mithra
Women's Health

Investor Presentation

March 2021

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Mithra

1

2 Innovative E4 platform

3 Complex Therapeutics

4 Mithra CDMO

5 Summary Highlights

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Women's Health

Transforming women's health through innovation

mithra
Women's Health

Created in
1999

At the heart of Europe
Belgium (Liège)

Biotech

Specialists in
Women's Health

Partnerships
>100 countries

Euronext Brussels
MITRA

> 300 Staff members

Co-founders

François Fornieri
Board member

- Over 30 years in the Pharma industry
- Founder & CEO of Uteron Pharma (sold to Watson/Actavis)
- Master in Chemical Engineering

Jean-Michel Foidart
Scientific Committee & Board member

- Former CSO of Uteron Pharma & Actavis Belgium
- Former Head of the Gynecology and Obstetrics Department of the University of Liège
- MD & PhD in Cell Biology & Biochemistry


Our **Mission** is to develop **innovative products** offering better efficacy, safety and convenience, meeting women's needs throughout their life span
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Women's Health

Women's health market is huge and growing…

> US$ 40bn

Growing above GDP at c. 4.2% CAGR

…with major opportunities

- **Contraceptives** represent the **largest sub-segment** of the women's health market with **no innovation in decades**
- Demographic trends increase the **relevance of age related medical treatments**

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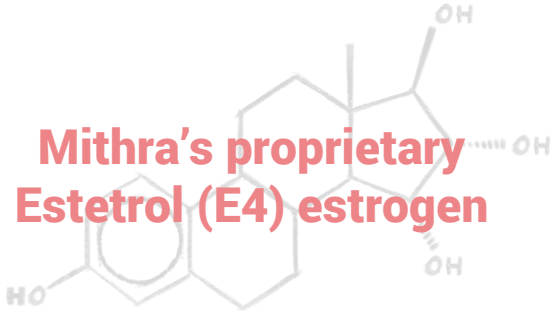
Source: Grand View Research, Women's health market size, 2020-2027

Existing solutions do not meet women's needs

Existing solutions:
EE and E2 estrogen



Mithra's proprietary
Estetrol (E4) estrogen

Key medical risks of EE and E2 estrogens	⟷	Similar medical benefits at an improved safety profile
Side effects negatively impact women's quality of life	⟷	Studies show reduced side effects and impact on quality of life
Negative environmental impact, e.g. on marine wildlife	⟷	In line with international sustainable development goals

Investment case highlights

1. Breakthrough innovation with a unique hormone : E4
2. 1 filing and 2 late-stage E4-based potential blockbusters
3. Worldwide specialist in polymer technology
4. Unique facility with specialist research, development and manufacturing capabilities

Mithra has 2 complementary innovation platforms powered by a unique CDMO facility: its novel E4-based pipeline and its portfolio of Complex Therapeutics

Advanced pipeline offering multiple near-term catalysts

E4

Product	Indication	Phase 1	Phase 2	Phase 3	Market Approval
Estelle®	Contraception				2021
PeriNesta®	Perimenopause				2023
Donesta®	Menopause				Q4 2023/Q1 2024
COVID-19 Treatment®	COVID-19				2022
Under development	CNS, dermatology, etc.	Various stages of non-clinical development of future E4-based pipeline			

Complex Therapeutics

Product	Indication	Formulation / Clinical	Filing	Market Approval
Myring®	Contraception	EU / RoW		Commercialized
		US		US : Q4 2021/Q1 2022
Tibelia®	Menopause			Commercialized
Zoreline®	Oncology			2024

Partnering strategy with leaders in Women's Health

Commercial Agreements in 100+ countries

An innovative E4 platform

1 Mithra

2

3 Complex Therapeutics

4 Mithra CDMO

5 Summary Highlights

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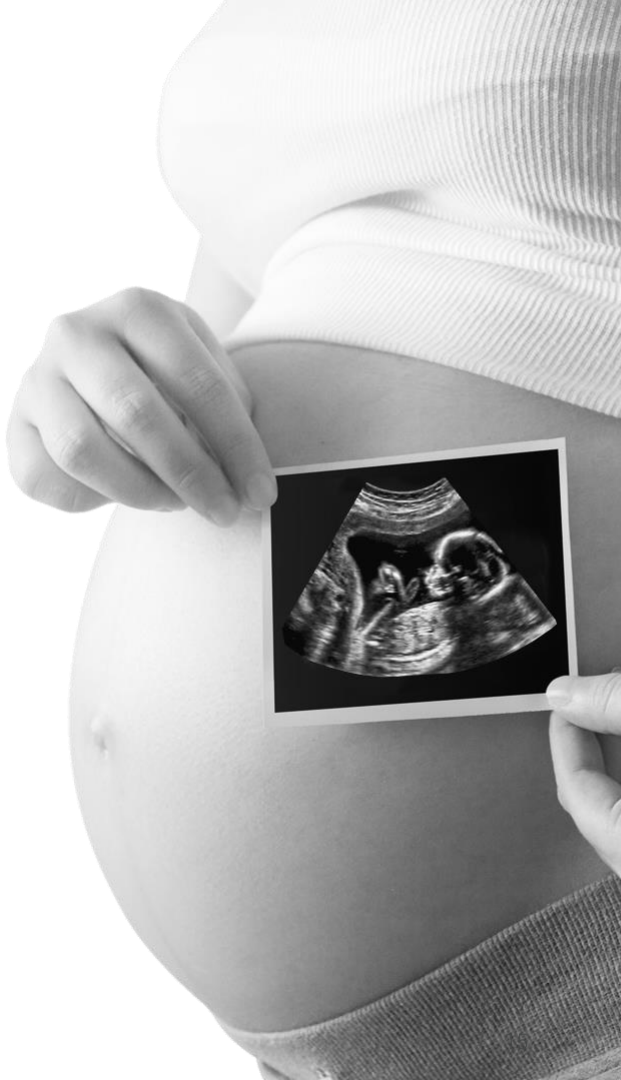
Women's Health


E4 (Estetrol)
a new estrogen with an
improved benefit/risk profile

What is Estetrol (E4) ?

An answer from nature with unique potential

- Initially discovered in Sweden in 1965
- Produced by human fetus around week 9
  - Fetal plasma levels 12x higher than those of mother
- Unique selective tissue action
- Could be applied in a broad range of indications beyond women's health, *i.e.* neuroprotection, dermatology, COVID-19, etc.
- Protected by 35 patent families
- Synthesized from soy beans



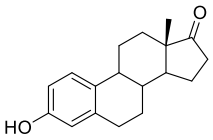
From Phytosterols to Estetrol (E4)

Soy

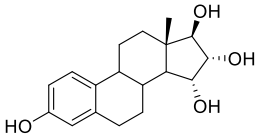
extraction

Phytosterols

Estrone (E1)



Estetrol (E4)



E4 : An environmentally-friendy estrogen

EE (ethynyl estradiol)

- 97% of current marketed Combined Oral Contraceptives are based on EE
- Known as a major Endocrine Disrupting Chemical

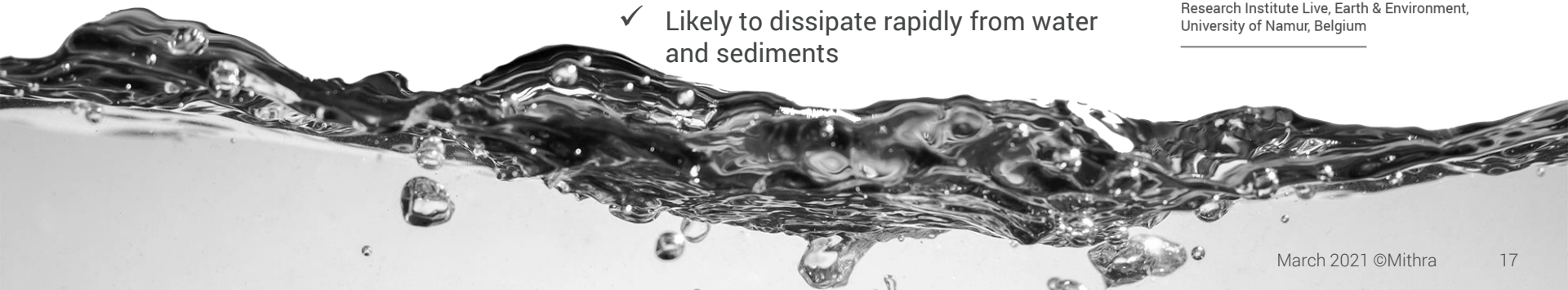
vs

E4 (Estetrol)

- ✓ Insignificant endocrine disruptor effects, whether in aquatic organisms or organisms living in the sediment
- ✓ Amount of biologically active E4 released in the wastewaters after human use expected to be minimal
- ✓ Does not accumulate in living organisms
- ✓ Likely to dissipate rapidly from water and sediments

> “All biotests carried out show without ambiguity that the endocrine disruptor effects of Estetrol are insignificant in comparison with those observed for natural or synthetic estrogens, whether in aquatic organisms or organisms living in the sediment.”

Prof. Patrick Kestemont, President of the Research Institute Live, Earth & Environment, University of Namur, Belgium



The role of estrogens in the human body

E4, a Native Estrogen with Selective action in Tissues supported by a unique mode of action

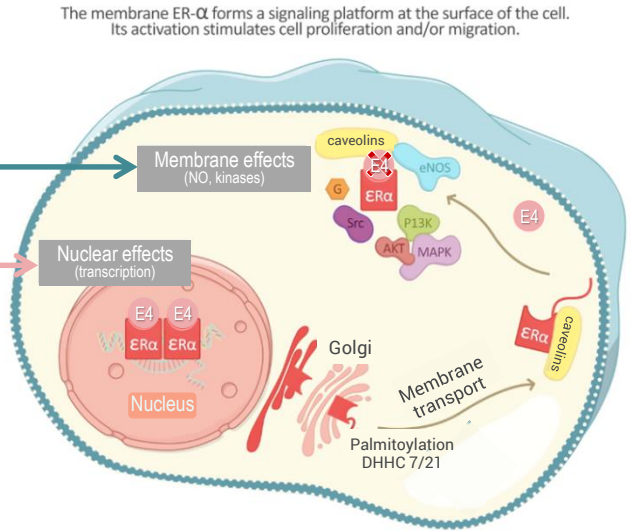
Unlike other estrogens, E4 acts differently depending on the tissue

Antagonist on the membrane receptor

- ✓ E4 blocks the membrane estrogen receptor
- ✓ E4 has a neutral effect on the liver unlike other estrogens
- ✓ E4 has a low impact on normal and malignant breast

Agonist on the nuclear receptor

- ✓ E4 activates the nuclear estrogen receptor
- ✓ E4 has important estrogenic activity on the vagina, endometrium, bone, and cardio-vascular system to provide beneficial effects



Safety concerns of estrogens:
an unmet clinical need potentially addressed by E4

Estrogen's systemic effects:

- **Heart and liver:** increased risk of myocardial infarction, thromboembolism
- **Brain:** increased risk of stroke
- **Uterus:** increased risk of endometrial cancer
- **Breast:** increased risk of breast cancer
- **Quality of life :** bleeding, cycle control

E4 has the potential to address most of these concerns:

+ Favorable **VTE** risk profile[1,#]
+ Favorable **drug-drug interaction** profile[4]
+ Minimal increase of **triglycerides**[5,‡]
+ Lower **breast** pain[6] and lower **carcinogenic** potential*[,2,3,7]
+ Good **user acceptability**, excellent cycle control, improved spotting and general well-being[6,8]

https://investors.mithra.com/wp-content/uploads/2018/03/2018-03-08-Hemostasis-ISGE-en-final.pdf
‡ https://investors.mithra.com/wp-content/uploads/2018/06/e-Poster-Mithra-IMS-2018.pdf

1 *Kluft C et al., Contraception 2016.;* ***2*** *Gerard C et al., Oncotarget 2015;6(19):17621-36.;* ***3*** *Visser M et al., Horm Mol Biol Clin Invest. 2012;9:95-103.;* ***4*** *Visser M et al., Climacteric 2008; 11 Suppl 1:64-8.;* ***5*** *Mawet M et al., Eur. J. Contracept. Reprod. Healthcare 2015:1-13.;* ***6*** *Apter D. et al., Contraception 2016;94(4):366-73;* ***7*** *Abot et al., EMBO 2014: 6 (10);* ***8*** *Apter et al., Eur. J. Contracept. Reprod. Healthcare 2017:22(4)*

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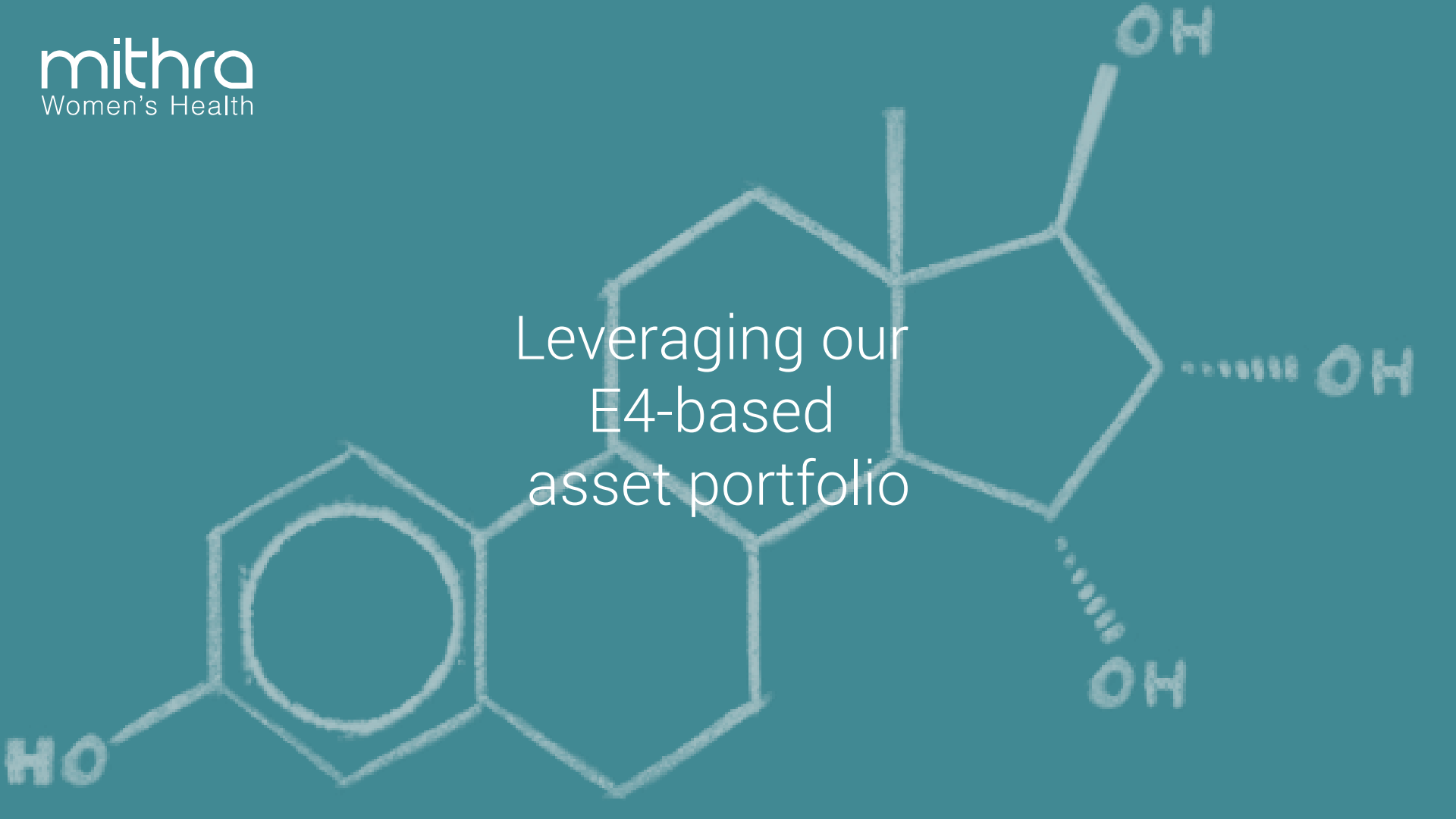
Leveraging our E4-based asset portfolio



3 potential E4-based blockbusters for each stage of women's hormonal life span

CONTRACEPTION

PERIMENOPAUSE

MENOPAUSE

>Teens

Estelle®
A new era in Combined Oral Contraception (COC)

Mid 40's

PeriNesta®
the 1st complete oral treatment targeting perimenopause

>50 years

Donesta®
Next generation Hormone Therapy (HT) for VMS relief

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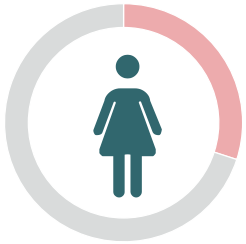
Teens & beyond

Estelle® (15mg E4 / 3mg DRSP)

A new era in Combined Oral Contraception (COC)



30%
of US women not taking pill mainly due to safety or convenience[1]

" Women are seeking **new contraceptive solutions** offering an improved safety profile and tolerability for better reproductive health"

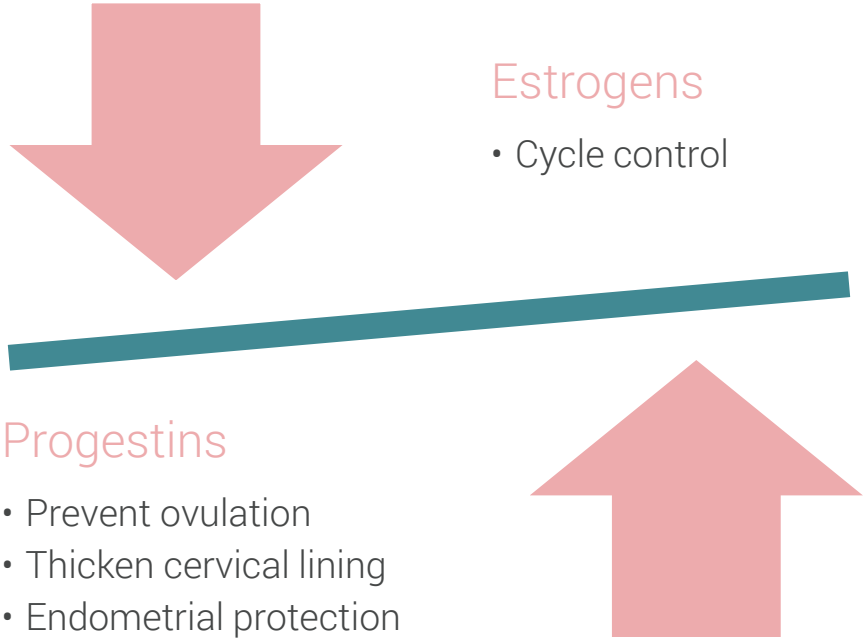
Celmatix Press Release
December 2018

1 K. Daniels et al., National Health Statistics report n° 62, 2013

OBJECTIVE

Optimize women's physiological hormonal balance by combining the best progestin & estrogen according to their profile

The role of female sex hormones in COCs



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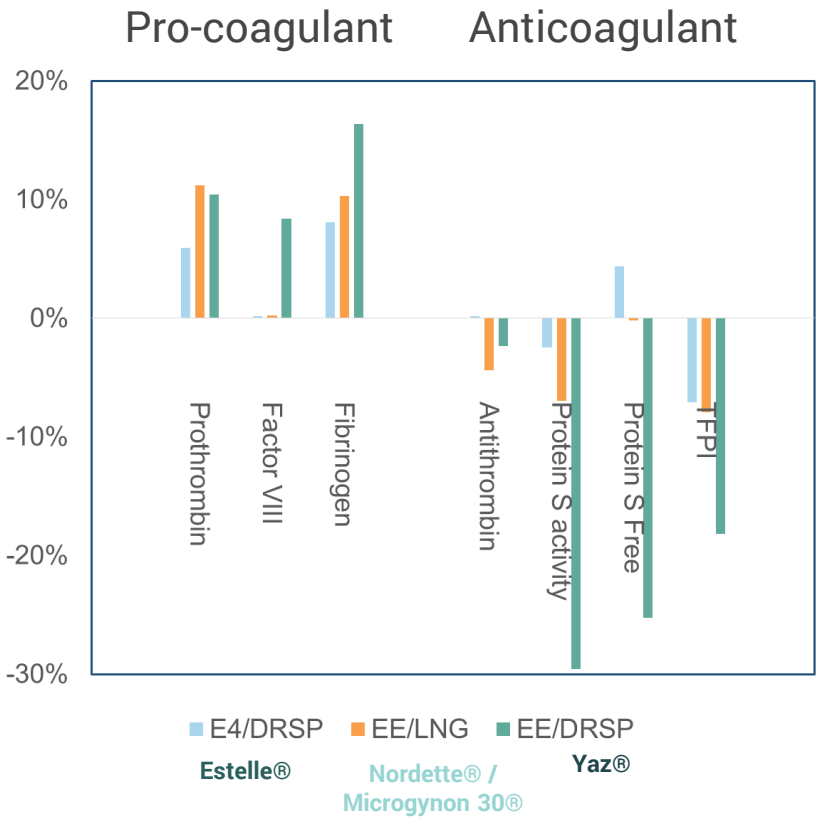
Estelle® for Contraception

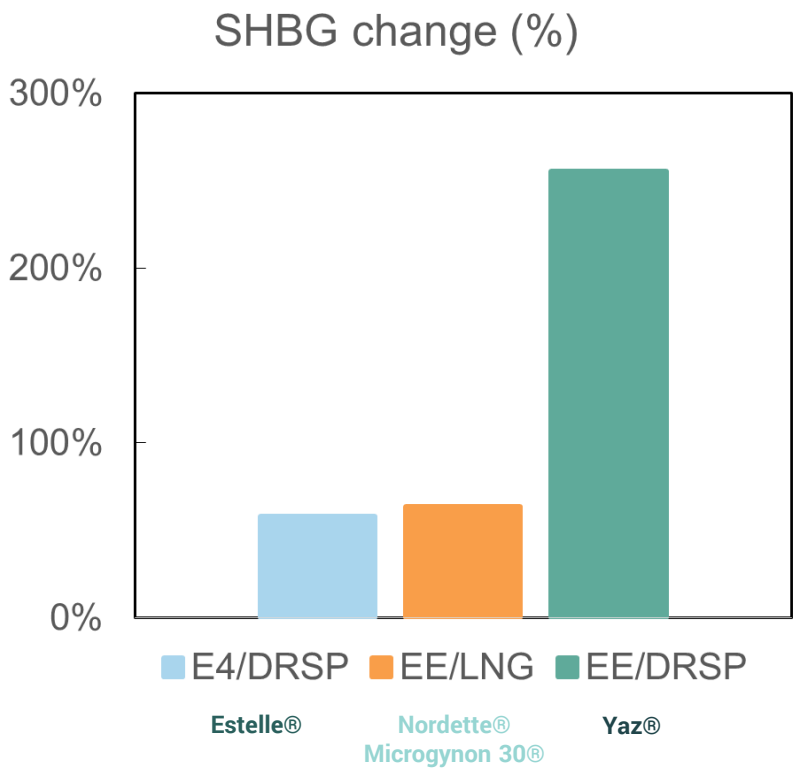
A real game changer with improved safety profile : the first N.E.S.T

Oral Contraception	*Estrogen*	*Progestin*	Better user acceptability	Improved safety profile
1960' - 1980'	Ethinylestradiol (EE)	Levonogestrel (LNG)	✗	✓
1990'	Ethinylestradiol (EE)	Drospirenone (DRSP)	✓	✗
2000's	Estradiol valerate (EV)	Nomegestrol acetate (NOMA), Dienogestate (DMG)	✗	✓
Estelle®, a NEW ERA, first NEST	**Estetrol (E4)**	Drospirenone (DRSP)	Estelle®	Estelle®

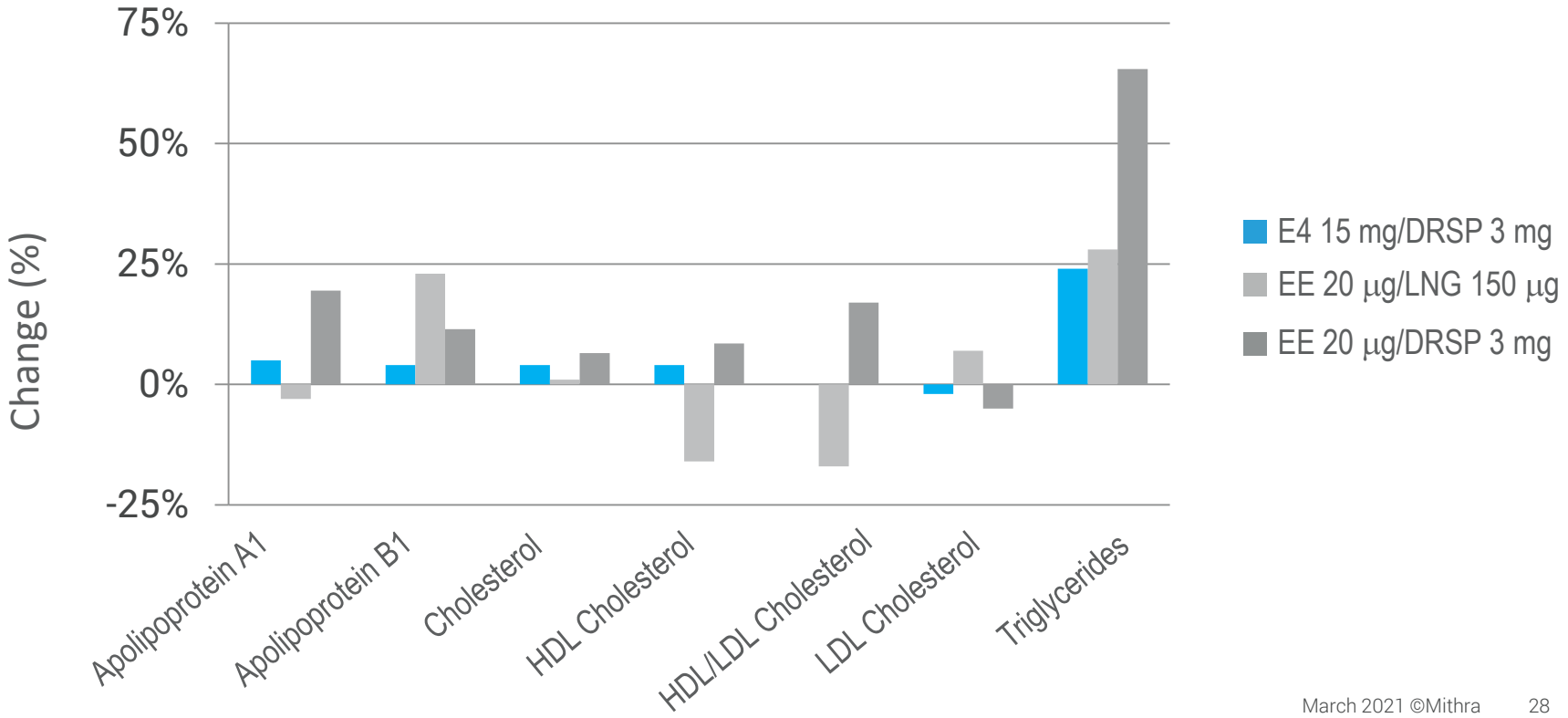
> No real innovation in estrogens for 90+ years !

Limited impact on hemostatic profile





Favorable lipid metabolism



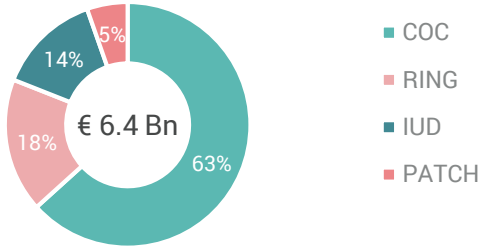
Estelle® in contraception potential benefits

- Excellent contraceptive efficacy
- Improved cycle control
- Favorable VTE risk profile
- Favorable breast profile
- Favorable CV safety profile with minimal increase of lipids (triglycerides)
- Neutral impact on body weight
- High user satisfaction with improved quality of life
- Lower risk of drug-drug interaction
- Environmentally friendly

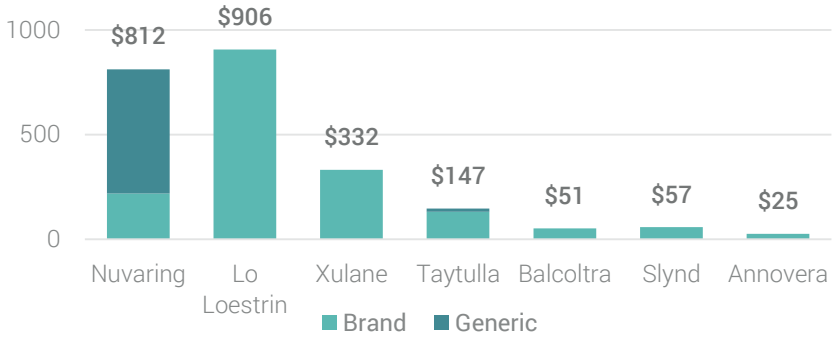
Strong demand for oral contraceptives

- EUR 6.4 Bn EU/US/Canada Hormonal Contraceptive Market driven by oral contraceptives
- **+50% women using COC's** between 1994-2019[1]
- **TOP 2** of most commonly used contraception WW
- Drospirenone : an important driver of choice for its anti androgenic and anti water retention properties[2]
  - Above 12% of oral contraceptives today in USA[2] and 20% in EU[2]
- USA: Lo Loestrin® in the # 1 top selling brand with US $ 906 million sales[3] including generics

Hormonal contraceptive Market
MAT Q3 / 2020



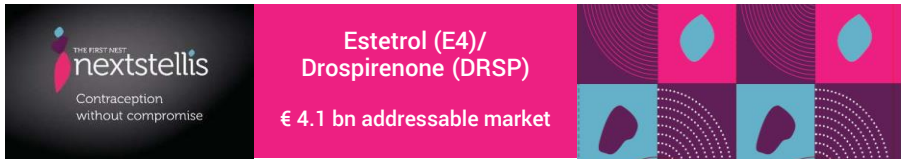
MAT sales of key CHC products(1)



1) WHO, Contraception Use 2019 / 2) IQVIA, Value MAT Q3 2020 / 3) IQVIA, Value FY 2020

Estelle® (E4/DRSP) a novel oral contraceptive

- Estetrol (E4) : unique, Native Estrogen with Selective action in Tissues (NEST)
  - Potential to be the first new estrogen introduced in ~50 years
  - Potential to have a lower adverse impact on the environment
- Licensed to 15 partners worldwide
- E4/DRSP oral contraceptive now filed in US (Nextstellis™), Europe, Switzerland, Brazil, Russia and Australia



Estimated launch timelines worldwide for Estelle

US & Canada

KSA/UAE

EAEU

Taiwan - Thailand

2021

2022

BeLux & EU

Russia

Australia

NON EU : Brazil - Israel

Bahrain, Kuwait, Qatar, Oman, Lebanon, Jordan

80% Worldwide Market

Estelle® Commercial Partnership Strategy - United Global Approach -

- Global marketing approach under Mithra's leadership
- Alignment of multiple commercial partners
- Single branding with limited number of brand names worldwide
- Single positioning / messaging
- Unified launch campaign and storyline

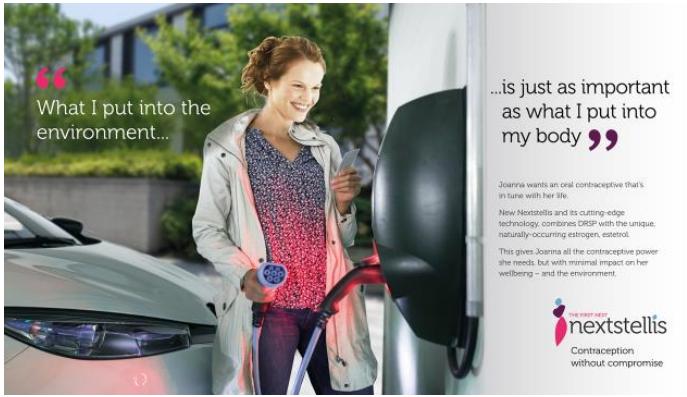
Estelle® Phase 3 study
on 3,725 women

Program	Trial	Subjects	Characteristics	Objectives	Results
Estelle®	Phase 3 US/Canada study	2,148	• Healthy premenopausal women of childbearing potential • 16-50 years	• Contraceptive efficacy -Pearl Index (PI) • Cycle control, general safety and acceptability	• Excellent efficacy pearl index of 2.41 (1.56-3.54) • Efficacy rate : 98 % • Excellent regular bleeding pattern • Well tolerated - Safety profile: no unexpected events • QoL maintained
Estelle®	Phase 3 European / Russia study	1,577	• Healthy premenopausal women of childbearing potential • 18-50 years	• Contraceptive efficacy -Pearl Index (PI) • Cycle control, general safety and acceptability • Endometrial safety (EU)	• Excellent efficacy pearl index of 0.47 (0.15-1.11) • Efficacy rate > 99,5 % • Excellent regular bleeding pattern • Well tolerated - Safety profile: no unexpected events • QoL maintained

** Sex Binding Hormone Globulin*

Estelle® clinical trial results

- ✓ Phase 3 trials in 3,725 women demonstrated contraceptive efficacy safety and tolerability
  - including women with BMI 30-35 kg/m2
- ✓ Good menstrual cycle control was demonstrated
- ✓ QoL and well being maintained
- ✓ Neutral impact on lipids and and glucose[1]
- ✓ A phase 2 trial showed a low effect of E4/DRSP on certain markers of coagulation



1: Clinical implications of these are to be determined
2: Creinin, M. et al: Obstetrics and gynecology, May 2019, Vol 133 No 5 (Supplement)

Estelle® Insights

- Contraception survey among 2000 US women confirm intent to opt for COC with an improved benefit/risk profile[1]
- HCP Global Estelle® positioning research[2] confirm:
  1. Very positive product profile
  2. Very motivating positioning statements
  3. High intentions to prescribe for 18 – 44 year olds

Medical/Commercial

- MSL's in place for scientific exchange with HCPs in EU, US and Canada
- Commercial launch in US supported by new dedicated women's health sales force, medical affairs, market access and marketing teams.
- Strong competitive positioning of licensees
- Omnichannel access
- Global marketing campaign in development
- Focus on all high prescribing physicians

1: Berenberg data on file, December 2019
2: BrainSell Ltd. April 2020: Estelle Positioning Market Research

Mid
40's

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PeriNesta®

1st complete oral treatment targeting perimenopause

What is perimenopause?

- Perimenopause, or menopause transition, begins several years before menopause when the ovaries gradually begin to make less estrogen
- Starts in a woman's 40's (average age is 45.5) and ends at menopause
- It's important to note that during perimenopause, women are still fertile

What are the symptoms?

- Symptoms seriously impact the quality of life*
- Contraception is needed alongside hot flushes relief
- While COC's can alleviate these symptoms, guidance advises the use of the lowest hormonal dose to limit VTE risks (which is increased at age > 40)
- Pregnancy above 40 presents a safety risk for the women, as well the baby

*Vasomotor symptoms , bad cycle control, psychological changes, bone loss, UCLA HEALTH

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Need for approved treatment providing both VMS relief and effective contraception, while addressing increased safety concern for women in perimenopause

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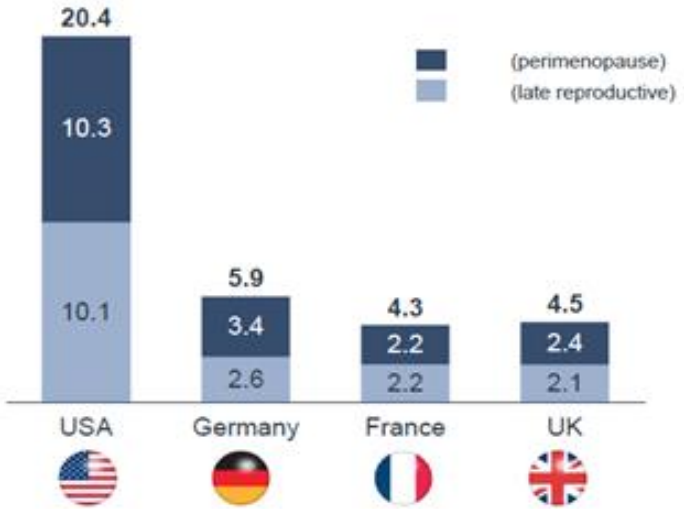
An under estimated market opportunity

- Estimated adressable population in menopausal transition ranges from 17-35 million in a selection of key major markets
- A multi-billion EUR market opportunity
- No approved treatment currently exists



Estimated Population in Menopausal transition (million, women 40-52 years of age) [1]

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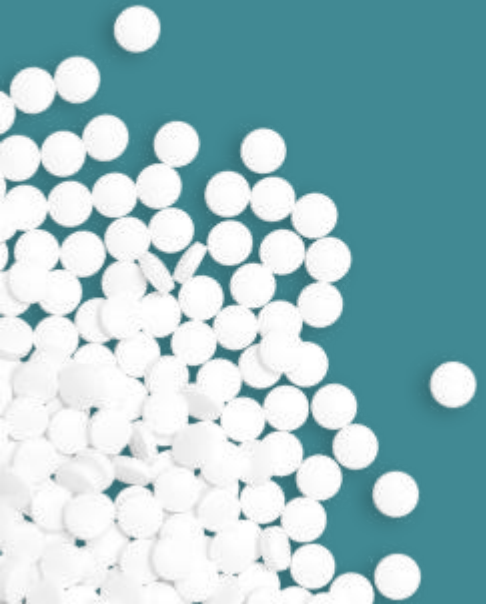
1. IQVIA Jan 19

PeriNesta®



- Potential to be the first complete oral treatment to address women's QoL needs in perimenopause
- VMS relief and contraceptive efficacy
- Improved safety profile

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Donesta® (E4 only)

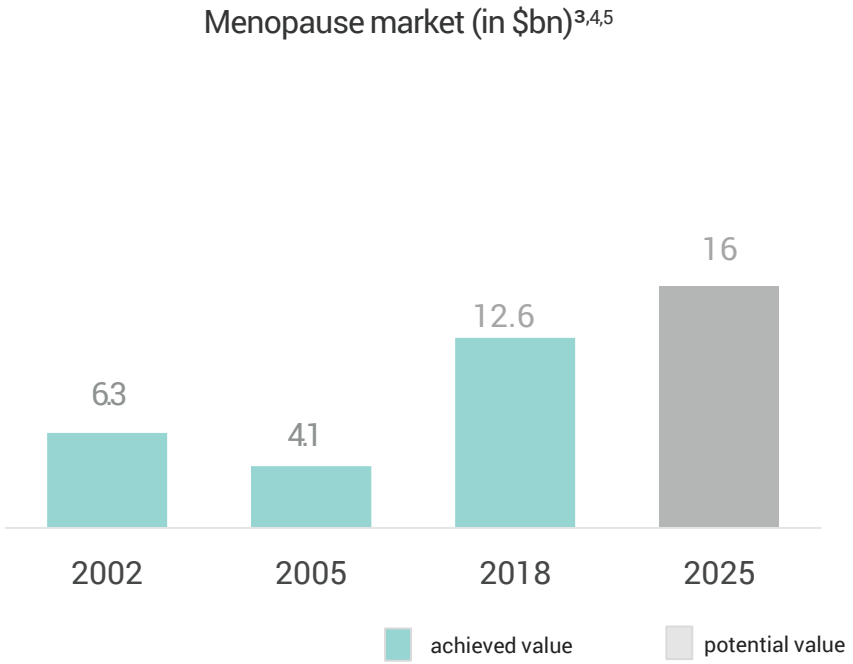
Next generation Hormone Therapy (HT) for VMS relief

What is menopause?

- **Menopause** is a natural part of the ageing process that occurs in all women
- It is defined as the point in time when **menstrual cycles permanently cease** due to the natural depletion of ovarian oocytes from aging. It is associated with lower levels of reproductive hormones, especially estrogen
- The diagnosis is typically made retrospectively after the woman has missed menses for 12 consecutive months
- It marks the permanent end of fertility and the average age of menopause is **51 years**

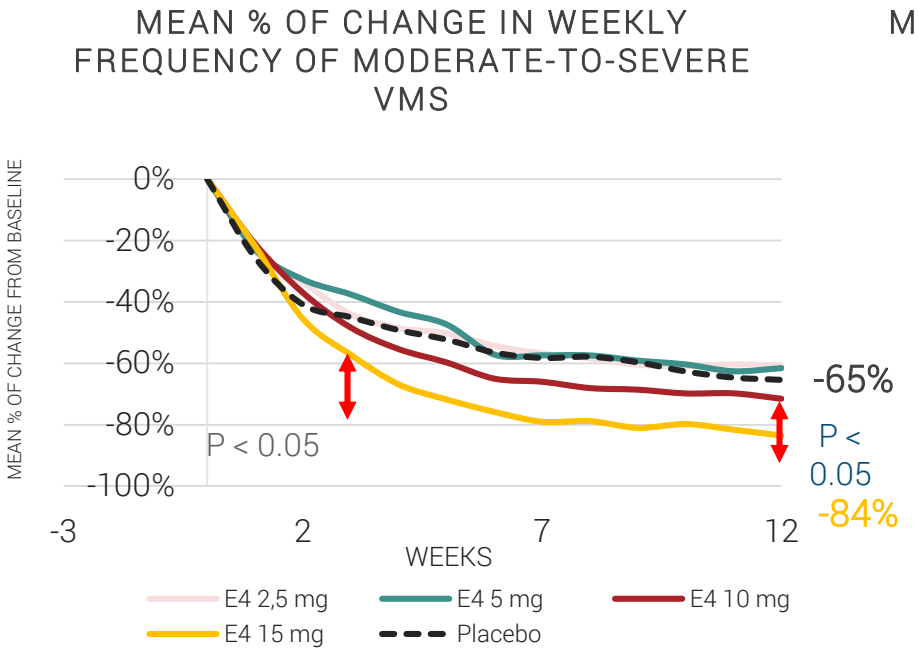
Donesta® for menopause and HT
an estimated $ 12.6 bn blockbuster market[1,5]

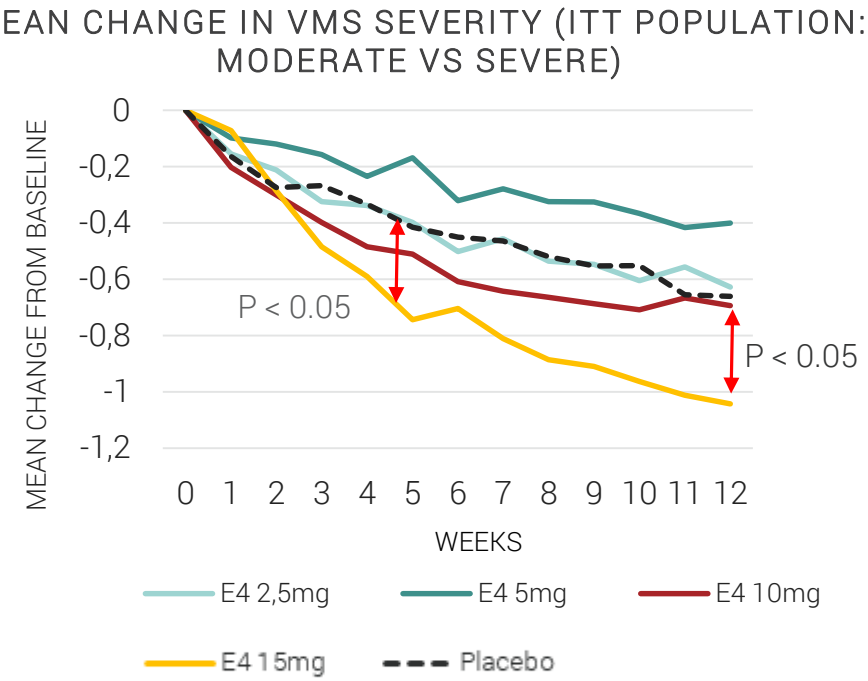
- 78%[1] of menopausal women suffer VMS (hot flushes) - only 7.8% receive HT[2]
- Increased safety issues:
  VTE, stroke, breast cancer risks
- No new estrogen-based products
  for more than 10 years, but renewed interest & developments (hormonal & non-hormonal)
- $16 bn billion potential HT Market in 2025 – VMS potential with safer alternative



*Sources: (1) **Transparency Market Research 2017**; (2) KBC company report Aug 2015; (3) IMS link Q2 2016; (4) TMR 2017 (5) IQVIA analysis 2019*

Donesta® Phase 2b: Positive Top-line Results: Significant effect on frequency of hot flushes





Donesta® - Phase III (E4Comfort) program design

2 multicenter, randomized, double-blind, placebo-controlled trials in post-menopausal women

E4 Comfort – C302 [1] October 2019		
Study	VMS Efficacy Study	Safety Study
Target population	Post-menopause H and NH* 40-65 years	Post-menopause H and NH [3] 40-65 years
Trial Size	600 subjects	400 subjects
Dosing	15 / 20 mg E4	20 mg E4
Follow-up	52 weeks	52 weeks

E4 Comfort – C301 [2] December 2019		
Study	VMS Efficacy Study	Safety Study
Target population	Post-menopause H and NH* 40-65 years	Post-menopause NH [4] 40-65 years
Trial Size	600 subjects	600 subjects
Dosing	15 / 20 mg E4	20 mg E4 + 100 mg P4
Follow-up	12 weeks	52 weeks

Study objectives

Primary endpoint:

Measure effect of treatment with **15mg and 20mg** of E4 on frequency and severity of VMS at weeks 4 and 12

Secondary Endpoint:

Effect of treatment on additional key efficacy and safety parameters (lipid, glucose metabolism, endometrial safety, health-related quality of life and treatment satisfaction)

[1] US, Canada [2] EU, Russia, Latam (+US, Canada) [3,4] Hysterectomized and Non-Hysterectomized

Donesta® a promising new oral HRT based on E4

- Phase 2 study successfully completed in 2018
- Results presented at Congresses in the US and EU
- Positive topline Phase 2b data strongly support further Donesta® development, as a unique next-generation hormone therapy
- Recruitment of Phase 3 trials ongoing since H2 2019 (last patient in expected in Q2 2021)
- Commercialization expected in 2024

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Women's Health

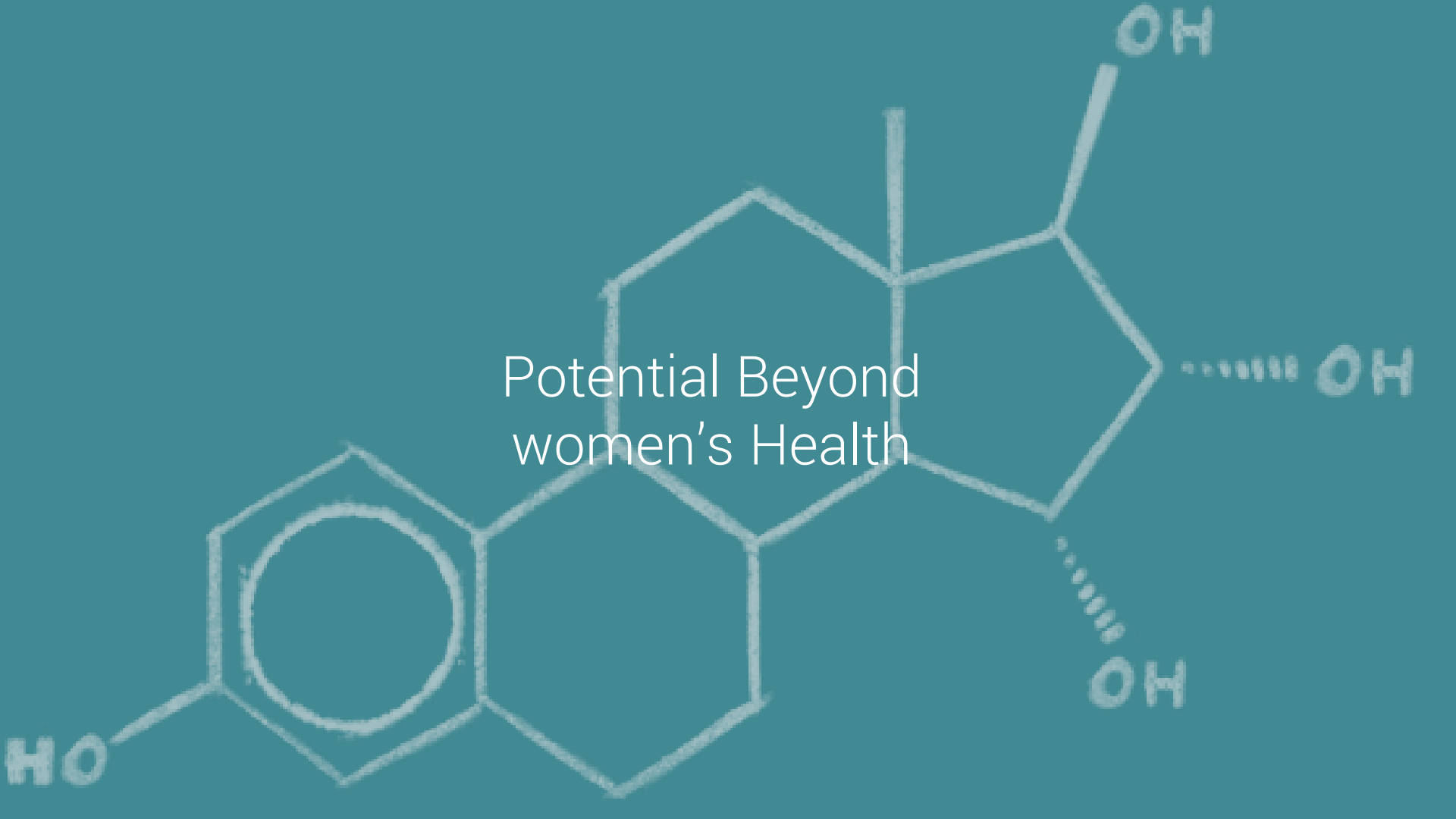
Blockbuster potential

- Women's health market has regained attention from large/spec pharma
- $16 billion potential HT Market in 2025
- Management estimates potential value of Donesta® to be worth multiples of the value of Estelle®
- Meet the high need for a natural and evidence based oral HRT with an improved benefit/risk profile
- Will make prescribers' decisions easier, as Donesta® offers a HT with fewer safety concerns

Three potential blockbusters offering solutions throughout a woman's hormonal life span

	Estelle®	PeriNesta®	Donesta®
Key Value Proposition	A new era in combined oral contraception	Innovative peri-menopausal treatment	Next generation Menopausal Hormone Therapy
Affected Population	Fertile women aged 14 – 51, BMI ≤ 35.0 kg/m^2	Active women aged 45 -- 51 that are still fertile and have first signs of menopause (hot flushes and irregular cycles)	Hysterectomized and non-hysterectomized women aged 51 – 65, suffering of symptoms of menopause
Market Opportunity	$ 22 bn (WW contraceptive market)	Multi-billion (under evaluation)	$ 12.6 bn (WW menopause market)
Status	Commercialization expected in 2021 / >€450 million licensing milestones contracted	Market approval expected in 2023	Phase 3 ongoing; commercialization expected in 2024

Potential Beyond women's Health



Additional promising solutions beyond Women Health

	COVID-19 Treatment	Neonatal Encephalopathy (NE)	Wound Healing
Key Value Proposition	1st oral estrogen (E4) treatment to improve recovery of hospitalized patients with SARS-CoV-2 infection	Add-on therapy to hypothermia reduces the incidence of death or neurodevelopmental impairment at 24 months of age	1st E4 treatment for acute / chronic wound healing to address the underlying mechanisms that contribute to wounds
Affected Population	Men > 18 y Post-menopausal women	Newborns (> 36 weeks)	Adult males and females
Market Opportunity	Multi million (under evaluation)	NE incidence is ~0.7 to 1.5 per 1,000 live births resulting on a patient pool of 15.1 k in 2020	$ 25 bn (WW wound care market Chronic/Acute 75/25)
Status	Phase 2 ongoing with read-out in H2 2021	Preclinical stage EMA & FDA ODD granted	Pre clinical + formulation Clinical PoC 2022

COVID-19 Treatment (E4 15 mg)

E4 15 mg 1st oral estrogen (E4) treatment to improve recovery of hospitalized patients with SARS-CoV-2 infection

Sustained Medical need despite vaccine

- COVID 19 pandemic :
  - > 25 million cases on worldometer currently not declining
  - 847,391 deaths globally likely to increase per annum even when vaccine is found
  - Approximately 1% mortality overall, and up to ~30% in high risk age groups age group (>80y)
- Influenza deaths ~250,000 – 650,000 per annum in spite of vaccination (WHO)
- Public health bodies are afraid of further pandemics
- Risk of respiratory viruses not covered by vaccine is high *(RSV, Rhinovirus, other coronavirus etc)*
- Virus is a major cause of asthma and COPD exacerbations
- Public health need is underpinned by funding availabilities

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Women's Health

Gender differences in COVID-19 morbity and mortality (F< M)

Table 1: in 10 year age bands by sex, population, deaths, mortality per 100,000, risk ratio in England & Wales, France, Germany, Italy, Netherlands, Portugal, Korea and Spain

	Population		Deaths		Deaths per 100,000		Sex ratio (M:F)
Age group	Male	Female	Male	Female	Male	Female	
0-9	19923780	18935073	6	7	0.03	0.04	**0.81**
10-19	21333098	20087329	14	9	0.07	0.04	**1.46**
20-29	23719884	22435304	94	50	0.40	0.22	**1.78**
30-39	25310993	25157644	282	170	1.11	0.68	**1.65**
40-49	27912903	27945866	993	531	3.56	1.90	**1.87**
50-59	29327752	29834735	3776	1661	12.9	5.57	**2.31**
60-69	22611177	24271853	9590	4024	42.4	16.6	**2.56**
70-79	15668774	18552985	21830	10940	139.3	59.0	**2.36**
80+	8541230	14494575	41067	42199	480.8	291.1	**1.65**
ALL	194349591	201715364	77652	59591	40.0	29.5	**1.35**

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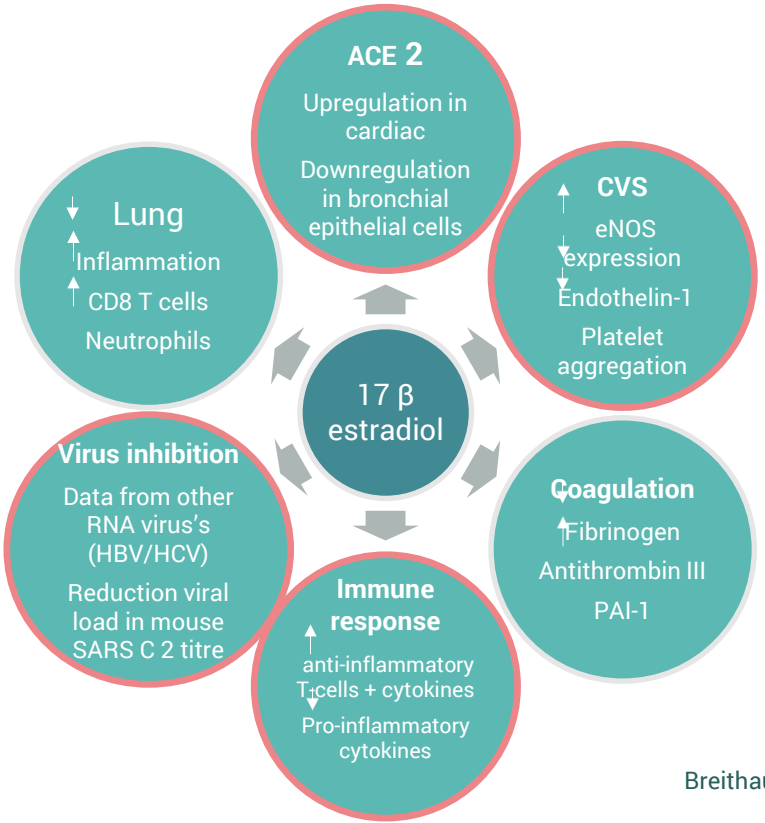
Bhopal and Bhopal, 2020;

King's College study show protective effect of estrogens against COVID-19 infection

- Total of 295,689 women aged 18-45y fielded data of whom 64,253 were combined oral contraception (COC) users
  - Women aged 18-45 years taking COC had a significantly lower predicted COVID-19 (P=8.03E-05), with a reduction in hospital attendance (P=0.023). Rate of hospitalisation for COC users was significantly lower than for non COC users - Odds Ratio 0.79 (0.64-0.97)
- A total of 44,268 post menopausal women were studied
  - Post-menopausal women using HRT or hormonal therapies did not exhibit consistent associations, including increased rates of predicted COVID-19 (P=2.22E-05) for HRT users alone

Costeira et., 2020, https://doi.org/10.1101/2020.07.30.20164921

Estrogen are antiviral in general but those ring in red are key in SARS CoV 2 infection



Breithaup-Faloppa et al, 2020
Li et al 2020
Mauvais-Jarvis, 2020

Antiviral effects of estrogen

(supported by E4 in vitro and in vivo data to confirm)

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Women are less **susceptible to viral infections** thanks to immune system differences between men and women

- Genes on the X chromosome are associated with regulation of immune functions and expression is orchestrated by sex hormones – in particular estrogen
  - ACE 2
  - interleukin (IL)-2R γ chain, IL-3R α chain, IL-13 α chain, IL1R kinase 1
  - Toll like receptors and IFN
- Results in enhanced immune innate (immediate) and immune adaptive (antibodies) capabilities
- Women are therefore less susceptible to viral infections
- Downside for women is more autoimmune disease such as rheumatoid arthritis multiple sclerosis, thyroid disease etc.

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Why E4 ?

- Past MHT studies
  - ↑ risk Hazard Ratio of >2 for VTE for women on MHT compared to not and an increased risk of stroke and cancer in the past but…
  - recent studies have shown equal risk for conjugated equine estrogen (Premarin) (Manson et al, 2017)
- ↑ risk of VTE for CEE was 45 versus 33 per 10,000 person-years (Premarin label) compared to placebo.
- E4 shows has the same or lesser effect on coagulation parameters compared to second generation ethinyl estradiol based pills

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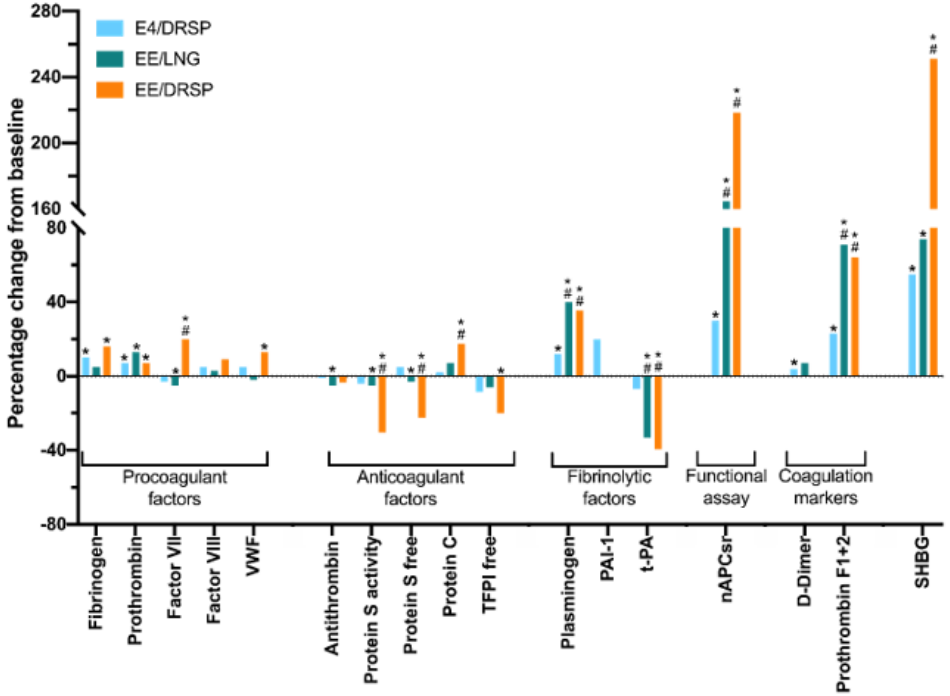
Women's Health

Effect of E4 on coagulation

Douxfils, 2020 (in press)

Supplemental Figure 1 **Effect of study treatment at cycle 6 on relevant hemostasis biomarkers and SHBG**



*The columns represent the median of the percent change from baseline (cycle 6 – baseline) - *different versus baseline, $p < 0.05$; # different from treatment with 15 mg E4/ 3 mg DRSP, $p<0.05$*

Abbreviations: DRSP, drospirenone; E4, estetrol; EE, ethinyl estradiol; LNG, levonorgestrel; nAPCsr, normalized activated protein C sensitivity ratio; PAI-1, plasminogen activator inhibitor type 1; SHBG, sex hormone binding protein; t-PA, tissue plasminogen activator; TFPI, tissue factor pathway inhibitor; VWF, von Willebrand factor

Benefits of a E4 Treatment

- Strong in vitro and in vivo evidence that oestrogens will reduce risk of viral disease (confirmatory studies with E4 on going currently)
- E4 has excellent CVS risk profile compared to other estrogens
- Additional clinical evidence that E4 may have treatment or prophylactic advantages for serious respiratory infection could be valuable for
  - Raising brand recognition
  - Sales
  - Pricing
- Risk of increasing incidence of VTE would appear small and inhibition of platelets could improve treatment.

Phase 2 study ongoing

A Randomized, Double Blind, Placebo Controlled Trial to Determine the Safety and Efficacy of Estetrol (E4) for the Treatment of Patients with Confirmed SARS-CoV-2 Infection

Sample size : 300 patients (ratio 1:1) – post menopausal women and men aged > 18 y

Study objectives:

- To confirm whether E4 improves recovery of patients with SARS-CoV-2 infection (COVID-19) who are hospitalized with moderate disease before potential further clinical development in COVID-19
- To assess prevention of development of severe disease or worsening of disease
- To assess the changes in viral load
- To assess safety, tolerability and efficacy

>>> Phase 2 results expected H2 2021

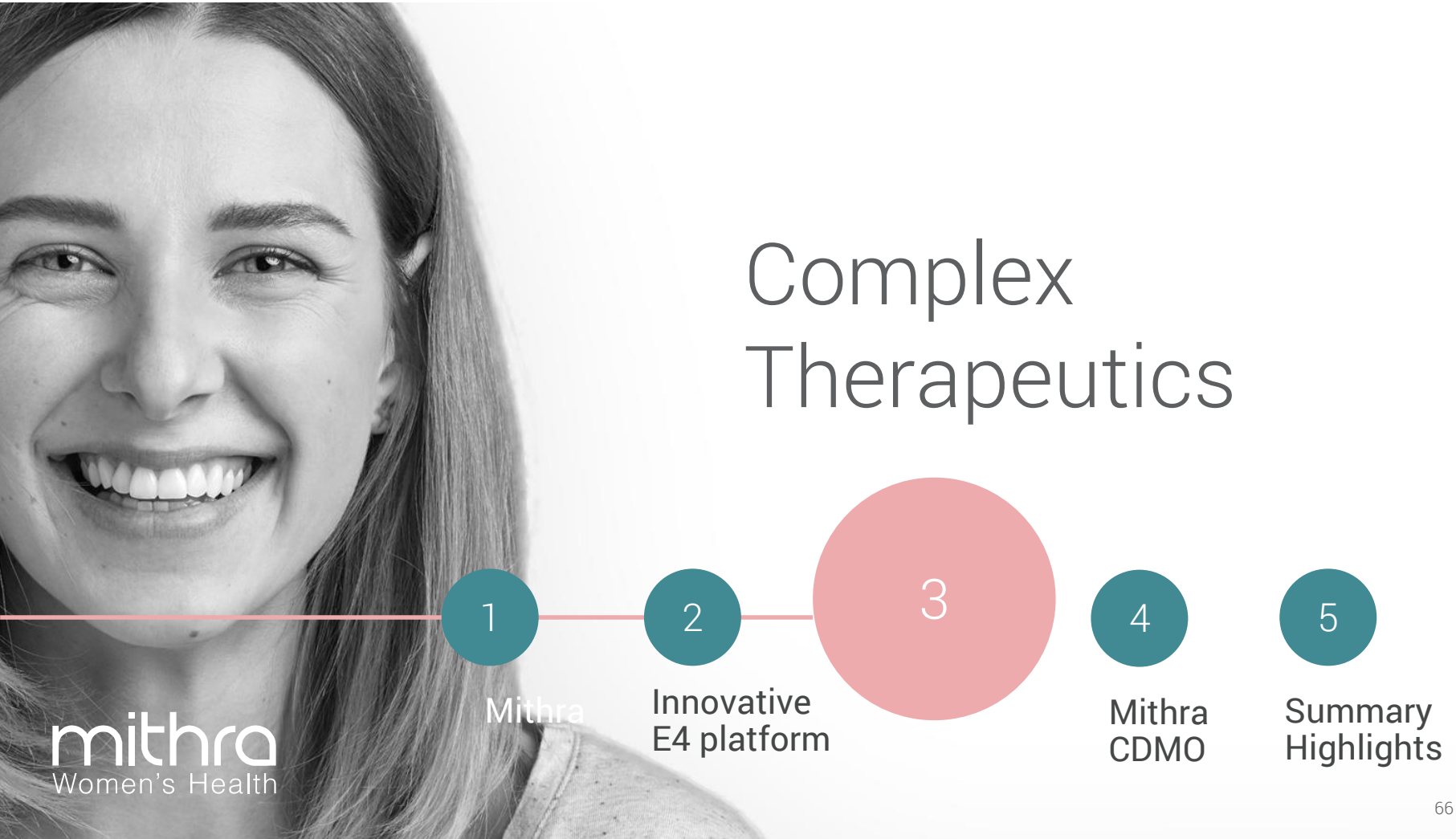
E4 in neuroprotection and Wound healing

E4 for Neonatal Encephalopathy

- Neonatal Encephalopathy is a type of brain damage caused by oxygen deprivation (hypoxia) and limited blood flow (ischemia) in newborns and entailing high mortality among <5 year old children and chronic neurological disability
- ODD designation granted in EMA (2017) and US (2019)
- Incidence range of 0.7 to 1.5 per 1,000 live births resulting on a patient pool of 15.1 k in 2020 and it is expected to remain stable (-0.4% p.a. by 2050)
- NE holds a clear unmet medical need as there is no FDA /EMA-approved medicines specifically intended for its treatment – lifetime costs estimated at EUR 0.9 m per patient
- E4 has shown neuroprotective activity in non clinical models
- KOLs expect a high added value of E4 in HIE treatment
- Status: non clinical study in large animals – Formulation E4 I.V.

E4 for Wound healing

- Current SoC entails compression, wound dressings and invasive treatment
- No EMA-approved drugs for advanced wound healing
- Multi billion market opportunity
- Mithra is developing an E4-based product enabling skin regeneration and wound closure
- Programme starting with clinical PoC programme in Acute Wound Healing: topical formulation of E4 to address surgical wounds for adult males and females undergoing general, cosmetic or orthopaedic surgery.
- Additional indications in Chronic Wound Care (VLU-DFU) considered
- Status: Initiation of non-clinical program and formulation development



Complex Therapeutics

1 Mithra

2 Innovative E4 platform

3

4 Mithra CDMO

5 Summary Highlights

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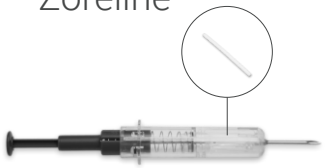
Leveraging know-how of Complex Therapeutics

- Expertise in developing complex and innovative polymer products
- Targeting safer, long-lasting delivery and controlled release of established approaches to **contraception, menopause and hormone-dependent cancers**
- Manufactured in-house at Mithra CDMO

Advancing our complex therapeutics business

Products	*Description*	*Indication*	*Opportunity*	*Status*
Myring™ 	Contraceptive vaginal ring (based on etonogestrel/ EE/polymers)	Contraception	Circa $902m Original product: NuvaRing® from Merck	EU : Launched US : Q4 2021/Q1 2022
Zoreline® 	Biodegradable SQ implant (goserelin)	For prostate & breast cancer and benign gynecological indications	Circa $623m Original product: Zoladex® from AstraZeneca	PK/PD on humans started
Tibelia® 	Therapeutic solution for HT Composed of tibolone (synthetic steroid)	Menopause	Circa $126m Original product: Livial® from Merck	Launched

Mithra CDMO

1 Mithra

2 Innovative E4 platform

3 Complex Therapeutics

4

5 Summary Highlights

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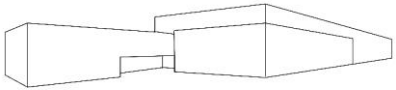
Women's Health

mithra cdmo



Ideally located in Europe, at the intersection of major **European biopharma clusters**

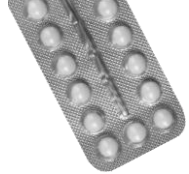
An integrated R&D and manufacturing platform

Specialized pharmaceutical ecosystem, to take products from POC to market

- 15,000 m² state-of-the art facilities
- Dedicated R&D and production areas
- Pilot, clinical & commercial batches
- GMP Standards compliance
- > 200 people on site

3 production units for complex dosage forms

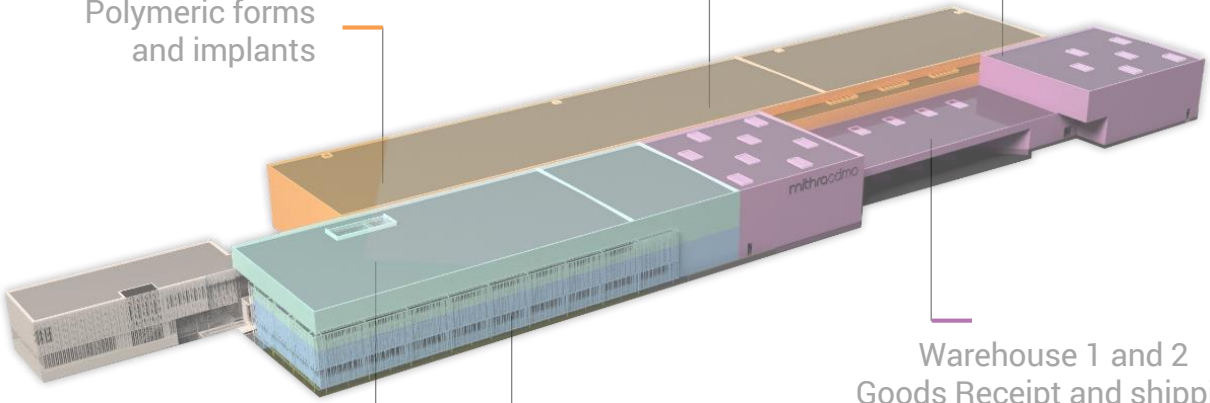
mithracdmo



Hormonal tablets

Sterile injectables

Polymeric forms and implants

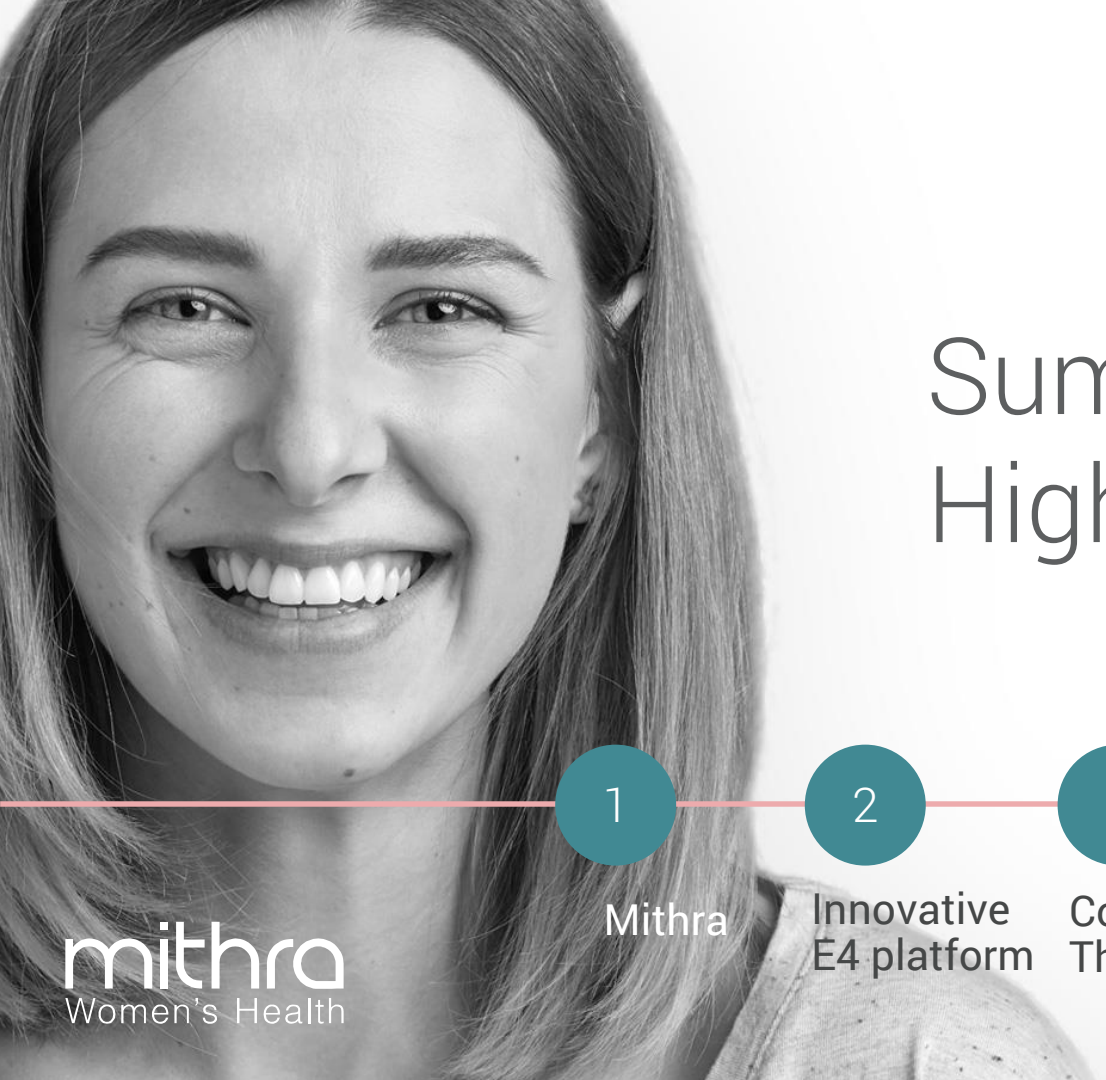


Warehouse 1 and 2
Goods Receipt and shipping

QC laboratories

R&D platform

- R&D
- QC
- Production
- Warehouse
- Admin



Summary Highlights

1. Mithra
2. Innovative E4 platform
3. Complex Therapeutics
4. Mithra CDMO
5.

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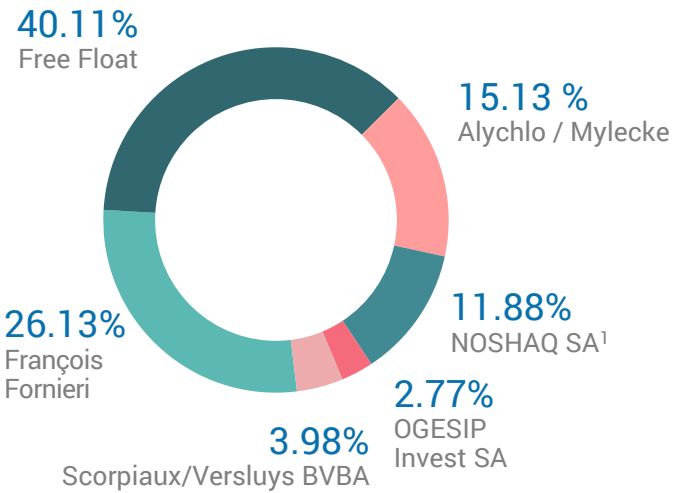
Women's Health

Summary financial information

Share capital

as of December 30, 2020 *



** Shareholdership in accordance with transparency declarations received by the company and notified managers' transactions. Weighted average shares outstanding: 42,554,297 as of June 30, 2020. / ** 1. François Fornieri holds warrants entitling him to subscribe still 1,023,000 additional shares of Mithra.*
1) Formerly MeusInvest

IFRS P&L and cash balance

(in m€, FY as of 31/12/2020)

	FY 2019	FY 2020
Revenues	96.5	9.0
R&D Expenses	(57.1)	(78.5)
G&A	(14.8)	(15.9)
Selling Expenses	(1.5)	(1.4)
EBITDA	32.7	(73.8)
Net Loss	(26.6)	(92.1)

	FY 2019	FY 2020
Total Equity	163.3	157.7
Cash & Equivalents	49.7	138.7

- Revenues in 2019 were exceptionally high thanks to the Estelle® LSA agreements – 2020 revenues are linked to the Donesta® strategy
- Increase in R&D spend due to Ph3 of Donesta®, launch of Covid study & slight increase in G&A
- EBITDA is negative as a result of the lower revenues and the increase in R&D expenses
- Record high cash position with convertible bond issue
- Substantial unused funding facilities
- Strong Equity despite R&D expenses incurred

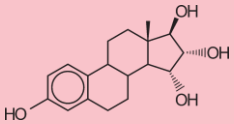
Expected newsflow 2021

- Estelle®
  - MA in EU & USA expected in H1 2021
  - Commercialization in Canada and potentially in Europe & US
  - LSA in new geographies (India & China)
- Donesta® Ph3, last patient in & continuation of business development strategy
- Coronesta – Results expected begin H2 2021
- Myring ®

Why invest in **Mithra**?

Belgian Biotech dedicated to **Women's Health** for 20 years

1



Breakthrough innovation with the unique hormone Estetrol (E4)

2

Estelle®
A new era in oral contraception on the market in 2021

3

1 filing stage and 2 late-stage E4-based potential blockbusters

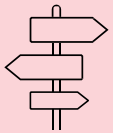
4

Expertise in polymers and formulation

5

Mithra CDMO unique platform with specialist research, development and manufacturing capabilities

6



Additional pipeline based on E4 outside women's health

Contact Us

Mithra
MITRA (Euronext)
Rue Saint-Georges 5/7
4000, Liège
Belgium

Benoît Mathieu
Investor Relations Officer
investorrelations@mithra.com

Website: investors.mithra.com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Women's Health
Thank you

APPENDIX

Advisory boards and clinical collaborations[1]

- EU and US-based advisory boards of key opinion leaders for both Donesta® and Estelle®
- Endorsement of the major potential of E4, providing strategic guidance on clinical programs
- Clinical collaborations with world renowned leaders in women's health

[1]Non-exhaustive list

Estelle® - Phase III program design

Two multicenter, open-label, single arm studies, 13 cycles

EU / Russia : Completed

Contraceptive Efficacy Study	1,577 subjects, 18-50 years	✓
	1,350 subjects, 18-35 years	✓
Endometrial Safety Substudy	175 subjects, 18-50 years	✓

US / Canada : Completed

Contraceptive Efficacy Study	2,148 subjects, 16-50 years	✓
	1,940 subjects, 16-35 years	✓
PK Substudy (body weight, race, smoking)	500 subjects, 16-50 years	✓

Study objectives

Primary objective:

Contraceptive **efficacy** based on the **Pearl Index** (PI)

Secondary Endpoints:

Cycle control – bleeding pattern; Safety – S(AE) reporting; Subject's well being; Population PK substudy (US/CA); Endometrial safety (EU)

Estelle®

Program	Trial	Subjects	Characteristics	Objectives	Results
Estelle®	Phase 3 US/Canada study	2,148	• Healthy premenopausal women of childbearing potential • 16-50 years	• Contraceptive efficacy -Pearl Index (PI) • Cycle control, general safety and acceptability	• Excellent efficacy pearl index of 2.41 (1.56-3.54) • Efficacy rate : 98 % • Excellent regular bleeding pattern • Well tolerated - Safety profile: no unexpected events • QoL maintained
Estelle®	Phase 3 European / Russia study	1,577	• Healthy premenopausal women of childbearing potential • 18-50 years	• Contraceptive efficacy -Pearl Index (PI) • Cycle control, general safety and acceptability • Endometrial safety (EU)	• Excellent efficacy pearl index of 0.47 (0.15-1.11) • Efficacy rate > 99,5 % • Excellent regular bleeding pattern • Well tolerated - Safety profile: no unexpected events • QoL maintained
Estelle®	Phase 2 Hemostasis study	98	• Healthy premenopausal women of childbearing potential • 3 treatment groups: 15 mg E4/3 mg DRSP 30 µg EE/150 µg LNG 20 µg EE/3 mg DRSP	• Analyze impact on coagulation (blood clotting) and fibrinolysis (breakdown of clots) of Estelle®, • Determine the risk profile of a novel COC for deep venous thrombosis (DVT) and pulmonary embolism.	• Less pronounced effects of E4/DRSP and EE/LNG on hemostasis parameters than those of EE/DRSP. • Comparable effects of E4/DRSP to EE/LNG (second generation COC). • Lower impact of E4/DRSP vs EE/DRSP on a number of hemostatic parameters confirms the importance of the estrogen selected for COC use

** Sex Binding Hormone Globulin*

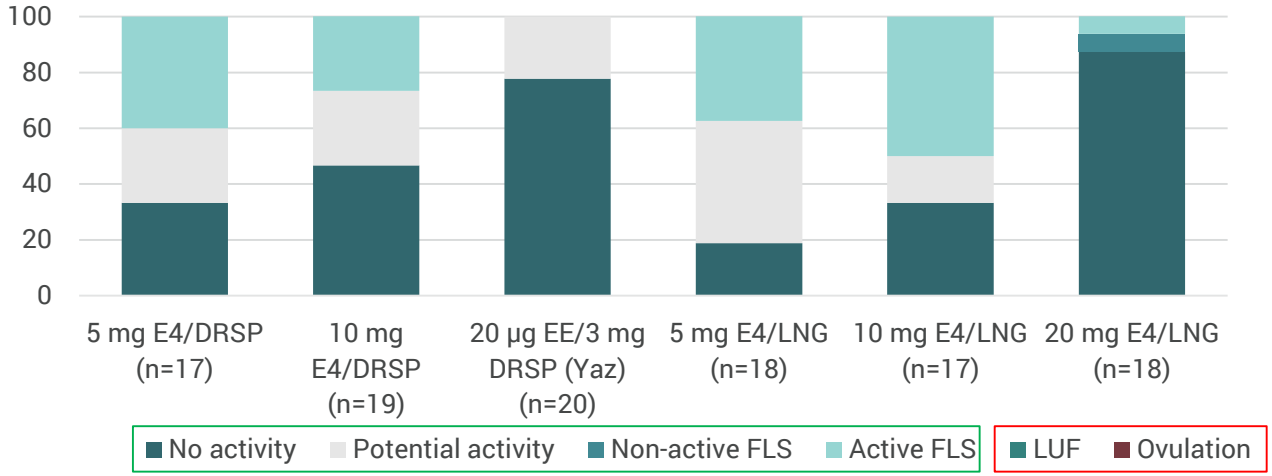
Estelle®

Program	Trial	Subjects	Characteristics	Objectives	Results
Estelle®	Phase 2b	389	• Healthy premenopausal women of childbearing potential	• Vaginal bleeding profile • Cycle control	• Well controlled bleeding pattern • Indications of reduced VTE risks
Estelle®	Phase 2a	109	• Healthy premenopausal women of childbearing potential	• Ovulation inhibition • Effect on liver function (surrogate markers of VTE)	• No ovulation • Only slight increase vs EE of SHBG* plasmatic concentration (surrogate marker of VTE risk)

** Sex Binding Hormone Globulin*

Estelle® Phase 2a: no ovulation

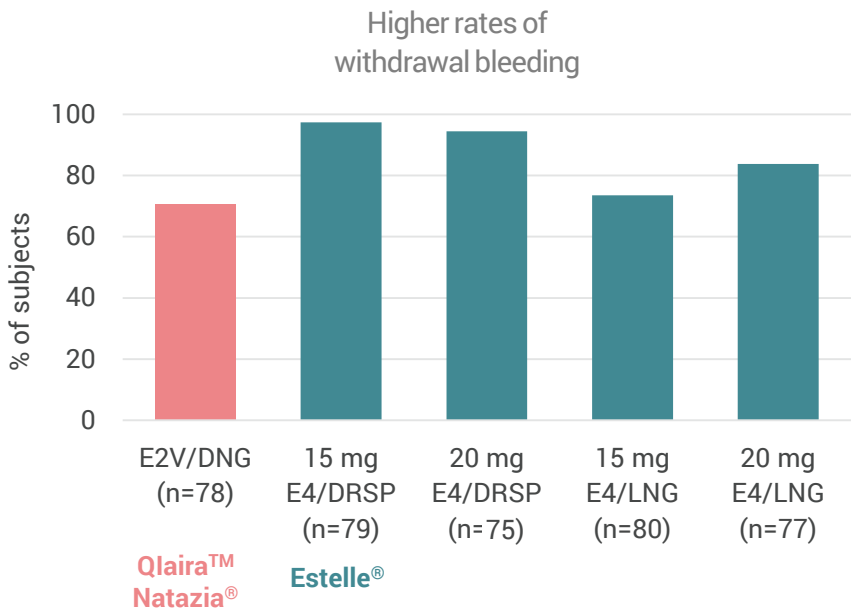
Evaluation of ovulation inhibition: % of patients scored according to Hoogland score (treatment cycle 3; n= 109 healthy premenopausal women of child bearing age)[1]

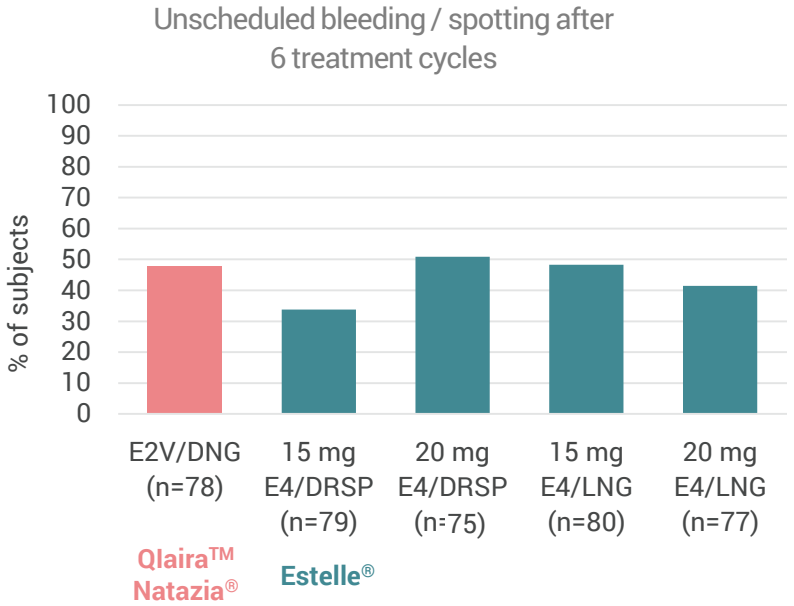


E4 inhibits ovulation in association with a progestin and **allows rapid & complete return to fertility**

- *Note: Hoogland score is a validated tool to assess ovarian function and evaluate ovulation inhibition, which is assessed by transvaginal ultrasounds (TVUS) monitoring of follicle size and analysis of serum E2 and progesterone levels, and consequently classified according to a 6-point scoring (1 = no ovarian activity; 2 = potential activity; 3 = non-active follicle-like structure (FLS); 4 = active FLS; 5 = luteinised unruptured follicle (LUF); 6 = ovulation).*
- *[1] Duijkers et al. 2015, Eur.J. Contracept. Reprod. Healthcare*

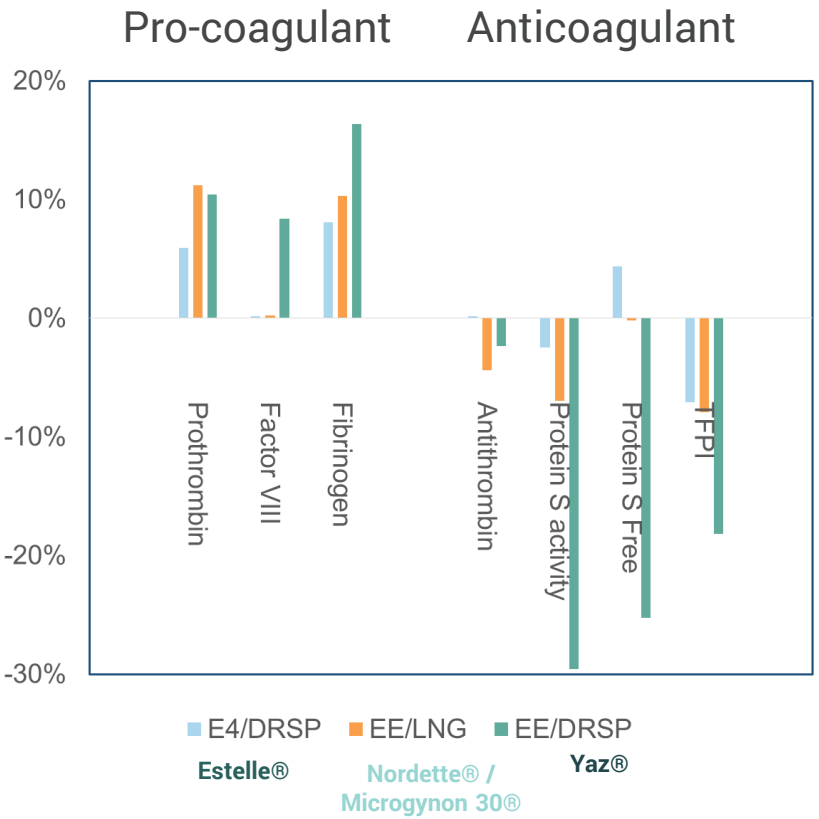
Estelle® Phase 2b: Dose-finding study shows well-controlled bleeding pattern[1]





[1] *Apter D. et al., Contraception. 2016;94(4):366-73*

Estelle® Phase 2 substudy: Reduced VTE* risk profile



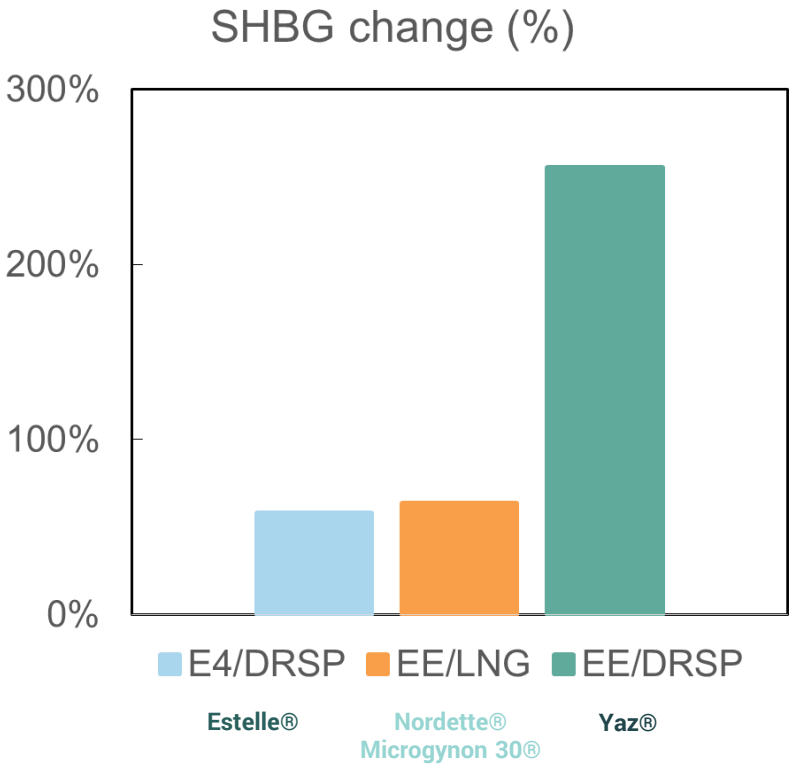
Effect of COCs on VTE Risk Factors

Cycle 6 – Baseline (Mean % change)

- **Limited hemostatic impact** for Estelle® (E4/DRSP)
- Comparable to EE/LNG (Nordette®/Microgynon 30®) the 'safest' 2nd generation pill
- Much lower than 4th generation benchmark EE/DRSP (Yaz®)

Venous Thromboembolism

Estelle® Phase 2 substudy: Reduced VTE risk profile



Change of SHBG (Sex-hormone binding globulin) plasma levels as marker of VTE risk[1]

Cycle 6 – Baseline (Mean change)

- **Limited impact on SHBG levels** for Estelle® (E4/DRSP)
- In line with EE/LNG (Nordette®/Microgynon-30®), the 'safest' 2nd generation pill
- Much lower than 4th generation benchmark EE/DRSP (Yaz®)

[1]Change of APC resistance (Thrombin generation).

Donesta®

- [1]Sex hormone-binding globulin

Program	Trial	# Subjects	Characteristics	Objectives	Results
Donesta®	Phase 2b	260	Healthy postmenopausal women	E4 Dose-finding study placebo/2.5 /5/10/15 mg Frequency & severity of hot flushes	15 mg minimally effective dose Significant reduction in VMS & VVA
Donesta®	Phase 1b	49	Healthy postmenopausal women	Safety and tolerability Number of hot flushes & sweating	Decrease in number of hot flushes Effective reduction of hot flushes with E4 – first efficacy evidence
Donesta®	Phase 1a	32	Healthy postmenopausal women	Safety and tolerability	Fast oral absorption Half life +/- 28 hours

Excellent safety and efficacy results for Estelle® (15 mg E4/3mg DRSP) & Donesta® (E4 alone)