg/kg/day (relative exposure, ≥4) and this was responsible for decreased survival. Female mice treated at 50 mg/kg/day (relative exposure, 15) also showed an increase in the incidence of pituitary adenomas. Treatment related tumours were not observed in male mice. Relative exposure at the No Observable Effect Level (NOEL) for carcinogenicity in the mouse (8 mg/kg/day) is 1.9. The findings are consistent with extensive endocrine disruption and have been observed with various other progestogens (administered without an oestrogen) in rodents.

Assessment of the human relevance of findings of mammary gland tumourigenicity in rodents is complicated by significant species differences in hormonal regulation and function. Mammary neoplasms are common spontaneous tumours in many strains of rodents and can be induced quite readily with alteration of hypothalamic-pituitary-gonadal function. Mammary gland tumourigenesis by progestogens in rodent species is thought to involve hyperstimulation of mammary tissue through elevation of endogenous oestrogen and prolactin levels; prolactin stimulates the development of corpora lutea, which results in high endogenous progesterone levels, compounding disruption of hormonal homeostasis. Prolactin apparently does not have this effect in primates. The monkey mammary gland is considered a better model for humans, based on the closer resemblance in terms of physiology and anatomy. As noted above, NOMAC did not cause proliferative changes in the mammary gland of cynomolgus monkeys with treatment at up to 20 mg/kg/day for 12 months (relative exposure, ≤3.5). In addition, NOMAC (≤1 μM) was shown not to stimulate the proliferation of the human breast cancer cell lines MCF-7 and T47D:A18 *in vitro* in a published study[3].

No carcinogenicity studies with NOMAC in combination with E2 were conducted. Given the existing data, that pharmacologically equivalent combinations are registered, and the predictive value of such studies being low, this is considered acceptable.

Reproductive toxicity

An extensive set of reproductive toxicity studies was submitted. Pivotal studies covered effects of NOMAC with and without E2 on fertility and early embryonic development in rats and on embryofetal development in rats and rabbits and effects of NOMAC alone on pre/postnatal development in rats and monkeys. The fertility studies did not involve treatment of males; this is acceptable given the indication. Standard study designs were appropriately modified to avoid the expected NOMAC induced impairment of fertility and parturition, thereby allowing effects on all stages of development to be assessed (that is, treatment was temporarily suspended at critical times such as the mating phase or just prior to parturition in the various studies).

A study in monkeys showed NOMAC crosses the placenta, with fetal plasma levels comparable to maternal levels. No nonclinical studies were conducted to determine if

[3] Catherino WH, Jordan VC. Nomegestrol acetate, a clinically useful 19-norprogesterone derivative which lacks estrogenic activity. J Steroid Biochem Mol Biol 1995; 55: 239–246.

NOMAC and/or its metabolites are excreted in milk; however, some excretion is assumed to be probable.

NOMAC alone or in combination with E2 inhibited oestrus cycling in rats (as expected), causing infertility which was reversible within 1–2 weeks. Embryolethality, evident as marked increases in post implantation loss (mainly early resorptions) and increased abortions, was observed in rats treated with E2 alone (≥1 mg/kg/day) and E2 (4 or 10 mg/kg/day) in combination with NOMAC (2.4 mg/kg/day; relative exposure, ≥3) but not with NOMAC alone (10 mg/kg/day; relative exposure, 15). No adverse effects on fetal development were found with NOMAC alone in rats (≤10 mg/kg/day; including no evidence for masculinisation of the female fetus), while decreased fetal weight, feminisation of male fetuses, malformations (cleft palate and bent tail) and increased fetal variations (bifid centrum in thoracic vertebrae, wavy ribs and incomplete ossification at several sites) were observed with the combination (in conjunction with maternotoxicity). In rabbits, embryolethality was observed with single agent NOMAC at 8 mg/kg/day and with the combination at ≥0.5/0.83 mg/kg/day E2/NOMAC. Treatment with NOMAC at 6 mg/kg/day did not affect fetal development in the species, while the combination decreased fetal weight (at all doses; ≥0.1/0.17 mg/kg/day E2/NOMAC) and reduced the proportion of male fetuses (≥0.5/0.83 mg/kg/day); teratogenicity was not observed in the rabbit. NOELs for effects on embryofetal development in studies with the combination were 0.6/1 mg/kg/day E2/ NOMAC in the rat (relative exposure to NOMAC, 0.2–1.0) and <0.1/0.17 mg/kg/day in the rabbit (relative exposure, <0.1).

Pre/postnatal development studies were conducted in rats and monkeys with NOMAC alone. Treatment was suspended from the day before expected parturition in the definitive studies because of the known inhibitory effect that progestogens have on uterine contractions (prolonged, difficult or failed parturition were observed with the drug in pilot studies in rats). No effects on offspring development were observed at doses up to 10 mg/kg/day in rats (including on reproductive function; estimated relative exposure, 15) or in monkeys at 15 mg/kg/day (estimated relative exposure, 2.6).

As with other oral contraceptives, Zoely is to be contraindicated in pregnancy and not recommended for use during lactation.

Pregnancy classification

The sponsor proposed Pregnancy Category B3. This was in accordance with the nonclinical findings and matched the categorisation of other combined oral contraceptives.

Use in children

No relevant nonclinical data were provided.

Nonclinical Summary and Conclusions

NOMAC was shown to possess nanomolar affinity for the progesterone receptor and act as a full agonist. Progestogenic activity was also demonstrated in various *in vivo* experiments. Of relevance to contraceptive use, oral treatment with NOMAC was shown to inhibit ovulation in rats and monkeys. Abolition of fertility in rats treated with NOMAC and E2 in combination was fully restored within 1–2 weeks following the withdrawal of treatment. The demonstration of inhibition of ovulation and fertility, support the product's use as a contraceptive.

Secondary pharmacodynamic studies revealed no agonist or antagonist activity for NOMAC at oestrogen or mineralocorticoid receptors, no or weak antagonist activity at glucocorticoid receptors and weak antagonist activity at androgen receptors. NOMAC did

not interfere with the beneficial effects of E2 on bone density or vascular reactivity in ovariectomised rats and monkeys. Safety pharmacology studies covered the central nervous system (CNS), cardiovascular, respiratory and gastrointestinal systems, with only slight/weak effects observed. Effects observed with NOMAC (hERG K^+ channel inhibition, anticonvulsant activity and acceleration of gastrointestinal transit) were slight/weak and are not considered to indicate risks relevant to clinical use.

Pharmacokinetic studies indicated rapid absorption of NOMAC in mice, rats, monkeys and humans. Plasma AUC was dose proportional. Clearance was considerably faster in the laboratory animal species compared with humans. Plasma protein binding by NOMAC was high in animals and humans; no binding to sex hormone binding globulin or corticosteroid binding globulin was found. PO administration of radiolabelled NOMAC resulted in widespread tissue distribution in rats and monkeys. Metabolism of NOMAC involved hydroxylation at various sites and subsequent conjugation, with roles for human CYPs 2C19, 3A4 (and possibly 3A5) and 2C8 identified. Excretion was via both urine and faeces, with little NOMAC excreted unchanged.

NOMAC alone and in combination with E2 displayed a low order of acute oral toxicity in mice and rats.

Pivotal repeat dose toxicity studies were conducted with NOMAC alone in rats and monkeys (12 months duration), supplemented by 3 month studies with the combination. Findings in the repeat dose studies were consistent with those seen previously in animal studies with progestogens and progestogen/oestrogen combinations. Mammary gland stimulation by NOMAC (hyperplasia in rats and increased secretory activity in monkeys) did appear to be more striking than typical however (in terms of incidence and persistence following treatment withdrawal). Repeat dose toxicity studies revealed only class effects of progestogens and oestrogens. Treatment was well tolerated. Mammary gland stimulation by NOMAC in the repeat dose studies was more striking compared to typical progestogens but was not of a proliferative nature in primates.

NOMAC was negative in a full set of assays for genotoxicity. NOMAC was not carcinogenic in a 2 year dietary study in rats, while increases in the incidence of mammary gland carcinoma and pituitary adenoma were observed in female mice receiving NOMAC in the diet for 88 weeks. Positive findings with NOMAC in the mouse carcinogenicity study (increased mammary gland carcinoma and pituitary adenoma) were consistent with extensive endocrine disruption and have been observed with other progestogens. Rodents are poor models for carcinogenicity with such hormonal agents owing to substantial differences in reproductive physiology compared with humans. Ultimately, assessment of the product's carcinogenicity will rely on human epidemiological data.

Placental transfer of NOMAC was demonstrated in the monkey; excretion in milk was not investigated. NOMAC and E2 in combination had adverse effects on embryofetal development in the rat and rabbit, including embryolethality, teratogenicity, feminisation of male fetuses and decreased fetal weight. Consistent with its progestogenic activity, NOMAC alone delayed and impaired parturition in rats. Postnatal development was unaffected by NOMAC in rats and monkeys. Findings of significant adverse effects on embryofetal development in rats and rabbits receiving the combination, with exposure to NOMAC at the NOELs similar or less than the clinical exposure level, support the proposed contraindication in pregnancy.

There were no nonclinical objections to the registration of Zoely for the proposed indication.

IV. Clinical Findings

Introduction

The clinical Phase III program was initiated in May 2006. The program included two controlled, pivotal efficacy and safety trials (292001 and 292002). These two trials together were designed to provide a sufficient number of evaluable cycles of exposure to obtain evidence of contraceptive efficacy and sufficient general safety data. In addition, the clinical Phase III program included three clinical pharmacology trials (292003, 292004 and 292005). Four additional Phase I trials (292006, 292007, 292008 and 292011) within the Phase III development program were initiated to complete the clinical development for the contraceptive application of NOMAC-E2.

Pharmacokinetics

Introduction

The section describing the pharmacokinetics of oral NOMAC-E2 consists of a total of 38 human studies. There are 26 pharmacokinetic (PK) studies including two intravenous studies and five *in vivo* metabolism studies. There are 10 pharmacodynamic (PD) studies of which three also contributed to the PKs. In addition, there are 25 *in vitro* human biomaterial studies.

Methods

Pharmacokinetic data analysis

The single and multiple dose pharmacokinetics of the combination of NOMAC-E2 were evaluated in the target population of women of childbearing potential in the principal PK trial **292006** (conducted with batch CA057). Supplemental data from studies **292002** (population PK), **292007** and **292011** were also provided. In addition, supportive pharmacokinetic data were provided from the development of Lutenyl (5 mg and 3.75 mg) and Naemis (NOMAC 3.75 mg + E2 1.5 mg). These supportive PK studies investigated different oral doses and/or formulations of NOMAC alone and NOMAC in combination with E2 and were evaluated in both women of childbearing potential and postmenopausal women (not part of the target population).

The pharmacokinetic profiles of E2 and oestrone (E1) were associated with very high degrees of variability most likely due to the fact that E2 levels measured in women of childbearing potential are a composite of endogenous E2 produced by the ovaries and E2 derived from NOMAC-E2 administration, which affects the interpretation of the E2 pharmacokinetics

In the principal PK trial **292006**, the pharmacokinetic parameters were determined from the plasma concentrations of NOMAC, E2 and E1 following single and multiple dose administration for each subject using noncompartmental techniques and the actual sampling times.

Statistical analysis

For the principal PK trial **292006,** the descriptive statistics for the pharmacokinetic parameters comprised the number of observations, arithmetic and geometric mean, standard deviation, arithmetic and geometric coefficient of variation, minimum, median and maximum. The pharmacokinetic parameters calculated after single dosing and at steady state were compared formally by means of a paired t-test on the log transformed parameters. Contrast statements were used to obtain point estimates and 95% confidence intervals (CI) for the parameter ratios of steady state over single dose. Effects were considered statistically significant if $p \leq 0.05$ (p: two-sided tail probability). Time

independent pharmacokinetics was concluded if the regimen effect for all parameters analysed were not statistically significant. Correlation analyses and scatter plots of the NOMAC pharmacokinetic parameters versus age were presented in order to explore the relation of the pharmacokinetics with age.

Absorption

Bioavailability

Study **INT00104097** assessed the absolute bioavailability of NOMAC and E2 in an oral combination tablet (2.5 mg/1.5 mg) compared to a combined 30 minute intravenous infusion of 1.15 mg NOMAC/0.40 mg E2 in young healthy females of childbearing potential. The absolute oral bioavailability of NOMAC was 63.4% (95% CI: 51.7 - 77.8%) and for E2 was 4.6% (95% CI: 3.5 - 6.1%). The oral absolute bioavailability of baseline corrected E2 was 0.8% (95% CI: 0.6-1.2%).

Bioequivalence

The initial dose finding studies (96-ESC/NOM-1-RD and 98) used a formulation that consisted of two individual tablets of nomegestrol acetate (NOMAC) (Lutenyl 0.625, 1.5 and 2.5 mg) and oestradiol (E2) (Estreva 1.5 mg) within a hard gelatin capsule. Subsequently, two NOMAC-E2 combination tablets were evaluated in two PK bridging trials (Trials 02--TX127066-1-RD and 02-TX133066-1-RD). It was concluded that the formulation TX127066 exhibited acceptable comparability for both NOMAC and E2 with the capsule formulation and this TX127066 formulation was selected as the contraceptive combination tablet formulation for use in subsequent trials. The combination tablet formulation TX127006 was then used in the regimen validation trial and the supportive coagulation trial in women of childbearing potential (Trials 02-ESC/NOM-1-RD and 02-ESC/NOM-2-RD, respectively). After completion of these trials a film coat was applied to the formulation for health, safety and environment reasons as well as to improve the appearance of the tablet. This change was supported by a comparative *in vitro* dissolution study in different media which showed similar *in vitro* release rates for both active components. The film coated combination tablet formulation TX127066 was selected for final development. All subsequent trials, including Phase I trials and the well controlled Phase III trials, have been performed with the film coated combination oral NOMAC-E2 (2.5 mg–1.5 mg) tablet formulation. Two pivotal clinical batches (CZ189 and CA057) were used in the final development program for NOMAC-E2 for the contraception indication.

A number of changes were made to the manufacturing process between the batches used in the pivotal clinical trials (which were based on the TX127066 formulation) and the proposed market product including change in mixer type, change in manufacturing site, up-scaling of batch sizes and the use of fine NOMAC rather than coarse particles to improve the content uniformity of the combination tablet. In order to bridge between NOMAC-E2 combination tablets made with the intended commercial manufacturing process and the tablets used in the pivotal Phase III clinical trials, the *in vitro* dissolution curves were compared. In addition, a trial (Trial 292007) was conducted to investigate the relationship between the *in vitro* dissolution curves and the *in vivo* exposure.

Healthy young females of childbearing potential

Study **02-TX127066-1-RD** examined the bioequivalence of NOMAC and E2 in a new tablet combining 2.5 mg NOMAC and 1.5 mg E2 (Test treatment) to a capsule containing one 2.5 mg NOMAC tablet and one 1.5 mg E2 tablet (Reference treatment) under fasted and fed conditions. The test tablet used represented the base formulation for all ensuing clinical trials, including pivotal Phase III trials, however it differed from the marketing formulation (see above). This study was also discussed in *Section II.*

Although there was no significant difference in T_{max} and relative bioavailability of the Test treatment under fasted conditions (A) and the Reference treatment under fasted conditions (C), the C_{max} of treatment A was significantly higher than for treatment C (ratio = 1.29) and therefore the two treatments were not bioequivalent. When the Test formulation was administered concomitantly with a meal, although not significantly different, the median T_{max} was delayed by an hour, whereas, C_{max} and the area under the plasma concentration time curve from time zero to the last measured time point (AUC_{last}) were significantly increased by 29 % and 26%, respectively. For the E2 data, without baseline correction, the C_{max}, AUC_{last} and T_{max} of treatment A were lower than for treatment C (ratios: 0.84, 0.87 and 0.70, respectively) and the 90% confidence intervals were outside the level of bioequivalence for C_{max} and AUC_{last}. Due to the secretion of E2 during the menstrual cycle in non-menopausal women, the baseline corrected data calculated up to the 24 hours post administration were also examined. On this basis, the C_{max} for treatments A and C were similar (ratio: 0.97), however, the variability was large (90% CI: 0.58 - 1.36), the T_{max} was delayed by 6 to 8 hours following treatment A and the ratio of the mean AUC_{24h} (A/C) was 1.31. For the oestrone data, without baseline correction, the C_{max} of treatment A was lower when compared with treatment C (ratio: 0.78), T_{max} was non-significantly shorter (7.1 vs 4.8 hours) and the AUC_{last} were similar for the 2 treatments (ratio: 0.90, ratio: 0.75- 1.06). Food increased the C_{max} and AUC by 20% and 19%, respectively. Once again as oestrone is secreted during the menstrual cycle in non-menopausal women, baseline corrected data was also examined. Based on this analysis, the C_{max} was lower for treatment A compared to C (ratio: 0.75) whereas the T_{max} was not significantly different and the AUC was equivalent with a confidence interval ranging from 0.87 to 1.08. Administration of the Test formulation with a meal increased C_{max} (ratio: 1.16; CI: 0.98 – 1.35), however, there was no change in T_{max} or AUC (ratio: 0.89; CI: 0.80 – 0.99).

Study **02-TX133066-1-RD** examined the bioavailability 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 in healthy female volunteers. Treatment A corresponded to a tablet containing 1.5 mg 17β-estradiol + 2.5 mg NOMAC (TX133066) under fasting conditions, treatment B was a TX133066 tablet under fed conditions and treatment C was a 1.5 mg 17β-estradiol tablet (TX13323) and a 2.5 mg NOMAC tablet (TX69066) under fasting conditions. Treatment A was associated with a higher C_{max} (ratio = 1.40; 90% CI: 1.11 – 1.70) than treatment C whereas the T_{max} and AUC were similar. When taken with a meal, although T_{max} was not significantly modified, C_{max} and AUC were increased by 66% and 27% respectively. Following baseline correction, the AUC_{last} and C_{max} of E2 following administration of Treatment A were 38% and 37% higher than following Treatment C and the T_{max} was significantly higher (5.0 vs 4.3 h). Although a meal had little effect on the mean C_{max} compared to treatment A (ratio 1.10, 90% CI: 0.68 – 1.54) both T_{max} and AUC_{last} were significantly increased following a meal (+0.5 h and ratio of 1.24, respectively). Following baseline correction, although the oestrone T_{max} was unaltered the C_{max} and AUC_{last} were significantly higher, by 44% and 39%, respectively, following treatment A than treatment C. By contrast, compared to treatment A, food had little impact on the PKs of oestrone.

The pharmacokinetics of NOMAC after single oral dose administration of several NOMAC-E2 batches differing in NOMAC particle size was examined in study **292007**. Particle size was generally inversely correlated with C_{max}, whereas it did not affect the area under the plasma concentration time curve from time zero to infinity (AUC_{∞}) or T_{max}. This study also investigated separately the relationship between the pharmacokinetics of NOMAC, the *in vitro* dissolution (percentage dissolved NOMAC after 10 min [D10]) and the particle size (μm) of each batch. For C_{max}, the percentage dissolved and particle size presented

statistically significant regression coefficients (slopes) indicating that these variables explain a significant proportion of the total variation of the C_{max} (35% and 29%). For AUC_{∞}, none of the regression coefficients (slopes) were statistically significantly different from zero. This study was also discussed in *Section II.*

Study **LUT 4-28-01** compared the pharmacokinetics after single dose administration of tablets containing 5 mg of pulverized NOMAC (Lutenyl) or non-pulverized crystallised NOMAC (TX47066) in healthy young women. The C_{max} (ranging from: 11.1 – 12.4 ng/mL, AUC (257 – 265 ng.h/mL), T_{max} (2 – 2.5 h) and half-life ($t_{1/2}$) (approx 42 h) were similar for both the microcrystalline (TX47066) and pulverised forms (Lutenyl).

Influence of food

Young women of child bearing potential

The influence of food on the PKs of NOMAC-E2 is described in two studies described in more detail in the preceding sections. In study 02-TX127066-1-RD, when the Test formulation was administered concomitantly with a meal, although not significantly different, the median NOMAC T_{max} was delayed by an hour, whereas C_{max} and AUC_{last} were significantly increased by 29 % and 26%, respectively. Administration of the Test formulation with a meal increased oestrone C_{max} (ratio: 1.16; confidence interval: 0.98 – 1.35) but there was no change in oestrone T_{max} or AUC (ratio: 0.89; confidence interval: 0.80 – 0.99).

In study 02-TX133066-1-RD**,** concomitant administration of NOMAC-E2 with a meal increased NOMAC C_{max} and AUC by 66% and 27% respectively, although NOMAC T_{max} was not significantly modified. Although a meal had little effect on the mean E2 C_{max} compared to fasting (ratio fed/ fasted: 1.10, 90% CI: 0.68 – 1.54), both T_{max} and AUC_{last} were significantly increased following a meal (+0.5 h and ratio of 1.24, respectively). By contrast, food had little impact on the PKs of oestrone.

Distribution

The apparent volume of distribution ($V_{ss,z/f}$) of NOMAC at steady state is 1645 ± 576 L.

Approximately 97-98% of circulating NOMAC is bound to plasma proteins including albumin, the remaining fraction of 2-3% is unbound. Sex hormone binding globulin (SHBG) and corticosteroid binding globulin (CBG) showed no detectable NOMAC binding. E2 and derived metabolites are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. E2 circulating in the blood is bound to SHBG (37%) and to albumin (61%), while only approximately 1-2% is unbound.

Elimination

In women of childbearing potential (**INT00104097**), the $t_{1/2}$ of NOMAC was 41.9 ± 16.2 h for a single dose and 45.9 ± 15.3 h for multiple doses. NOMAC had a clearance of 15.6 L/h. The weight normalised apparent clearance at steady state was 0.415 ± 0.166 L/h/kg in Trial **292006**, or 26.0 ± 9.15 L/h when presented as apparent clearance. Using the estimate of absolute bioavailability (63.4%; **INT00104097**), the clearance of this analysis was calculated to be ~16.5 L/h, which is similar to that of the intravenous administration.

In postmenopausal women (**Trial LUT 4-35-01**), NOMAC had a half-life of 37.3 h and clearance of 12.9 L/h.

In **the combined analysis**, the half-life of E2 was 8.43 h. When corrected for baseline E2, in an attempt to eliminate the influence of endogenous E2, a half-life of 3.62 h was determined. Without baseline correction the clearance of E2 was 53.4 L/h and with baseline a value for clearance of 65.7 L/h was calculated. The elimination of E2 was shown to be highly variable.

Excretion

NOMAC is excreted via faeces and urine. Studies in postmenopausal women showed that the major route of excretion for NOMAC and/or its metabolites was via the faeces. The mean terminal half-life based on total NOMAC radioactivity was 62.1 h and 77.6 h. A mean of 89.9% - 95.6% of the administered total NOMAC radioactivity was recovered with 54.8 - 67.0% recovered in faeces within 10 days post dose (22.9 - 40.8% was recovered in urine) (**Trials LUT 4-06-01, LUT 4-12-01 and LUT 4-13**).

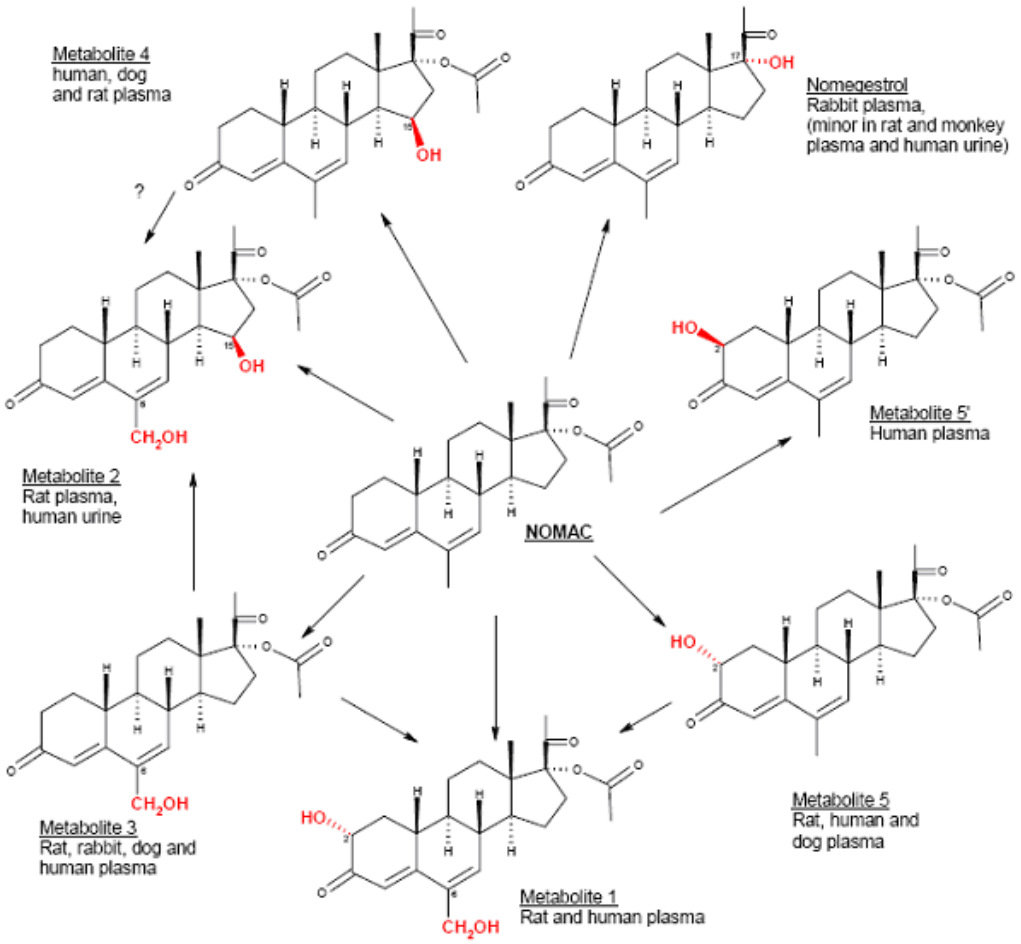
The major proportion of the total NOMAC radioactivity (79.4%) was eliminated within 4 days of dosing. Low levels of total NOMAC radioactivity were excreted in urine (<0.5%) and faeces (<1.5%) between 216-240 h post dose (**Trials LUT 4-06-01 and LUT 4-12-01 and LUT 4-13**). A mean of 2.1% (14 to 48 h) and 2.9% (96 to 144 h) of the recovered urinary radioactivity corresponded to unchanged [^{14}C]-NOMAC (**Trials LUT 4-06-01 and LUT 4-12-01**), whereas in **Trial LUT 4-13** a TLC analysis of 12 to 48 h and 96 to 144 h urine samples did not detect unchanged [^{14}C]-NOMAC.

Metabolism

NOMAC is metabolised in the liver by hydroxylation, glucuronide and sulphate conjugation and to a minor extent by deacetylation. Several pharmacologically inactive hydroxylated metabolites are formed by liver CYP enzymes (CYP2C8, CYP2C19, CYP3A4 and CYP3A5). NOMAC and its hydroxylated metabolites undergo extensive phase 2 metabolism to form glucuronide and sulphate conjugates (Figure 1). Only 2-3% of recovered urinary radioactivity corresponds to unchanged NOMAC. The apparent clearance ($CL_{ss/f}$) of NOMAC at steady state is 26.0 ± 9.15 L/h.

The metabolism of E2 is known and therefore no trials on the metabolism of E2 were performed. In summary, orally administered E2 is extensively metabolised (first pass effect) and a significant component of the dose administered is metabolised in the gastrointestinal mucosa. E2 is rapidly transformed in several metabolites, mainly oestrone (E1), which is subsequently conjugated and undergoes enterohepatic circulation. There is a dynamic equilibrium between E2, E1 and E1-Sulfate (E1-S) due to various enzymatic activities including E2-dehydrogenases, sulfotransferases and aryl sulphatases. Oxidation of E1 and E2 involves cytochrome P450 enzymes, mainly CYP1A2, CYP1A2 (extra hepatic), CYP3A4, CYP3A5, and CYP1B1 and CYP2C9.

Figure 1: Proposed metabolism scheme for NOMAC



Dose proportionality and time dependency

Dose proportionality

Healthy female subjects of childbearing potential

A combined multiple dose and single dose trial (**292006)** assessed the pharmacokinetic profile of NOMAC, E2 and E1 after oral administration of NOMAC-E2 in healthy female volunteers of childbearing potential. The C_{max}, AUC_{0-24}, T_{max} and $t_{1/2}$ of NOMAC following a single dose of NOMAC-E2 was 7.2 ng/mL, 50.4 ng.h/mL, 2 h and 41.9 h, respectively. At steady state, the C_{max}, AUC_{0-24}, T_{max} and $t_{1/2}$ of NOMAC was 12.3 ng/mL, 106 ng.h/mL, 1.5 h and 44 h, respectively. Following once daily treatment with NOMAC/E2, steady state of NOMAC based on pre-dose concentrations was attained after five days of dosing. The mean accumulation ratio (based on AUC) was 2.0, indicating that the NOMAC concentrations in plasma at steady state are approximately twice as high as those after single dosing. At steady state of NOMAC, the exposure of E2 was approximately 55% lower than after single dosing, whereas, at steady state NOMAC, the exposure of E1 was approximately 25% higher than after single dosing.

Study **LUT 4-29-01** examined the steady state pharmacokinetics of NOMAC in young healthy women following 14 consecutive days of once daily oral administration of a 5 mg

NOMAC alone tablet (Lutenyl) during the second part of an ovarian cycle. NOMAC steady state was attained five days following the commencement of once daily dosing. At steady state, the plasma peak concentration was reached in approximately three hours. Elimination was biphasic and the terminal elimination half-life was approximately 41 h. The mean accumulation ratio (RA) was 2.26, indicating that the NOMAC concentrations at steady state are approximately twice as high as those following a single administration.

Postmenopausal women

Another 3 trials examined the pharmacokinetic profile of NOMAC-E2 combined in postmenopausal women after single and multiple dosing. They are not discussed in this AusPAR as these subjects do not fall within the scope of proposed indication for registration.

NOMAC alone

Six studies examined the pharmacokinetics of NOMAC alone in healthy postmenopausal women and a single study examined the pharmacokinetics of NOMAC in healthy men. As these subjects do not fall within scope of the proposed indication for registration they are not discussed in this AusPAR.

Intra and inter-individual variability

Inter-subject and intra-subject variability for NOMAC was estimated based on an analysis of variance (ANOVA) analysis of data from **Trial 292006** conducted in women of childbearing potential. Inter-subject variability on C_{max} was 29.2% and for $AUC_{(0\text{-}24,\ \infty)}$ this was 35.1%. Within-subject variability on C_{max} was 15.4% and on $AUC_{(0\text{-}24,\ \infty)}$ 11.3%. Total variability on C_{max} and $AUC_{(0\text{-}24,\ \infty)}$ was therefore 33.3% and 37.0%, respectively.

For E2 a measure of total variability was presented by the arithmetic coefficient of variation (CV) on C_{max}, which was 71.0% after a single dose (n=19) and 59.7% at steady state (n=23). For $AUC_{0\text{-}24}$ the total variability was 65.2% CV (n=19) after a single dose and 51.0% CV at steady state (n=23). This overall variability presents a composite measure of exogenous and endogenous E2 levels. The pharmacokinetics of E2 was also shown to be highly variable in postmenopausal women with a between-subject variability of approximately 60% for $AUC_{0\text{-}24}$ and 100% for C_{max} (**Trials LUT 4-36 and LUT 4-37**).

Pharmacokinetics in the target population

Population pharmacokinetics

Study INT00101987 examined the covariate relationships (age, race and body mass index [BMI]) in a population PK model of NOMAC. The analysis was based on the results of two clinical trials: one Phase I study (292006) and one Phase III study (292002). In both studies a daily dose of 2.5 mg NOMAC /1.5 mg E2 was administered to a total of 81 healthy female subjects of childbearing potential. The population PK analysis was performed using a non-linear mixed effects modelling approach using NONMEM VI with FOCEI. Model selection was based on the Log-Likelihood Criterion, goodness of fit plots and scientific plausibility. Identification of covariates was performed using an automated procedure (Stepwise Covariate Model building as implemented in Perl-speaks-NONMEM) and the reliability of the final model was verified using diagnostic plots and bootstrap analysis.

The NOMAC pharmacokinetics were best described by a two compartmental model with first order absorption, a lag time on absorption and first order elimination from the central compartment. The food status at the time of dosing of the subjects included in this analysis was not equal for the Phase I (and within; single dose versus multiple dose) and Phase III data. Introduction of separate Ka's to reflect the fed or fasted status of the

subject and different residual errors to account for study and study-part differences improved the model fit substantially. Of the evaluated covariates, BMI was included as a covariate on CL and F. CL/F decreased slightly (0.8 L·hr-1 per BMI unit) with BMI. No effect of age (range: 18 -47) or race (groups; 4 Black, 2 Asian, 75 Caucasian) was identified. However, the number of non-Caucasians (see above) was too small to allow analysis of effect of race on PKs.

Special populations

Children

As the combination NOMAC-E2 is to be used in women of childbearing potential no combination contraceptive has been evaluated in paediatric populations before menarche or geriatric populations. A pharmacokinetic trial with NOMAC-E2 to compare the pharmacokinetics in post-menarcheal adolescents with adult women is planned (Trial 292008) but this submission does not contain any data in post-menarcheal adolescents aged 12-17 years.

Impaired renal function

Clinical data are not available to evaluate the effect of renal disease on the pharmacokinetics, safety and efficacy of the combination NOMAC-E2.

Impaired hepatic function

Clinical data are not available to evaluate the effect of hepatic disease on the pharmacokinetics, safety and efficacy of the combination NOMAC-E2. However, steroid hormones may be poorly metabolized in women with impaired liver function.

Population Pharmacokinetics

A population analysis, study **INT00105057**, examined the pharmacokinetics of NOMAC, with special emphasis on the effects of age and BMI, in post-menarcheal females. Data was taken from three trials (**307001, 292006 and 292002**) comprising a total of 98 healthy female patients of childbearing potential. The adult PK model was developed using the PK-Sim software package for single intravenous (IV) and subsequently expanded to single oral and multiple oral administration of NOMAC. A PBPK model describing the pharmacokinetics of NOMAC following single IV, single PO and multiple PO administration in adult women was successfully established and validated on a separate multiple PO data set.

The PK model was then extended to adolescent post menarche girls using data from a virtual post menarche adolescent population and by applying physiological scaling. The post menarche NOMAC PK model was then used to explore the pharmacokinetics in this age group compared to female adults. Using this analysis the investigators identified that adolescent girls have a similar exposure, similar maximum plasma concentrations, similar time at maximum plasma concentrations, similar trough concentrations, and terminal half life on the first day of administration and at steady state.

In addition, the influence of age and BMI on the pharmacokinetics of NOMAC were studied. Exposure ($AUC_{0-\infty}$) was shown not to be correlated with BMI. Body weight normalised plasma clearance was inversely correlated with BMI, whereas terminal half life and volume of distribution were found to be positively correlated with BMI and these correlations were found to be independent of age. The impact of a missed pill on different days in the administration cycle was also studied using the established PK models. As a consequence of a missed pill on Day 4, trough levels 36 and 60 hours after the last administration tended to be slightly lower in the older girls and adult women compared to younger girls but were found to be largely independent of BMI. After missing a pill at

steady state (Day 21), trough concentrations after 36 and 60 hours were slightly lower at older age compared to younger girls and lower in females with a lower BMI.

Interactions

In vitro studies

In vitro studies **PR8039/CC0021** and **PR8040/CC0022** investigated CYP inhibition and induction by NOMAC. No significant inhibition or dose dependent decrease of any CYP activity was observed at any NOMAC concentration either by direct or by mechanism based inhibition. Moreover, NOMAC did not act as a CYP inducer.

In vivo studies

Two interaction studies were conducted in healthy postmenopausal women (**NOM-OEST 4-04 and NOM-OEST 4-05**). These studies examined the interaction between NOMAC-E2 and the CYP3A4 inducer, rifampicin, and the CYP3A4 inhibitor, ketoconazole.

In the presence of rifampicin (**NOM-OEST 4-04)**, the C_{max} of NOMAC decreased by 85%, AUC_{∞} decreased by 95 % and the $t_{1/2}$ was reduced. Following rifampicin administration, C_{max} was increased for both E2 and E1 by 165% and 70%, respectively and the time to C_{max} was reduced. The AUC for E2 was increased by 25%, while the AUC for E1 was relatively unaffected.

In the presence of ketoconazole (**NOM-OEST 4-05)**, the C_{max} of NOMAC increased by 85% with an increase in the time to maximum concentration and AUC_{∞} increased by 115%, whereas the elimination half-life of NOMAC was unaltered. For E2, C_{max} and time to reach maximum concentration were unchanged, however, $AUC_{0\text{-}tlast}$ increased by 25 %. There was a small increase in the C_{max} and $AUC_{0\text{-}tlast}$ of E1 and a shorter time to T_{max}.

Exposure relevant for safety evaluation

Steady state following administration of proposed daily dose of NOMAC (2.5 mg) is achieved after 5 days; maximum plasma concentrations of NOMAC of about 12 ng/mL are reached 1.5 hours after dosing and average steady state concentrations are 4 ng/mL. The exposure to NOMAC after a single dose is 112 ± 40.4 ng.h/mL (AUC_{∞}) and at steady state 106 ± 33.1 ng.h/mL ($AUC_{ss,0\text{-}24}$ [$AUC_{0\text{-}24}$ at steady state]). Maximum serum concentrations of E2 are about 90 pg/mL and are reached 6 hours after dosing; average E2 levels are 50 pg/mL, which correspond with the early and late phase of a woman's menstrual cycle.

No formal studies were done to assess effects of race, renal/hepatic impairment on PKs of NOMAC-E2. Whole body physiologically based PK modelling and simulation showed no difference in the NOMAC PKs between post-menarcheal adolescents aged 12-17 years and adult women; however no studies were conducted to evaluate safety, efficacy and tolerability of NOMAC-E2 in this subset of the target population.

Evaluator's overall pharmacokinetic conclusions

Absorption, Distribution, Metabolism and excretion:

In studies of NOMAC-E2 in women of childbearing potential, the absolute oral bioavailability of NOMAC was 63.4% and for E2 was 4.6%. The oral absolute bioavailability of baseline corrected E2 was 0.8%.

Orally administered NOMAC is rapidly absorbed with maximum concentrations of 7.19 ± 2.04 ng/mL ($C_{sd,max}$) after a single dose and 12.3 ± 3.50 ng/mL ($C_{ss,max}$) at steady state, reached at 2 h ($T_{sd,max}$) and 1.5 h ($T_{ss,max}$), respectively. Steady state is achieved after 5 days of dosing.

Orally administered E2 is subject to a substantial first pass effect during absorption by the intestinal mucosa and/or during first liver passage. At steady state, in the presence of NOMAC, maximum concentrations of E2 are reached at 6 h ($T_{ss,max}$) with maximum concentrations ($C_{ss,max}$) of 86.0 ± 51.3 pg/mL after administration of the NOMAC-E2 (2.5mg/1.5mg) film coated combined tablet formulation.

Concomitant administration of test treatment (uncoated TX127066) with a meal increased the subject's exposure to NOMAC, E2 and oestrone.

NOMAC pharmacokinetics showed considerable variability, 33.3% and 37.0% for C_{max} and $AUC_{(0\text{-}24,\infty)}$, respectively. In addition, due to the presence of endogenous E2, the pharmacokinetics of E2 also demonstrated substantial variability.

NOMAC is extensively bound to albumin (97-98%), but does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). The apparent volume of distribution of NOMAC at steady state is 1645$\pm$576 L.

NOMAC is metabolised in the liver into several pharmacologically inactive hydroxylated metabolites by CYP2C8, CYP2C19, CYP3A4 and CYP3A5. NOMAC does not act as either an inhibitor or inducer of CYP.

Oxidation of E1 and E2 involves mainly CYP1A2, CYP1A2 (extra hepatic), CYP3A4, CYP3A5, and CYP1B1 and CYP2C9.

NOMAC is excreted predominantly via faeces and urine. In women of childbearing potential (target patient population), the $t_{1/2}$ of NOMAC was 47hours.

Drug interactions and PKs in special populations

Drug interaction studies were not performed with Zoely, but due precautions have been included in the proposed PI regarding concomitant administration with drugs that induce or inhibit CYP450 enzymes. As no clinical data exists on the pharmacokinetics of NOMAC-E2 in subjects with impaired hepatic or renal function NOMAC-E2 should not be prescribed to individuals that fall within these groups. There is no or very little data concerning the pharmacokinetics of NOMAC-E2 in special populations or its interactions with other drugs in the target population.

Bioequivalence

After initial formulation development, two formulations (TX133066, TX127066) were made of the combination NOMAC-E2 tablet. Tablet formulation TX127066 was selected for contraceptive development because of the acceptable comparability between the capsule and tablet formulation with respect to bioavailability for both components (NOMAC and E2). Finally a film coat was applied and all subsequent Phase III trials and additional Phase I trials were performed with this film coated combined tablet formulation. During pharmaceutical development, data indicated that in order to obtain a robust manufacturing process it was required to reduce the particle size of the coarse NOMAC. For E2, already material of reduced particle size is used in the manufacture NOMAC-E2 tablets.

In order to bridge between NOMAC-E2 combination tablets made with the intended commercial manufacturing process and the tablets used in the pivotal Phase III clinical trials, the *in vitro* dissolution curves were compared. In addition, a trial was conducted to investigate the relationship between the *in vitro* dissolution curves and the *in vivo* exposure; results from this study showed that particle size is inversely correlated with C_{max} but did not affect AUC or T_{max} of NOMAC.

The sponsor claimed that from a contraceptive efficacy perspective, the most important parameter is AUC_{∞}, which was neither affected by the differences in the *in vitro* dissolution

profiles nor by differences in NOMAC particle size as used for the various clinical batches. The sponsor further claimed that although the C_{max} showed differences, this would not be an issue from a safety/tolerability perspective due to 2 reasons:

(1) the extent of the dissolution differences in C_{max} for the different batches decreases from a single dose to a multiple dose steady state situation, which is clinically relevant given the intended use of NOMAC-E2 in a 24/4 day multiple dose regimen, and

(2) multiple doses up to five times the contraceptive daily dose of NOMAC-E2 (2.5 mg-1.5 mg) and single doses up to 40 times the daily dose of NOMAC alone have been used in women and men, respectively, without safety concerns.

However, there was no bridging study to unequivocally establish bioequivalence between the clinical trials formulation and the proposed marketing formulation of NOMAC-E2.

The sponsor indicated that a full bioequivalence study (P06328) comparing Phase III pivotal clinical batches and drug product manufactured using the proposed commercial process was submitted later. This was evaluated by the quality evaluator, as discussed on pages 7-9 and 75 of this AusPAR.

Pharmacodynamics

Introduction

NOMAC has a strong affinity for the human progesterone receptor, a strong antigonadotropic and moderate anti-androgenic activity, anti-oestrogenic activity on the endometrium and is devoid of any oestrogenic, androgenic, glucocorticoid or mineralocorticoid activity.

The pharmacodynamic effects of NOMAC and E2 on the hormones regulating ovulation were studied in 4 dose finding trials (**LUT 5-24-01, LUT 5-22-01, 96-ESC/NOM-1-RD and 98-ESC/ NOM-1-RD**).

Mechanism of Action

The contraceptive effect of NOMAC-E2 is primarily achieved by inhibition of ovulation and increased viscosity of cervical mucus (which increases the difficulty of sperm entry into the uterus), effects already achieved by NOMAC (2.5 mg) alone. E2 enhances the contraceptive efficacy of NOMAC and has been added to restore NOMAC induced suppression of E2 levels. The effects on vaginal bleeding are considered to be the result of the combination of NOMAC and E2.

The principle mechanism of action of oral contraceptives is the inhibition of ovulation, which can be determined by the absence of the steep and sustained rise in progesterone serum levels. In addition, the extent of residual ovarian activity can be determined by measuring ovarian E2 hormone production and ultrasound monitoring of follicular growth. Determining the levels of the gonadotropins luteinising hormone (LH) and follicle stimulating hormone (FSH) aids in understanding the interference of the contraceptive with hypothalamic-pituitary-ovarian function.

Primary pharmacology

NOMAC alone

Trial **LUT 5-24-01** examined the effects of NOMAC administration on gonadotropins in 10 women of childbearing potential who were receiving 5 mg NOMAC per day. Compared to baseline, NOMAC caused a significant decrease in LH pulsatility, basal LH levels and LH response to exogenous gonadotrophin releasing hormone (GnRH), suggesting NOMAC has effects at both at the hypothalamic and pituitary level. In contrast, basal FSH secretion and the FSH response to GnRH were significantly increased by NOMAC, possibly as a result of

reduced ovarian E2 synthesis and associated negative feedback. The latter is compatible with the existence of an additional effect of NOMAC on the ovary, as has been observed for several other progestogens.

Trial **LUT 5-22-01** investigated the oral dose of NOMAC effective for inhibiting ovulation. Subjects were treated with oral dosages of 1.25 mg, 2.5 mg or 5 mg NOMAC for 20-21 days. The 2.5 mg dosage was identified as the optimum dose, being effective in suppressing ovulation as judged by suppressed progesterone levels and absence of LH peaks as well as in inhibiting follicular growth as judged by decreased E2 concentrations. The 5 mg dosage did not add to the effect of 2.5 mg, while the 1.25 mg dosage, although inhibiting ovulation, resulted in higher E2 blood levels, indicating this dose was less able to inhibit follicular growth.

NOMAC-E2

Study **96-ESC/NOM-1-RD** was the first trial with the NOMAC-E2 combination, in which the effective dose of NOMAC (2.5 mg - treatment 4, T4) alone was compared to NOMAC-E2 combinations containing NOMAC 0.625 mg (T1), 1.25 mg (T2) and 2.5 mg (T4) plus 1.5 mg E2. Plasma progesterone (P) levels were equal to or below 0.8 ng/mL in all measurements performed daily in the 38 subjects, without statistically significant difference between the four groups. Comparison between the three groups treated with NOMAC combined with E2 showed that, despite extremely low results in all groups, P levels were almost always highest in T1 and, although the difference was not statistically significant between the three groups, the decrease in P levels was significantly correlated to the increase in the NOMAC dose. Comparison between the two groups T3 and T4 showed a significantly higher maximum P level in the NOMAC only group. Compared to the control cycle, plasma E2 levels were significantly lower during treatment in all groups, with a decrease ranging from 57.5% in T2 to 72.9% in T4. Comparison between the four groups showed that the mean E2 levels were significantly higher in T1 at 62.0 pg/mL and lower in T4 at 31.9 pg/mL. There was no statistically significant difference between the three groups treated with NOMAC combined with E2 in daily plasma E2 levels but the E2 C_{max} and AUC calculated from Day 12 to Day 28 were significantly and negatively correlated to the dose of NOMAC. E2 levels were consistently higher in T3 compared to T4, although the difference was not always significant.

Maximum FSH level was lower during the treatment cycle in all groups but the decrease was not significant in any group. There was no statistically significant difference between the three groups treated with NOMAC combined with E2 and no correlation was found with the NOMAC dose. The lowest FSH levels were found in T3 and the highest in T4 with a statistically significant difference between the two groups. The LH peak was suppressed in all groups but the greatest LH suppression was observed in the NOMAC-E2 2.5/ 1.5mg (T3) group. There was a statistically significant difference between the four groups due to a higher LH level in T4 compared to T2 and T3. Comparison between the three groups treated with NOMAC combined with E2 showed a significant difference between T1 and T3, regarding mean LH levels and AUC but no correlation with the NOMAC dose, although daily LH levels were consistently higher in T1. All LH parameters were significantly higher in T4 compared to T3. In accord with the hormonal results, cervical mucus scores decreased significantly between control and treatment cycles, in all groups and without significant difference between the groups. Inter-current bleeding occurred in all treatment groups and no difference was found between the four groups regarding bleeding pattern.

Trial **98-ESC/ NOM-1-RD** evaluated the optimal daily dose of NOMAC (0.625 mg, 1.25 mg or 2.5 mg) in combination with 1.5 mg E2 (21/7 regimen) that would achieve progesterone suppression and regular menstrual cycles in healthy female volunteers

following treatment over six consecutive cycles of 28 days**.** Ovulation in this study was defined as at least one progesterone blood level ³ 3 ng/mL during the treatment cycle and it occurred in 13.1%, 19.4% and 20.3% of the women (per protocol [PP] analysis) in the NOMAC 2.5 mg, 1.25 mg, 0.625 mg groups, respectively (15.2%, 17.2% and 24.7%, respectively in the "intent to treat" (ITT) analysis. Ovulation tended to be less frequent in the 2.5 mg NOMAC group as compared to the other two treatment groups, although the difference was not statistically significant.

NOMAC levels were retrospectively measured in the women who ovulated and these showed that 5 women were non-compliant with treatment (2, 1 and 2 in 2.5 mg, 1.25 mg and 0.625 mg NOMAC groups, respectively); the incidence of ovulation in women whose NOMAC compliance was checked was 10%, 18% and 18%, respectively. Suppression of follicle development was better in the 2.5 mg NOMAC group as compared to the other groups, as assessed by unruptured follicle (UF) and E2 levels**.**

All NOMAC doses significantly decreased the endometrial thickness compared to the pre-treatment values. Significantly better menstrual cycle control was obtained with 2.5 mg NOMAC as compared to the other two treatment groups. The highest NOMAC dose resulted in a higher percentage of cycles with withdrawal bleeding, a lower incidence of breakthrough bleeding/spotting, and a shorter mean duration of breakthrough bleeding/spotting.

Evaluator's Comments:

> Overall, this study demonstrated that the NOMAC-E2 (2.5 mg-1.5 mg) combination produced the best ovarian suppression and bleeding control; however, the regimen used in this dose response study was the 21/7 NOMAC-E2/ placebo regimen, while the proposed regimen is 24/4.

Finally, the selected dose combination was investigated in trial **02-ESC/NOM-1-RD** to compare the effects on ovarian activity of two regimens (NOMAC-E2/ placebo: 21/7 and 24/4 regiments)**.** In both regimen groups, neither ovulation nor LUF syndrome (blood progesterone > 3 ng/mL) occurred and progesterone blood levels remained very low throughout the treatment period. Compared to the 21 day regimen, the 24 day regimen resulted in a significantly stronger inhibition of follicular growth. This effect was illustrated by the statistically lower diameter of the largest follicle at the end of the pill free interval and at the beginning of the consecutive cycle. The lowest E2 blood levels found at the end of the second pill free interval and during treatment Cycle 3 in the 24 day regimen group could also account for the stronger inhibition of follicular growth. The 24 day regimen delayed the increase in FSH during the pill free interval. LH and FSH were found significantly lower with this regimen, at least at one measurement in each pill free interval. The 24 day regimen also resulted in a better bleeding pattern. The total number of genital bleeding was found significantly lower than with the 21 day regimen. The bleeding duration was shorter for both withdrawal and intermenstrual bleeding/ spotting but the difference reached statistical significance only for withdrawal bleeding. There was no significant difference between the two groups in the incidence of intermenstrual bleeding, but the duration of intermenstrual bleeding per cycle was significantly shorter with the 24 day regimen.

The two regimens showed similar reduction in the cervical mucus index and the endometrial thickness. Furthermore, return to fertility was evaluated in all women during the post treatment cycle by measuring blood progesterone around Day 20 post treatment and if necessary again a few days later (> 3 ng/mL equivalent to 9.6 nmol/L) and by recording the occurrence of spontaneous menstruation after the end of treatment. The incidence of post-treatment blood progesterone > 3 ng/mL was 71% and 73% in the 21/7

and 24/4 regimens, respectively. The incidence of withdrawal bleeding was 92% in both groups and median duration of withdrawal bleeding was 5 and 4 days in 21/7 and 24/4 regimen groups, respectively. There was one pregnancy in the post-treatment period (subject chose to abort).

Study **292003** evaluated the effects on ovarian function of a monophasic combined oral contraceptive (COC) containing 2.5 mg NOMAC and 1.5 mg E2, compared to a monophasic COC containing 3 mg drospirenone (DRSP) and 30 µg ethinyl oestradiol (EE). Ovarian function was effectively suppressed by NOMAC-E2, as no ovulations or suspected ovulations (that is, assessed by the investigator on the basis of USS alone or suspected because of progesterone values greater than 16 nmol/L) occurred during the trial. In both treatment groups, the mean diameter of the leading follicle started to increase during the placebo pill period reaching its maximum on the second and fifth day of Cycle 2 in the NOMAC-E2 and DRSP-EE groups, respectively. The mean maximum follicle diameter in Cycle 2 was 8.2 mm in the NOMAC-E2 group and 10.8 mm in the DRSP-EE group. In all other treatment cycles the mean maximum follicle diameter was lower for both treatment groups. None of the subjects in the NOMAC-E2 group had a maximum follicle diameter of 15 mm or more. The mean maximum progesterone values were below 2 nmol/L in both treatment groups during the in-treatment period. For all subjects, the maximum progesterone value in any treatment cycle was far below the cut off value of 16 nmol/L for (suspected) ovulation (≤5 ng/mL).

Mean FSH and LH values continuously decreased during active tablet intake and increased during the placebo pill period. Peak values were reached at the end of the placebo period (FSH) or in the beginning of the next cycle (LH). Slightly higher peak mean values were seen in the DRSP-EE group as compared to the NOMAC-E2 group. Mean E2 values were reduced in both treatment groups compared to the screening cycle but higher E2 values were found in the NOMAC-E2 group during active tablet intake due to the exogenous administration of E2 of the investigational product.

A clear decrease in mean E2 values was seen at the end of the placebo pill period in the NOMAC-E2 group, in contrast to the clear increase in the DRSP-EE group. Cervical mucus receptivity was reduced as shown by decreased Insler scores in both treatment groups. In Cycle 1, the mean Insler score was decreased from 8.9 to 2.3 in the NOMAC-E2 group and from 7.3 to 3.2 in the DRSP-EE group. The mean endometrial thickness was reduced during treatment compared to screening, with slightly smaller values in the NOMAC-E2 group compared to the DRSP-EE group. The (mean) maximum endometrial thickness was similar between the groups in Cycles 1 and 6, and slightly smaller in the NOMAC-E2 group (5.3 mm) compared to the DRSP-EE group in Cycle 2 (6.8 mm). Persistently high values in individual subjects were not observed. No pregnancies occurred during the trial.

The occurrence of breakthrough bleeding/spotting was higher in the NOMAC-E2 group as compared to the DRSP-EE group. This was predominantly due to spotting days. Similarly, the occurrence of absence of withdrawal bleeding was higher in the NOMAC-E2 group.

For all androgens, a decrease from baseline in mean values was seen at Cycle 6, which was smaller in the NOMAC-E2 group as compared to the DRSP-EE group. SHBG was increased in both treatment groups at Cycle 6 as compared to baseline, with the increase in the DRSP-EE group being more pronounced as compared to the NOMAC-E2 group (321.3% versus 51.3%, respectively).

No clinically relevant changes were found in folic acid values during treatment and post-treatment. Post-treatment return of ovulation was detected in 22 subjects (78.6%) on NOMAC-E2 and in 12 subjects (75%) on DRSP-EE; for most of the remaining subjects LH peaks and/or ultrasound evidence of (imminent) ovulation were observed, but

progesterone levels had not (yet) reached 16 nmol/L by the end of the post-treatment cycle.

Relationship between plasma concentration and effect

Trial **98-ESC/ NOM-1-RD** examined a range of NOMAC doses (0.625 mg, 1.25 mg or 2.5 mg) in combination with 1.5 mg E2 (21/7 regimen). Although, all doses significantly decreased the endometrial thickness compared to the pre-treatment values, ovulations tended to be less frequent, suppression of follicle development was greater, significantly better menstrual cycle control was obtained, a higher percentage of cycles with withdrawal bleeding, a lower incidence of breakthrough bleeding/spotting, and a shorter mean duration of breakthrough bleeding/spotting was obtained with the 2.5 mg NOMAC compared to the other two treatment groups.

Evaluator's overall conclusions on pharmacodynamics

The PD studies in women of childbearing potential strongly suggest that NOMAC-E2 combination (2.5 mg/1.5 mg) was effective in suppressing ovarian function as measured by progesterone, LH, FSH and E2 levels, follicle diameter, endometrial thickness and cervical mucus score. Return of ovulation was detected in the first cycle following cessation of administration of NOMAC-E2 in 70- 79% of the subjects. Both the 21/7 and 24/4 NOMAC-E2 regimen was associated with similar inhibition of ovulation and return to fertility; the only difference between the 2 regimens was slightly shorter duration of withdrawal bleeding (median of 5 and 4 days with 21/7 and 24/4 regimen, respectively). Return of ovulation after stopping NOMAC-E2 intake takes at least 16 days after the last active tablet intake.

Efficacy

Introduction

Two dose finding studies (96-ESC and 98-ESC) were performed with combinations of 1.5 mg E2 and 3 doses of NOMAC and another study (compared the regimen of 21 active and 7 placebo tablets (21/7) with that of 24 active and 4 placebo (24/4) regimen. Two pivotal studies compared efficacy/ safety of proposed NOMAC-E2 (24/4 regimen) with that of DRSP-EE over 13 cycles (of 28 days each) in 4433 healthy females aged >18 years (<50 years).

Dose response studies

Dose finding trials for contraception were initially performed with NOMAC alone and identified 2.5 mg NOMAC as the optimum dose for ovulation inhibition. In the Phase IIa, randomised, double blind, dose finding study **96-ESC/NOM-1-RD**, there was a trend for the higher doses of NOMAC to be associated with lower plasma levels of LH, P and E2. The combination of 2.5 mg NOMAC with 1.5 mg E2 resulted in statistically significantly lower mean levels of P, LH and FSH as compared to 2.5 mg NOMAC alone. In accord with the hormonal results, cervical mucus scores decreased significantly between control and treatment cycles in all groups but without significant difference between the groups. Intercurrent bleeding occurred in all treatment groups and no difference was found between the four groups regarding bleeding pattern.

Evaluator Comments

Blood sampling times in the study were adequate (from Days 5 to 25) so that LH peaks were not missed. As all study treatments (0.625 mg, 1.25 mg and 2.5 mg NOMAC in combination with 1.5 mg E2) led to inhibition of ovulation, the minimal effective dose of NOMAC inhibiting ovulation when combined with a fixed dose of E2 was not determined in this study. Although 2.5 mg NOMAC alone also inhibited

ovulation, it did not produce the same hormone profile to that observed following treatment in combination with 1.5 mg E2; the combination resulted in statistically lower mean levels of P, LH and FSH. The 3 doses of NOMAC combined with 1.5 mg E2 produced similar suppression of ovulation but there was a trend for the higher doses of NOMAC to be associated with lower plasma levels of LH, P and E2. These findings might suggest that unlike the inhibition of ovulation, the degree of inhibition of follicular development is related to the dose of NOMAC.

The Phase II, randomised, double blind, comparative, multicentre dose finding trial **98-ESC/ NOM-1-RD** evaluated the optimal daily dose of NOMAC (0.625 mg, 1.25 mg or 2.5 mg) in combination with 1.5 mg E2 (21/7 regimen) that would achieve progesterone suppression and regular menstrual cycles in 306 healthy female volunteers following treatment over six consecutive cycles of 28 days each. Results from this study have been discussed in detail above.

Evaluator Comments:

Overall, this study demonstrated that the NOMAC-E2 (2.5 mg-1.5 mg) combination produced the best ovarian suppression and bleeding control; however, the regimen used in this dose-response study was the 21/7 NOMAC-E2/ placebo regimen, while the proposed regimen is 24/4.

Finally, the selected dose combination was investigated in a Phase II, randomized, double blind, comparative, three cycle, single centre trial (**02-ESC/NOM-1-RD**) to compare the effects on ovarian activity of two regimens of 2.5 mg NOMAC and 1.5 mg E2 in healthy female volunteers ; a regimen of 21 active tablets NOMAC-E2 2.5-1.5 mg followed by 7 placebo tablets (21/7 regimen) to the proposed a regimen of 24 tablets NOMAC-E2 2.5-1.5 mg followed by 4 placebo tablets (24/4 regimen) (discussed above). In both regimen groups, no ovulation and LUF syndrome (blood progesterone > 3 ng/mL) occurred and progesterone blood levels remained very low throughout the treatment period. Compared to the 21 day regimen, the 24 day regimen resulted in a significantly stronger inhibition of follicular growth. This effect was illustrated by the statistically lower diameter of the largest follicle at the end of the pill free interval and at the beginning of the consecutive cycle. The 24 day regimen delayed the increase in FSH during the pill free interval; LH and FSH were also significantly lower with this regimen.

Evaluator Comments:

On the basis of a better bleeding profile as judged by a shorter duration of withdrawal bleeding and a lower overall number of days with vaginal bleeding over three cycles of use and increased suppression of ovulation, the 24/4 regimen (02-ESC/NOM-1-RD) was selected for further development.

Main (pivotal) studies

The two pivotal studies (292001 and 292002) were designed as randomized, open label, comparative, multicentre twin trials in 4433 healthy female subjects to evaluate the contraceptive efficacy, cycle control, safety and acceptability of 2.5 mg NOMAC and 1.5 mg E2 (Zoely 24/4 regimen) in comparison to 3 mg drospirenone (DRSP) and 30 µg ethinyl oestradiol (EE) (Yasmin 21/7 regimen). The duration of treatment was 13 consecutive cycles of 28 days.

Study 292001 involved approximately 95 study centres in Europe, Asia and Australia, while study 292002 involved approximately 90 trial centres in Latin America, Canada and the United States. DRSP-EE was chosen as comparator for the pivotal trials because this contraceptive is very commonly used and has been approved in many countries worldwide, including Australia.

The trials were conducted in an open label fashion, as the differences in regimen between the NOMAC-E2 COC (24 active plus 4 placebo tablets per cycle) and comparator drug (21 active plus 7 placebo tablets per cycle) would lead to obvious differences in the timing of withdrawal bleeding, which would then reveal the treatment.

Study population

Both pivotal studies included sexually active women (aged ≥18 and ≤50 years), at risk for pregnancy and not planning to use condoms; in need for contraception and willing to use an oral contraceptive (OC) for 12 months (13 cycles). Other inclusion criteria were BMI ≥17 and ≤35 kg/m^2 and good physical and mental health. Important exclusion criteria were contraindications for contraceptive steroids such as risk factors for arterial/venous thrombosis, severe hypertension or dyslipoproteinaemia, diabetes with vascular involvement, contraindications related to the anti-mineralocorticoid activity of DRSP-EE (as specifically indicated in the approved product label texts such as renal/ hepatic/ adrenal insufficiency), previous use of an injectable hormonal method of contraception (within six months of an injection with a three month duration, within four months of an injection with a two month duration and within two months of an injection with a one month duration), abnormal cervical smears and clinically relevant abnormal laboratory results as judged by the investigator at screening; postpartum, post-abortion or breastfeeding within two months of the start of trial medication; or use of drugs that interfere with the metabolism of contraceptive hormones

Study treatments, randomisation

In Trial 292001, 2080 women were planned to be randomly assigned in a 3:1 ratio to either NOMAC-E2 (Zoely) or DRSP-EE (Yasmin), leading to 1560 women using NOMAC-E2 (1260 subjects aged 18-35 years and 300 subjects aged >35 years) and 520 women using DRSP-EE (420 subjects aged 18-35 years and 100 subjects aged >35 years).

In Trial 292002, a total of 2320 subjects were planned to be enrolled of which 1740 subjects were to receive NOMAC-E2 (1410 subjects aged 18-35 years and 330 subjects aged >35 years) and 580 subjects were to receive DRSP-EE (470 subjects aged 18-35 years and 110 subjects aged >35 years).

Subjects were instructed to take one tablet per day at approximately the same time every day. Subjects not using a hormonal contraceptive were to start the trial medication on the first day of her menstrual period; subjects using a Progestogen-Only Pill (POP) were to stop taking the POP and start the trial medication on the next day (immediate switch), while those using an implant or hormone medicated IUD were to start on the day of its removal. In all of these cases a condom was used until the subject had completed seven days of uninterrupted active tablet intake. Subjects using a COC were to start the trial medication anytime within seven days after the last active tablet but at the latest on the day following usual tablet-free or placebo tablet interval of her previous COC. Management of missed tablets in pivotal studies was clearly stated in the study protocol.

To exclude enrolment bias, the randomization process was done by making use of an interactive voice response system (IVRS). Randomization was performed with an allocation ratio of 3:1 (NOMAC-E2: DRSP-EE) and was stratified by age class (≤35 years and >35 years).

[4] Present use or use within two months prior to the start of the trial medication of the following drugs: phenytoin, barbiturates, primidone, carbamazepine, oxcarbazepine, topiramate, felbamate, rifampicin, nelfinavir, ritonavir, griseofulvin, ketoconazole, sex steroids (other than pre- and post treatment contraceptive method) and herbal remedies containing Hypericum perforatum (St John's Wort).

Outcomes/endpoints, sample size and statistical methods

The subject was given an electronic diary on which she was asked to document on a daily basis whether a tablet was taken or not. This information was used as a measure for the extent of exposure and dosing compliance. The first day of each of the Cycles 2 to 13 was determined from the electronic diary. The following types of (individual) compliance were calculated:

(1) Compliance to the 28-day regimen (yes/no).[5]

(2) Overall compliance to tablet intake (%).[6]

Major discrepancies between this overall (per subject) compliance and the number of dispensed and returned tablets (more than 28 tablets difference in the number of tablets taken) were reported. Contraceptive efficacy was assessed from the occurrence of in treatment 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 two days (according to EU/Rest of the World definition) or 14 days (FDA definition). This complied with requests from regulatory authorities.

Cycle control was evaluated on the basis of vaginal bleeding pattern as recorded daily by subjects using electronic diaries. Acceptability was evaluated on the basis of discontinuation rates and reasons for discontinuation. All questionnaires were to evaluate symptoms at the beginning of the trial, after one and three cycles of use (to explore possible effects in the early stage of pill-use), after six cycles and after 13 cycles (to explore possible changes over longer periods of time). Acne was assessed by regular skin examinations. Endometrial biopsy classification (at screening and at the end of the trial) and population pharmacokinetics of NOMAC-E2 were assessed in subsets of subjects in Trial 292002.

The primary efficacy parameter in both pivotal studies was contraceptive efficacy, that is, the prevention of in treatment pregnancies, based on the Pearl Index (the number of 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 subgroup of women in the age class of ≤35 years. Secondary efficacy parameters were contraceptive efficacy analyses for the Restricted ITT Analysis Set for the age class of >35 years and for the overall age class; in additional contraceptive efficacy analyses, Pearl Index and life table methods were applied to the full ITT group in which all exposure was taken into account.

Other secondary parameters were vaginal bleeding patterns (cycle analysis, cumulative amenorrhea, reference period analysis). Satisfaction and health related quality of life, libido and menstrual symptoms were assessed by Patient Reported Outcome questionnaires (PROs) using the following questionnaires: the short form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), the McCoy Female Sexuality Questionnaire (MFSQ) and the Menstrual Distress Questionnaire (MDQ); skin (acne) examination and post-treatment evaluations were also done.

The "All Subjects Treated" (AST) group consisted of all randomized subjects who took at least one dose of trial medication. This population was used for all safety analyses. The

[5] Cycle length within 28±2 days. The overall subject compliance to the 28 day regimen was defined as the percentage of compliant cycles over all cycles of the subject. Summary statistics across subjects per cycle are presented showing the number and percentage of compliant cycles.

[6] Number of days with a tablet taken divided by the number of days where tablets should have been taken (times 100). The overall compliance to tablet intake was summarized by treatment group.

"intent to treat" (ITT) group used for contraceptive efficacy consisted of all subjects from the AST group with the exception of two subjects for whom it was decided to exclude all diary data from the analyses. The ITT analysis of vaginal bleeding patterns was based on all subjects in the ITT group who had at least one evaluable cycle (cycle analysis) or reference period (reference period analysis).

In addition, for the contraceptive efficacy analysis (Pearl Index), cycles expected not to be at risk for pregnancy (with recorded use of condoms or without confirmed sexual intercourse, as determined from the electronic diary data) were excluded from the ITT analysis. Assuming that the Pearl Index is in the range of 0.0 to 2.0 (for sample size purposes), an exposure of 16675 evaluable cycles to NOMAC-E2 in both trials together was required in women ≤35 years, resulting in an exposure of 642 woman years per trial. Each pivotal trial was designed to contribute half of the required exposure. Assuming 35% discontinuations (contributing an average of three cycles of exposure) and up to 30% non-evaluable cycles, approximately 1260 subjects were to be randomized to NOMAC- E2 in this age subset (18-35 years) and 420 subjects to the DRSP-EE comparator group.

Results of pivotal study 292001

Participant flow

Of the 2126 randomised and treated subjects (NOMAC-E2=1591, DRSP-EE= 535), 1552 subjects completed the trial (1142 on NOMAC-E2 and 410 subjects on DRSP-EE). Of the 574 subjects (27.0%) who discontinued prematurely from treatment, 449 subjects (28.2%) were randomized to NOMAC-E2 and 125 subjects (23.4%) to DRSP-EE (Table 3).

Table 3: Number (%) of subjects who discontinued prematurely from treatment (all subjects group)

Primary reason for discontinuation[a]	NOMAC-E2 (N=1591)		DRSP-EE (N=535)		Total (N=2126)	
	n	%	n	%	n	%
Adverse Event / Serious Adverse Event	290	18.2	56	10.5	346	16.3
Unacceptable vaginal bleeding	63	4.0	4	0.7	67	3.2
Other (S)AEs	227	14.3	52	9.7	279	13.1
Withdrawal of informed consent	19	1.2	4	0.7	23	1.1
Pregnancy	6	0.4	3	0.6	9	0.4
Pregnancy wish	16	1.0	8	1.5	24	1.1
Lost to follow-up	40	2.5	17	3.2	57	2.7
Other reason	78	4.9	37	6.9	115	5.4
Total discontinuations	449	28.2	125	23.4	574	27.0

[a] According to the investigator's judgment.

Subjects discontinued most frequently due to (serious or non-serious) adverse events (AEs) (16.3%) with a higher percentage in the NOMAC-E2 group (18.2%) compared to DRSP-EE (10.5%). The second most frequently reported reason for premature discontinuation was 'other reasons' (4.9% in the NOMAC-E2 group and 6.9% in the DRSP-EE group). Overall, 43 patients (2%) had a major protocol violation with similar incidence in the two treatment groups.

The demographics of the subjects between the treatment groups were similar with respect to age, race, ethnicity, body weight and height, and BMI at screening. The mean (standard deviation [SD]) age was 28.0 (7.0) years, body weight was 63.5 (10.4) kg, and BMI was 23.0 (3.5) $kg/m^{2.}$ Most of the subjects were White (94.2%), with moderate menstrual flow for about 5 days and had used COC (66-67%) as prior contraception.

Overall, the regimen compliance defined by a cycle length of 28±2 days was high and did not differ between the treatment groups (96.6% and 96% of all cycles in the NOMAC-E2 and DRSP-EE groups, respectively). Regimen compliance expressed for each subject as the percentage of compliant cycles out of all cycles of the subject was also similar in both groups.

In contrast, daily tablet intake compliance (based on the electronic diaries) was expressed for each subject as the percentage of days with tablet taken over all cycles of the subject. In both treatment groups, the tablet intake compliance appeared to be low; only 81.7% in the NOMAC–E2 group and 75.5% in the DRSP-EE group had at least 75% overall tablet intake compliance. However, in most cases non-compliance to tablet intake was based on missing data rather than tablets entered as 'not taken'. However, drug accountability data showed that more than 90% of the subjects (94.8% in the NOMAC–E2 group and 91.4% in the DRSP-EE group) had a tablet intake compliance of at least 95%.

Furthermore, the compliance decreased steadily over time in both treatment groups. In the NOMAC-E2 group, the percentage of subjects with more than two days with forgotten (or missing) tablets increased from 11.2% in Cycle 1 to 38.8% in Cycle 6 to 43.7% in Cycle 9 to 52.9% in Cycle 13. A similar trend was observed in the analysis of vaginal bleeding patterns where the non-evaluability of cycles (that is, more than two consecutive days with missing bleeding information) steadily increased over time from 4.8% in Cycle 1 to 36.8% in Cycle 13. Similar trends over time with only slightly higher non-evaluability rates were observed for the DRSP-EE group both for tablet data as well as bleeding data. Overall, the intake compliance was slightly higher in the NOMAC-E2 group than in the DRSP-EE group independent of the method of calculation (diary data or drug accountability data).

Primary efficacy results

Overall, seven in-treatment pregnancies occurred between the first and last day of trial medication (active or placebo) extended with a maximum of two days (4/1442 in the NOMAC-E2 group and 3/486 in the DRSP-EE group). Overall, 16 treatment pregnancies occurred with an estimated date of conception more than 14 days after last day of trial medication (13/1442 in the NOMAC-E2 group and 3/486 in the DRSP-EE group). In total, nine pregnancies occurred in non-treated subjects (8 in the NOMAC-E2 group and 1 in the DRSP-EE group) and pregnancy was the primary reason for not being treated in all the cases.

For the NOMAC-E2 group (and overall age class), 35.8% of all cycles were considered as 'not at risk' (20.2% missing responses, 13.0% of cycles without intercourse and 2.5% of cycles with intercourse, but always use of condoms). Similar results were observed for the DRSP-EE group. Furthermore, no major differences were observed between the two age groups (≤ or >35 years) in the number of cycles "not as risk".

For the primary efficacy analysis, when using the two day extension of the in treatment period, the estimated Pearl Indices in the age class of ≤35 years were 0.57 (95% CI: [0.16; 1.46]) for the NOMAC-E2 group and 1.26 (95% CI: [0.26; 3.69]) for the DRSP-EE group. When using the 14 day extension period, the estimated Pearl Indices were 1.0 (95% CI: [0.40; 2.06]) for the NOMAC-E2 group and 1.68 (95% CI: [0.46; 4.31] for the DRSP-EE group (Table 4).

Table 4: Contraceptive efficacy: Pearl index with 95% CI – primary efficacy analysis (restricted ITT set)

Age	Treatment group	N	Exposure		In-treatment pregnancies (with +2-day window)[a]			In-treatment pregnancies (with +14-day window)[b]		
			28-day cycles	WY	Pregnancies	Pearl Index estimate	95 % CI	Pregnancies	Pearl Index estimate	95 % CI
Overall	NOMAC-E2	1442	11143	857.2	4	0.467	[0.1271, 1.1948]	7	0.817	[0.3283, 1.6826]
	DRSP-EE	486	3836.2	295.1	3	1.017	[0.2097, 2.971]	4	1.356	[0.3693, 3.4707]
≤ 35	NOMAC-E2	1193	9110.7	700.8	4	0.571	[0.1555, 1.4614]	7	0.999	[0.4016, 2.058]
	DRSP-EE	402	3092.3	237.9	3	1.261	[0.2601, 3.6858]	4	1.682	[0.4582, 4.3056]
> 35	NOMAC-E2	249	2032.5	156.3	0	0.000	[0, 2.3594]	0	0.000	[0, 2.3594]
	DRSP-EE	84	743.9	57.2	0	0.000	[0, 6.4466]	0	0.000	[0, 6.4466]

[a] Pregnancies with conception date from the day of first intake of trial medication up to and including the days of last intake of trial medication extended with a maximum of 2 days.
[b] Pregnancies with conception date from the day of first intake of trial medication up to and including the days of last intake of trial medication extended with a period of 14 days.
WY = woman year (defined by 13 x 28 days).
Confidence intervals are based on Poisson (λT) distribution, where λ denotes the Pearl Index and T is the total extent of exposure. For Pearl Index=0 an upper confidence limit of 97.5% was used.

The ratio of Pearl Indices of the two treatment groups was not statistically significantly different from 1 in either analysis (Table 5).

Table 5: Pearl index with 95% CI in treatment pregnancies with maximum extension of 14 days including ratio of NOMAC-E2 vs DRSP-EE

Ageclass	Treatment group	Number of subjects	Total extent of exposure		In-treatment pregnancies	Pearl Index estimate	95% Confidence interval	Ratio of Pearl Indices NOMAC-E2 vs DRSP-EE		
			28-day cycles	Woman years				Estimate	95% Confidence interval	p-value
Overall	NOMAC-E2	1442	11143.2	857.2	7	0.817	(0.3283, 1.6826)	0.602	(0.1532, 2.8065)	0.607
	DRSP-EE	486	3836.2	295.1	4	1.356	(0.3693, 3.4707)			
> 35	NOMAC-E2	249	2032.5	156.3	0	0.000	(0, 2.3594)			
	DRSP-EE	84	743.9	57.2			(0,)			
<= 35	NOMAC-E2	1193	9110.7	700.8	7	0.999	(0.4016, 2.058)	0.594	(0.151, 2.767)	0.592
	DRSP-EE	402	3092.3	237.9	4	1.682	(0.4582, 4.3056)			

Supportive evidence was provided by the primary efficacy analysis in the ITT group (in which all exposure was taken into account) and the PP analysis (Table 6).

Table 6: Contraceptive efficacy: Pearl index with 95% CI – supportive efficacy analysis (ITT and PP sets)

Analysis	Age	Treatment group	N	Exposure (WY)	In-treatment pregnancies (with +2-day window)[a]		
					Pregnancies	Pearl Index estimate	95% CI
ITT	Overall	NOMAC-E2	1589	1326.8	4	0.301	[0.0821, 0.7719]
		DRSP-EE	535	466.1	3	0.644	[0.1327, 1.8808]
	≤ 35	NOMAC-E2	1317	1089.7	4	0.367	[0.1, 0.9399]
		DRSP-EE	443	383.0	3	0.783	[0.1615, 2.2892]
	> 35	NOMAC-E2	272	237.2	0	0.000	[0, 1.5555]
		DRSP-EE	92	83.2	0	0.000	[0, 4.4364]
PP	Overall	NOMAC-E2	1560	570.8	4	0.701	[0.1909, 1.7941]
		DRSP-EE	521	197.4	2	1.013	[0.1227, 3.6607]
	≤ 35	NOMAC-E2	1292	458.9	4	0.872	[0.2375, 2.2318]
		DRSP-EE	430	154.4	2	1.296	[0.1569, 4.6802]
	> 35	NOMAC-E2	268	111.9	0	0.000	[0, 3.2952]
		DRSP-EE	91	43.0	0	0.000	[0, 8.5804]

[a] In-treatment pregnancies are 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.
WY = woman year (defined by 13 x 28 days).
Confidence intervals are based on Poisson (λT) distribution, where λ denotes the Pearl Index and T is the total extent of exposure. For Pearl Index=0 an upper confidence limit of 97.5% was used.

In additional analyses, Pearl Index and life table methods were applied to the full ITT group in which all exposure was taken into account. Since the number of pregnancies in the ITT analyses and in the restricted ITT analyses were to be the same per analysis rules, these analyses differed only in the decreased exposure in the Restricted ITT Analysis Set compared to the ITT group. For the ITT group, when using the two day extension of the in-treatment period, the estimated Pearl Indices for the overall age class were 0.30 (95% CI: [0.08; 0.77]) for the NOMAC-E2 group and 0.64 (95% CI: [0.13; 1.88]) for the DRSP-EE group. The Kaplan-Meier estimates (and 95% CI) of the cumulative probabilities of pregnancy at Day 364 were 0.33 (95% CI: [0.12; 0.87]) for the NOMAC-E2 group and 0.64 (95% CI: [0.21; 1.96]) for the DRSP-EE group. These results were consistent with the Pearl Index analyses. Similarly, in the age class of ≤35 years the estimated Pearl Indices were 0.37 (95% CI: [0.1; 0.94]) for the NOMAC-E2 group and 0.78 (95% CI: [0.16; 2.29]) for the DRSP-EE group, resulting in cumulative probabilities of pregnancy at Day 364 of 0.40 (95% CI: [0.15; 1.06]) for the NOMAC-E2 group and 0.77 (95% CI: [0.25; 2.38]) for the DRSP-EE group; similar results were observed when using the 14 day extension for the in-treatment period.

Secondary efficacy analyses

Vaginal bleeding patterns

For the ITT analysis, the relative number of evaluable cycles ranged from 93.1% (Cycle 1) to 60.7% (Cycle 13) in the NOMAC-E2 group and from 88.7% (Cycle 1) to 60.4% (Cycle 13) in the DRSP-EE group.[7] The occurrences of breakthrough bleeding/spotting were slightly higher in the NOMAC-E2 group (from 14.1% to 32.9% from Cycles 1 to 13) compared to the DRSP-EE group (10.5% to 27.7%), especially in the first few cycles (Table 7).

Table 7: Occurrence of breakthrough bleeding/spotting (ITT group)

	Treatment group								Difference NOMAC-E2 minus DRSP-EE (%)	
	NOMAC-E2				DRSP-EE					
Cycle	N	n	%	95% CI	N	n	%	95% CI	Estimate	95% CI
1	1466	483	32.9	[30.5, 35.4]	470	130	27.7	[23.7, 31.9]	NA	NA
2	1339	289	21.6	[19.4, 23.9]	440	75	17.0	[13.6, 20.9]	4.5	[0.4, 8.7]
3	1233	297	24.1	[21.7, 26.6]	398	54	13.6	[10.4, 17.3]	10.5	[6.4, 14.6]
4	1135	231	20.4	[18.0, 22.8]	389	59	15.2	[11.8, 19.1]	5.2	[0.9, 9.5]
5	1064	221	20.8	[18.4, 23.3]	368	62	16.8	[13.2, 21.1]	3.9	[-0.6, 8.5]
6	982	182	18.5	[16.1, 21.1]	349	53	15.2	[11.6, 19.4]	3.3	[-1.1, 7.8]
7	931	165	17.7	[15.3, 20.3]	320	45	14.1	[10.4, 18.4]	3.7	[-0.9, 8.2]
8	874	127	14.5	[12.3, 17.0]	298	47	15.8	[11.8, 20.4]	-1.2	[-6.0, 3.5]
9	861	129	15.0	[12.7, 17.5]	295	47	15.9	[11.9, 20.6]	-0.9	[-5.8, 3.9]
10	809	121	15.0	[12.6, 17.6]	271	32	11.8	[8.2, 16.3]	3.1	[-1.4, 7.7]
11	770	125	16.2	[13.7, 19.0]	277	29	10.5	[7.1, 14.7]	5.8	[1.3, 10.2]
12	743	110	14.8	[12.3, 17.6]	259	30	11.6	[8.0, 16.1]	3.2	[-1.4, 7.9]
13	666	94	14.1	[11.6, 17.0]	241	33	13.7	[9.6, 18.7]	0.4	[-4.7, 5.5]

N = Number of subjects with evaluable cycles; NA= Not applicable.
Note: No comparison was done for Cycle 1 due to the different starting procedures related to the pre-trial use of contraceptives.

[7] Electronic diaries did not utilize any built-in tools to trigger subjects to enter data. Therefore, the information on the start of a new tablet strip was not always correctly available in the diary (either sometimes forgotten or entered more than once for a cycle). Since this information was the basis for numbering the cycles for the cycle analysis, data handling conventions were defined in the SAP to avoid that very long or very short cycles led to a wrong classification (i.e., were assigned to a wrong cycle number). Among other rules, short cycles of <14 days length were ignored for the cycle numbering and received fractional cycle numbers.

The occurrences of absence of withdrawal bleeding was statistically significantly higher in the NOMAC-E2 group (ranged over the Cycles 1 to 12 from 17.7% to 30.6%) compared to the DRSP-EE group (from 2.9% to 6.1%); the occurrences of absence of withdrawal bleeding in the NOMAC-E2 group tended to increase over the cycles (Table 8).Table 8: Occurrence of absence of withdrawal bleeding (ITT group)

	Treatment group								Difference NOMAC-E2 minus DRSP-EE (%)	
	NOMAC-E2				DRSP-EE					
Cycle	N	n	%	95% CI	N	n	%	95% CI	Estimate	95% CI
1	1466	284	19.4	[17.4, 21.5]	470	14	3.0	[1.6, 4.9]	NA	NA
2	1339	237	17.7	[15.7, 19.9]	440	17	3.9	[2.3, 6.1]	13.8	[11.1, 16.6]
3	1233	258	20.9	[18.7, 23.3]	398	18	4.5	[2.7, 7.1]	16.4	[13.3, 19.5]
4	1135	244	21.5	[19.1, 24.0]	389	20	5.1	[3.2, 7.8]	16.4	[13.1, 19.6]
5	1064	245	23.0	[20.5, 25.7]	368	17	4.6	[2.7, 7.3]	18.4	[15.1, 21.7]
6	982	249	25.4	[22.7, 28.2]	349	10	2.9	[1.4, 5.2]	22.5	[19.3, 25.7]
7	931	245	26.3	[23.5, 29.3]	320	11	3.4	[1.7, 6.1]	22.9	[19.4, 26.3]
8	874	235	26.9	[24.0, 30.0]	298	9	3.0	[1.4, 5.7]	23.9	[20.3, 27.4]
9	861	245	28.5	[25.5, 31.6]	295	13	4.4	[2.4, 7.4]	24.0	[20.2, 27.9]
10	809	245	30.3	[27.1, 33.6]	271	12	4.4	[2.3, 7.6]	25.9	[21.9, 29.9]
11	770	232	30.1	[26.9, 33.5]	277	17	6.1	[3.6, 9.6]	24.0	[19.7, 28.3]
12	743	227	30.6	[27.3, 34.0]	259	12	4.6	[2.4, 8.0]	25.9	[21.7, 30.1]
13	666	279	41.9	[38.1, 45.7]	241	14	5.8	[3.2, 9.6]	36.1	[31.3, 40.9]

N = Number of subjects with evaluable cycles; NA = Not applicable.
Note: No comparison was done for Cycle 1 due to the different starting procedures related to the pre-trial use of contraceptives.

The occurrences of breakthrough bleeding (separate from spotting) ranged over the Cycles 1 to 13 from 2.8% to 8.8% in the NOMAC-E2 group and from 1.7% to 5.1% in the DRSP-EE group. Breakthrough spotting (spotting only) occurred more frequently than breakthrough bleeding in both treatment groups, ranging from 11.4% to 27.8% in the NOMAC-E2 group and from 6.9% to 25.1% in the DRSP-EE group. The occurrences of early withdrawal bleeding were low in both treatment groups, ranging from 2.3% to 9.7% in the NOMAC-E2 group and from 3.2% to 11.1% in the DRSP-EE group. The occurrences of continued withdrawal bleeding were also lower in the NOMAC-E2 group (23.7% to 30.8%) compared to the DRSP-EE group (54.6% to 62.7%) for all thirteen cycles. The medians of the number of withdrawal bleeding/ spotting days were slightly lower for subjects in the NOMAC-E2 group (3-4 days) compared to the DRSP-EE group (4-5 days).

In a subset of 589 subjects, the incidence of cumulative amenorrhea (the absence of bleeding or spotting in a given cycle up to the end of the trial) increased steadily over time, from 1.8% in Cycle 1 (that is, amenorrheic from Cycle 1 through Cycle 13) up to 7.9% in Cycle 9 (amenorrheic from Cycle 9 through Cycle 13) and 24.9% in Cycle 13 in the NOMAC-E2 group.[8] For the DRSP-EE group, the incidence of cumulative amenorrhea was low (≤1.4%). For the lower age class ≤35 years, the incidences of cumulative amenorrhea in the NOMAC-E2 group was similar to the overall age group, with a tendency to slightly lower percentages; for the upper age class (>35 years), the incidences of cumulative amenorrhea was markedly higher compared to the lower age class for all cycles, increasing from 5.7% in Cycle 1 to 17.0% in Cycle 9 to 29.2% in Cycle 13. No cumulative amenorrhea was observed for the upper age class in the DRSP-EE group.

[8] The analysis of cumulative amenorrhea (the absence of bleeding or spotting in a given cycle up to the end of the trial) required complete information on bleeding/spotting among the women who completed the trial (up to Day 364).

The analysis of bleeding patterns was also performed by a reference period analysis (RPA), which divides the subject's bleeding information into consecutive periods of 91 days. Reference period analysis was only performed for subjects in the ITT group who had at least one evaluable reference period. A reference period was considered to be non-evaluable in case of insufficient bleeding data, improper length of the reference period or both and was similar in both treatment groups. Across the different reference periods (RPs), the medians for the number of bleeding/spotting days, episodes or length of bleeding/ spotting episodes were slightly lower for the NOMAC-E2 group than the DRSP-EE group. The incidences of amenorrhea (neither bleeding, nor spotting throughout the reference period) were higher in the NOMAC-E2 group (range 6.1% in RP 1 to 13.4% in RP 4) compared to the DRSP-EE group (range 0.3% in RP 2 to 1.3% in RP5). Infrequent bleeding (less than three bleeding/spotting episodes starting within a reference period) also occurred more frequently in the NOMAC-E2 group (15.4% in RP 1 to 21.3% in RP 3) compared to the DRSP-EE group (2.4% in RP 1 to 3.8% in RP 2). For prolonged bleeding, the incidences ranged from 1.1% to 6.5% and 1.7% to 4.3%, respectively. Results of the reference period analysis for the lower and upper age classes were comparable to the overall age class.

Patient reported outcomes and acne

In both treatment groups, a small decrease from baseline in the Q-LES-Q global score (worsening) to last measurement was observed within the overall age class in both groups with no statistically significant difference (mean change from baseline $\pm$SD was -3.4 $\pm$13.9 and -2.5$\pm$14 in the NOMAC-E2 and DRSP-EE groups, respectively). For the McCoy Female Sexuality Questionnaire (MFSQ), a significantly greater decrease from baseline (worsening) to last measurement was observed within the overall age class in the NOMAC-E2 group compared to the DRSP-EE group (mean $\pm$SD=-5.2 $\pm$13.6 and -1.5$\pm$13.1, respectively, p<0.0001).[9] Worsening of each of the domain scores of the MFSQ (sexual interest, satisfaction, vaginal lubrication, orgasm and sexual partner) was greater with NOMAC-E2 compared with DRSP-EE. The 'imputed cases analysis' was also consistent with the 'complete cases analysis', both at Cycles 1, 3, 6, and 13 as within age classes and overall.

For the menstrual score of MDQ at last measurement, patients treated with NOMAC-E2 showed a statistically significant reduction of pain (mean$\pm$SD: NOMAC-E2 vs DRSP-EE -3.2 $\pm$19.6 vs +0.9$\pm$16.9, p<0.0001) and decrease in water retention (-4.3$\pm$19.4 vs -1.4 $\pm$19.2, p=0.0064). There were no statistically significant differences between treatment groups in MDQ Domain Score 3 (autonomic reactions), MDQ Domain Score 5 (impaired concentration), MDQ Domain Score 6 (behaviour change), MDQ Domain Score 8 (control). However, for the MDQ Domain Score 7 (arousal), significantly greater decrease (worsening) from baseline was observed for the NOMAC-E2 group compared with the DRSP-EE group (-4.9 $\pm$7.5 vs -1.7$\pm$16.3, p=0.0008).

Overall, 67% of the patients in both the treatment groups did not have acne at baseline (25% had mild acne, 7% had moderate acne, and 0.5% had severe acne). The distributions of acne presence and severity at last measurement showed a tendency towards improvement of acne in both treatment groups, but the difference in acne distributions at last measurement (adjusted for baseline values) was statistically significantly in favour of DRSP-EE (p<0.0001).

[9] Two types of analyses were performed, a 'complete cases analysis' which required all responses for a specific domain score to be present, and an 'imputed cases analysis' in which missing values were imputed

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Participant flow

Overall, a total of 2220 subjects were randomized and treated (1666 and 554 subjects on NOMAC-E2 and DRSP-EE, respectively) but only 1332 subjects completed the trial (988 and 344 subjects, respectively). Overall, 888 subjects discontinued prematurely from treatment (678 and 210 subjects in the NOMAC-E2 and DRSP-EE groups, respectively) (Table 9). Subjects discontinued most frequently due to serious AEs as primary reason (15.5%) with a higher percentage in the NOMAC-E2 group (17.3%) compared to DRSP-EE (10.1%).

Table 9: Number (%) of subjects who discontinued prematurely from treatment (all subjects group)

Primary reason for discontinuation [a]	NOMAC-E2 (N=1666)		DRSP-EE (N=554)		Total (N=2220)	
	n	%	n	%	n	%
Adverse event / serious adverse event	289	17.3	56	10.1	345	15.5
Unacceptable vaginal bleeding	64	3.8	10	1.8	74	3.3
Other (S)AEs	225	13.5	46	8.3	271	12.2
Pre-treatment (serious) adverse event	1	0.1			1	0.0
Withdrawal of informed consent	111	6.7	36	6.5	147	6.6
Pregnancy	15	0.9	5	0.9	20	0.9
Pregnancy wish	17	1.0	6	1.1	23	1.0
Lost to follow-up	175	10.5	73	13.2	248	11.2
Other reason	70	4.2	34	6.1	104	4.7
Total discontinuations	678	40.7	210	37.9	888	40.0

[a] According to the investigator's judgment.

During regular review of data before database lock a number of sites were identified to be excluded from all or specific analyses based on diary data (PROs, compliance) due to limited credibility of their electronic diary data. Overall, 153 subjects (7.0%) had a major protocol violation with slightly higher incidence in the DRSP-EE group (8.7%) compared with NOMAC (6.4%); the most common protocol violations were no diary data or one or more minor violations resulting in exclusion from efficacy analysis.

Baseline patient characteristics

The demographics of the subjects between the treatment groups were similar with respect to age, race, ethnicity, body weight and height, and BMI at screening. The mean (SD) age was 28.0 (7.0) years, body weight was 65.8 (12.6) kg and BMI was 24.5 (4.2) kg/m^2. Most of the subjects were White (85%) with moderate menstrual flow for about 5 days and had used COC (58%) as prior contraception.

Overall, the regimen compliance defined by a cycle length of 28±2 days was high and similar between the treatment groups (91.8% and 92.2% of all cycles in the NOMAC-E2 and DRSP-EE groups, respectively). Regimen compliance expressed for each subject as the percentage of compliant cycles out of all cycles of the subject was also similar in both groups.

In contrast, overall tablet intake compliance (based on the electronic diaries) appeared to be low in both treatment groups; only 60.8% in the NOMAC–E2 group and 55% in the DRSP-EE group had at least 75% overall tablet intake compliance. However, in most cases

non-compliance to tablet intake was based on missing data rather than tablets entered as 'not taken'. Drug accountability data showed that more than 90% of the subjects (94.8% in the NOMAC–E2 group and 91.4% in the DRSP-EE group) had a tablet intake compliance of at least 95%. Furthermore, the compliance decreased steadily over time in both treatment groups.

In the NOMAC-E2 group, the percentage of subjects with more than two days with forgotten (or missing) tablets increased from 11.2% in Cycle 1 to 38.8% in Cycle 6 to 43.7% in Cycle 9 to 52.9% in Cycle 13. A similar trend was observed in the analysis of vaginal bleeding patterns where the non-evaluability of cycles (more than two consecutive days with missing bleeding information) steadily increased over time from 4.8% in Cycle 1 to 36.8% in Cycle 13. Similar trends over time with only slightly higher non-evaluability rates were observed for the DRSP-EE group both for tablet and bleeding data. Overall, the tablet intake compliance was slightly higher in the NOMAC-E2 group than in the DRSP-EE group, independent of the method of calculation (diary data or drug accountability data).

Primary efficacy results

Overall, 19 in-treatment pregnancies occurred between the first and last day of trial medication (active or placebo) extended with two days after end of treatment (12 in the NOMAC-E2 group and 7 in the DRSP-EE group). Overall, 16 treatment pregnancies occurred with an estimated date of conception more than 14 days after last day of trial medication (13/1442 in the NOMAC-E2 group and 3/486 in the DRSP-EE group.

In the NOMAC-E2 group (and overall age class), 43.1% of all cycles were considered as 'not at risk' (29.0% missing responses, 10.2% of cycles without intercourse and 3.9% of cycles with intercourse but always use of condoms). Similar results were observed in the DRSP-EE group and there were no major differences between the two age classes. For the main analysis population (NOMAC-E2 group with ≤35 years), the percentage of cycles not at risk was 43.7%. For the primary efficacy analysis, when using the two day extension of the in-treatment period, the estimated Pearl Indices in the age class of ≤35 years were 1.96 (95% CI: [0.98; 3.51]) in the NOMAC-E2 group and 3.09 (95% CI: [1.13; 6.73]) in the DRSP-EE group. When the in-treatment period was extended with a period of 14 days, the estimated Pearl Indices in the age class of ≤35 years were 2.50 (95% CI: [1.37; 4.19]) in the NOMAC-E2 group and 4.64 (95% CI: [2.12; 8.80]) in the DRSP-EE group (Table 10). The NOMAC-E2 to DRSP-EE ratio of Pearl Indices of the two treatment groups was not statistically significantly different from one in either analysis (Table 11).

Table 10: Contraceptive efficacy: Pearl index with 95% CI – primary efficacy analysis (restricted ITT set)

Age	Treatment group	N	Exposure		In-treatment pregnancies (with +2-day window) [a]			In-treatment pregnancies (with +14-day window) [b]		
			28-day cycles	WY	Pregnancies	Pearl Index estimate	95 % CI	Pregnancies	Pearl Index estimate	95 % CI
Overall	NOMAC-E2	1370	8896.0	684.3	12	1.754	[0.9061, 3.0632]	15	2.192	[1.2268, 3.6154]
	DRSP-EE	444	3028.1	232.9	7	3.005	[1.2082, 6.1917]	10	4.293	[2.0587, 7.8951]
≤35	NOMAC-E2	1158	7285.6	560.4	11	1.963	[0.9798, 3.5119]	14	2.498	[1.3657, 4.1913]
	DRSP-EE	378	2522.7	194.1	6	3.092	[1.1347, 6.7299]	9	4.638	[2.1208, 8.8042]
>35	NOMAC-E2	212	1610.4	123.9	1	0.807	[0.0204, 4.4977]	1	0.807	[0.0204, 4.4977]
	DRSP-EE	66	505.5	38.9	1	2.572	[0.0651, 14.33]	1	2.572	[0.0651, 14.33]

[a] Pregnancies with conception date from the day of first intake of trial medication up to and including the days of last intake of trial medication extended with a maximum of 2 days.
[b] Pregnancies with conception date from the day of first intake of trial medication up to and including the days of last intake of trial medication extended with a period of 14 days.
WY = woman years (defined by 13 x 28 days).
Confidence intervals are based on Poisson (λT) distribution, where λ denotes the Pearl Index and T is the total extent of exposure. For Pearl Index=0 an upper confidence limit of 97.5% was used.

Table 11: Pearl index with 95% CI in treatment pregnancies with maximum extension of 14 days including ratio of NOMAC-E2 vs DRSP-EE

Ageclass	Treatment group	Number of subjects	Total extent of exposure		In-treatment pregnancies	Pearl Index estimate	95% Confidence interval	Ratio of Pearl Indices NOMAC-E2 vs DRSP-EE		
			28-day cycles	Woman years				Estimate	95% Confidence interval	p-value
Overall	NOMAC-E2	1370	8896.0	684.3	12	1.754	(0.9061, 3.0632)	0.584	(0.2118, 1.7494)	0.372
	DRSP-EE	444	3028.1	232.9	7	3.005	(1.2082, 6.1917)			
> 35	NOMAC-E2	212	1610.4	123.9	1	0.807	(0.0204, 4.4977)	0.314	(0.004, 24.638)	0.841
	DRSP-EE	66	505.5	38.9	1	2.572	(0.0651, 14.33)			
<= 35	NOMAC-E2	1158	7285.6	560.4	11	1.963	(0.9798, 3.5119)	0.635	(0.2152, 2.0905)	0.514
	DRSP-EE	378	2522.7	194.1	6	3.092	(1.1347, 6.7299)			
Overall	NOMAC-E2	1370	8896.0	684.3	15	2.192	(1.2268, 3.6154)	0.511	(0.2146, 1.2709)	0.156
	DRSP-EE	444	3028.1	232.9	10	4.293	(2.0587, 7.8951)			
> 35	NOMAC-E2	212	1610.4	123.9	1	0.807	(0.0204, 4.4977)	0.314	(0.004, 24.638)	0.841
	DRSP-EE	66	505.5	38.9	1	2.572	(0.0651, 14.33)			
<= 35	NOMAC-E2	1158	7285.6	560.4	14	2.498	(1.3657, 4.1913)	0.539	(0.2171, 1.4107)	0.223
	DRSP-EE	378	2522.7	194.1	9	4.638	(2.1208, 8.8042)			

Supportive evidence was provided by the primary efficacy analysis in the ITT group (in which all exposure was taken into account) and the PP analysis (Table 12).

Table 12: Contraceptive efficacy: Pearl index with 95% CI – supportive efficacy analysis (ITT and PP sets)

Analysis	Age	Treatment group	N	Exposure (WY)	In-treatment pregnancies (with +2-day window) [a]		
					Pregnancies	Pearl Index estimate	95% CI
ITT	Overall	NOMAC-E2	1644	1194.8	12	1.004	[0.519, 1.7544]
		DRSP-EE	549	402.8	7	1.738	[0.6986, 3.5803]
	≤35	NOMAC-E2	1385	985.1	11	1.117	[0.5574, 1.9981]
		DRSP-EE	466	334.0	6	1.796	[0.6593, 3.9102]
	>35	NOMAC-E2	259	209.7	1	0.477	[0.0121, 2.6567]
		DRSP-EE	83	68.8	1	1.452	[0.0368, 8.0926]
PP	Overall	NOMAC-E2	1539	363.2	10	2.753	[1.3201, 5.0628]
		DRSP-EE	501	117.3	6	5.115	[1.8772, 11.133]
	≤35	NOMAC-E2	1291	285.0	9	3.158	[1.4441, 5.9951]
		DRSP-EE	423	91.9	5	5.442	[1.7669, 12.699]
	>35	NOMAC-E2	248	78.3	1	1.278	[0.0323, 7.1188]
		DRSP-EE	78	25.4	1	3.934	[0.0996, 21.92]

[a] In-treatment pregnancies are 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.
WY = woman years (defined by 13 x 28 days).
Confidence intervals are based on Poisson (λT) distribution, where λ denotes the Pearl Index and T is the total extent of exposure. For Pearl Index=0 an upper confidence limit of 97.5% was used.

In additional analyses, Pearl Index and life table methods were applied to the full ITT group in which all exposure was taken into account. For the ITT group, when using the two day extension of the in treatment period, the estimated Pearl Indices for the overall age class were 1.0 (95% CI: [0.52; 1.75]) in the NOMAC-E2 group and 1.74 (95% CI: [0.70; 3.58]) in the DRSP-EE group. The PP analyses showed similar results, although the Pearl Index was almost double that observed in the ITT analyses. The Kaplan-Meier estimates (and 95% CI) of the cumulative probabilities of pregnancy at Day 364 were 1.01 [0.57; 1.79] in the NOMAC-E2 group and 1.74 [0.83; 3.64] in the DRSP-EE group. Similar results were observed in the age class ≤35 years resulting in cumulative probabilities of pregnancy at Day 364 of 1.13 (95% CI: [0.62; -2.06]) in the NOMAC-E2 group and 1.81 (95% CI: [0.81; -4.04]) in the DRSP-EE group.

Secondary efficacy results

Vaginal bleeding patterns

For the ITT analysis, the relative number of evaluable cycles steadily decreased from 77.5% (Cycle 1) to 44.1% (Cycle 13) in the NOMAC-E2 group and from 77.4% (Cycle 1) to 43.8% (Cycle 13) in the DRSP-EE group.

The occurrences of breakthrough bleeding/spotting ranged over thirteen cycles of treatment from 16.2% to 30.8% in the NOMAC-E2 group and from 8.7% to 21.1% in the DRSP-EE group and were statistically significantly higher in the NOMAC-E2 group compared to the DRSP-EE group in Cycles 2, 3, 4, 5, 6, 8 and 12 (Table 13). The occurrences of breakthrough bleeding/spotting in the NOMAC-E2 group gradually decreased from Cycle 1 to Cycle 13, whereas the occurrences in the DRSP-EE group fluctuated over the thirteen cycles. Breakthrough spotting (spotting only) occurred more frequently than breakthrough bleeding in both treatment groups, ranging from 12.0% to 25.5% in the NOMAC-E2 group and from 7.7% to 18.1% in the DRSP-EE group.

Table 13: Occurrence of breakthrough bleeding/spotting (ITT group)

	Treatment group								Difference NOMAC-E2 minus DRSP-EE (%)	
	NOMAC-E2				DRSP-EE					
Cycle	N	n	%	95% CI	N	n	%	95% CI	Estimate	95% CI
1	1202	370	30.8	(28.2, 33.5)	398	84	21.1	(17.2, 25.4)	NA	NA
2	950	243	25.6	(22.8, 28.5)	308	55	17.9	(13.7, 22.6)	7.7	(2.6, 12.8)
3	812	196	24.1	(21.2, 27.2)	256	40	15.6	(11.4, 20.7)	8.5	(3.2, 13.8)
4	739	152	20.6	(17.7, 23.7)	236	34	14.4	(10.2, 19.5)	6.2	(0.8, 11.5)
5	671	139	20.7	(17.7, 24.0)	229	29	12.7	(8.6, 17.7)	8.1	(2.8, 13.3)
6	628	125	19.9	(16.8, 23.2)	207	18	8.7	(5.2, 13.4)	11.2	(6.3, 16.2)
7	565	104	18.4	(15.3, 21.9)	196	25	12.8	(8.4, 18.3)	5.7	(-0.0, 11.3)
8	543	97	17.9	(14.7, 21.3)	189	23	12.2	(7.9, 17.7)	5.7	(0.0, 11.4)
9	507	85	16.8	(13.6, 20.3)	173	30	17.3	(12.0, 23.8)	-0.6	(-7.1, 5.9)
10	491	93	18.9	(15.6, 22.7)	170	29	17.1	(11.7, 23.6)	1.9	(-4.7, 8.5)
11	456	83	18.2	(14.8, 22.1)	160	27	16.9	(11.4, 23.6)	1.3	(-5.5, 8.1)
12	428	70	16.4	(13.0, 20.2)	152	15	9.9	(5.6, 15.8)	6.5	(0.6, 12.4)
13	383	62	16.2	(12.6, 20.3)	133	20	15.0	(9.4, 22.3)	1.2	(-6.0, 8.3)

N = Number of subjects with evaluable cycles; NA= Not applicable.
Note: No comparison was done for Cycle 1 due to the different starting procedures related to the pre-trial use of contraceptives.

The occurrences of absence of withdrawal bleeding in the NOMAC-E2 group tended to increase over the cycles, which were not observed for the women in the DRSP-EE group. The occurrences of the absence of withdrawal bleeding were statistically significantly higher in the NOMAC-E2 group (17.6% to 34.2%) compared to the DRSP-EE group (3.8% to 8.5%) for all cycles (Table 14).

Table 14: Occurrence of absence of withdrawal bleeding (ITT group)

	Treatment group								Difference NOMAC-E2 minus DRSP-EE (%)	
	NOMAC-E2				DRSP-EE					
Cycle	N	n	%	95% CI	N	n	%	95% CI	Estimate	95% CI
1	1202	216	18.0	(15.8, 20.3)	398	23	5.8	(3.7, 8.5)	NA	NA
2	950	167	17.6	(15.2, 20.2)	308	15	4.9	(2.8, 7.9)	12.7	(9.3, 16.1)
3	812	178	21.9	(19.1, 24.9)	256	15	5.9	(3.3, 9.5)	16.1	(12.0, 20.1)
4	739	184	24.9	(21.8, 28.2)	236	16	6.8	(3.9, 10.8)	18.1	(13.6, 22.6)
5	671	169	25.2	(21.9, 28.7)	229	13	5.7	(3.1, 9.5)	19.5	(15.1, 24.0)
6	628	166	26.4	(23.0, 30.1)	207	9	4.3	(2.0, 8.1)	22.1	(17.7, 26.5)
7	565	139	24.6	(21.1, 28.4)	196	13	6.6	(3.6, 11.1)	18.0	(13.0, 22.9)
8	543	152	28.0	(24.3, 32.0)	189	16	8.5	(4.9, 13.4)	19.5	(14.0, 25.0)
9	507	151	29.8	(25.8, 34.0)	173	8	4.6	(2.0, 8.9)	25.2	(20.1, 30.2)
10	491	147	29.9	(25.9, 34.2)	170	8	4.7	(2.1, 9.1)	25.2	(20.1, 30.4)
11	456	156	34.2	(29.9, 38.8)	160	6	3.8	(1.4, 8.0)	30.5	(25.2, 35.7)
12	428	141	32.9	(28.5, 37.6)	152	10	6.6	(3.2, 11.8)	26.4	(20.4, 32.3)
13	383	187	48.8	(43.7, 54.0)	133	7	5.3	(2.1, 10.5)	43.6	(37.3, 49.8)

N = Number of subjects with evaluable cycles; NA = Not applicable.
Note: No comparison was done for Cycle 1 due to the different starting procedures related to the pre-trial use of contraceptives.

The occurrences of early withdrawal bleeding were low in both treatment groups, ranging from 2.3% to 14.6% in the NOMAC-E2 group and from 3.8% to 11.6% in the DRSP-EE group. The occurrences of continued withdrawal bleeding were lower in the NOMAC-E2 group (19.8% to 32.9%) compared to the DRSP-EE group (52.3% to 62%) for all thirteen cycles. The medians of the number of withdrawal bleeding/ spotting days were slightly lower for subjects in the NOMAC-E2 group (2-4 days) compared to the DRSP-EE group (4-5 days).

In a subset of 256 subjects (194 in the NOMAC-E2 group and 62 in the DRSP-EE group), the incidence of cumulative amenorrhea increased steadily over time (2.6%, 11.3% and 27.3% in cycle 1, 9 and 12, respectively). For the DRSP-EE group, no cumulative amenorrhea was observed (0.0%).

The analysis of bleeding patterns was also performed by a reference period analysis (RPA). A reference period was considered to be non-evaluable in case of insufficient bleeding data, improper length of the reference period or both and this was similar in both treatment groups. Across the different reference periods (RPs), the medians for the number of bleeding/spotting days, episodes or length of bleeding/ spotting episodes for the NOMAC-E2 group were slightly lower than for the DRSP-EE group. The incidences of amenorrhea (neither bleeding, nor spotting throughout the reference period) were higher in the NOMAC-E2 group (range 4.5% to 13.7%) compared to the DRSP-EE group (range 0.8% to 3.2%). Infrequent bleeding (less than three bleeding/spotting episodes starting within a reference period) also occurred more frequently in the NOMAC-E2 group (15.8% to 21.6%) compared to the DRSP-EE group (1.3% to 2.7%). For prolonged bleeding, the incidences ranged from 0.8 to 6% and 0 to 6%, respectively. Results of the reference period analysis for the lower and upper age classes were comparable to the overall age class.

Patient reported outcomes and acne

A decrease from baseline (worsening) to last measurement in Q-LES-Q global score was observed within the overall age class and the difference between the two treatment groups in changes from baseline was statistically significant in favour of DRSP-EE (p=0.0038). For the MFSQ, a non-significantly greater decrease from baseline (worsening)

to last measurement was observed within the overall age class in the NOMAC-E2 group compared to the DRSP-EE group (mean ±SD=-3.2 ±13.8 and -1.4±13.1, respectively); a statistically significant difference in decrease from baseline between the treatment groups in favour of DRSP-EE was only observed at Cycle 3 (p=0.0087. Worsening of each of the domain scores of the MFSQ (satisfaction, vaginal lubrication, orgasm and sexual partner) showed no statistically significant difference between the NOMAC-E2 and DRSP-EE groups; the only exception was statistically significantly greater worsening in 'sexual interest' with NOMAC-E2. The 'imputed cases analysis' was also consistent with the 'complete cases analysis', both at Cycles 1, 3, 6 and 13 as within age classes and overall.

For the MDQ score at last measurement, a statistically significant decrease from baseline (reduction of pain) was observed for the NOMAC-E2 group compared with the DRSP-EE group (mean±SD: NOMAC-E2 vs DRSP-EE -4.1 ± 20.8 vs -0.9±19.2, p<0.0074). There were no statistically significant differences between treatment groups in MDQ Domain Scores of water retention, autonomic reactions, impaired concentration, behaviour change, control). However, for the MDQ Domain Score 7 (arousal), significantly greater decrease (worsening) from baseline was observed for the NOMAC-E2 group compared with the DRSP-EE group (-5.6 ±19.6 vs -0.1±17.4, p=0.012).

Overall, 67% of the patients in both the treatment groups did not have acne at baseline (27% had mild acne, 5.6% had moderate acne and 0.3% had severe acne). The distributions of acne presence and severity at last measurement showed a tendency towards improvement of acne in both treatment groups, but the difference in acne distributions at last measurement (adjusted for baseline values) was statistically significant in favour of DRSP-EE (p<0.0001).

Supportive studies

292004 was a non-inferiority, Phase III study comparing the effects of NOMAC-E2 (2.5 mg-1.5 mg; 24/4 regimen) versus a COC containing 150 µg levonorgestrel (LNG) and 30 µg EE (21/7 regimen) on haemostasis, lipid and carbohydrate metabolism in 118 healthy female volunteers over 6 treatment cycles. The sample size calculation was based on a one-sided 97.5% CI for the difference between the two treatment groups with respect to the absolute change from baseline in SHBG, in view of the assumed (non causal) association between SHBG and VTE risk.[10,11] Assuming absolute changes from baseline of 30 nmol/L in each group with a common single dose of 40 nmol/L estimated from previous trials, a sample size of 42 evaluable subjects per group was necessary to show that NOMAC-E2 was not inferior to LNG-EE 150/30 with respect to an absolute increase from baseline up to a margin (delta) of 25 nmol/L, with a power of 80% and a one-sided significance level of 0.025. This margin was less than half of the reported difference in absolute SHBG changes from baseline between LNG-EE 150/30 (30 nmol/L increase) and most other COCs (90 nmol/L increase). Assuming a 20% risk of discontinuations, a sample size of 60 women in each group was considered adequate. The treatment duration of six months was considered to be sufficiently long to establish the effects on all parameters. To exclude enrolment bias, the randomization process was done by making use of an interactive voice response system (IVRS). However, this study did not comply with the

[10] Odlind V, Milsom I, Persson I and Victor A. Can changes in sex hormone binding globulin predict the risk of venous thromboembolism with combined oral contraceptive pills? Acta Obstet Gynecol Scand 2002; 81: 482-90.

[11] EMEA Scientific advice NOMAC-E2. EMEA/CHMP/SAWP/148162/2006. Procedure no. EMEA/H/SA/705/1/2006/II.

CHMP Guidelines which states that such biomarker comparative studies should have a crossover design.[12]

Only 3 subjects had major protocol violations, while 22% (26/118) had minor protocol violations with similar incidence in both treatment groups. The treatment groups were similar with respect to baseline demographics, haemostasis, lipid, carbohydrate, adrenal/ thyroid and androgen parameters, and use of prior contraceptives. The most commonly used concomitant medications were antiinflammatory drugs, analgesics and antihistamines with no significant difference between treatment groups. The regimen compliance was very high in both treatment groups; furthermore, 93.1% and 87.7% of the subjects in the NOMAC-E2 and LNG-EE groups, respectively, took at least one tablet on at least 95% of the days during the treatment period. The primary endpoints for the study were special safety parameters which are discussed in the next section.

The number of cycles, regardless of cycle length, that were considered not to be at risk for pregnancy and therefore excluded from the restricted ITT analysis was 31 (9.4%) for the NOMAC-E2 group and 45 (13.8%) for the LNG-EE group. No pregnancies occurred during the trial and the upper limits of the 95% CI of the Pearl Index were similar between the two treatment groups for all three analyses (ITT, Restricted ITT and PP analysis). The occurrence of breakthrough bleeding/ spotting was similar in NOMAC-E2 and LNG-EE groups for the first 3 cycles, but higher in the NOMAC-E2 group for the Cycles 4, 5 and 6. The absence of withdrawal bleedings was statistically significantly higher in the NOMAC-E2 (maximally 19.2% per cycle) group compared with the LNG-EE group (maximally 2.0% per cycle).

Study **292005** was an open label, group comparative, randomized, single centre trial which evaluated the effect on bone mineral density (BMD) following 2 years of treatment with NOMAC-E2 2.5 mg – 1.5 mg in comparison to LNG-EE 0.150 mg – 0.030 mg in 110 young, healthy female volunteers. Of the 35 subjects (31.8%) who discontinued the trial prematurely, 13 subjects (23.2%) were randomized to NOMAC-E2 and 22 subjects (40.7%) were randomized to LNG-EE; AEs were the most common reason for discontinuation with slightly higher incidence in the LNG-EE group (24.1%, 13/54) compared with the NOMAC-E2 group (20.9%, 23/56). Discontinuation due to unacceptable vaginal bleeding occurred in two subjects (3.6%) in the NOMAC-E2 group and in one subject (1.9%) in the LNG-EE group. In both treatment groups, more than 90% of the subjects (92.9% in the NOMAC–E2 group and 98.1% in the LNG-EE group) had at least 90% compliant cycles. In the NOMAC-E2 and LNG-EE groups 94.6% and 94.2% of the subjects, respectively, took at least one tablet on at least 90% of the days during the treatment period.

No pregnancies were reported in the NOMAC-E2 group and one in treatment pregnancy was reported in the LNG-EE group during the trial analysis. The total exposure was higher in the NOMAC-E2 group (71.9 woman years) compared to the LNG-EE group (57.7 woman years) for the restricted ITT analysis set. The estimated Pearl Indices were 0.00 (95% CI: [0, 5.13]) for the NOMAC-E2 group and 1.73 (95% CI: [0.04, 9.66]) for the LNG-EE group.

The occurrence of breakthrough bleeding/spotting ranged over Cycles 2 to 26 from 2.3% to 27.3% in the NOMAC-E2 group and from 0.0% to 20.0% in the LNG-EE. The occurrence of absence of withdrawal bleeding was statistically significantly higher in the NOMAC-2 group (ranged over Cycles 2 to 25 from 16.4% to 48.8%) compared with the LNG-EE group (0.0% to 11.4%).

[12] EMEA, Committee for Medicinal Products for Human use (CHMP), 27 July 2005. Guideline on clinical investigation of steroid contraceptives in women. EMEA/CPMP/EWP/519/98 Rev 1.

With a standard deviation of the changes from baseline of the Z-scores in the range of 0.30 to 0.50, the number of completers in the study gave a detectable difference of 0.20 to 0.34 with a power of 80% and p=0.05. The bone mineral density (BMD) and Z-scores at baseline were higher in the NOMAC-E2 group compared to the LNG-EE group (Table 13). The mean (SD) Z-scores for lumbar spine were 0.351 (1.008) in the NOMAC-E2 group and -0.106 (1.125) in the LNG-EE group. The Z-scores for femoral neck were 0.321 (0.886) and 0.035 (1.071), respectively. These unbalances were not likely to affect the BMD analyses since the baseline adjusted ANCOVA was used. Following 2 years treatment, there was no statistically significant difference in effect on bone mineral density between NOMAC-E2 and LNG-EE groups.

Table 15: Summary statistics of BMD at screening (all subjects treated)

Site	Value	Statistic	NOMAC-E2 (N=56)	LNG-EE (N=54)
Lumbar spine (L_2-L_4)	BMD (final) (g/cm^2)	Mean (SD)	1.242 (0.121)	1.187 (0.135)
		Median (Min, Max)	1.255 (0.924,1.524)	1.169 (0.937,1.546)
	Z-score	Mean (SD)	0.351 (1.008)	-0.106 (1.125)
		Median (Min, Max)	0.450 (-2.30,2.70)	-0.265 (-2.19,2.88)
Femoral neck	BMD (final) (g/cm^2)	Mean (SD)	1.032 (0.107)	0.999 (0.129)
		Median (Min, Max)	1.044 (0.779,1.303)	0.982 (0.701,1.258)
	Z-score	Mean (SD)	0.321 (0.886)	0.035 (1.071)
		Median (Min, Max)	0.410 (-1.80,2.54)	-0.090 (-2.44,2.20)

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

Database used for meta-analysis of efficacy

Data from the two pivotal trials (292001 and 292002) and two supportive studies (292003 and 292004) provided the data for the efficacy meta-analyses. However, contraceptive efficacy was not the primary objective of the supportive trials.

During regular review of the data before database lock, it was decided to exclude 29 subjects (two subjects in Trial 292001 and 27 subjects in Trial 292002) from the ITT group due to limited credibility of their electronic data. In Trial 292002, all subjects (20 in total) from site 416 (centre MX 042) were identified before database lock to be excluded from all analyses due to non-reliability of all data, including two subjects (416007 and 416017) that were reported to be pregnant. The ITT was the basis for the efficacy analysis (contraceptive efficacy and vaginal bleeding patterns). From the ITT Group, subjects without at least one cycle at risk for pregnancy (with recorded use of condoms, or without confirmed vaginal intercourse, as determined from the patient diary data) were excluded, leading to the restricted ITT Group, which was the primary analysis dataset for Pearl Index analysis.

For the combined pivotal studies, 1123 of 3233 subjects (34.7%) in the NOMAC-E2 group and 335 of 1084 subjects (30.9%) in the DRSP-EE group discontinued prematurely from treatment with the most common reason for discontinuation being SAEs (NOMAC-E2: 17.9% vs DRSP-EE: 10.3%); discontinuations due to unacceptable vaginal bleeding occurred in slightly more subjects in the NOMAC-E2 group compared with the DRSP-EE group (3.9% vs 1.3%). The discontinuation rates as observed in the two pivotal trials were slightly lower compared to the discontinuation rates assumed in the sample size calculations (35% for Trial 292001 and 45% for Trial 292002).

In general, the trial populations were well balanced between the two treatments groups for all four individual trials with respect to gynaecological history, contraceptive history and socioeconomic data. A majority of the subjects had never been pregnant (52-61%), most had moderate menstrual flow (59-75%) for a median of 4-5 days and majority used

some form of contraception before start of study [COCs (32-72%), foam, condom, suppositories (6-43%) were most commonly used)]. In the two pivotal trials, majority of the subjects (64% NOMAC-E2 group and 63% in the DRSP-EE group) were switchers as they had used hormonal contraceptive method in the two months before the start of study treatment.

Contraceptive efficacy

The combined exposure to NOMAC-E2 (age group 18-35 years) of the two pivotal studies was 16396 cycles, equivalent to 1261 woman years and that to DRSP-EE was 5615 cycles, equivalent to 432 woman years. For the overall age class (18-50 years), the combined exposure to NOMAC-E2 was 20039 cycles (equivalent to 1542 woman years). The extent of exposure to NOMAC-E2 was 105 and 298 cycles in the supportive trials 292003 and 292004, respectively. Compliance to the recommended 28 day regimen (cycle length of 28±2 days) differed in the two pivotal trials. For NOMAC-E2 regimen compliance was 96.6% and 91.8% in studies 292001 and 292002, respectively; regimen compliance for DRSP-EE was 96.0% and 92.2%, respectively. No differences were observed with respect to regimen compliance between the treatment groups (NOMAC-E2 versus DRSP-EE) in both trials. In both pivotal studies, tablet intake compliance based on electronic diaries (days with missing tablet entry excluded) as well as the intake compliance derived from the Drug Accountability Form (dispensed minus returned tablets) was high with mean values of 98% or more for both treatment groups (NOMAC-E2 and DRSP-EE). In the pivotal studies, 39.2% of all cycles in the NOMAC-E2 group were considered as 'not at risk' with similar results in the DRSP-EE group. In addition, no major differences were observed between the two age classes (18-35 years and 35-50 years).

For the primary analysis population (restricted ITT aged 18-35 years), when using the two day extension of the in-treatment period, the estimated Pearl Indices were 1.19 (95% CI: [0.67; 1.96]) for the NOMAC-E2 group and 2.08 (95% CI: [0.95; 3.96]) for the DRSP-EE group; the estimated ratio of Pearl Indices of NOMAC-E2 versus DRSP-EE for the ITT Group for the adequate and well controlled trials combined in the age class 18-35 years was 0.58 (95% CI: [0.24;1.49], p-value=0.277). If the in treatment period was extended with a period of 14 days, the estimated Pearl Indices for the primary analysis population were 1.67 (95% CI: [1.03; 2.55]) for the NOMAC-E2 group and 3.01 (95% CI: [1.60; 5.15]) for the DRSP-EE group; the estimated ratio of Pearl Indices of NOMAC-E2 versus DRSP-EE for the ITT Group in the age class 18-35 years was 0.56 (95% CI: [0.27; 1.21], p-value=0.147).

Similar results were observed in the overall age class (18-50 years). The overall Pearl Index (method failure and user failure) 18-50 years of age was: 0.64 (upper limit 95% CI 1.03).

Since the number of pregnancies in the ITT analysis and restricted ITT analysis were the same, the ITT analyses differed only in the increased exposure in the ITT group compared to the restricted ITT analysis set and hence had slightly lower Pearl Indices. However, the estimated Pearl Indices for NOMAC-E2 and DRSP-EE in the PP analysis were higher compared to those in the restricted ITT and ITT analyses, since the PP exposure not only excluded cycles not at risk but also exposure days with defined protocol violations.

Table 16: Contraceptive efficacy: Ratio of Pearl index with 95% CI age class 18-35 years – restricted ITT and ITT sets

Analysis	Trial	In-treatment pregnancies[a] (with +two-day window)			In-treatment pregnancies[b] (with +14-day window)		
		Ratio of Pearl Indices NOMAC-E2 versus DRSP-EE	95 % CI for ratio	p-value[c]	Ratio of Pearl Indices	95 % CI for ratio	p-value[c]
Restr ITT analysis set	Combined	0.571	(0.234, 1.4792)	0.268	0.553	(0.2643, 1.2025)	0.140
	292001	0.453	(0.0766, 3.0894)	0.501	0.594	(0.151, 2.767)	0.592
	292002	0.635	(0.2152, 2.0905)	0.514	0.539	(0.2171, 1.4107)	0.223
ITT Group	Combined	0.576	(0.2361, 1.4926)	0.277	0.558	(0.2668, 1.2134)	0.147
	292001	0.469	(0.0793, 3.1992)	0.530	0.615	(0.1564, 2.8653)	0.630
	292002	0.622	(0.2107, 2.0469)	0.489	0.527	(0.2126, 1.3813)	0.206

[a] Pregnancies with conception date from the day of first intake of trial medication up to and including the days of last intake of trial medication extended with a maximum of two days
[b] Pregnancies with conception date from the day of first intake of trial medication up to and including the days of last intake of trial medication extended with a period of 14 days
[c] Equality of the Pearl Indices is tested by conditioning on the total number of pregnancies in both treatment groups (resulting in a binomial distribution) and rejecting for large and small relative number of pregnancies in one arm (two-sided, α=0.05).
CI = Confidence Interval.

Table 17: Contraceptive efficacy: Ratio of Pearl index with 95% CI age class 18-50 years – restricted ITT and ITT sets

Analysis	Trial	In-treatment pregnancies [a] (with +two-day window)			In-treatment pregnancies [b] (with +14-day window)		
		Ratio of Pearl Indices NOMAC-E2 versus DRSP-EE	95 % CI for ratio	p-value [c]	Ratio of Pearl Indices NOMAC-E2 versus DRSP-EE	95 % CI for ratio	p-value[c]
Restr ITT analysis set	Combined	0.548	(0.2338, 1.351)	0.203	0.536	(0.2633, 1.1376)	0.108
	292001	0.459	(0.0777, 3.1335)	0.513	0.602	(0.1532, 2.8065)	0.607
	292002	0.584	(0.2118, 1.7494)	0.372	0.511	(0.2146, 1.2709)	0.156
ITT Group	Combined	0.551	(0.2353, 1.3592)	0.208	0.542	(0.2649, 1.1445)	0.111
	292001	0.468	(0.0792, 3.1978)	0.529	0.615	(0.1563, 2.864)	0.629
	292002	0.576	(0.2098, 1.7327)	0.362	0.506	(0.2125, 1.2568)	0.150

[a] Pregnancies with conception date from the day of first intake of trial medication up to and including the days of last intake of trial medication extended with a maximum of two days.
[b] Pregnancies with conception date from the day of first intake of trial medication up to and including the days of last intake of trial medication extended with a period of 14 days.
[c] Equality of the Pearl Indices is tested by conditioning on the total number of pregnancies in both treatment groups (resulting in a binomial distribution) and rejecting for large and small relative number of pregnancies in one arm (two-sided, alpha=0.05).
CI = Confidence Interval.

The life table analysis for the restricted ITT Group, 18-35 years (pivotal studies combined), using the two day extension of the in treatment period showed that Kaplan-Meier estimates (and 95% CI) of the cumulative probabilities of pregnancies at Day 364 were 0.80 (95% CI: [0.48; 1.34]) for the NOMAC-E2 group and 1.34 (95% CI: [0.70; 2.56]) for the DRSP-EE group. When the in-treatment period was extended with a period of 14 days, the Kaplan-Meier estimates for the age class 18-35 years, adequate and well controlled trials combined, were: 1.12 (95% CI: [0.73; 1.72]) for the NOMAC-E2 group and 1.97 (95% CI: [1.15; 3.39]) for the DRSP-EE group. There were no statistically significant differences (α=0.05) between the treatment groups with respect to cumulative probability of in-treatment pregnancies at Day 364. For the restricted ITT Group, when using the two day extension of the in-treatment period, the Hazard ratios (for risk of in-treatment pregnancies) of NOMAC-E2 versus DRSP-EE were <0.60 using the 2 day and 14 day extension window.

Evaluator's comments:

For NOMAC-E2 the difference between the upper 95% CI and the Pearl Index estimate is 0.77 and 0.88 for the two day and 14 day extension in-treatment period, respectively. These differences are both smaller than 1.0 and thus satisfy

the criterion for the precision of the two-sided 95% CI for the Pearl Index estimate according to the CHMP Guidelines. Furthermore, the Pearl Index results in the restricted ITT population were confirmed by similar results in the life table analysis, which included all treatment cycles reflecting real world usage.

Return of fertility

In trials 292001 and 292002, for more than 97% of the subjects in both treatment groups, who switched to no contraceptive or a non-hormonal contraceptive method (and who were not pregnant), menses had returned at the post-treatment assessment; post-treatment was scheduled six weeks after end of treatment visit (either after Cycle 13 or early discontinuation).

Vaginal bleeding pattern

The occurrences of breakthrough bleeding/spotting in the NOMAC-E2 group were slightly higher as compared to the DRSP-EE group in the first cycles of use. The incidence of breakthrough bleeding/spotting gradually decreased in the following cycles, although the occurrences of breakthrough bleeding/spotting were statistically significantly higher in the NOMAC-E2 group as compared to the DRSP-EE group in Cycles 2, 3, 4, 5, 6, 7, 11 and 12 (Table 18).

Table 18: Occurrence of breakthrough bleeding/spotting (ITT group)

Cycle	NOMAC-E2				DRSP-EE				NOMAC-E2 minus DRSP-EE (%)	
	N	n	%	95% CI	N	n	%	95% CI	Estimate	95% CI
1	2668	853	32.0	(30.2, 33.8)	868	214	24.7	(21.8, 27.7)	–	–
2	2289	532	23.2	(21.5, 25.0)	748	130	17.4	(14.7, 20.3)	5.9	(2.6, 9.1)
3	2045	493	24.1	(22.3, 26.0)	654	94	14.4	(11.8, 17.3)	9.7	(6.5, 13.0)
4	1874	383	20.4	(18.6, 22.3)	625	93	14.9	(12.2, 17.9)	5.6	(2.2, 8.9)
5	1735	360	20.7	(18.9, 22.7)	597	91	15.2	(12.5, 18.4)	5.5	(2.0, 9.0)
6	1610	307	19.1	(17.2, 21.1)	556	71	12.8	(10.1, 15.8)	6.3	(2.9, 9.7)
7	1496	269	18.0	(16.1, 20.0)	516	70	13.6	(10.7, 16.8)	4.4	(0.9, 8.0)
8	1417	224	15.8	(13.9, 17.8)	487	70	14.4	(11.4, 17.8)	1.4	(-2.2, 5.1)
9	1368	214	15.6	(13.8, 17.7)	468	77	16.5	(13.2, 20.1)	-0.8	(-4.7, 3.1)
10	1300	214	16.5	(14.5, 18.6)	441	61	13.8	(10.7, 17.4)	2.6	(-1.2, 6.4)
11	1226	208	17.0	(14.9, 19.2)	437	56	12.8	(9.8, 16.3)	4.2	(0.4, 7.9)
12	1171	180	15.4	(13.4, 17.6)	411	45	10.9	(8.1, 14.4)	4.4	(0.8, 8.1)
13	1049	156	14.9	(12.8, 17.2)	374	53	14.2	(10.8, 18.1)	0.7	(-3.4, 4.8)

N = number of subjects with evaluable cycle; n = number of evaluable cycles with breakthrough bleeding/spotting; CI= Confidence Interval.
Note: No comparison was done for Cycle 1 due to the different starting procedures related to the pre-trial use of contraceptives.

The occurrences of the absence of withdrawal bleeding were statistically significantly higher in the NOMAC-E2 group (17-44%) compared to the DRSP-EE group (4-6%) for all cycles (Table 19).

Table 19: Occurrence of absence of withdrawal bleeding (ITT group)

Cycle	NOMAC-E2				DRSP-EE				NOMAC-E2 minus DRSP-EE (%)	
	N	n	%	95% CI	N	n	%	95% CI	Estimate	95% CI
1	2668	500	18.7	(17.3, 20.3)	868	37	4.3	(3.0, 5.8)	--	--
2	2289	404	17.6	(16.1, 19.3)	748	32	4.3	(2.9, 6.0)	13.4	(11.2, 15.5)
3	2045	436	21.3	(19.6, 23.2)	654	33	5.0	(3.5, 7.0)	16.3	(13.8, 18.7)
4	1874	428	22.8	(21.0, 24.8)	625	36	5.8	(4.1, 7.9)	17.1	(14.4, 19.7)
5	1735	414	23.9	(21.9, 25.9)	597	30	5.0	(3.4, 7.1)	18.8	(16.2, 21.5)
6	1610	415	25.8	(23.7, 28.0)	556	19	3.4	(2.1, 5.3)	22.4	(19.7, 25.0)
7	1496	384	25.7	(23.5, 28.0)	516	24	4.7	(3.0, 6.8)	21.0	(18.2, 23.9)
8	1417	387	27.3	(25.0, 29.7)	487	25	5.1	(3.3, 7.5)	22.2	(19.1, 25.2)
9	1368	396	28.9	(26.6, 31.4)	468	21	4.5	(2.8, 6.8)	24.5	(21.4, 27.5)
10	1300	392	30.2	(27.7, 32.7)	441	20	4.5	(2.8, 6.9)	25.6	(22.5, 28.8)
11	1226	388	31.6	(29.1, 34.3)	437	23	5.3	(3.4, 7.8)	26.4	(23.0, 29.7)
12	1171	368	31.4	(28.8, 34.2)	411	22	5.4	(3.4, 8.0)	26.1	(22.6, 29.5)
13	1049	466	44.4	(41.4, 47.5)	374	21	5.6	(3.5, 8.5)	38.8	(35.0, 42.6)

N = number of subjects with evaluable cycles; n = number of evaluable cycles with absence of withdrawal bleeding.
Note: No comparison was done for Cycle 1 due to the different starting procedures related to the pre-trial use of contraceptives.

For those subjects who had breakthrough bleeding/spotting, the medians of the number of breakthrough bleeding/spotting days were similar between the two treatment groups, ranging from 2.0 to 3.0 days. For those subjects who had a withdrawal bleeding/spotting, the medians of the number of withdrawal bleeding/spotting days were slightly lower for subjects in the NOMAC-E2 group (3-4 days) as compared to the DRSP-EE group (4-5 days). Breakthrough spotting (spotting only) occurred more frequently than breakthrough bleeding in both treatment groups, ranging over the Cycles 2 to 13 from 20.8% to 11.6% in the NOMAC-E2 group and from 14.4% to 7.3% in the DRSP-EE group.

The occurrences of early withdrawal bleeding were low in both treatment groups, ranging over the Cycles 1 to 12 from 11.9% to 2.4% in the NOMAC-E2 group and from 11.3% to 3.6% in the DRSP-EE group. The occurrences of continued withdrawal bleeding were lower in the NOMAC-E2 group as compared to the DRSP-EE group for all thirteen cycles. The percentage of subjects with a continued withdrawal bleeding was lower in the NOMAC-E2 group (31.7% to 23.3% over Cycles 1 to 12) compared to the DRSP-EE group (61.0% to 56.2%).

The analysis of cumulative amenorrhea required complete information on bleeding/ spotting among the women who completed the trial (up to Day 364). In a subset of 845 subjects (635 in the NOMAC-E2 group and 210 in the DRSP-EE group), the incidence of cumulative amenorrhea in the NOMAC-E2 group increased steadily over time (2.0%, 9% and 25.7% in Cycle 1, 9 and 13, respectively. For the DRSP-EE group, the incidence of cumulative amenorrhea was low (≤1.0%). For the age class ≤35 years the incidences of cumulative amenorrhea in the NOMAC-E2 group were slightly lower as compared to the overall age class, whereas for the age class >35 years the incidences of cumulative amenorrhea were higher as compared to the overall age class, increasing from 4.9% in Cycle 1 to 17.1% in Cycle 9 to 28.7% in Cycle 13). No cumulative amenorrhea was observed for the upper age class of DRSP-EE.

RP analysis showed that the number of bleeding/ spotting episodes was similar in the NOMAC-E2 and DRSP-EE groups, although the median duration of bleeding/ spotting

episodes was slightly longer in the DRSP-EE group. The incidence of amenorrhea was much higher in the NOMAC-E2 group.

Patient reported outcomes and acne

Baseline levels of the Q-LES-Q global score, measuring Satisfaction and Health Related Quality of Life, were high in both treatment groups reflecting a healthy population. At last measurement, both treatment groups showed a small decrease (worsening) in the Satisfaction and health related quality of life (Q-LES-Q) global score. This decrease was less pronounced in the DRSP-EE group.

Both treatment groups showed small decreases (worsening) in the MFSQ at last measurement as indicated by the global score. This decrease was less pronounced in the DRSP-EE group and was reflected mainly in MFSQ domain score 'sexual interest'. The results for the menstrual symptoms and mood (MDQ) questionnaire showed that both NOMAC-E2 and DRSP-EE were effective in reducing pre-menstrual and menstrual symptoms. NOMAC-E2 was more effective in reducing menstrual 'pain' compared to DRSP-EE, while DRSP-EE had a more neutral effect on 'arousal' in the menstrual phase as compared to NOMAC-E2.

In both treatment groups, the majority of the subjects with no acne at baseline were free from acne at last measurement (88.2% in the NOMAC-E2 group and 95.3% in DRSP-EE group). New acne developed in 11.8% of the subjects in the NOMAC-E2 group versus 4.7% of the subjects in the DRSP-EE group. In both treatment groups, more subjects with acne at baseline showed an improvement of acne (than a worsening of acne) at last measurement (50.9% and 62.3% in the NOMAC-E2 and DRSP-EE groups, respectively); worsening of acne was observed for 6.8% and 3.3% of the subjects, respectively, whereas 42.3% and 34.3%, respectively showed no changes in the severity of their acne.

Clinical studies in special populations

The subgroups analysed for efficacy were: age: ≤24, 25-35, ≥36 years; race: White, Asian, Black/African American, Other; smoking: yes/no; body weight: <60, 60-80, 80 kg; BMI: <18.5, 18.5-<25, 25-<30, ≥30 kg/m^2; Starters/switchers (switchers are subjects who used a hormonal contraceptive method within two months before the start of NOMAC-E2 treatment). There was a higher estimated Pearl Index in women aged <24 years, Black/ Asian or other races, those with BMI<18.5 kg/m^2 and those starting with oral COC (rather than switching from other COC). However, the contraceptive efficacy of NOMAC-E2 relative to the comparator DRSP-EE appeared to be independent of the subgroups analysed.

All the studies were conducted in women aged ≥18 to <50 years with childbearing potential and requiring oral contraception. No studies were conducted in post-menarcheal adolescent girls aged 12-17 years. The sponsor has undertaken a study comparing the pharmacokinetics of NOMAC-E2 in post-menarcheal adolescent girls aged 12-17 years vs that in women aged 18-50 years (292011), although results of this study were not provided in this submission.

No relevant differences were found for any of the subgroups analysed with respect to the incidence of breakthrough bleeding/spotting. The incidences of absence of withdrawal bleeding were slightly higher in NOMAC-E2 users in the highest body weight/BMI category as compared to the other categories. In addition, absence of withdrawal bleeding was less frequently reported for starters than for switchers as well as the lowest age subgroup (≤24 years). The differences observed between the different subgroups were small and therefore not considered to be clinically relevant.

Evaluator's overall conclusions on clinical efficacy

Two dose finding studies (96-ESC and 98-ESC) were performed with combinations of 1.5 mg E2 and three doses of NOMAC, which led to the selection of NOMAC-E2 2.5 mg-1.5 mg, being the combination providing the optimum balance between ovulation inhibition and cycle control. Another study (02-ESC) comparing a regimen of 21 active tablets NOMAC-E2 2.5-1.5 mg followed by 7 placebo tablets (21/7 regimen) to the proposed regimen of 24 tablets NOMAC-E2 2.5-1.5 mg followed by 4 placebo tablets (24/4 regimen) for three cycles showed a better bleeding profile (shorter duration of withdrawal bleeding and a lower overall number of days with vaginal bleeding over three cycles of use) and increased contraceptive robustness for the 24/4 regimen. The dose of 1.5 mg E2 was selected based on its provision of adequate oestrogen levels for treating oestrogen deficiency symptoms (Naemis; sequential E2 1.5 mg for 10 days, followed by NOMAC-E2 3.75 mg - 1.5 mg for 14 days) and oestrogen replacement therapy and prevention of osteoporosis (Estreva; E2 1.5 mg) in postmenopausal women, as well as the absence of hypo- and hyperoestrogenic side effects at this dose in a large number of published trials employing various progestagen-E2 combinations in fertile women.

The 2 pivotal studies (292001 and 292002) involving 4433 healthy females aged 18-50 years were designed to obtain a sufficient number of evaluable cycles (cycles at risk for pregnancy) of exposure to NOMAC-E2 in the subset of women of 35 years or younger to fulfil both the FDA (two independent trials with 10,000 completed cycles) and the TGA-adopted EU criteria.[12] The study population in the pivotal studies was generally representative of the target patient population, although patients under 18 years were not evaluated. The majority of the women were experienced COC users with 60 to 66% having used a COC prior to the study. The active comparator used in the pivotal studies is available in Australia as Yasmin containing DRSP 3 mg+EE 30 µg (Bayer Schering); another similar COC available in Australia is Yaz (Bayer Schering), but the dose of EE (20 µg) in this preparation is less than that used in the Zoely pivotal studies. The efficacy endpoints and methods applied in the pivotal studies are generally considered standard approaches in the field of contraception.

NOMAC-E2 was effective as a contraceptive, as shown by the Pearl Index and the Life Table analysis. The criterion for the precision of the two-sided 95% CI for the Pearl Index estimate according to the TGA-adopted EU guideline was met. The estimated Pearl Indices (restricted ITT analysis set) in the age class 18-35 years (2-day window) were 1.19 (95% CI: [0.67; 1.96]) for the NOMAC-E2 group and 2.08 (95% CI: [0.95; 3.96]) for the DRSP-EE group. Life Table analysis showed that the Kaplan-Meier estimates (restricted ITT Group) at Day 364 in the age class 18-35 years were 0.80 (95% CI: [0.48; 1.34]) for the NOMAC-E2 group and 1.34 (95% CI: [0.70; 2.56]) for the DRSP-EE group. Similar results were observed with the 14 day extended in-treatment period (FDA definition).

The use of the Restricted ITT analysis (or calculation of the Pearl Index for method failure) as the primary efficacy endpoint was justified as the studies employed reliable methods for recording of compliance (electronic patient diaries). Furthermore, results observed in the Life Table analysis which included all cycles of the subjects and reflected real world usage were similar to those observed in the restricted patient group with exclusion of cycles expected not to be at risk for pregnancy (recorded use of condoms or without confirmed sexual intercourse from the electronic diary data). Robustness of the contraceptive efficacy primary results was confirmed by similar results in the overall ITT Group (18-50 years) analysis; the estimated Pearl Indices (2 day window) were 0.64 (95% CI: [0.36; 1.03]) for the NOMAC-E2 group and 1.15 (95% CI: [0.55; 2.12]) for the DRSP-EE group with similar results using the FDA-defined 14 day window.

The incidence of breakthrough bleeding/ spotting and of 'absence of withdrawal bleeding' was statistically significantly higher in women treated with NOMAC-E2 compared to those treated with DRSP-EE. Discontinuation due to 'unacceptable vaginal bleeding' was also higher in the NOMAC-E2 group compared to the DRSP-EE group (4.0% versus 0.7%). The incidence of cumulative amenorrhea was also higher in the women treated with NOMAC-E2 compared with DRSP-EE.

Overall, the PROs showed that there was no significant difference between NOMAC-E2 and DRSP-EE in terms of overall QOL (Q-LES-Q) and in fact showed worsening of sexual parameters (MFSQ). However, treatment with NOMAC-E2 did show significant reduction of pain and water retention (MDQ). Interpretation of the PRO measures was limited by the fact that the studies were open label due to different schedules of the two treatments (24/4 and 21/7 regimens). In both treatment groups, more subjects with acne at baseline showed an improvement of acne (than a worsening of acne) at last measurement (50.9% and 62.3% in the NOMAC-E2 and DRSP-EE groups, respectively).

Return to fertility: In the Phase II study 98-ESC/NOM-1-RD, return to fertility following 3 treatment cycles (with the 21/7 and 24/4 regimen of NOMAC-E2) was shown in all women during the post-treatment cycle; this was checked by measuring blood progesterone around Day 20 and if necessary a few days later (>3 ng/mL) and by recording occurrence of spontaneous menstruation at end of treatment. In the pivotal studies, 292001 and 292002, for more than 97% of the subjects in both treatment groups, who switched to no contraceptive or a non-hormonal contraceptive method (and who were not pregnant), menses had returned at the post-treatment assessment; post-treatment was scheduled six weeks after end of treatment visit (either After Cycle 13 or early discontinuation).

Safety

Introduction

The safety data of eight completed trials and in addition the serious adverse events (SAEs) of one ongoing trial (292005) are discussed in this section; more than 95% of all patients exposed to NOMAC-E2 were in the two pivotal Phase III studies 29001 and 29002. The safety data of the clinical pharmacology trials performed with a formulation and/or dose regimen different from the coated tablet formulation of NOMAC-E2 (2.5 mg-1.5 mg) and/or 24/4 cycle regimen are not discussed in this section. Safety data were obtained by determination of routine laboratory parameters, vital signs and cervical smear, by performing physical, gynaecological and breast examinations and by monitoring SAEs. Acceptability was evaluated on the basis of discontinuation rates and reasons for discontinuation. In study 292002, cervical smear and endometrial biopsies were performed in a subset of women (as requested by the FDA). In study 292004, the primary objective was evaluation of effect of NOMAC-E2 on specific safety parameters of haemostasis, lipid/ carbohydrate parameters and adrenal/ thyroid function. Study 292003 evaluated effects of NOMAC-E2 on androgen parameters, serum concentrations of SHBG and folic acid.[13] The occurrence of (S)AEs, vital signs, routine laboratory parameters, and blood carrier proteins SHBG, corticosteroid binding globulin (CBG) and TBG were evaluated in the dose response studies 02-ESC/NOM-1-RD, 02-ESC/NOM-2-RD. Cardiac safety was assessed by safety ECGs, cardiac telemetry and continuous ECG monitoring in study 292011. Study 292005 specifically evaluated effects of 2 years treatment with NOMAC-E2 on BMD.

[13] Free testosterone, total testosterone, dihydrotestosterone (DHT), androstenedione and dehydrepiandrosterone sulfate (DHEAS).

Patient exposure

Overall, 3434 subjects were exposed to NOMAC-E2 (2.5 mg-1.5 mg) for a total of 2602.2 woman years in the Integrated Safety Data Set (ISDS); the majority of exposure to NOMAC-E2 (94.8%) was in the two pivotal studies 292001 and 292002. Overall, 1105 subjects were exposed to DRSP-EE (98.5% in the pivotal studies); only a few subjects of the ISDS were exposed to LNG-EE (150 µg-30 µg) (n=58, study 292004) and to LNG-EE (100 µg-20 µg) (n=45, study 02-ESC/NOM-2-RD) (Table 20). In the ISDS, the total extent of exposure (in number of woman years) to DRSP-EE (3 mg-30 µg) was approximately one third of the exposure to NOMAC-E2 due to the randomization ratio of 3:1 (NOMAC-E2 vs DRSP-EE) in the pivotal trials.

Table 20: Extent of exposure in cycles and woman years - ISDS

Parameter		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)
Extent of exposure (in 28-day cycles)	n	3434	1105	58	45
	Mean	9.9	10.4	5.6	3.0
	SD	4.5	4.3	1.3	0.0
	Min	0.0	0.0	0.0	3.0
	Median	13.0	13.0	6.0	3.0
	Max	15.3	14.0	6.1	3.0
Number of woman years		2602.2	881.8	25.0	10.4
Number of 28-day cycles		33828.5	11464.0	325.6	135.0

The combined exposure in the pivotal studies to NOMAC-E2 was 2545.1 woman years and to DRSP-EE was 874.8 woman years. The mean exposure to NOMAC-E2 and DRSP-EE was slightly higher in pivotal study 292001 compared to 292002**.** The total extent of exposure to NOMAC-E2 was much lower in the clinical pharmacology and pharmacokinetic trials compared to the pivotal studies.

Overall, 1399 subjects (40.7%) in the age category of 18-24 years were exposed for a total of 1005.9 woman years, 1484 subjects (43.2%) in the age category of 25-35 years were exposed for 1141.3 woman years and 551 subjects (16.0%) in the age category of 36-50 years were exposed for 454.9 woman years. The median of the individual extent of exposure (in 28 day cycles) was 13.0 cycles in each of the three age categories. The majority of the NOMAC-E2 exposed subjects were White (n=3073, about 90% of the total subjects and exposed for 2357.4 woman years) and had BMI ≥18.5 - <25 kg/m^2 (65.9%) or BMI ≥25 - <30 kg/m^2 (22.3%). The median extent of exposure to NOMAC-E2 was 13.0 cycles in each of the four BMI categories.

Adverse events

A majority of the subjects in all treatment groups experienced at least one AE during the in-treatment period with a slightly higher incidence in the NOMAC-E2 group compared to DRSP-EE (75.3% vs 69.0%); similar results were observed for treatment related AEs (49.1% vs 37.3%). The majority of the AEs were of mild to moderate intensity with only 11.3% in the NOMAC-E2 group reporting at least one AE with a severe intensity (compared with 10.1% in the DRSP-EE group) (Table 21). In the NOMAC-E2 group, four AEs were reported with an incidence higher than or equal to 10% (vs DRSP-EE, all causalities): acne (18.1% vs 9.8%), weight increased (10.9% vs 6.9%), headache (10.5% vs

10.6%) and withdrawal bleeding irregular (10.0% vs 0.5%). The majority of these four AEs were related to trial medication as judged by the investigator.

Table 21: Number (%) of subjects with various types of adverse events occurring during the in treatment period (ISDS)

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

[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.

Two other AEs were reported with an incidence between 5 and 10% in the NOMAC-E2 group (vs DRSP-EE), that is, nasopharyngitis (6.7% vs 7.2%) and cervical dysplasia (5.5% vs 6.6%). Other common AEs were (NOMAC-E2 vs DRSP-EE) libido decreased (4.3% vs 2.4%), metrorrhagia (4.3% vs 2.4%), dysmenorrhoea (2.0% vs 1.4%), mood altered (1.9% vs 0.9%), nausea (1.6% vs 3.7%), menorrhagia (1.5% vs 0.8%,), genital haemorrhage (1.3% vs 0.6%,), breast pain (1.3% vs 1.7%), mood swings (1.1% vs 0.9%), migraine (1.1% vs 1.4%,), depression (1.1% vs 1.2%) and depressed mood (1.0% vs 0.6%).

The AE profile in the pivotal studies was similar to that described above in the ISDS as >98% of the exposure in the ISDS was derived from the pivotal studies 292001 and 292002. The overall incidence in subjects experiencing at least one AE was higher in pivotal study 292001 compared to study 292002 for both the NOMAC-E2 (81.9% vs 70.6%, respectively) and DRSP-EE group (75.0% vs 62.5%, respectively). Within each trial the percentage of subjects with at least one AE was higher in the NOMAC-E2 treatment group compared to the DRSP-EE group.

NOMAC-E2 was well tolerated in all clinical pharmacology and pharmacokinetic trials and had a similar AE profile as NOMAC-E2 in the ISDS.

The onset of the majority of these AEs was during the first six cycles (Days 1-168), although new occurrences were also observed during the remaining cycles of the trials for weight increase and acne, although the frequencies were lower and decreased over time. The prevalence of the AE weight increase stabilized around slightly above 10%, while the prevalence of acne tended to decrease again after peaking around 15% between Cycles 6 and 9. The prevalence of nasopharyngitis, headache and withdrawal bleeding irregular was evenly distributed over time, indicating a balance between new occurrences and resolution of existing events.

Serious adverse events and deaths

Two subjects in the NOMAC-E2 group died (0.1%), one in each pivotal study. The deaths were due to a metastatic gastric cancer and a road traffic accident, both of which were considered unrelated to study medication. None of the subjects died in any of the other treatment groups.

During the in-treatment period (extended by 28 days after the last day of trial medication intake), the percentage of subjects that experienced a SAE was low in both the NOMAC-E2 (1.8%) and DRSP-EE group (1.4%). No SAEs were reported in the two LNG-EE groups. SAEs were only reported in studies 292001, 292002, 292003 and 292004. In the two pivotal studies, SAEs were reported for a total of 77 subjects (42 in Trial 292001 and 35 in Trial 292002 during the treatment period (extended by 28 days after the last day of trial medication intake); the incidence of subjects who experienced an SAE was low and similar between the treatment groups in study 292001 (about 2%). In study 292002, the incidence of subjects with an SAE was 1.8% in the NOMAC-E2 group and 0.9% in the DRSP-EE group. The SAEs related to the trial medication in the NOMAC-E2 group were migraine (in 1 patient), optic neuritis (1), cholelithiasis (2), cholecystitis (1), menorrhagia (1) and congenital mitral valve incompetence (1). The SAEs related to the trial medication in the DRSP-EE group were deep vein thrombosis (1) and systemic lupus erythematosus (1). The SAE profile was similar between the NOMAC-E2 and DRSP-EE groups with the exception of a slightly higher incidence of hepatobiliary disorders in the NOMAC-E2 group. No serious cardiac related AEs were reported in both treatment groups, except for cardiac aneurysm in 1 subject of the NOMAC-E2 group (not related to trial medication). No in-treatment deep vein thrombosis occurred during the NOMAC-E2 clinical trial, compared to 1 case with DRSP-EE.

The incidence of SAEs was very low in the clinical pharmacology and pharmacokinetic trials with only 2 SAEs reported in the NOMAC-E2 group in studies 292003 and 292004 (appendicitis and worsening of congenital mitral valve leak).

In the ongoing trial 292005, a total of three SAEs in two subjects (ear pain and dehydration in one subject on LNG-EE [0.150 mg-0.030 mg] and appendicitis in another subject on NOMAC-E2 [2.5 mg-1.5 mg]) were reported up to the clinical cut-off date of 1 February 2009. These three SAEs were not related to the trial medication as judged by the investigator.

Laboratory findings

Haematology and biochemistry

In the ISDS, the majority of the haematology parameters were within normal limits following treatment with NOMAC-E2 and were similar to changes observed with DRSP-EE. Similar results were observed in the pivotal studies or the clinical pharmacology/ PK studies. Overall, no apparent mean changes and no obvious shifts from baseline to values below or above safety ranges were observed in any of the treatment groups for any of the haematology parameters.

None of the biochemical parameters showed obvious differences between treatment groups with respect to median relative changes from baseline to last measurement. For all parameters, median relative changes from baseline were less than 10% in the NOMAC-E2 group. This was similar in the DRSP-EE group with the exception of a median decrease of 16.5% for total bilirubin.

Special laboratory parameters

Special laboratory parameters (lipid metabolism, haemostasis, carbohydrate metabolism, effects on adrenal and thyroid function, androgens, SHBG and folic acid) were assessed in studies 292003, 292004, 02-ESC/NOM-1-RD and 02-ESC/NOM-2-RD.

Lipid metabolism

In study 292004, no relevant changes from baseline were observed for total cholesterol in either treatment group but in the respective sub fractions differences were apparent. The high density lipoprotein (HDL) cholesterol did not change in the NOMAC-E2 group but it was significantly reduced in the LNG-EE group. This difference was particularly due to a more pronounced statistically significantly ($p<0.0001$) greater decrease in HDL2-cholesterol in the LNG-EE group compared to the NOMAC-E2 group. The total cholesterol/ HDL cholesterol ratio did not change in the NOMAC-E2 group, whereas a statistically significant increase was noted in the LNG-EE group (p-value <0.0001). Low density lipoprotein (LDL) cholesterol was unchanged in the NOMAC-E2 group, while a small increase was noted in the LNG-EE group (p-value=0.0455). The total cholesterol/LDL cholesterol ratio did not change in the NOMAC-E2 group, as opposed to a small decrease in the LNG-EE group, which was statistically significantly different between the treatment groups (p-value = 0.0008).

Apolipoprotein A-1 (relates to HDL) showed a more pronounced increase in the NOMAC-E2 group compared to the LNG-EE group, while apolipoprotein B (relates to LDL) did not change in the NOMAC-E2 group and increased in the LNG-EE group. Total triglycerides showed a small increase in both groups, which was less pronounced in the NOMAC-E2 group compared to the LNG-EE group (p-value=0.0078).

In study 02-ESC/NOM-2-RD, small changes from baseline were observed for total cholesterol in both treatment groups at Cycle 3. Total triglycerides did not change in the NOMAC-E2 group, whereas an increase was observed in the LNG-EE group. This difference between the treatment groups was statistically significant (p-value=0.0094).

Haemostasis

Haemostasis parameters were evaluated in Trials 292004 and 02-ESC/NOM-2-RD. Trial 292004 was designed to investigate the effects of NOMAC-E2 on haemostasis in comparison to a monophasic COC containing LNG-EE (150 µg-30 µg). In study 292004, the baseline distributions of all haemostasis parameters were similar between the treatment groups. In general, the changes from baseline observed at Cycle 3 were similar to those found at Cycle 6.

Prothrombin fragments 1+2, a measure of thrombin formation, showed an increase in both treatment groups, which was less pronounced with NOMAC-E2. D-dimer, indicating the overall setting point for fibrin turnover, was essentially unchanged in the NOMAC-E2 group and increased in the LNG-EE group.[14] Coagulation factors II (prothrombin), VIIa, VIIc and VIII all showed small increases from baseline in both treatment groups with the exception of statistically significantly greater decrease in the LNG-EE group for factor VIIc. The anticoagulant parameters antithrombin III, protein C and protein S (free and total) all showed small changes (increases) from baseline in both groups. The activated Protein C (APC) resistance ratio (endogenous thrombin potential [ETP]-based), which measures the anticoagulant response of plasma to activated protein C (APC) after activation of the extrinsic coagulation pathway, was increased in both treatment groups, although the

[14] Because more than half of the subjects had D-dimer values below the lower limit of quantification (LLOQ) at any assessment in both treatment groups, further statistical analysis of between-group differences was not meaningful.

increase for NOMAC-E2 was statistically significantly lesser than that observed for LNG-EE. The APC resistance ratio (activated partial thromboplastin time [APTT]-based), which measures the anticoagulant response of plasma to activated protein C (APC) after activation of the intrinsic coagulation pathway, was essentially unchanged in both treatment groups. C-reactive protein **(**CRP) was elevated in both treatment groups, with a statistically significantly higher increase in the LNG-EE group.

In study 02-ESC/NOM-2-RD, the effects of NOMAC-E2 on haemostasis were compared to a monophasic COC containing LNG-EE (100 µg-20 µg). For all haemostasis parameters, the baseline distributions were similar between the treatment groups. Prothrombin fragments 1+2 essentially did not change in the NOMAC-E2 and a small increase was observed in the LNG-EE group. The difference between the treatment groups was statistically significant (p-value=0.0056). D-dimer decreased in the NOMAC-E2 group, while an increase was observed in the LNG-EE group with statistically significantly difference between the two treatment groups (p-value=0.0006). The procoagulation Factor VIII showed a minimal increase from baseline to Cycle 3 in both treatment groups. Factors II (prothrombin) was increased in both groups but the increase was significantly less in the NOMAC-E2 group compared to the LNG-EE group (p-value=0.0390). The anticoagulant parameters antithrombin III and protein S (free and total) all showed small changes from baseline in both groups. Differences in change from baseline to Cycle 3 between the NOMAC-E2 and LNG-EE groups were statistically significant for antithrombin III (p-value=0.007), and for protein S (free) (p-value=0.0342). In the NOMAC-E2 group, a small increase was observed for APC resistance ratio, which was statistically significantly lower compared to the increase in the LNG-EE group (p-value=0.0194).

Carbohydrate metabolism

In study 292004, all carbohydrate parameters at baseline were similar between the NOMAC-E2 and LNG-EE treatment groups. In general, the changes from baseline observed at Cycle 3 were similar to those found at Cycle 6. NOMAC-E2 did not induce changes in the AUC3 and incremental AUC3 for glucose, while notable increases were observed in the LNG-EE group with statistically significant difference between groups (p-values$\leq$0.0016). NOMAC-E2 did not induce changes in the AUC3 and incremental AUC3 for insulin, while there was statistically significant increase in the LNG-EE group (p-values $\leq$0.0024). No effects were observed in either group for glycosylated haemoglobin (HbA1c)

In study 02-ESC/NOM-1-RD, there were no clinically relevant changes from baseline in the fasting blood glucose after three cycles of treatment between the NOMAC-E2 24/4 regimen and the NOMAC-E2 21/7 regimen groups. In study 02-ESC/NOM-2-RD, no clinically relevant changes from baseline were observed in the fasting blood glucose between the NOMAC-E2 and LNG-EE (100 µg-20 µg) groups after three cycles of treatment.

Effects on adrenal and thyroid function

In study 292004, the baseline distributions were similar between the treatment groups for all adrenal and thyroid function parameters. The changes from baseline observed at Cycle 3 were similar to those found at Cycle 6. Total cortisol, CBG and TBG increased in both treatment groups but the increase was statistically significantly greater in the LNG-EE group compared to the NOMAC-E2 group (p-value<0.0001). There were no differences between the NOMAC-E2 and LNG-EE groups in changes from baseline for free thyroxine (T4) and thyroid stimulating hormone (TSH).

In study 02-ESC/NOM-1-RD, the baseline distributions were similar between the treatment groups for all parameters. In both NOMAC-E2 regimen (24/4 and 21/7) groups, the levels of CBG and TBG showed a mean increase from baseline to Cycle 3 during

treatment of about 14% and 9%, respectively with no statistically significant difference between the two NOMAC-E2 groups.

Effects on Androgens, SHBG and folic acid

The effect of NOMAC-E2 on androgen levels was investigated in the comparative trials 292003 and 292004. Samples were taken at Cycle 0 (pre-treatment), Cycle 1, Cycle 6 and post-treatment (Cycle 7, between Days 6 and 27) in Trial 292003 and at Cycle 0, Cycle 3 and Cycle 6 in Trial 292004. The androgen parameters evaluated were free testosterone, total testosterone, DHT, androstenedione and DHEAS. In addition to androgen parameters, serum concentration of SHBG and folic acid were measured at Cycle 0 (pre-treatment), Cycle 1, Cycle 6 and post-treatment in Trial 292003. SHBG was also measured in Trials 02-ESC/NOM-1-RD, 02-ESC/NOM-2-RD and 292004, at pre-treatment and during treatment at Cycle 3, and in Trial 292004 also at Cycle 6.

In study 292003, the baseline distributions were similar between the treatment groups for all androgens and SHBG parameters. The changes observed at Cycle 1 were similar to those found at Cycle 6. For all androgens, a statistically significant (or nearly significant) decrease in mean values from baseline to Cycle 6 was observed, which was smaller in the NOMAC-E2 group compared to the DRSP-EE group. Median androgen values increased after treatment discontinuation in the post-treatment cycle and were similar to baseline levels for total and free testosterone in the NOMAC-E2 group. SHBG values were increased in both treatment groups at Cycle 6 compared to baseline, with a more pronounced median increase in the DRSP-EE group compared to the NOMAC-E2 group (282% vs 46%, $p<0.0001$). The median SHBG value decreased again in the post treatment cycle and was similar to baseline levels in the NOMAC-E2 group, whereas it was still higher compared to baseline in the DRSP-EE group. No relevant changes were found in mean folic acid values during treatment and post treatment.

In study 292004, the baseline distributions were similar between the treatment groups for all parameters. The changes observed at Cycle 3 were similar to those found at Cycle 6. For all androgens, a decrease from baseline was observed, which was statistically significantly smaller in the NOMAC-E2 group compared to the LNG-EE group. The differences between the treatment groups in changes from baseline were statistically significant (p-value≤0.05) for all parameters except for free testosterone. The carrier protein SHBG was increased in both treatment groups at Cycle 6, with a statistically significantly more pronounced median increase in the NOMAC-E2 group (44%) compared to the LNG-EE group (22%)(p-value=0.0187).

In Trial 02-ESC/NOM-1-RD the SHBG levels in the NOMAC-E2 24/4 regimen and NOMAC-E2 21/7 regimen groups showed a median increase from baseline to Cycle 3 of about 22% and 38%, respectively with no statistically significant difference between the two treatment regimens (p-value=0.2573). In Trial 02-ESC/NOM-2-RD, the SHBG levels in the NOMAC-E2 group and LNG-EE group showed a similar median percent increase from baseline to Cycle 3 of about 38% and 37%, respectively (p-value=0.6164).

Vital signs, ECG

Overall, the mean changes from baseline to last measurement for both systolic and diastolic blood pressure were small over the studied period. The percentage of subjects with markedly abnormal systolic or diastolic blood pressure was small for subjects treated with NOMAC-E2 and DRSP-EE (≤2.4%).

In both the NOMAC-E2 and DRSP-EE groups a small increase in body weight from baseline to the last measurement was observed, with median changes of 1.00 kg and 0.20 kg, respectively. At least once during the in-treatment period, a relative increase of at least 7%

in body weight was observed for slightly more women in the NOMAC-E2 group compared with the DRSP-EE group (16% vs 11%). The incidence of relative decrease of at least 7% in body weight was similar in both groups (6-7%). There were no apparent changes in body weight in the LNG-EE groups, which originated from small and shorter trials (292004 and 02-ESC/NOM-2-RD).

The results of study 292006 showed that the time matched mean effects of NOMAC-E2 on the Fridericia corrected QT interval (QTcF) and Individual corrected QT interval (QTcI) compared to placebo, were below 5 milliseconds (ms). Furthermore, no individual QTcI or QTcF values exceeding 480 ms or time matched changes from baseline exceeding 30 ms were observed. The thorough QTc trial 2920011 was negative according to the definitions of the TGA-adopted EU guideline and it was concluded that therapeutic and supra-therapeutic doses of NOMAC-E2 are not associated with QTc prolongation of regulatory concern. The sensitivity analyses performed for the primary parameter, the alternative QT correction methods and categorical QTc analyses confirmed the robustness of results of the primary analysis. Moreover, the PK-QTc model confirmed the absence of a relationship between NOMAC levels and QTc prolongation.

Effects on cervical smears and endometrium

Clinically relevant shifts from a normal cervical smear result at screening to an abnormal cervical smear result (mild, moderate or severe dysplasia) at last measurement were observed for a small number of subjects. Both NOMAC-E2 and DRSP-EE groups showed similar incidence of clinically relevant shifts to mild dysplasia (NOMAC-E2 vs DRSP-EE: 4.1% vs 4.0%), to moderate dysplasia (0.4% vs 0.6%) and to severe dysplasia (0.1% vs 0.1%).

Overall, 107 subjects participated in the endometrial biopsy sub-study of 292002 (85 in the NOMAC-E2 group and 22 in the DRSP-EE group). Only 42 subjects provided both a baseline and a Cycle 13 (or early discontinuation, with at least six cycles of trial medication intake) sample (34 in the NOMAC-E2 group and eight in the DRSP-EE group). The mean (SD) age of the subjects who participated in this endometrial sub-study was 29.1 (7.2) years, the mean (SD) body weight was 70.3 (13.8) kg, and the mean (SD) BMI was 25.6 (4.6) kg/m^2. In the NOMAC-E2 group, the majority of the endometrial samples (19 out of 34) were classified as 'Secretory' at baseline of which 12 were classified as 'Other', five as 'Secretory', and two as 'Normally proliferative' at the Cycle 13 assessment. Thirteen samples were classified as 'Other' both at baseline and at Cycle 13. Two samples were classified as 'Normally proliferative' at baseline of which one was classified as 'Normally proliferative' and one as 'Other' at Cycle 13. In the DRSP-EE group the majority of the endometrial samples (five out of eight) were classified as a 'Secretory' at baseline, of which three were classified as 'Other', and two as 'Secretory' at Cycle 13. Three samples were classified as 'Other' at baseline of which two samples were classified as 'Other' and one as 'Normally proliferative' at the Cycle 13 assessment.

The dose of NOMAC used in the Naemis development program (3.75 mg NOMAC sequentially combined with 1.5 mg E2) in postmenopausal women was shown suitable for suppressing endometrial proliferation since no endometrial hyperplasia was reported in 385 women treated for one year and 159 women treated for two years.

Frequent ultrasound assessment of endometrial thickness was performed in Trial 292003, which showed that NOMAC-E2 induced a thin endometrium (around 4 mm thickness) throughout six cycles of treatment.

Safety in special populations

Effect of intrinsic factors on safety of NOMAC-E2

The influence of demographic factors on the safety outcomes of NOMAC-E2 was assessed by subgroup analyses on the pooled NOMAC-E2 data of the ISDS. The most frequently observed AEs (nasopharyngitis, headache, acne, withdrawal bleeding irregular, cervical dysplasia and weight increased) were examined to determine if they occurred at differential rates in subjects of different age, body weight, BMI, race, or ethnicity. Except for nasopharyngitis and cervical dysplasia, in most instances the AEs were considered related to the trial medication as judged by the investigator. The subgroups analysed were: Age: ≤24, 25-35, ≥36 years; Body weight: <60, 60-80, >80 kg; BMI: <18.5, 18.5-<25, 25-<30, ≥30 kg/m^2; Race: White, Asian, Black/ African American, Other; Ethnicity: Hispanic or Latino, Not Hispanic or Latino. Furthermore, the effect of age on lipid and haemostasis parameters was examined in subjects of Trial 292004.

Effect of age, BMI and race

The incidence of acne was slightly higher in subjects of the younger and middle age subgroups (n=280 [20.0%] and n=269 [18.1%]), respectively) compared to the subjects in the older age subgroup (n=71 [12.9%]). The incidences of weight increased, headache and withdrawal bleeding irregular were evenly distributed over the three different age classes. The incidence nasopharyngitis slightly decreased from the younger (8.1%) to the older age group (4.5%). The incidences of cervical dysplasia were very similar between the age classes.

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. The incidence of cervical dysplasia was slightly higher in the lower and middle body weight subgroups (5.2% and 6.3%, respectively) as compared to the higher body weight subgroup (2.6%). Similar results were found between these AEs and BMI. Overall, the results did not show any clinically relevant associations between these AEs within the NOMAC-E2 group and body weight/BMI. At baseline, incidences of acne, weight increase and withdrawal bleeding irregular were higher in Asian subjects 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. Overall, the AE incidence in Black/African Americans was either similar or lower as compared to white subjects.

Discontinuation due to Adverse Events

In the ISDS, the overall incidence of subjects who discontinued NOMAC-E2 treatment due to an AE (17.1%; 588/3434) was higher compared to the DRSP-EE (10.1%; 112/1105) and the LNG-EE 150 µg-30 µg (6.9%; 4/58) groups. None of the 45 subjects treated with LNG-EE (100 µg-20 µg) discontinued treatment prematurely. In the NOMAC-E2 group, the System Organ Class (SOC) *Psychiatric Disorders* was the most frequent reported SOC (5.9%) in which AEs were reported that resulted in premature discontinuation. The incidences of discontinuations due to an AE in *Psychiatric Disorders* for the DRSP-EE (2.9%) and LNG-EE (150 µg-30 µg) (1.7%) groups were lower compared to the NOMAC-E2 group. The most frequent reported AEs leading to discontinuation in *Psychiatric Disorders* (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%). Most of these AEs in both treatment groups were considered related to the trial medication as judged by the investigators. The second most frequent reported SOC in which AEs were reported that resulted in premature discontinuation for the NOMAC-E2 group was *Reproductive System and Breast Disorders* (5.2%) and most of

these AEs were considered related to the trial medication as judged by the investigators. A lower percentage of subjects on DRSP-EE (2.2%) discontinued treatment prematurely due to an AE in this SOC. 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%). None of the subjects in the LNG-EE groups discontinued treatment prematurely due to AEs in this SOC.

A total of six AEs leading to premature discontinuation from NOMAC-E2 treatment were reported with an incidence of 1% or more (NOMAC-E2 vs DRSP-EE, all causalities). These were acne (2.5% vs 0.2%), libido decreased (2.0% vs 1.0%), weight increased (1.6% vs 0.9%), metrorrhagia (1.4% vs 0.8%), withdrawal bleeding irregular (1.3% vs 0%) and headache (1.0% vs 1.2%).

For all other AEs leading to premature discontinuation, the incidence rates were lower than 1% in the NOMAC-E2 group.

The percentage of subjects that discontinued due to an AE showed similar results between Trials 292001 and 292002, in both the NOMAC-E2 group (18.2% and 17.3%, respectively) and the DRSP-EE group (10.5% and 10.1%, respectively). Overall, the incidences and type of AEs leading to premature discontinuation in the combined pivotal studies were similar to the ISDS described earlier.

In the clinical pharmacology studies 292003 and 292004, the incidence of subjects who discontinued prematurely from treatment due to an AE was low and similar between the treatment groups, and the type of AEs was consistent with the events observed in the two pivotal trials. None of the subjects in Trials 02-ESC/NOM-1-RD, 02-ESC/NOM-2-RD and 292006 discontinued treatment prematurely due to an AE.

Evaluator's overall conclusions on clinical safety

NOMAC-E2 was well tolerated and showed a similar overall safety profile to DRSP-EE. The AE profile was similar between the treatment groups with the exception of higher incidences of acne, weight increased and withdrawal bleeding irregular in the NOMAC-E2 group as compared to the DRSP-EE group. However, active monitoring of acne, weight and bleeding pattern, as well as the open label design of these trials may have introduced bias in the spontaneous reporting of AEs.

NOMAC-E2 showed a similar SAE profile to DRSP-EE, with the exception of a slightly higher incidence of hepatobiliary disorders in the NOMAC-E2 group compared to the DRSP-EE group. However, taking into account the non-serious AEs, overall incidences of cholelithiasis/cholecystitis were similar between both treatment groups. No serious cardiac related AEs were reported in both treatment groups, except for cardiac aneurysm in one subject of the NOMAC-E2 group (not related to trial medication). No in-treatment deep vein thromboses on NOMAC-E2 have occurred during the clinical trials, compared to one case on DRSP-EE. Two subjects in the NOMAC-E2 group died during the in-treatment period, but their cause of death was not related to the trial medication.

In the NOMAC-E2 group, discontinuations due to the following AEs were higher compared to the DRSP-EE group: acne (2.5% vs 0.2%), libido decreased (2.0% vs 1.0%),weight increased (1.6% vs 0.9%), metrorrhagia (1.4% vs 0.8%) and withdrawal bleeding irregular (1.3% vs 0%). Discontinuations due to unacceptable vaginal bleeding also occurred in slightly more subjects in the NOMAC-E2 group compared with the DRSP-EE group (3.9% vs 1.3%), although overall incidence was still low.

Trials evaluating the effect of new hormonal contraceptives on haemostasis parameters, plasma lipid parameters and carbohydrate metabolism and on endocrine systems like adrenal and thyroid function are required for registration and the sponsor did conduct

such a parallel group, non-inferiority study (292004) in 121 women treated over 6 treatment cycles. LNG-EE 150 µg - 30 µg was chosen as the active comparator as its effects on above mentioned parameters and systems have been well established in many trials. In addition, LNG-EE 150 µg - 30 µg is also mentioned in the TGA-adopted EU guideline as an appropriate comparator for trials evaluating the effect of a new combined contraceptive product on haemostasis.[12] All haemostatic parameters mentioned in this guideline were included in Trial 292004. However, this study did not comply with the guidelines which clearly state that such biomarker comparative studies should have a crossover design. The changes compared to baseline at Cycle 3 and Cycle 6 for surrogate markers of coagulation in NOMAC-E2 treated subjects were consistent in Trials 292004 and 02-ESC/NOM-2-RD. In general, NOMAC-E2 induced smaller changes in haemostasis parameters compared to LNG-EE (150 µg-30 µg) and LNG-EE (100 µg-20 µg). In Trial 292004 at both Cycle 3 and Cycle 6, the acute phase reactant CRP was elevated in the NOMAC-E2 and LNG-EE (150 µg-30 µg) groups, with a much higher increase in the LNG-EE group. No SAEs related to the cardiovascular or venous thromboembolism (VTE) events were reported in this study.

For NOMAC-E2 no relevant changes from baseline were observed for the lipid parameters total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides. LNG-EE treatment did not change total cholesterol either, but decreased HDL-cholesterol and HDL-2 cholesterol, and increased LDL cholesterol and triglycerides. Except for total cholesterol, all differences between NOMAC-E2 and LNG-EE were statistically significant. Lipoprotein (a) levels were unchanged by either treatment. NOMAC-E2 slightly increased the total cortisol, CBG and TBG levels at Cycle 3 and Cycle 6. This increase, however, was more pronounced in the LNG-EE group as compared to the NOMAC-E2 group; it had no consequences on the thyroid function as demonstrated by the lack of influence on free T4 and TSH.

For all androgens, a decrease from baseline in mean values was observed at Cycle 1 (Trial 292003 only), Cycle 3 (Trial 292004 only) and Cycle 6 (both trials), which was significantly smaller in the NOMAC-E2 group as compared to the DRSP-EE and the LNG-EE groups. After trial medication discontinuation, mean androgen values increased again in the post-treatment cycle and all androgen levels in the NOMAC-E2 group were similar to baseline levels (Trial 292003 only). Compared to baseline, SHBG was increased in the NOMAC-E2, DRSP-EE and LNG-EE groups. The increase of SHBG in the NOMAC-E2 group was similar across the four trials (292003, 292003, 02-ESC/NOM-2-RD, and 02-ESC/NOM-1-RD), with median increases from baseline of 22 to 46%. However, the increase in the DRSP-EE group was much more pronounced and statistically different compared to the NOMAC-E2 group (282% median increase from baseline). For the LNG-EE groups, median increases of 37% (LNG-EE [100 µg-20 µg], Cycle 3) and 22% (LNG-EE [150 µg-30 µg], Cycle 6) were observed. The difference between LNG-EE (150 µg-30 µg) and NOMAC-E2 at Cycle 6 was statistically significant. At post-treatment, SHBG levels decreased to baseline values in the NOMAC-E2 group (Trial 292003). No relevant changes were found in folic acid values during NOMAC-E2 treatment and post-treatment.

Histopathology of endometrial biopsies and ultrasound measurements of endometrial thickness did not indicate an untoward effect of NOMAC-E2 on the endometrium. All endometrial biopsies at Cycle 13 or early discontinuation showed classifications compatible with the intake of oral contraceptives.

During this clinical development program, 22 in-treatment pregnancies (treatment period + 14 days post-treatment) were reported. In-treatment pregnancies were followed-up for final outcome. No untoward effects of NOMAC-E2 on pregnancy, health of the fetus or neonate were found.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Pharmacokinetics

Currently, warnings and precautions for post-menarcheal adolescents are identical to those described for adults. However, PK/PDs of NOMAC-E2 have not been evaluated in post-menarcheal adolescent females aged 12 to 17 years. Therefore the lack of trial data examining this group should be clearly stated in the PI. Although one trial is being planned (**Trial 292008**) to investigate the contraceptive NOMAC-E2 (2.5 mg-1.5 mg) product in young adolescent females, aged 12-17 years, no information on the PKs and PDs of NOMAC-E2 is provided in adolescent females aged 12-17 years other than whole body physiologically-based PK modelling data.

Summary results of one (previously unevaluated) single dose PK study comparing the PK of adults and adolescents was submitted to support the sponsor's claim that the actions are similar in these two subpopulations, as discussed on page 83 of this AusPAR.

Results of 29007 suggest no clinically relevant differences between the "clinical trial" and proposed marketing formulation. However, there is no bridging study to unequivocally establish bioequivalence between the clinical trials formulation and the proposed marketing formulation of NOMAC-E2.

A full bioequivalence study (P06328) comparing Phase III pivotal clinical batches and drug product manufactured using the proposed commercial process was submitted. This was evaluated by the quality evaluator, as discussed on page 75 of this AusPAR.

Efficacy

Although the proposed indication states that Zoely can be used in post-menarcheal adolescent girls aged >12 years, the sponsors have not conducted any studies evaluating efficacy or safety of NOMAC-E2 in women aged <18 years.

Clinical Summary and Conclusions

Clinical aspects

Clinical efficacy

Dose finding trials for the indication of contraception were initially performed with NOMAC alone and identified 2.5 mg NOMAC as the optimum dose for ovulation inhibition (Trial LUT 5-22-01). Subsequently, two dose finding trials were performed with combinations of 1.5 mg E2 and three doses of NOMAC, with the meanwhile established optimum dose of NOMAC as the highest dose (Trials 96-ESC/NOM-1-RD and 98-ESC/NOM-1-RD). These trials led to the selection of NOMAC-E2 2.5 mg-1.5 mg, being the combination providing the optimum balance between ovulation inhibition and cycle control.

Finally, the selected dose combination was investigated in a trial comparing a regimen of 21 active tablets NOMAC-E2 2.5-1.5 mg followed by 7 placebo tablets (21/7 regimen) to the proposed regimen of 24 tablets NOMAC-E2 2.5-1.5 mg followed by 4 placebo tablets (24/4 regimen) for three cycles (Trial 02-ESC/NOM-1-RD). The 24/4 regimen was selected for further development on the basis of a better bleeding profile (shorter duration of withdrawal bleeding and a lower overall number of days with vaginal bleeding over three cycles of use) and statistically significantly stronger inhibition of follicular growth.

The two pivotal studies (292001 and 292002) involving 4433 healthy females aged 18-50 years were designed to obtain a sufficient number of evaluable cycles (cycles at risk for pregnancy) of exposure to NOMAC-E2 in the subset of women of 35 years or younger to fulfil both the FDA (two independent trials with 10,000 completed cycles) and the TGA-adopted EU criteria.[11] NOMAC-E2 was effective as a contraceptive, as shown by the Pearl Index and the Life Table analysis. The criterion for the precision of the two-sided 95% CI for the Pearl Index estimate according to the TGA-adopted guideline was met. The estimated Pearl Indices (restricted ITT analysis set) in the age class 18-35 years (2 day window) were 1.19 (95% CI: [0.67; 1.96]) for the NOMAC-E2 group and 2.08 (95% CI: [0.95; 3.96]) for the DRSP-EE group. The overall Pearl Index (method failure and user failure) 18-50 years of age was: 0.64 (upper limit 95% CI 1.03). Life Table analysis showed that the Kaplan-Meier estimates (restricted ITT Group) at Day 364 in the age class 18-35 years were 0.80 (95% CI: [0.48; 1.34]) for the NOMAC-E2 group and 1.34 (95% CI: [0.70; 2.56]) for the DRSP-EE group. Similar results were observed with the 14 day extended in-treatment period (FDA definition).

Results observed in the Life Table analysis which included all cycles of the subjects and reflected real world usage were similar to those observed in the restricted patient group with exclusion of cycles expected not to be at risk for pregnancy (recorded use of condoms and without confirmed sexual intercourse from the electronic diary data). Robustness of the contraceptive efficacy primary results was confirmed by similar results in the overall ITT Group (18-50 years) analysis.

The incidence of breakthrough bleeding/ spotting, absence of withdrawal bleeding and cumulative amenorrhea was significantly higher in women treated with NOMAC-E2 compared to those treated with DRSP-EE. Overall, the PROs showed that there was no significant difference between NOMAC-E2 and DRSP-EE in terms of overall QOL (Q-LES-Q), although treatment with NOMAC-E2 did show significant reduction of pain and water retention (MDQ). Interpretation of the PRO measures was limited by the fact that the studies were open label due to different schedules of the two treatments (24/4 and 21/7 regimens). In both treatment groups, more subjects with acne at baseline showed an improvement of acne (than a worsening of acne) at last measurement.

In the pivotal studies, 292001 and 292002, for more than 97% of the subjects in both treatment groups, who switched to no contraceptive or a non-hormonal contraceptive method (and who were not pregnant), menses had returned at the post-treatment assessment; post-treatment was scheduled six weeks after end of treatment visit (either after Cycle 13 or early discontinuation).

Clinical safety

NOMAC-E2 was well tolerated and showed a similar overall safety profile to DRSP-EE. The AE profile was similar between the treatment groups with the exception of higher incidences of acne, weight increased and withdrawal bleeding irregular in the NOMAC-E2 group as compared to the DRSP-EE group.

NOMAC-E2 showed a similar SAE profile to DRSP-EE, with the exception of a slightly higher incidence of hepatobiliary disorders in the NOMAC-E2 group compared to the DRSP-EE group. However, taking into account the non-serious AEs, overall incidences of cholelithiasis/cholecystitis were similar between both treatments groups. In the NOMAC-E2 group, discontinuations due to the following AEs were higher compared to the DRSP-EE group: acne (2.5% vs 0.2%), libido decreased (2.0% vs 1.0%), weight increased (1.6% vs 0.9%), metrorrhagia (1.4% vs 0.8%), withdrawal bleeding irregular (1.3% vs 0%). Discontinuations due to unacceptable vaginal bleeding also occurred in slightly more subjects in the NOMAC-E2 group compared with the DRSP-EE group (3.9% vs 1.3%).

The effect of NOMAC-E2 on haemostasis parameters, plasma lipid parameters, carbohydrate metabolism and on endocrine systems like adrenal and thyroid function was more favourable compared to that with LNG-EE. However, the study evaluating the effects on metabolic parameters was a non-inferiority study and not a crossover study as suggested in the TGA-adopted guideline. The incidence of abnormal vital sign findings was low. A slight trend of body weight gain (approximately 1 kg) was noted over one year of treatment. Clinically significant abnormalities for haematology and biochemistry did not occur.

During this clinical development program, 22 in-treatment pregnancies (treatment period + 14 days post-treatment) and 16 in-treatment pregnancies (treatment period +2 days post-treatment) were reported. In-treatment pregnancies were followed up for final outcome. No untoward effects of NOMAC-E2 on pregnancy, health of the fetus or neonate were found.

Benefit risk assessment

Benefits

NOMAC-E2 is a novel combination for oral contraception containing the progesterone derived progestogen, NOMAC and the natural oestrogen, 17ß-estradiol. It appears to be unique in providing both ovulation inhibition and an acceptable vaginal bleeding pattern. Ovulation inhibitory properties are primarily ascribed to NOMAC, whereas the effects on vaginal bleeding are considered to be the result of the combination of NOMAC and E2.

Dose finding for NOMAC (in combination with a fixed dose of 1.5 mg E2) has resulted in the selection of a daily dose of 2.5 mg for this progestogen. Dose finding for E2 was not performed. However, based on clinical observations (data with P/E2 combinations as described in the literature), that is, the absence of hypo- and hyperoestrogenic side effects in a large number of clinical studies, the 1.5 mg dose was considered justified.[15,16]

A regimen validation study, comparing a 21/7 regimen to a 24/4 regimen for NOMAC (2.5 mg) combined with 1.5 mg E2, justified the selected monophasic 24/4 regimen on the basis of stronger suppression of ovulation (based on significantly greater inhibition of follicular growth (as well as from E2 and FSH levels) and a better bleeding profile (shorter duration of withdrawal bleeding and a lower overall number of days with vaginal bleeding over three cycles of use). Cervical mucus scores and endometrial thicknesses were similarly suppressed with both regimens. Furthermore, the 24 day regimen delayed the increase in FSH during the pill free interval and LH and FSH were found significantly lower with this regimen, at least at one measurement in each pill free interval. Overall, it appears that the 24/4 regimen, that is, daily intake of one active tablet for 24 days followed by daily intake of one placebo tablet for four days is likely to result in a robust concept for contraception, especially in 'real life' where tablets are easily forgotten, which compromises contraceptive efficacy particularly around the "pill free" period.

In the 2 pivotal studies (292001 and 292002) involving 4433 healthy females aged 18-50 years, the estimated Pearl Indices (restricted ITT analysis set) in the age class 18-35 years (2 day window) were 1.19 (95% CI: [0.67; 1.96]) for the NOMAC-E2 group and 2.08 (95% CI: [0.95; 3.96]) for the DRSP-EE group. The overall Pearl Index (method failure and user failure) 18-50 years of age was: 0.64 (upper limit 95% CI 1.03). Life Table analysis showed

[15] Lindberg UB, Crona N, Stigendal L, Teger-Nilsson AC, Silfverstolpe G. A comparison between effects of E2 valerate and low dose ethinyl E2 on haemostasis parameters. Thrombosis and Haemostasis 1989; 61: 65-69.

[16] Csemicsky G, Dieben T, Coelingh Bennink HJ, Landgren BM. The pharmacodynamic effects of an oral contraceptive containing 3 mg micronized 17ß E2 and 0.150 mg desogestrel for 21 days, followed by 0.030 mg desogestrel only for 7 days. Contraception 1996, 54: 333-338.

that the Kaplan-Meier estimates (restricted ITT Group) at Day 364 in the age class 18-35 years were 0.80 (95% CI: [0.48; 1.34]) for the NOMAC-E2 group and 1.34 (95% CI: [0.70; 2.56]) for the DRSP-EE group. Results observed in the Life Table analysis which included all cycles of the subjects and reflected real world usage were similar to those observed in the restricted patient group with exclusion of cycles expected not to be at risk for pregnancy (recorded use of condoms or without confirmed sexual intercourse from the electronic diary data). Robustness of the contraceptive efficacy primary results was confirmed by similar results in the overall ITT Group (18-50 years) analysis.

The incidence of breakthrough bleeding/ spotting, absence of withdrawal bleeding and cumulative amenorrhea was significantly higher in women treated with NOMAC-E2 compared to those treated with DRSP-EE; however, the duration of these bleeding episodes were shorted in the NOMAC-E2 group. Furthermore, treatment with NOMAC-E2 showed significant reduction of pain (dysmenorrhoea) and water retention although interpretation of the PRO measures was limited by the fact that the studies were open label due to different schedules of the two treatments (24/4 and 21/7 regimens). An overall positive effect on acne was shown on the basis of specific acne assessments, which is consistent with the observed effects on androgen levels.

NOMAC-E2 was found to be safe and well tolerated and demonstrated an overall safety profile typical for combined hormonal contraceptives. In comparison to LNG-EE, NOMAC-E2 was shown to induce less changes in the overall activity of the coagulation system and in APC resistance (ETP based), indicating a lower coagulation tendency for NOMAC-E2. In addition, NOMAC-E2 did not induce changes in lipid metabolism, while LNG-EE tended to decrease HDL-cholesterol and increase LDL-cholesterol, changes considered unfavourable with regard to cardiovascular risk. Both NOMAC-E2 and LNG-EE appeared to increase CRP, but the effect was much more pronounced with LNG-EE. Carbohydrate metabolism appeared unchanged with NOMAC-E2, as suggested by unchanged glucose and insulin parameters after oral glucose loading; LNG-EE on the other hand was associated with an increased insulin response and higher glucose levels, suggestive of some peripheral insulin resistance. Altogether, NOMAC-E2 has been shown to have less pronounced effects on metabolic parameters as compared to baseline as well as compared to the well established LNG-EE comparator. However, clinical relevance for the actual risks of VTE based on these surrogate endpoints is not generally agreed upon and considered indicative at most.

NOMAC-E2 did not show any deleterious effects on blood pressure or ECG or other laboratory parameters. No untoward effects of NOMAC-E2 on pregnancy, health of the fetus or neonate were found in the 22 In-treatment pregnancies which were followed up for final outcome.

Risks

NOMAC-E2 was associated with a greater incidence of acne, increased weight and unacceptable vaginal bleeding (leading to discontinuation in about 3-4% of the patients) compared with DRSP-EE. Discontinuations due to AEs, especially unacceptable vaginal bleeding, were higher in patients treated with NOMAC-E2 compared to those treated with DRSP-EE. In the pivotal studies, the overall incidence of absence of withdrawal bleeding and cumulative amenorrhea was significantly higher in the NOMAC-E2 group compared with the DRSP-EE group.

Although, there were no drug interaction studies conducted with the proposed NOMAC-E2 (2.5 mg/1.5 mg) oral contraceptive combination tablet, general precautions regarding drug interactions with COCs were included in the proposed PI.

All the studies in the NOMAC-E2 clinical development program included females aged >18 and <50 years. The safety and efficacy of NOMAC-E2 was not evaluated in post-menarcheal adolescents aged 12-17 years, although the originally proposed indication of prevention of pregnancy in this submission included this subgroup of females.

Balance

With combined hormonal contraceptives (CHCs), the main goals are inhibition of ovulation, good cycle control and safety. The early contraceptive preparations contained high doses of the synthetic oestrogen 17-α ethinyl oestradiol (EE), in combination with a high dose of a 19-nortestosterone derived progestogen. The presence of the 17-α ethinyl group in EE increased its oral bioavailability but is also associated with alterations in hepatic metabolism. The high dose early contraceptives were therefore associated with a variety of side effects, including some rare but serious thrombotic effects. To improve the clinical profile, the EE dose was reduced and more selective progestogens were developed, the latter also allowing further EE dose reduction. The use of oestrogens and progestogens that are similar to the endogenously produced hormones 17β-estradiol and progesterone (whose action is intended to be mimicked) is expected to have less impact on haemostasis, lipid and carbohydrate metabolism compared to their synthetic analogues.[15,16,17] In the past several attempts have been made to replace EE in COCs by E2, which is the natural endogenously produced oestrogen. However, no E2-containing combinations or regimens explored so far resulted in an acceptable clinical profile, that is, providing both contraceptive efficacy and an acceptable vaginal bleeding pattern for the target population.

NOMAC is a highly selective progestogen derived from, and structurally similar to, the naturally occurring steroid hormone, progesterone. Like progesterone, it has strong affinity for the human progesterone receptor and displays strong anti-gonadotropin activity, an anti-oestrogenic effect on the uterus, and some anti-androgenic activity. NOMAC is devoid of oestrogenic, androgenic, glucocorticoid and mineralocorticoid activity. The use of a potent and highly selective progestogen like NOMAC allows the replacement of EE by the natural oestrogen, E2 in a monophasic regimen that is easy to adhere to.

The proposed 24/4 regimen of NOMAC-E2 showed stronger suppression of ovulation (based on significantly greater inhibition of follicular growth (as well as from E2 and FSH levels) and a better bleeding profile (shorter duration of withdrawal bleeding and a lower overall number of days with vaginal bleeding over three cycles of use) compared to the traditional 21/7 regimen. Furthermore, women using NOMAC-E2 experienced a low number of bleeding events, and the withdrawal bleedings tending to be light and of short duration (on average for 3-4 days) compared with DRSP-EE. In addition, NOMAC-E2 was found to reduce menstrual pain (dysmenorrhoea).

Missed withdrawal bleedings were seen more frequently in users of NOMAC-E2 compared to DRSP-EE, so potential users of NOMAC-E2 should be counselled regarding this phenomenon. However, the proposed PI does contain adequate instructions in case of absence of withdrawal bleeding.

NOMAC-E2 was found to be safe and well tolerated and demonstrated an overall safety profile typical for combined hormonal contraceptives. The most frequently reported adverse events attributed to NOMAC-E2 were acne, headache, weight increase and

[17] Astedt B, Svanberg L, Jeppsson S, Liedholm P, Rannevik G. The natural oestrogenic hormone E2 as a new component of combined oral contraceptives. Br Med J 1977; 6056; 269.

irregular withdrawal bleeding. NOMAC-E2 has been shown to have less pronounced effects on metabolic parameters (haemostasis, lipid and carbohydrate metabolism) compared to baseline as well as compared to the well established LNG-EE comparator.

Apart from overall safety and tolerability in the intended population, the clinical development program for NOMAC-E2 demonstrated (1) a strong suppression of ovarian function and robust and good contraceptive efficacy, (2) a stable vaginal bleeding profile, and (3) less pronounced effects on metabolic parameters than traditional combined hormonal contraceptives (LNG-EE). Overall, NOMAC-E2 has a favourable benefit-risk ratio for oral contraception. However, there is no safety and efficacy data to justify use in post-menarcheal adolescents aged 12-17 years.

Conclusions

The overall risk benefit balance of NOMAC-E2 2.5mg/ 1.5mg (Zoely) was considered positive for the indication of oral contraception.

The proposed indication was as follows:

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

However, all studies in the NOMAC-E2 clinical development program included females aged ≥18 and ≤50 years and the safety and efficacy of NOMAC-E2 was not evaluated in post-menarcheal adolescents aged 12-17 years. Hence, ZOELY can only be granted approval for the following modified indication:

Oral contraception. Zoely is indicated in fertile women aged ≥18 years.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

The sponsor identified the following Ongoing Safety Concerns as indicated in Table 22.

Table 22: Ongoing safety concerns

Important Identified Risks	Migraine Depression/Depressed mood
Important Potential Risks	Venous thromboembolic events Cholelithiasis/Cholecystitis Inflammatory bowel disease
Important Missing Information	Safety in post-menarcheal adolescents Safety in women aged over 50 years Safety in women during pregnancy Safety in women during lactation Safety in women with metabolic dysfunctions Safety in women with a history of or risk factors for VTE and ATE

ATE = arterial thromboembolic events; VTE = venous thromboembolic events.

The clinical evaluator noted that the safety of NOMAC-E2 was not evaluated in post-menarcheal adolescents aged 12-17 years. The OPR reviewer recommended that the important missing information be updated to reflect that this fact.

The clinical evaluator also commented that the incidence of hepatobiliary disorders was higher in NOMAC-E2 group compared to the DRSP-EE group. The hepatobiliary disorders noted in the clinical evaluation report were cholelithiasis and cholecystitis; these are already included as important potential risks.

Pharmacovigilance Plan

The sponsor stated that routine pharmacovigilance (PhV) activities are suitable for monitoring of all of the important identified and potential risks and the important missing information and that updates will be provided in the PSUR.[18]

In addition to routine PhV the sponsor was proposing to undertake a Post-Authorisation Safety Study (PASS) in the form of a large prospective non-interventional cohort study to further investigate the important potential risk: "venous thromboembolic events" and the important missing information: "safety in post-menarcheal adolescents", "safety in women during pregnancy" and "safety in women with a history of or risk factors for VTE and arterial thromboembolic events (ATE)".

In principle the OPR reviewer had no objection to the sponsor implementing the proposed application of routine PhV activities and undertaking a PASS as detailed above. However, the full study protocol for the PASS was not provided making review of the pharmacovigilance actions difficult. It was recommended that the sponsor be required to provide a full copy of the study protocol to the TGA for assessment.

The sponsor indicated that a copy of the final CELINA study protocol was provided to the TGA on 19 July 2011.

The sponsor stated that the PASS study will also be used to monitor the safety in post-menarcheal adolescent subjects as they will not be excluded from the study, however, none of the objectives provided in the study synopsis relate to this safety concern. It was difficult to determine if the PASS will provide safety information on post-menarcheal adolescent subjects. Furthermore, in light of the comments made by the clinical evaluator, that the use of Zoely in post-menarcheal female adolescents aged 12-17 years is not justified due to lack of safety or efficacy data in these patients, a PASS would not be suitable to obtain safety information in this population. It was recommended that the sponsor be required to undertake a specific study to assess the safety of NOMAC-E2 in post-menarcheal adolescent subjects aged 12-17.

Risk Minimisation Activities

The sponsor stated that routine risk minimisation activities are sufficient for the specified ongoing safety concerns. This was considered acceptable by the OPR reviewer.[19]

[18] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[19] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

All chemistry and quality control aspects were satisfactorily addressed, except for particle size distribution of NOMAC; the evaluator noted that the acceptability of the limits set would depend on the safety findings from the pivotal clinical studies.

Bioavailability

Study PO6328 was submitted after the clinical evaluation report was finalised and was evaluated by the quality evaluator only. This study compared the Phase III pivotal study batches with the formulation proposed for marketing. The evaluator stated that the Phase III efficacy studies were conducted using batch CZ189 (**Study 292001**) and batch CA 057 (**Study 292002**). The particle size distribution of NOMAC used in the pivotal studies was *coarse* and the particle size distribution in the formulation to be registered is *fine*. There was also a difference in manufacturing process, the film coats were slightly different; however the core formulations are the same.

Study P06328 compared the tablet for registration (batch CD 078) to batches CZ189 and CA057 used in Phase III efficacy studies 292001 and 292002 respectively. The issue of note was that the C_{max} was outside the generally accepted range (90% CI within 80 to 125% of the test vs reference) compared to batch CZ189 from study 292001 and not in relation to CA 057 from study 292002, as indicated in Table 23. However, AUC values were bioequivalent.

Table 23: Results from Study PO6328

Batches	Studies	Particle size distribution	Bioequivalence re C_{max}
CZ189	Pivotal study 292001	coarse	Not bioequivalent
CA057	Pivotal study 292002	coarse	Bioequivalent
CD 078	To be marketed formulation	Fine	-

The evaluator opined that, if the safety profile observed in the clinical efficacy study 292002 performed with batch CA057 of tablets (where C_{max} was bioequivalent to the proposed tablets) was similar to that observed in the clinical efficacy study 292001 performed with batch CZ189 of tablets (where C_{max} was not bioequivalent), the proposed particle size distribution limits for the 'fine' NOMAC used in the commercial tablets will be acceptable. *The sponsor noted that this was reviewed and accepted by the Delegate as discussed on page 82 of this AusPAR.*

Study 02-TX-127066 compared the bioavailability of a tablet (similar to that used in Phase III studies without the coating) vs capsule formulation (used in Phase II studies) with and without food. Food increased the bioavailability of NOMAC by 25-30%. There was a concomitant increase in bioavailability of E2 and oestrone.

A cross study comparison estimated absolute bioavailability of NOMAC at 63% and that of E2 at 0.8% after baseline correction. This was a combined PK analysis: NOMAC+E2 oral data from Study 292006 and intravenous data from Study **307001** (which involved a combined IV infusion of 1.15 mg NOMAC and 0.4 mg E2 in 23 subjects).

The sponsor's attempt to determine whether there was correlation between bioavailability and dissolution rates fell short, because an IVIVC according to the guidance was not obtained; the evaluator cautioned that dissolution methods should not be used to support any subsequent bioavailability issues.

The PSC agreed that the attention of the Delegate be drawn to the increased C_{max} observed in Study P06328 for the tablet proposed for registration compared to the tablets used in the clinical study.

The evaluator recommended approval of this submission, "only if the safety profile observed in the clinical efficacy study (292002) performed with batch CA057 of tablets was similar to that observed in the clinical efficacy study (292001) performed with batch CZ189 of tablets. Specifically, if the safety profiles are worse in study 292001 than study 292002, the proposed particle size distribution limits of NOMAC will not be acceptable".

Nonclinical

The evaluator noted that the studies were of "high quality" and were satisfactory in scope.

NOMAC was shown to possess nanomolar affinity for the progesterone receptor and is a full agonist. NOMAC inhibited ovulation in rats and monkeys. Restoration of fertility was seen in rats 1-2 weeks after cessation of treatment with NOMAC and E2. In relation to secondary pharmacodynamic studies NOMAC displayed no activity at oestrogen, mineralocorticoid or glucocorticoid receptors. There was weak antagonist activity at the androgen receptors. There was no interaction noted with E2.

Pharmacokinetic studies of NOMAC were conducted in mice, rats and monkeys. Absorption of NOMAC after oral dosing was rapid in mice, rats and cynomolgus monkeys, with peak plasma concentrations reached within 0.25–2 h. Plasma AUC was dose proportional (mice, rats, monkeys) and consistently higher in female animals compared with males. Coadministration of E2 did not appear to have a significant effect on exposure to NOMAC (assessed in mice and rats). Plasma protein binding was high in animals and humans. There was no binding to SHBG or CBG. Clearance in laboratory animals was faster than in humans. There was widespread distribution in tissues in rats and monkeys after PO administration.

The evaluator stated that "metabolism of NOMAC involved hydroxylation at various sites and subsequent conjugation, with roles for human CYPs 2C19, 3A4 (and possibly 3A5) and 2C8 was identified". No (or negligible) inhibition of human CYPs 1A2, 2A6, 2C8, 2C9, 2D6, 3A4, 3A4/5, 2B6, 2C19 and 2E1, and no induction of CYP1A2 or CYP3A4, were seen with NOMAC at concentrations up to 120 ng/mL (almost 10-times the clinical C_{max}). There were several metabolites detected; they had (none or) weak progestogenic activity compared to the parent compound. Oestrogenic or androgenic activity of the metabolites is not mentioned. *The sponsor should clarify this in the pre-ACPM response: do the metabolites have such activity? The sponsor noted that this was clarified as discussed on page 84 of this AusPAR.* Excretion was via both urine and faeces, with little NOMAC excreted unchanged.

The evaluator also stated that repeat dose toxicity findings (12 month studies in rats and monkeys) were in line with previous studies on progesterone and progesterone plus oestrogen combinations. Mammary gland stimulation that was more than typical was seen in relation to hyperplasia in rats and increased secretory activity in monkeys (NOMAC alone). Clearly, human epidemiological studies need to validate these findings.

Genotoxicity assays were negative. NOMAC was not carcinogenic in a two year oral study in rats. In an 88 week study (oral NOMAC) in female mice there was an increase in incidence of mammary gland carcinoma and pituitary adenoma. The evaluator noted that

rodents are poor models for carcinogenicity with hormonal agents and ultimately the product's carcinogenicity needs to rely on human epidemiological data.

There was placental transfer of NOMAC seen in monkeys. NOMAC plus E2 had significant adverse findings on embryofetal development in rats and rabbits: embryolethality, teratogenicity, feminisation of male foetuses and decreased fetal weight. These were observed at NOELs similar to or less than clinical exposure levels and support the proposed contraindication in pregnancy.

Overall, there were no nonclinical objections to the registration of Zoely.

Clinical

Pharmacodynamics

Study **LUT 5 -24-10** assessed the effect of NOMAC on gonadotrophins in 10 women administered 5mg/day. NOMAC had effects on pituitary and hypothalamic function. This study showed an increase in FSH, compatible with an additional effect on the ovary.

Study **5-22-01** assessed the dose of NOMAC required to inhibit ovulation. The minimum effective dose was 2.5 mg as judged by suppressed progesterone levels, absence of LH peaks and inhibition of follicular growth (and reduced oestrogen levels).

Study **96-ESC/NOM-1-RD** used combinations of NOMAC and E2. Dose response was seen in relation to all endpoints except E2.

Study **98-ESC/NOM-1-RD** evaluated optimal daily dose of NOMAC (0.625 mg, 1.25 mg or 2.5 mg) in combination with 1.5 mg E2 (21/7 day regimen) for six 28 day cycles in healthy females. Dose response was seen in relation to suppression of ovulation (progesterone level ≥ 3 ng/mL). Suppression of follicle development was better with 2.5 mg NOMAC group. The evaluator also stated that better bleeding control was seen with 1.5- 2.5 mg NOMAC.

The two regimens (NOMAC –E2/placebo: 21/7 and 24/4 days) were compared in **02-ESC/NOM-1-RD**. The evaluator noted a stronger inhibition of follicle growth in the 24 day treatment regimen. There was better bleeding pattern and lower levels of LH and FSH observed with the 24/4 regimen. There was similar reduction in cervical mucus index and endometrial thickness observed with both regimens.

Study **292003** examined the effects of a monophasic combined oral contraceptive containing 2.5 mg NOMAC plus 1.5 mg E2 (n=32) vs 3mg drospirenone plus 30 µg EE (n=16) for six treatment cycles. There was suppression of ovulation in all cycles. There was a decrease in mean FSH and LH. Though the values tended to be lower in the drospirenone group, there was considerable overlap in both treatment groups. The evaluator noted a "clear decrease in mean E2 was at the end of the placebo pill period in the NOMAC-E2 group compared with the DRSP group". Reduction in cervical receptivity and cervical thickness was also seen. Breakthrough bleeding/spotting and the absence of withdrawal bleeding were greater in the NOMAC –E2 group.

The evaluator noted that return of ovulation was detected in the first cycle following cessation of NOMAC-E2 in 70-79% of the subjects. Both regimens 21/7 and 24/ 4 had similar incidence of return of ovulation.

Pharmacokinetics

The absolute bioavailability of the combination product (2.5 mg/1.5 mg) was assessed in study **INT 00104097 (**which was a cross study comparison of **Study 292006** and **Study 307001**) in young healthy females of child bearing potential. The absolute bioavailability of NOMAC was 63.4% (95% CI: 51.7-77.8) and for E2 was 4.6% (95% CI: 3.5-6.1).

The evaluator discussed the development of the formulation proposed for marketing. There was a bridging study (Study **292007**) that was conducted to assess the relationship regarding *in vitro* dissolution curves and *in vivo* exposure between the formulation used in the Phase III studies and the "to market" formulation. The evaluator noted that particle size inversely correlated with C_{max} but did not affect AUC or T_{max} of NOMAC. However, the quality evaluator recorded a need for caution in relation to the interpretation on this correlation.

One bioequivalence study **02-TX127066-1-RD** examined the bioequivalence of capsule vs tablet in fed and fasted condition. In relation to C_{max} the formulations were not bioequivalent. In study **02-TX 133066-1-RD**, which was also of similar design, the formulations were not found to be bioequivalent.

The sponsor stated that efficacy is unlikely to be affected as AUC was not affected. The changes in C_{max} reduce with multiple dosing and this is more clinically relevant than single dosing. The sponsor stated that there have been no safety concerns identified in studies using 5 times the multiple dose and 40 times the single dose in other studies.

Study **02-TX127066-1-RD** was conducted in young healthy women of childbearing potential where food delayed T_{max} by an hour in relation to NOMAC; C_{max} and AUC increased by 29% and 26%. There was no significant change in relation to E2 and oestrone. In Study **02-TX133066-1-RD**, NOMAC C_{max} and AUC increased by 66% and 27% respectively.

The evaluator noted that orally administered NOMAC is rapidly absorbed with a C_{max} of 7.19 ±2.04 ng/mL after a single dose and 12.3 ± 3.50 ng/mL at steady state. Steady state is achieved after 5 days of dosing. The E2 component undergoes significant first pass effect. T_{max} is 6 hours and Css_{max} is 86 ± 51.3 pg/mL. There was significant variability seen with NOMAC PKs. There was also significant variability seen with E2 pharmacokinetics.

NOMAC is extensively bound to albumin (97%-98%). It does not bind to sex hormone binding globulin or corticoid binding globulin. The apparent volume of distribution is 1645 ± 576 L.

NOMAC is metabolised in the liver to inactive metabolites by CYP 2C8, CYP2C19, CYP 3A4 and CYP 3A5. It does not act as inducer or inhibitor to cytochrome P450.

The $t_{1/2}$ of NOMAC in the target patient population is 47 hours. It is excreted via faeces and urine.

No studies have been conducted in those with hepatic or renal impairment.

Efficacy

Dose response studies

96-ESC-NOM-1-RD and **98-ESC-NOM-1-RD** were discussed under *Pharmacodynamics*. Both studies showed that a combination of NOMAC 2.5 mg and 1.5 mg E2 fared better than lower doses of NOMAC (0.625 and 1.25 mg) plus 1.5 mg E2. Both these studies used 21/7 day cycles, however. The selected dose combination was studied using the two different cycle regimens in a Phase II randomised double blind three cycle single centre study (**02-ESC/NOM-1-RD**). The 24/4 day regimen resulted in stronger inhibition of follicular growth with shorter duration of withdrawal bleeding. These findings were the basis for selecting the 24/4 day regimen for the pivotal studies.

Pivotal studies

The two pivotal studies (**292001 and 292002**) were both randomised, open label studies comparing the efficacy, cycle control and safety of 2.5 mg NOMAC + 1.5 mg E2 (Zoely 24/4

regimen) vs 3 mg drospirenone + 30 µg ethinyl oestradiol (Yasmin 21/7 regimen). The treatment duration was 13 consecutive cycles of 28 days.

The primary efficacy endpoint in both pivotal studies was contraceptive efficacy: prevention of in-treatment pregnancies based on the Pearl Index for the restricted ITT (subgroup of women in the age class ≤ 35 years). It was stated that "contraceptive efficacy was assessed from the occurrence of in-treatment 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 two days (according to EU/Rest of the World definition) or 14 days (FDA definition), which complied with requests from regulatory authorities".

In relation to sample sizes, the following is extracted from the evaluation report: "Assuming that the Pearl Index is in the range of 0.0 to 2.0 (for sample size purposes), an exposure of 16675 evaluable cycles to NOMAC-E2 in both trials together was required in women ≤35 years, resulting in an exposure of 642 woman years per trial. Each pivotal trial was designed to contribute half of the required exposure. Assuming 35% discontinuations (contributing an average of three cycles of exposure) and up to 30% non-evaluable cycles, approximately 1260 subjects were to be randomized to NOMAC- E2 in this age subset (18-35 years) and 420 subjects to the DRSP-EE comparator group."

292001

Of the 2126 randomised and treated, 1591 were in the NOMAC-E2 group and 585 in the DRSP-EE group.1142 subjects in the NOMAC-E2 group and 410 in the DRSP-EE group completed the study. Overall, there were 4/1442 pregnancies in the NOMAC-E2 group and 3/486 in the DRSP-EE group when extended with a maximum of two days. When extended to 14 days after the last day of study medication, it rose to 13/1442 in the NOMAC-E2 group and 3/486 in the DRSP-EE group. The primary efficacy endpoint is shown in Table 23.

Table 23: Primary efficacy endpoint for study 292001

	NOMAC-E2	DRSP-EE
Age class 18-35 years:		
2 day extension of treatment	0.57 (95% CI: 0.16, 1.46)	1.26 (95% CI: 0.26, 3.69)
14 day extension of treatment	1.0 (95% CI: 0.4, 2.06)	1.68 (95% CI: 0.46, 4.31)
Age class 18-50 years:		
2 day extension of treatment	0.47 (95% CI: 0.13, 1.20)	1.02 (95% CI:0.21, 2.97)

The life table analysis was consistent with the Pearl Index.

The occurrence of breakthrough bleeding and absence of withdrawal bleeding were higher in the NOMAC-E2 group. Other irregular bleeding patterns were low in both groups.

Improvement in acne score (67% did not have acne at baseline) at last measurement was statistically significant in favour of DRSP-EE.

Study 292002

Overall 2220 subjects were randomised and treated (1666 in NOMAC-E2 and 554 in the DRSP-EE groups); 1332 completed the study. 678 subjects in the NOMAC-E2 and 210 in

the DRSP-EE group withdrew. Of these, 17.3% in NOMAC-E2 and 10.1% in DRSP-EE withdrew because of side effects.

Overall, 17 in-treatment pregnancies occurred between the first and last day of trial medication extended with two days after end of treatment (11 in the NOMAC-E2 group and 6 in the DRSP-EE group), in the restricted ITT group**.** 23 treatment pregnancies occurred with an estimated date of conception more than 14 days after last day of trial medication (14/1442 in the –E2 group and 9/486 in the DRSP-EE group. The primary efficacy endpoint is shown in Table 24.

Table 24: Primary efficacy endpoint for study 292002

	NOMAC-E2	DRSP-EE
Age class 18-35 years:		
2 day extension of treatment	1.96 (95% CI: 0.98, 3.51)	3.09 (95% CI: 1.13, 6.73)
14 day extension of treatment	2.50 (95% CI: 1.37, 4.19)	4.64 (95% CI: 2.12,8.80)
Age class 18-50 years:		
2 day extension of treatment	1.75 (95% CI: 0.91, 3.06)	3.01 (95% CI:1.21, 6.19)

The life table analysis reflected these findings.

The occurrences of breakthrough bleeding/spotting in the NOMAC-E2 group gradually decreased from Cycle 1 to Cycle 13, whereas the occurrences in the DRSP-EE group fluctuated over the thirteen cycles. Breakthrough spotting (spotting only) occurred more frequently than breakthrough bleeding in both treatment groups, ranging from 12.0% to 25.5% in the NOMAC-E2 group and from 7.7% to 18.1% in the DRSP-EE group.

The occurrences of absence of withdrawal bleeding in the NOMAC-E2 group tended to increase over the cycles, which were not observed for the women in the DRSP-EE group. The incidence of early withdrawal bleeding was low in both groups (2.3% to 14.6% in NOMAC-E2 and 3.8% -11.6% in DRSP-EE group). Patient reported outcomes were also discussed. There were no clinically significant differences seen. Improvement in acne was seen in the DRSP-EE group.

Supportive studies

Study **292004** was a Phase III study comparing NOMAC-E2 with 150 µg LNG + 30 µg EE (21/7 day regimen). This was considered a supportive study as the primary endpoints were safety endpoints relating to haemostasis, lipid and carbohydrate metabolism. There were no in-treatment pregnancies reported.

Study **292005** was an open, randomised, single centre study that compared the efficacy of NOMAC-E2 vs LNG+EE (150mg+30mg) on 110 healthy females over two years. Pregnancy was a secondary endpoint. There were no pregnancies reported in the NOMAC-E2 group. Pearl Index was 0 (95% CI: 0, 5.13).

Pooled analysis

The evaluator discussed the pooled analysis of the pivotal studies and also analysis with the inclusion of the supportive studies. In relation to the pooled analysis of the pivotal studies, discontinuations due to SAEs were 17.9% vs 10.3%; unacceptable vaginal bleeding was 3.9% vs 1.3%. The efficacy analysis is shown in Table 25.

Table 25: Efficacy from the pooled analysis

Analysis	Trial	Treatment group	N	Exposure		In-treatment pregnancies [a] (with +two-day window)			In-treatment pregnancies [b] (with +14-day window)		
				28-day cycles	WY	pregnancies	Pearl Index estimate	95 % CI [c]	pregnancies	Pearl Index estimate	95 % CI [c]
Restr ITT analysis set	Combined	NOMAC-E2	2351	16396.3	1261.3	15	1.189	(0.6656, 1.9616)	21	1.665	(1.0307, 2.5451)
		DRSP-EE	780	5615.0	431.9	9	2.084	(0.9528, 3.9555)	13	3.010	(1.6026, 5.1469)
	292001	NOMAC-E2	1193	9110.7	700.8	4	0.571	(0.1555, 1.4614)	7	0.999	(0.4016, 2.058)
		DRSP-EE	402	3092.3	237.9	3	1.261	(0.2601, 3.6858)	4	1.682	(0.4582, 4.3056)
	292002	NOMAC-E2	1158	7285.6	560.4	11	1.963	(0.9798, 3.5119)	14	2.498	(1.3657, 4.1913)
		DRSP-EE	378	2522.7	194.1	6	3.092	(1.1347, 6.7299)	9	4.638	(2.1208, 8.8042)
ITT Group	Combined	NOMAC-E2	2702	26971.9	2074.8	15	0.723	(0.4046, 1.1924)	21	1.012	(0.6265, 1.5472)
		DRSP-EE	909	9320.7	717.0	9	1.255	(0.574, 2.3829)	13	1.813	(0.9654, 3.1006)
	292001	NOMAC-E2	1317	14165.7	1089.7	4	0.367	(0.1, 0.9399)	7	0.642	(0.2583, 1.3236)
		DRSP-EE	443	4978.9	383.0	3	0.783	(0.1615, 2.2892)	4	1.044	(0.2846, 2.6741)
	292002	NOMAC-E2	1385	12806.2	985.1	11	1.117	(0.5574, 1.998)	14	1.421	(0.777, 2.3845)
		DRSP-EE	466	4341.8	334.0	6	1.796	(0.6593, 3.9102)	9	2.695	(1.2322, 5.1154)

[a] Pregnancies with conception date from the day of first intake of trial medication up to and including the days of last intake of trial medication extended with a maximum of two days.
[b] Pregnancies with conception date from the day of first intake of trial medication up to and including the days of last intake of trial medication extended with a period of 14 days.
[c] Note: Two sided 95% CI for Pearl Index was calculated by assuming underlying Poisson distribution. If PI=0 (no pregnancies), an upper confidence limit of 97.5% was used.
N = number of subjects; WY = Woman Year; CI = Confidence Interval.

The vaginal bleeding results reflected the results of the individual studies.

The evaluator concluded that adequate efficacy has been demonstrated in this submission. The use of the "Restricted ITT" was justified as the studies employed reliable methods for recording compliance. The results of life table analysis that included all cycles of the subjects and reflected real world usage were similar. The robustness of the efficacy results were confirmed by the overall results in the ITT population. The incidence of breakthrough bleeding/ spotting and of 'absence of withdrawal bleeding' was statistically significantly higher in women treated with NOMAC-E2 compared to those treated with DRSP-EE. Discontinuation due to 'unacceptable vaginal bleeding' was also higher in the NOMAC-E2 group compared to the DRSP-EE group (4.0% versus 0.7%). The incidence of cumulative amenorrhea was also higher in the women treated with NOMAC-E2 compared with DRSP-EE.

Return to fertility (Phase II study **98-ESC/NOM-1-RD**) was shown in all women during the post treatment cycle. This was verified by serum progesterone levels > 3 ng/mL approximately at Day 20 and the return of spontaneous menstruation. Over 97 % of subjects who switched to non-hormonal method of contraception, after study completion, had a return of menses, in the pivotal studies.

Safety

The evaluator noted a combined exposure of 2545.1 women years in NOMAC-E2 and 874.8 women years for DRSP-EE in the pivotal studies.

Those experiencing at least one AE during the in-treatment period was higher in the NOMAC-E2 group (75.3% vs 69% in the DRSP-EE group). Overall, treatment related events were similar in both groups. Four AEs were reported at a higher incidence ≥ 10% in the NOMAC-E2 group: acne (18.1% vs 9.8%), increased weight (10.9 vs 6.9%), headache (10.5 vs 10.6%) and irregular withdrawal bleeding (10% vs 0.5%).

Discontinuations due to adverse events were higher in the NOMAC-E2 group and included acne, decreased libido, increased weight, metrorrhagia and irregular withdrawal bleeding.

Study **29004** evaluated the effects on haemostasis, effect on the adrenal and thyroid functions. This was a 6 month study comparing LNG-EE of 150 µg -30 µg. NOMAC-E2 induced small changed in haemostasis parameters. Changes in lipid parameters favoured NOMAC-E2 over DRSP-EE. NOMAC-E2 decreased total cortisol, CBG and TBG. The changes were less than that reported with DRSP-EE. There were no changes seen in TFTs.

Endometrial biopsies were undertaken in 107 subjects at baseline and at cycle 13, in study 292002 (85=NOAMC-E2 and 22= DRSP-EE). No significant findings were reported.

There were no VTEs reported.

Overall conclusion and recommendation by the evaluator

The evaluator's conclusion was as follows:

- There were no efficacy and safety data submitted to recommend approval in 12-17 year olds
- NOMAC-E2 was effective as a contraceptive as seen in the PI and Life Table analysis in the two pivotal studies
- The incidence of break through bleeding/ spotting, absence of withdrawal bleeding and cumulative amenorrhoea was significantly higher in women treated with NOMAC-E2 compared to DRSP-EE.
- NOMAC-E2 was well tolerated; however, acne, weight increase and irregular bleeding was reported at a higher rate in the NOMAC-EE2 group.
- The safety profile was acceptable.

Overall, the risk benefit profile was acceptable and the evaluator recommended approval for oral contraception.

Risk Management Plan

There was no objection to the sponsor implementing routine pharmacovigilance activities and also undertaking a post authorisation safety study (PASS). This study is a large prospective non-interventional cohort study to investigate: 'safety in post-menarcheal adolescents', 'safety in women during pregnancy' and 'safety in women with a history of or risk factors for venous thromboembolic events (VTE) and arterial thromboembolic events (ATE).

Risk-Benefit Analysis

Delegate Considerations

Issues arising from evaluation

1. Attention was drawn by the quality evaluator to the lack of bioequivalence regarding C_{max} when comparing one batch (CZ189) used in the pivotal study (study 292001) vs the proposed formulation. Study 292002 which used batch CA057 showed bioequivalence with the proposed formulation. Hence that evaluator recommended approval provided the safety profiles using the two batches in the two pivotal studies are similar.

   The adverse events reported in each study were compared. Clearly, this is a crude index, as the progestogen related events in the limited subject population do not show an obvious trend. However, in practice, should they occur at a higher rate, it may lead to cessation of treatment with Zoely and switching to another COC with a more acceptable safety profile.

   The issue of increased bioavailability with food intake has not been addressed in the PI. *The sponsor should in its pre-ACPM response submit a summary of adverse events*

from the pivotal studies (with and without food) to support its claim that it is not of significance.

2. Study 292004 assessed the haemostasis endpoints for six months and showed no obvious effects. This needs confirmation in larger and long term studies. Thus, the issues of venous thromboembolism and arterial events are to be monitored by the conduct of a Phase IV study. *The protocol should be submitted to the OPR, when finalised.*
3. The amended indication was acceptable. However there should be a cross reference to Clinical Trials where the age range of the subject group is specified.

The Delegate proposed registration of Zoely (2.5 mg nomegestrol acetate and 1.5 mg oestradiol) for oral contraception.

Response from Sponsor

The indication has been amended to 'oral contraception'. The Delegate noted that this was in line with those approved for Qlaira and Yasmin.[20]

The sponsor addressed the issues raised by the Delegate.

Increased bioavailability with food intake

In response to this issue the sponsor indicated that all Phase III Trials (292001 – 292005; batches CZ189 and CA057) have been performed without restrictions with respect to intake of food. In the protocols women were advised to "take one tablet on each day and every day, preferably at the same time of the day". Thus, no advice in relation to food intake was given. Therefore, in the absence of data on daily food intake and timing, it is not possible to retrospectively analyse the adverse events profile with or without food intake.

Nevertheless, given that it is likely that many women will have taken their tablets both with and without food, the efficacy and safety data from the pivotal studies is considered to reflect typical use.

The sponsor advised that as a follow up measure for the European centralized registration procedure a food effect study was due to commence shortly. The title of this study is:

"A single dose, two-way, crossover study to assess the effect of food on the pharmacokinetics of the commercial NOMAC-E2 tablet formulation and of the Phase III pivotal clinical batches."

The objective of the study is to assess the effect of food on the PK of NOMAC, E2 and E1 after single dose administration of the NOMAC-E2 tablet formulation. The study was scheduled to start in May 2011. The final clinical trial report is planned to be ready by the end of March 2012 and will be submitted to the TGA thereafter.

Given the data presently available, the sponsor proposed to maintain the current text in the PI regarding timing of Zoely administration with respect to food intake. Reference was made to the original application where the food effect on the C_{max} (29%) and AUC (27%) of NOMAC was considered to be of minor clinical relevance. This conclusion is based on safety data obtained after multiple doses up to 5 times the contraceptive daily dose of NOMAC-E2 (2.5 mg-1.5 mg), single doses up to 40 times the daily dose of NOMAC alone, and supportive safety data as collected for two currently marketed higher dosed products for pre- and postmenopausal women: Lutenyl NOMAC (3.75 mg or 5 mg); and Naemis NOMAC-E2 (3.75 mg-1.5 mg).

[20] TGA. AusPAR for Qlaira, March 2011. Available at http://www.tga.gov.au/pdf/auspar/auspar-qlaira.pdf

Summary results of one (previously unevaluated) single dose PK study comparing the PK of adults and adolescents (study **292008**) was submitted as a part of the response. The similarity of the results in relation to these endpoints (and physiologically based modelling) was submitted to support the sponsor's claim that the actions are similar in these two subpopulations.

The lack of a bioequivalence study between the proposed formulation vs those used in the pivotal studies was addressed in the submission of Study PO6328. This was evaluated by the quality evaluator and discussed below.

Based on this data, statements have been included in the PI under the heading "Pharmacokinetic properties" that no clinically relevant effect of food was observed on the bioavailability of both NOMAC and E2. In addition, in the Dosage and Administration Section under "Dosage and Administration- how to take Zoely" the tablet intake instructions are as follows:

"Tablets must be taken every day at about the same time without regard to meals. Take tablets with some liquid as needed, and in the order as directed on the package."

As previously stated, the sponsor proposed no changes to this text at present.

The issues of venous thromboembolism and arterial events are to be monitored by the conduct of a Phase IV study. The protocol should be submitted to the OPR, when finalised.

Study (PASS). This will be a 5 year, large, multinational, observational study to assess VTE and ATE risk and other health risks associated with NOMAC-E2 use compared with other marketed COCs during standard clinical practice (CELINA). Approximately 16,500 subjects per cohort (33,000 subjects in total) will be recruited in 2 years and followed for 3-5 years. The sponsor indicated that the protocol will be finalised by the end of July 2011 and submitted as soon as possible thereafter. *The sponsor indicated that the CELINA protocol was submitted to the TGA on 19 July 2011.*

The amended indication is acceptable. However there should be a cross reference to Clinical Trials where the age range of the subject group is specified.

The sponsor proposed to align the text with the text from the Qlaira (oestradiol valerate / dienogest) PI where the indication is also "oral contraception", without cross reference to the Clinical Trials section.[20] Similar to the Qlaira PI, the Zoely PI contains clear information in the Clinical Trials section to enable determination of the age group of subjects participating in the clinical studies submitted in support of registration. For both Qlaira and Zoely, this is 18-50 years.

There were several metabolites detected; they had (none or) weak progestogenic activity compared to the parent compound. Oestrogenic or androgenic activity of the metabolites is not mentioned. The sponsor should clarify this in the pre-ACPM response: do the metabolites have such activity?

The sponsor indicated that the oestrogenic and androgenic activity of the metabolites has not been tested. Levels of individual metabolites were low: around 5% of NOMAC equivalents or lower. It should also be noted that no oestrogenic or androgenic side effects have been noted in the repeated dose toxicity studies with NOMAC.

The sponsor also made a number of comments with regard to the PI but these are beyond the scope of this AusPAR.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for the indication:

For oral contraception.

In making this recommendation, the ACPM considered that nomegestrol + oestradiol (NOMAC-E2) was shown to be effective as a contraceptive in the two pivotal studies evaluated.

The ACPM agreed with the Delegate that the use of the crude index of a comparison of safety profiles between the studies using the different formulas was less than ideal. NOMAC-E2 was well tolerated; however, acne, weight increase and irregular bleeding were reported at a higher rate in the NOMAC-E2 group. Although the safety profile was considered acceptable it was noted that the incidence of break through bleeding/spotting, absence of withdrawal bleeding and cumulative amenorrhoea were significantly higher in women treated with NOMAC-E2 compared to drospirenone+ethinylestradiol (DRSP-EE).

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy, considered there was a favourable benefit risk profile for this product. However, there were no efficacy and safety data submitted to recommend approval in 12-17 year olds.

The specific conditions of registration should include:

The protocol for the Phase IV study required for long term study and monitoring venous thromboembolism and arterial events (CELINA) should be submitted to the OPR, when finalised. The nonclinical data were not predicative of human carcinogenicity, so breast and cervical cancer should be explicitly included in the study's endpoints.

The ACPM also recommended changes to the PI and Consumer Medicines Information (CMI) document but these are beyond the scope of this AusPAR.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Zoely containing nomegestrol 2.5 mg and oestradiol 1.5 mg indicated for:

Oral contraception

Among specific conditions of registration were the following:

- The implementation in Australia of the latest nomegestrol acetate and 17β oestradiol Risk Management Plan (RMP), and any subsequent revisions, as agreed with the TGA and its Office of Product Review.
- The results of the CELINA clinical study report, including all information on breast and cervical cancer, are to be submitted to the TGA as soon as they become available.

Attachment 1. Product Information

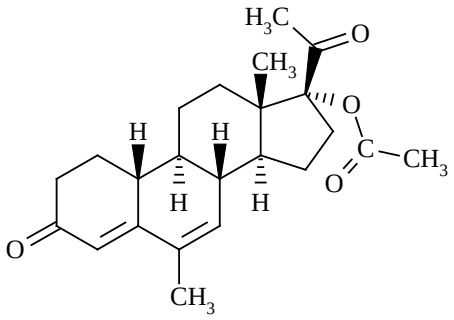
The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION
ZOELY®

NAME OF THE MEDICINE

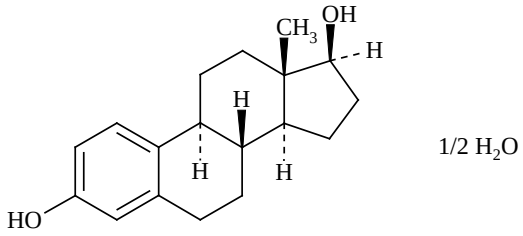
ZOELY
Each blister strip consists of 24 white active tablets each containing 2.5mg nomegestrol acetate and 1.5 mg oestradiol (as hemihydrate) and 4 yellow placebo tablets that do not contain active substances.

Nomegestrol acetate



Chemical name: 17a-acetoxy-6-methyl-19-norpregna-4,6-dien-3,20-dione
Molecular formula: $C_{23}H_{30}O_4$
Molecular mass: 370.48
CAS No.: 58652-20-3

Oestradiol



Chemical name: estra-1,3,5(10)-triene-3,17b-diol
Molecular formula: $C_{18}H_{24}O_2$
Molecular mass: 281.4
CAS No.: 50-28-2

DESCRIPTION

ZOELY is a combined oral contraceptive (COC) preparation containing the progestogen nomegestrol acetate and the natural oestrogen 17b-oestradiol as the active substances.

Nomegestrol acetate: a white to off white crystalline powder that is freely soluble in methylene chloride, acetone and ethyl acetate, soluble in dioxane and acetonitrile and sparing soluble in methanol and ethanol. Melting range is between 177 and 180^{o}C.

Oestradiol: a white to almost white, crystalline powder and is practically insoluble in water. Melting range is between 173 and 179^{o}C.

PHARMACOLOGY

Nomegestrol acetate is a highly selective progestogen derived from, and structurally similar to, the naturally occurring steroid hormone, progesterone. Nomegestrol acetate has a strong affinity for the human progesterone receptor and has strong anti-gonadotropic activity, moderate anti-androgenic activity, and is devoid of any oestrogenic, androgenic, glucocorticoid or mineralocorticoid activity.

The oestrogen contained in ZOELY is 17β-oestradiol, a natural oestrogen identical to the endogenous human 17β-oestradiol (E2). This oestrogen differs from the oestrogen ethinylooestradiol used in other combined oral contraceptives (COC) by the lack of the ethinyl group in the 17alpha position. During use of ZOELY, the average E2 levels are comparable to the E2 levels during the early follicular and late luteal phase of the menstrual cycle.

The contraceptive effect of ZOELY is based on the interaction of various factors, the most important of which are the inhibition of ovulation and the changes in the cervical secretion. During the use of ZOELY, nomegestrol acetate is primarily responsible for the suppression of ovulation, with 17β-oestradiol enhancing the suppressive effects of nomegestrol acetate.

After discontinuation of ZOELY, rapid return to ovulation was observed in most women.

Folic acid is an important vitamin in the early phase of pregnancy. Folic acid serum levels remained unchanged during and after ZOELY treatment for 6 consecutive cycles as compared to baseline.

Pharmacotherapeutic group: progestagens and oestrogens, fixed combinations, ATC code: G03A A14.

Pharmacokinetic properties

Nomegestrol acetate (NOMAC)

Absorption
Orally administered nomegestrol acetate (NOMAC) is rapidly absorbed. Maximum plasma concentrations of NOMAC of about 7 ng/mL are reached at 2 h after single administration. The absolute bioavailability of NOMAC after a single dose is 63 %.Administration of ZOELY with a high fat meal increased the bioavailability of NOMAC by 27-29% which was not considered clinically relevant.

Distribution
Nomegestrol acetate (NOMAC) is extensively bound to albumin (97-98%), but does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). The apparent volume of distribution of NOMAC at steady state is 1645 ± 576L.

Metabolism
Nomegestrol acetate (NOMAC) is metabolized into several hydroxylated metabolites without progestagenic activity, by liver cytochrome P450 enzymes, mainly CYP2C8, CYP2C19, CYP3A4 and CYP3A5. NOMAC and its hydroxylated metabolites undergo extensive phase 2 metabolism to form glucuronide and sulphate conjugates. The oestrogenic and androgenic activities of the metabolites are unknown. The apparent clearance at steady state is 26 L/h.

Elimination
The elimination half life ($t_{1/2}$) is 46 hours (ranging from 28-83 hours) at steady state. The elimination half-life of metabolites was not determined. NOMAC is excreted via urine and faeces. Approximately 80% of the dose is excreted in urine and faeces within 4 days. Excretion of NOMAC was nearly complete after 10 days and amounts excreted were higher in faeces than in urine.

Linearity
Dose-linearity was observed in the range 0.625 – 5mg (assessed in fertile and post-menopausal women).

Steady-State Conditions
The pharmacokinetics of nomegestrol acetate (NOMAC) are not influenced by SHBG. Steady-state is achieved after 5 days. Maximum plasma concentrations of NOMAC of about 12 ng/mL are reached 1.5 hours after dosing. Average steady state plasma concentrations are 4 ng/mL.

Drug-drug interactions
From *in vitro* studies, nomegestrol acetate causes no notable induction or inhibition of any cytochrome P450 enzymes and has no clinically relevant interaction with the P-gp transporter.

<u>Oestradiol (E2)</u>

Absorption
17β-Oestradiol (E2) is subject to a substantial first-pass effect after oral administration. The absolute bioavailability is approximately 5%. After administration of ZOELY with a high fat meal, the mean exposure to oestradiol (E2) was only marginally affected. Exposure to the major metabolite of E2, estrone (E1), was increased by about 20% which was not considered clinically relevant.

Distribution
The distribution of exogenous and endogenous 17β-oestradiol (E2) is similar. Oestrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Oestradiol circulates in the blood

bound to SHBG (37%) and to albumin (61%), while only approximately 1-2% is unbound.

Metabolism
Oral exogenous 17β-oestradiol (E2) is extensively metabolized. The metabolism of exogenous and endogenous E2 is similar. E2 is rapidly transformed in the gut and the liver in several metabolites, mainly estrone (E1), which are subsequently conjugated and undergo entero-hepatic circulation. There is a dynamic equilibrium between E2, E1 and E1-Sulfate (E1S) due to various enzymatic activities including E2-dehydrogenases, sulfotransferases and aryl sulfatases. Oxidation of E1 and E2 involves cytochrome P450 enzymes, mainly CYP1A2, CYP1A2 (extra hepatic), CYP3A4, CYP3A5, and CYP1B1 and CYP2C9.

Elimination
17β-Oestradiol (E2) is rapidly cleared from the circulation. Due to metabolism and enterohepatic circulation, a large circulating pool of oestrogen sulfates and glucuronides is present. This results in a highly variable elimination half-life of E2, which is calculated to be 8.4 ± 6.4 hours, after intravenous administration.

Steady-State Conditions
Maximum serum concentrations of 17β-oestradiol (E2) are about 90 pg/mL and are reached 6 hours after dosing. Average serum concentrations are 50 pg/mL and these E2 levels correspond with the early and late phase of a woman's menstrual cycle.

Special Populations
Paediatric population
Whole-body-physiologically based pharmacokinetic modeling and simulation showed that no difference in the nomegestrol acetate pharmacokinetics is expected between post-menarcheal adolescent women (aged 12-17 years) and adult women.

Effect of renal impairment
No studies were performed to evaluate the effect of renal disease on the pharmacokinetics of ZOELY.

Effect of hepatic impairment
No studies were conducted to evaluate the effect of hepatic disease on the pharmacokinetics of ZOELY. However, steroid hormones may be poorly metabolised in women with impaired liver function.

Ethnic groups
No formal studies were performed to assess pharmacokinetics in ethnic groups.

CLINICAL TRIALS

Contraceptive efficacy
Two randomized, open-label, comparative efficacy-safety trials (Study report 292001 and 292002) were conducted in more than 3200 women treated for 13 consecutive cycles with ZOELY. The primary efficacy and safety parameters were contraceptive efficacy, vaginal bleeding pattern (cycle control), general safety and acceptability. Women entering the study were aged between 18 and 50 years and women with a

BMI greater than 35 were excluded from the study. Women were excluded from the study if they had conditions which were listed as a contraindication for combined oral contraceptives. The overall Pearl Index (method failure and user failure) 18-50 years of age was: 0.64 (upper limit 95% CI 1.03).
In the pivotal efficacy and safety trials, women using ZOELY experienced overall a low number of bleeding events. Withdrawal bleedings were light and of short duration (on average 3-4 days) and often less painful (dysmenorrhea).

A randomized, open-label, comparative, multicenter trial (Study report 292004) was performed to assess effects of ZOELY on hemostasis, lipids, carbohydrate metabolism, adrenal and thyroid function and on androgens. Glucose tolerance and insulin sensitivity remained unaltered and no clinically relevant effects on lipid metabolism and hemostasis were observed with ZOELY. The comparator levonorgestrel 150µg + ethinyloestradiol 30µg was associated with more pronounced changes in these parameters. ZOELY increased the carrier proteins TBG and CBG, but to lesser extent than LNG-EE. ZOELY induced a small increase in SHBG, which was slightly higher than LNG-EE (20 to 30 µg EE). The androgenic parameters androstenedione, DHEA-S, total and free testosterone were significantly reduced during use of ZOELY.

Endometrial histology was investigated in a subgroup of women (n=32) in one clinical study after 13 cycles of treatment. There were no abnormal results.

INDICATIONS

Oral contraception.

CONTRAINDICATIONS

Combined hormonal contraceptives (COCs) should not be used in the presence of any of the conditions listed below. No epidemiological data are available with 17β-oestradiol containing COCs, but the contraindications for ethinyloestradiol containing COCs are also considered applicable to the use of ZOELY. Should any of the conditions appear for the first time during the use of ZOELY, the product should be stopped immediately:

- presence or history of venous thrombosis (deep venous thrombosis, pulmonary embolism);
- presence or history of arterial thrombosis (myocardial infarction, cerebrovascular accident) or prodromal conditions (e.g. transient ischaemic attack, angina pectoris);
- history of migraine with focal neurological symptoms;
- the presence of severe or multiple risk factor(s) for venous or arterial thrombosis (see *Precautions*) such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinemia
- hereditary or acquired predisposition for venous or arterial thrombosis, such as APC resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant);

- pancreatitis or a history thereof if associated with severe hypertriglyceridaemia;
- presence or history of severe hepatic disease as long as liver function values have not returned to normal;
- presence or history of liver tumours (benign or malignant);
- known or suspected sex steroid-influenced malignancies (e.g., of the genital organs or the breasts);
- known or suspected pregnancy;
- hypersensitivity to any of the active substances of ZOELY or to any of the excipients.

PRECAUTIONS

If any of the conditions/risk factors mentioned below is present, the benefits of the use of ZOELY should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using ZOELY. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether its use should be discontinued. All data presented below are based upon epidemiological data obtained with combined oral contraceptives (COCs) containing ethinyloestradiol. ZOELY contains 17β-oestradiol. No epidemiological data are available with oestradiol containing COC but the warnings are considered applicable to the use of ZOELY.

Circulatory Disorders

- Epidemiological studies have suggested an association between the use of combined oral contraceptives (COCs) containing ethinyloestradiol and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely.
- Use of any ethinyloestradiol-containing COC carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 per 100, 000 pregnant woman years. This compares with 5 to 10 cases per 100,000 woman-years for non-users. VTE is fatal in 1%-2% of cases. It is not known how ZOELY influences this risk compared with other COCs.
- Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.
- Symptoms of venous or arterial thrombosis can include: unilateral leg pain and/or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; ‘acute’ abdomen.

- The risk of venous thromboembolism increases with:
  - increasing age;
  - a positive family history (i.e. venous thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use;
  - prolonged immobilization, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilization.
  - obesity (body mass index over 30 kg/m^2);
  - and possibly also with superficial thrombophlebitis and varicose veins. There is no consensus about the possible role of these conditions in the etiology of venous thrombosis.
- The risk of arterial thromboembolic complications increases with:
  - increasing age;
  - smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
  - dyslipoproteinemia;
  - obesity (body mass index over 30 kg/m^2);
  - hypertension;
  - migraine;
  - valvular heart disease;
  - atrial fibrillation;
  - a positive family history (arterial thrombosis ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.
- Other medical conditions, which have been associated with adverse circulatory events, include diabetes mellitus, systemic lupus erythematosus, hemolytic uraemic syndrome, chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and sickle cell disease.
- The increased risk of thromboembolism in the puerperium must be considered (see *Use in Pregnancy*).
- An increase in frequency or severity of migraine (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of ZOELY use.
- Women using COCs should be specifically pointed out to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, COC use should be discontinued. Adequate contraception should be initiated because of the teratogenicity of anti-coagulant therapy (coumarins).

Neoplasms

- The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Epidemiological studies have indicated that long-term use of ethinyloestradiol-containing COCs contributes to this increased risk, but there continues to be uncertainty about the extent to which this finding is attributable to confounding effects, like increased cervical

screening and difference in sexual behaviour including use of barrier contraceptives, or a causal association.

- With the use of the higher-dosed COCs (50 μg ethinyloestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to 17β-oestradiol -containing COCs remains to be confirmed.
- A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using ethinyloestradiol-containing COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both.
- In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. Therefore, a hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

Other conditions

- Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.
- Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. A relationship between COC use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to suspend the intake of the tablets and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy. In seven multi-centre clinical trials of up to two years duration, no clinically relevant changes in blood pressure were observed with ZOELY.
- The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis related hearing loss; (hereditary) angioedema.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.
- There is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing <0.05 mg ethinyloestradiol). However, diabetic women should be carefully observed while taking a COC especially in the first months of use. ZOELY was shown to have no effect on peripheral

insulin resistance and glucose tolerance in healthy women (see *Clinical Trials*).

- Crohn's disease and ulcerative colitis have been associated with COC use.
- Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.
- ZOELY contains <60 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on lactose-free diet should take this amount into consideration.

Medical Examination/Consultation

Prior to the initiation or reinstitution of COC use, a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and if clinically indicated a physical examination should be performed, guided by the contraindications and precautions The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of further periodic checks should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

The efficacy of COCs may be reduced in the event of e.g., missed tablets (see *Dosage and Administration*), gastro-intestinal disturbances during active tablet taking (see *Dosage and Administration*), or use of concomitant medication (see *Interactions*).

Cycle control

As with all COCs, breakthrough bleeding or spotting may occur, especially during the first months of use. Therefore, the evaluation of any breakthrough bleeding or spotting is only meaningful after an adaptation interval of about three cycles. If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage. Women with undiagnosed abnormal vaginal bleeding should not start treatment with a COC until a possible underlying condition has been excluded.

In the pivotal efficacy and safety trials, women using ZOELY experienced overall a low number of bleeding events. Withdrawal bleedings were light and of short duration (on average 3-4 days) and often less painful (dysmenorrhea).

Some users of ZOELY have reported absence of withdrawal bleeding during the placebo yellow tablet phase although not being pregnant. In such cases, absence of withdrawal bleeding was not associated with a higher occurrence of breakthrough bleeding or spotting in the subsequent cycle.

If absence of withdrawal bleeding occurs and ZOELY is taken according to the instructions as described under *Dosage and Administration* it is unlikely that the woman is pregnant. However, pregnancy must be ruled out before ZOELY use is

continued if ZOELY has not been taken as directed or if two consecutive withdrawal bleeds are missed.

Genotoxicity

No evidence for genotoxicity was found with nomegestrol acetate in assays for bacterial and mammalian mutagenicity, yeast mitotic gene conversion, chromosomal aberrations and unscheduled DNA synthesis *in vitro* and clastogenicity *in vivo* (mouse and rat bone marrow micronucleus tests).

There is limited evidence available in the literature suggesting that oestradiol may be weakly genotoxic at high doses. No evidence could be found for an increase in the rate of gene mutation in bacterial or mammalian cells, but there was some evidence for the induction of chromosomal aberrations and aneuploidy and an increased incidence of sister chromatid exchanges (indicative of DNA damage) in mammalian cells. None of these effects were induced by oestradiol in human lymphocyte cultures. Importantly, there was no evidence for micronuclei formation in rodent bone marrow assays.

The genotoxic potential of the combination of nomegestrol acetate and oestradiol has not been investigated.

Carcinogenicity

Carcinogenicity studies have not been performed with the combination of nomegestrol acetate and oestradiol. However, studies have been performed for the two active components separately.

Supraphysiological doses of oestradiol have been associated with the induction of tumours in oestrogen-dependent target organs in all rodent species tested. The relevance of these findings with respect to humans has not been established. However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

In a long-term oral (dietary) carcinogenicity study in mice, nomegestrol acetate increased the incidence of mammary gland carcinoma and pituitary adenoma in females at doses ≥20mg/kg/day and 50 mg/kg/day, respectively. Systemic exposure to nomegestrol acetate (plasma AUC) in animals at these doses was 4 to 15 times higher than that of women treated with ZOELY. These findings are consistent with extensive endocrine disruption in the species caused by the progestagenic activity of nomegestrol acetate.

No evidence of tumourigenicity was found with nomegestrol acetate in a 2-year study in rats using dietary doses up to 10 mg/kg/day (yielding 30 times the expected human exposure level).

Use in pregnancy (Category B3)

ZOELY is not indicated during pregnancy. If pregnancy occurs during treatment with ZOELY, further intake should be stopped. Most epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used ethinyloestradiol-containing COCs prior to pregnancy, nor a teratogenic effect when ethinyloestradiol-containing COCs were taken inadvertently during early pregnancy.

Clinical data on a limited number of exposed pregnancies indicate no adverse effect of ZOELY on the foetus or neonate.

In rats, treatment with nomegestrol acetate and oestradiol in combination caused increased post-implantation loss, abortions, decreased fetal weight, feminisation of male fetuses, malformations (cleft palate and bent tail) and increased variations (vertebral and rib abnormailities and incomplete ossification). Nomegestrol acetate, given alone in rats, prolonged or impaired parturition. Post-implantation loss was increased and fetal weight was decreased in rabbits treated with the combination. Systemic exposure to nomegestrol acetate (plasma AUC) at no-effect doses in the animal embryofetal development studies was similar to or less than the expected human exposure level. Nomegestrol acetate was shown to cross the placenta in monkeys, with fetal plasm levels comparable to maternal drug levels.

Use in Lactation

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should not be recommended until the nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk, but there is no evidence that this adversely affects infant health.

Paediatric use

Warnings and precautions for post-menarcheal adolescents less than 18 years of age and women greater than 50 years of age are expected to be similar to those described for adults between these age groups although this has not been confirmed in clinical trials.

Interactions with other medicines

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

Influence of other medicinal products on ZOELY

Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature for COCs in general.

Hepatic metabolism: Interactions can occur with drugs that induce microsomal enzymes, which can result in increased clearance of sex hormones (e.g., phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, and products containing St. John's wort). Also HIV protease (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and combinations of them, have been reported to potentially affect hepatic metabolism. With microsomal enzyme-inducing drugs, a barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. In case of long-term treatment with microsomal enzyme inducing drugs another method of contraception should be considered. Drugs that inhibit microsomal enzymes (e.g. ketoconazole) may increase sex hormone plasma levels.

Antibiotics: Contraceptive failures of ethinyloestradiol-containing oral contraceptives have been reported with antibiotics, such as ampicillin and tetracyclines. The mechanism of this effect has not been elucidated and it is unknown whether interactions of antibiotics with a 17β-oestradiol-containing contraceptive occur. Women on treatment with antibiotics (except rifampicin and griseofulvin, see above) should use a barrier method until 7 days after discontinuation. If the period during which the barrier method is used extends beyond the end of the white tablets in the COC pack, the yellow placebo tablets must be discarded and the next COC pack should be started right away.

Drug interaction studies were not performed with ZOELY, but two studies with rifampicin and ketoconazole, respectively, were performed with a higher dosed NOMAC-E2 combination (NOMAC 3.75 mg + 1.5 mg E2) in post-menopausal women.

Influence of ZOELY on other medicinal products
Oral contraceptives may affect the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

Paediatric population
The interactions as described above are expected to be similar in postmenarcheal adolescent women.

Effect on Laboratory tests
The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g., corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

Effects on ability to drive and use machines
ZOELY has no influence on the ability to drive and use machines.

ADVERSE EFFECTS

Tabulated summary of adverse reactions
Seven multi-centre clinical trials of up to two years duration were used to evaluate the safety of ZOELY. In total 3,490 women, aged 18-50, were enrolled and completed 35,028 cycles.

ZOELY is well tolerated and demonstrates an overall safety profile similar to other combined oral contraceptives. Possibly related undesirable effects that have been reported in users of ZOELY are listed in the table below:

	Adverse reaction in MedDRA Term[1]			
Body system	**Very common ≥ 1/10**	**Common ≥ 1/100 to <1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥1/10,000 to < 1/1000**
Metabolism and nutrition disorders			increased appetite, fluid retention	decreased appetite
Psychiatric disorders		decreased libido, depression/ depressed mood, mood altered		increased libido
Nervous system disorders		headache migraine		disturbance in attention
Eye disorders				dry eye, contact lens intolerance
Vascular disorders			hot flush	
Gastrointestinal disorders		nausea	Abdominal distension	dry mouth
Skin and subcutaneous tissue disorders	acne[2]		hyperhydrosis, alopecia, pruritus, dry skin, seborrhea	chloasma, hypertrichosis
Musculoskeletal and connective tissue disorders			sensation of heaviness	
Reproductive system and breast disorders	abnormal withdrawal bleeding	metrorrhagia, menorrhagia, breast pain, pelvic pain	hypomenorrhoea, breast swelling, galactorrhoea, uterine spasm, premenstrual syndrome, breast mass, dyspareunia, vulvovaginal dryness	vaginal odour, vulvovaginal discomfort
General disorders and administrative site conditions			irritability, oedema	hunger
Investigations		weight increased	hepatic enzyme increased	

[1] The most appropriate MedDRA term (version 13.1) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

[2] Acne was a solicited rather than spontaneously reported event, being assessed at every study visit.

The adverse reaction rates for Zoely (N = 3490) in comparison to the reference COC containing drospirenone 3 mg – ethinylestradiol 30 µg (21/7 regimen) (N = 1105) in the integrated safety data set were:
acne (15.4 % versus 7.9 %), weight increased (8.5 % versus 5.9 %) and abnormal withdrawal bleeding (predominantly absence of withdrawal bleeding) (10.2 % versus 0.6 %).

Description of selected adverse reactions
A number of undesirable effects have been reported in women using combined oral contraceptives containing ethinyloestradiol, which are discussed in more detail in *Precautions*. These include:

- venous thromboembolic disorders;
- arterial thromboembolic disorders;
- hypertension;
- hormone-dependent tumours (e.g. liver tumours, breast cancer);
- chloasma.

The frequency of diagnosis of breast cancer is very slightly increased among COC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see *Contraindications* and *Precautions*.

Paediatric population
Frequency, type and severity of adverse reactions in post-menarcheal adolescents are expected to be the same as in adult women.

Other special populations
No studies have been performed with renally or hepatically impaired subjects. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

DOSAGE AND ADMINISTRATION

How to take ZOELY
Tablet intake instructions are the same for all users.

Tablets must be taken every day at about the same time without regard to meals. Take tablets with some liquid as needed, and in the order as directed on the package. One tablet is to be taken daily for 28 consecutive days. Each pill pack starts with 24 white active tablets, followed by 4 yellow placebo tablets; (see Picture 1). A subsequent pack is started immediately after finishing the previous pack, without a break in daily tablet intake and irrespective of presence or absence of withdrawal bleeding. Withdrawal bleeding usually starts on day 2-3 after intake of the last white tablet and may not have finished before the next pack is started. See also ‘Cycle control’ under *Precautions*.

How to start ZOELY

No preceding hormonal contraceptive use

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). When doing so, no additional contraceptive measures are necessary. Starting on days 2-5 is allowed, but during the first pill pack a barrier method should be used until the woman has completed 7 days of uninterrupted white tablet-taking (see Picture 1).

Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring or transdermal patch)

The woman should start with ZOELY preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using ZOELY preferably on the day of removal, but at the latest when the next application would have been due.

If the woman has been using her previous method consistently and correctly, and if it is reasonably certain that she is not pregnant, she may also switch on any day. The hormone-free interval of the previous method should never be extended beyond its recommended length.

Changing from a progestagen-only-method (minipill, implant, injectable) or from a hormone-medicated Intra Uterine System (IUS)

The woman may switch any day from the minipill and ZOELY should be started on the next day. An implant or IUS may be removed any day, and ZOELY should be started on the day of its removal. When changing from an injectable, ZOELY should be started on the day when the next injection would have been due. In all of these cases the woman should be advised to additionally use a barrier method until she has completed 7 days of uninterrupted white active tablet-taking.

Following first-trimester abortion

The woman may start immediately. When doing so, no additional contraceptive measures are necessary.

Following delivery or second-trimester abortion

For breast-feeding women see *Use in Lactation* under *Precautions*.

Women should be advised to start between day 21 and 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of white active tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

Management of missed tablets

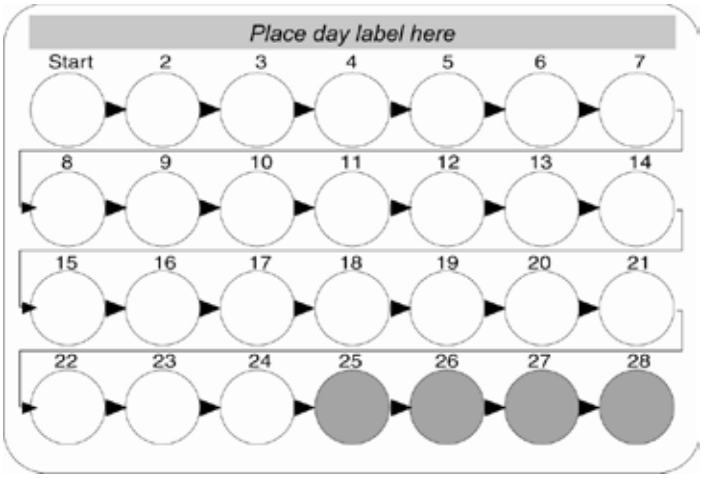
The following advice only refers to missed white active tablets:

If the user is **less than 12 hours** late in taking any active tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is **more than 12 hours** late in taking any active tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

- 7 days of uninterrupted 'white active tablet'-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.
- The more 'white active tablets' are missed and the closer the missed tablets are to the 4 yellow placebo tablets, the higher the risk of a pregnancy.

Picture 1



Missed tablet advice

One white active tablet missed
Contraceptive protection is not reduced. The user should take the last missed white tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. She does not need any additional contraceptive protection.

Two or more white active tablets missed
If the woman missed two or more white tablets and subsequently has no withdrawal bleed while taking the yellow placebo tablets, the possibility of a pregnancy should be considered (see also 'Cycle control' under *Precautions*).

Day 1-7
The user should take the last missed white tablet as soon as she remembers even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. A barrier method should be used until she has completed 7 days of uninterrupted white tablet-taking. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered.

Day 8-17
The user should take the last missed white tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. A barrier method should be used until she has completed 7 days of uninterrupted white tablet-taking.

Day 18-24

The risk of reduced reliability is higher because of the forthcoming yellow placebo-tablet interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. The user should take the last missed white tablet as soon as she remembers, even if this means taking two tablets at the same time. She should never take more than two white tablets at the same time. A barrier method should be used until she has completed 7 days of uninterrupted white tablet-taking. Thus, the next pack must be started the day after the white tablets in the current pack are finished, i.e., no yellow placebo tablets should be taken. The user is unlikely to have a withdrawal bleed until she takes the yellow tablets of the second pack, but she may experience breakthrough bleeding or spotting while taking white tablets.

Please note: If the user is not sure about the number or colour of tablets missed and what advice to follow, a barrier method should be used until she has completed 7 days of uninterrupted white active tablet-taking.

Yellow placebo tablets missed

Contraceptive protection is not reduced. Yellow tablets from the last (4th) row of the blister can be disregarded. However, the missed tablets should be discarded to avoid unintentionally prolonging the placebo tablet phase.

Advice in case of gastro-intestinal disturbances

In case of severe gastro-intestinal disturbance (e.g., vomiting or diarrhoea), absorption of the active substances may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after white tablet-taking, the tablet should be considered as missed. In case of one white tablet missed contraceptive protection is not reduced. If vomiting again takes place on the next day(s), the advice as given for 2 or more white tablets missed under *Dosage and Administration* ('Management of missed tablets') is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra white tablet(s) from another pack.

How to shift periods or how to delay a period

To delay a period the woman should continue with another blister pack of ZOELY without taking the yellow tablets from her current pack. The extension can be carried on for as long as wished until the end of the white tablets in the second pack. Regular intake of ZOELY is then resumed after the yellow placebo tablets have been taken of the second pack. During the extension the woman may experience breakthrough bleeding or spotting.

To shift her periods to another day of the week than the women is used to with her current scheme, she can be advised to shorten her forthcoming placebo tablet phase with a maximum of 4 days. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and may experience breakthrough-bleeding and spotting during the subsequent pack (just as when delaying a period).

OVERDOSAGE

There have been no reports of serious deleterious effects from overdose. Multiple doses up to five times the daily dose of ZOELY and single doses up to 40 times the

daily dose of nomegestrol acetate alone have been used in women without safety concern. On the basis of general experience with combined oral contraceptives, symptoms that may occur are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

PRESENTATION AND STORAGE CONDITIONS

Each blister of ZOELY contains:

- 24 white, round, film-coated tablets coded with 'ne' on both sides, each containing 2.5mg nomegestrol acetate and 1.5mg oestradiol. The tablets also contain the inactive ingredients lactose, cellulose microcrystalline, crospovidone, talc, magnesium stearate, silica colloidal anhydrous, polyvinyl alcohol, titanium dioxide and macrogol 3350.
- 4 yellow, round, film-coated tablets coded with 'p' on both sides. The tablets contain the inactive ingredients lactose, cellulose microcrystalline, crospovidone, talc, magnesium stearate, silica colloidal anhydrous, polyvinyl alcohol, titanium dioxide, macrogol 3350, iron oxide yellow E 172 and iron oxide black E 172.

Pack sizes: 1 x 28 and 3 x 28 tablets in PVC/aluminium blisters (transparent PVC thermoforming film with aluminium lidding foil). Not all pack sizes may be marketed.

The shelf life of ZOELY is 3 years when stored below 30^{o}C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods: 15 August 2011.

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