mithra
Women's Health

Investor Presentation

June 2020

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Mithra

1 Innovative E4 platform

2 Complex Therapeutics

3 Mithra CDMO

4 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

250 Staff members

Co-founders

François Fornieri
Chief Executive Officer

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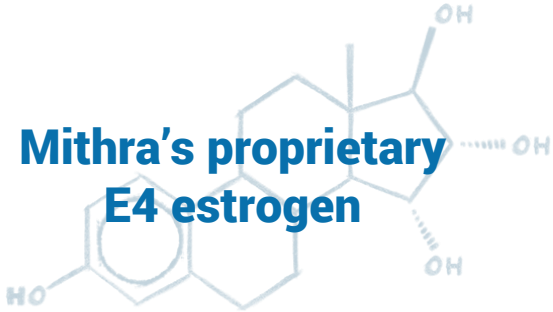
Source: Grand View Research, Women's health market size, 2020-2027

Existing solutions do not meet women's needs

Existing solutions:
EE and E2 estrogen



Mithra's proprietary
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. 3 late-stage potential blockbusters
3. Worldwide specialist in polymer technology
4. Unique facility with specialist research, development and manufacturing capabilities

Mithra has two 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				2023
Under development	CNS, dermatology, oncology, COVID-19, 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 : 2020
Tibelia®	Menopause			Commercialized
Zoreline®	Oncology			2024

An innovative E4 platform

1 Mithra

2

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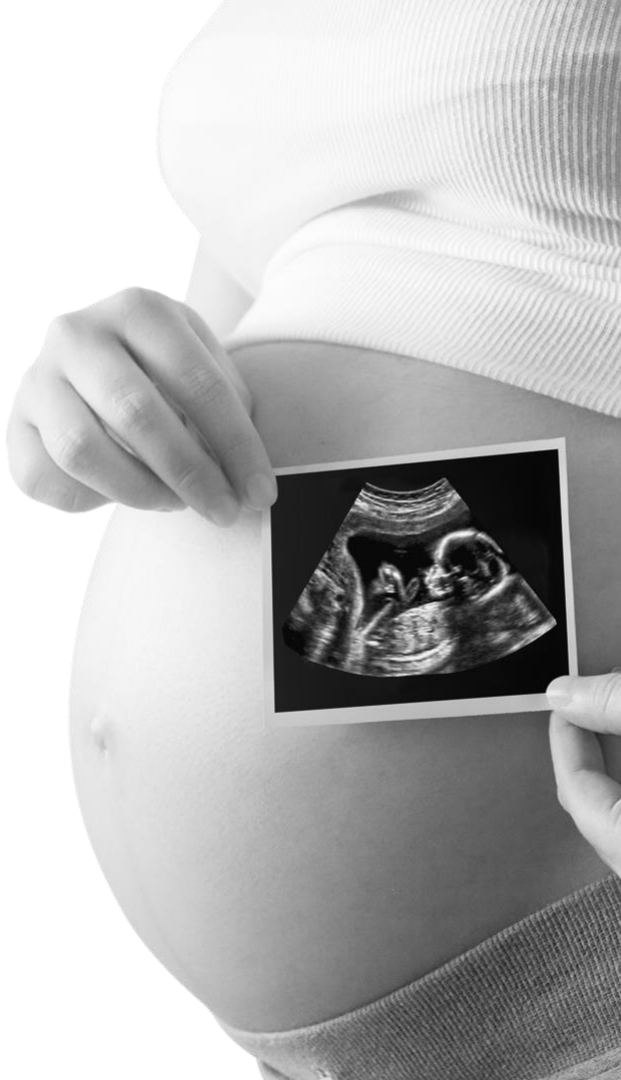
E4 (Estetrol)
a new estrogen with an
improved benefit/risk profile

What is Estetrol (E4) ?

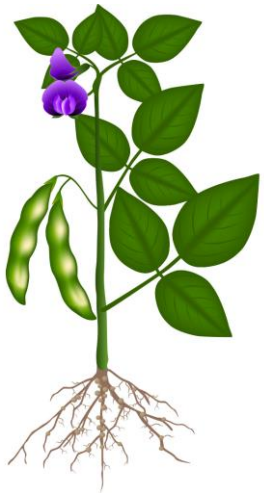
An answer from nature with unique potential

- 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, oncology, COVID-19, etc.
- Protected by 30 patent families
- Synthesized from soy beans



From Phytosterols to Estetrol (E4)

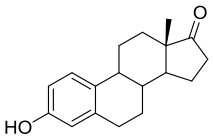
Soy



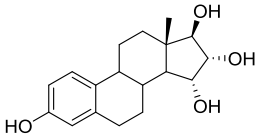
extraction

Phytosterols

Estrone (E1)



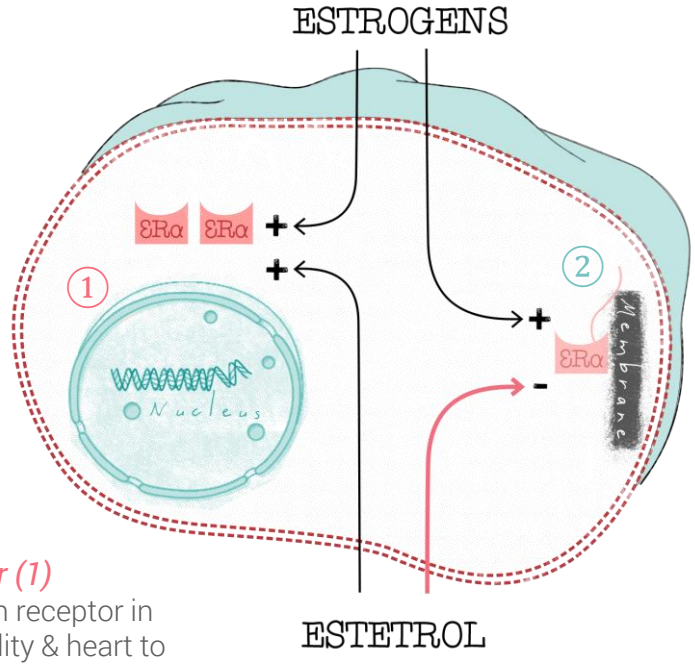
Estetrol (E4)



The role of estrogens in the human body

E4 : a unique mode of action

E4 acts differently compared to other estrogens depending on the tissue



Antagonist on the membrane receptor (2)
E4 blocks the estrogen receptor in breast and has a neutral effect on the liver (unlike other estrogens)

Agonist on the nuclear receptor (1)
E4 activates the nuclear Estrogen receptor in bone, vagina, endometrium stability & heart to provide beneficial effects (as other estrogens)

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 for 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)

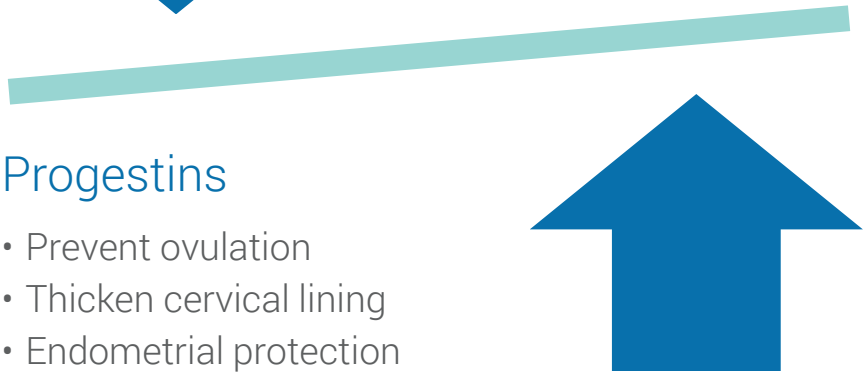
OBJECTIVE

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

The role of female sex hormones in COCs

Estrogens

- Cycle control



Progestins

- Prevent ovulation
- Thicken cervical lining
- Endometrial protection

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The impact of Progestin

Androgenic

Oily skin, acne, alopecia

Anti-androgenic

Sexual dysfunction, breast tendernes, fatigue, depression

Properties	Levonorgestrel / Norethindrone	Progesterone	Drospirenone	Cyproterone
Prevents ovulation	++	-	++	++
Endometrial safety	+	+	+	+
Androgenic activity	+	-	-	-
Anti-androgenic	-	-	+	+++
Glucocorticoid activity (favorise insulin resistance)	-	-	-	-
Antimineralocorticoid (sodium excretion)	-	+	++	-

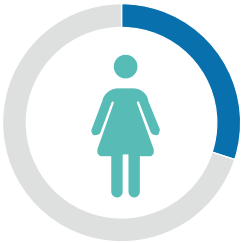
Masculinize metabolism & appearance

Demasculinize metabolism & appearance

Estelle® for Contraception
A real game changer with improved safety profile

Oral Contraception	Estrogen	Progestin	Better user acceptability	Improved safety profile
1st & 2nd generation (60' - 80')	Ethinylestradiol (EE)	Levonogestrel (LNG)	✗	✓
3rd & 4th generation (> 90')	Ethinylestradiol (EE)	Drospirenone (DRSP)	✓	✗
Estelle®, a NEW ERA	**Estetrol (E4)**	Drospirenone (DRSP)	Estelle®	Estelle®

> No real innovation in estrogens for 90+ years !



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

Benefits of Estelle®

- 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

E4 is set to be **a new paradigm** for Women's Health, allowing Mithra to re-energize a ~$22bn contraceptive market and outperform competition

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Mid
40's

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PeriNesta® (15 mg E4 + 3 mg DRSP + Food supplement)

1st complete oral treatment for 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 VMS 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 instability, 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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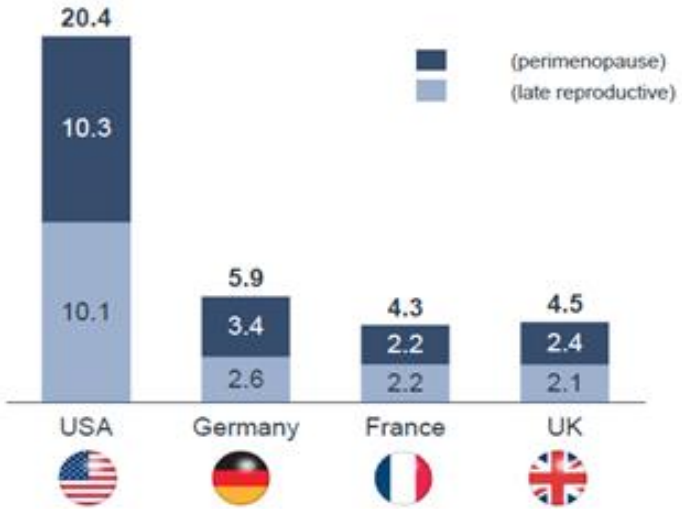
An under estimated market opportunity

- 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
- Formulation: 15 mg Estetrol (E4) and 3 mg Drospirenone + Food supplement
- Regimen : 28 tablets
- Next step: clinical trial to start
- Commercialization expected in 2023

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Donesta® (E4 only)

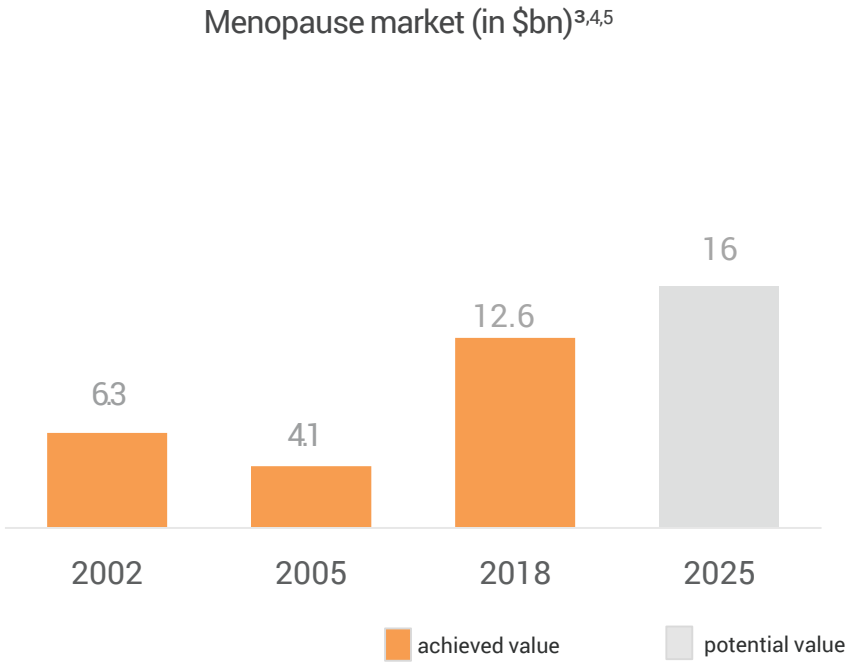
Next generation Hormone Therapy (HT) for VMS relief

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® 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
- Phase 3 trials ongoing since H2 2019*
- Commercialization expected in 2023

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* Potential recruitment delay due to Covid-19

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	Clinical trial to start; commercialization expected in 2023	Phase 3 ongoing; commercialization expected in 2023

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 : 2020
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

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5 Summary Highlights

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An integrated R&D and manufacturing platform

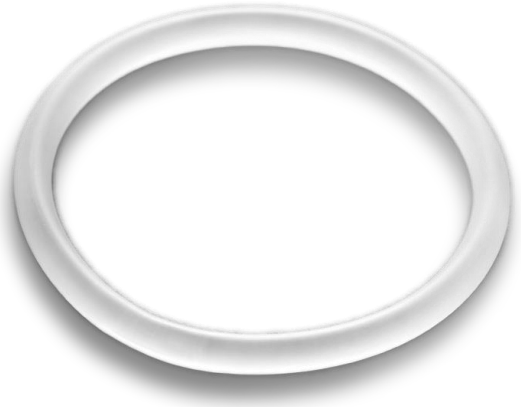
- Specialized pharmaceutical ecosystem, to take products from POC to market
- 15,000 m² facilities in Liège (Belgium)
- Dedicated R&D and production areas
- Pilot, clinical & commercial batches
- GMP Standards compliance
- Initiation of ramp-up of Estelle®

Mithra CDMO

3 production units

Sterile injectables

Polymeric forms



Hormonal tablets

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

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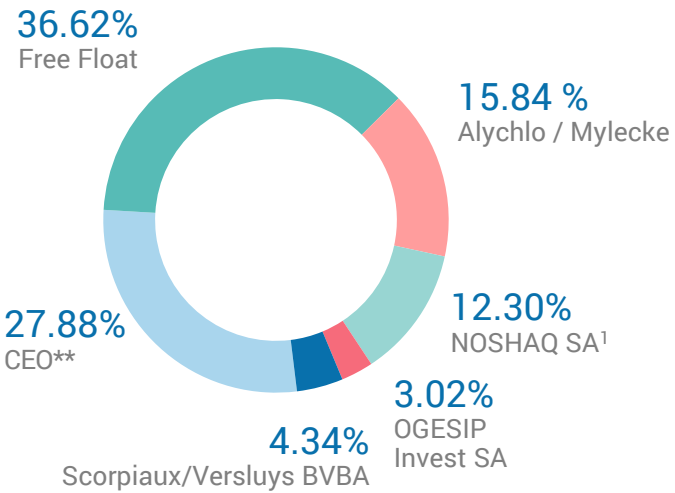
Summary financial information

Share capital
as of December 31, 2019 *



** Shareholdership in accordance with transparency declarations received by the company and notified managers' transactions. Weighted average shares outstanding: **39,133,245** as of December 31, 2019. / ** François Fornieri holds warrants entitling him to subscribe 1,023,000 additional shares of Mithra through himself and 752,790 additional shares of Mithra through Yima SPRL, a company fully owned by Mr Fornieri. / 1) Formerly MeusInvest*

IFRS P&L and cash balance
(in m€, FY as of 31/12/2019)

	FY 2018	FY 2019
Revenues	65.4	96.5
R&D Expenses	(33.4)	(52.6)
G&A	(9.0)	(13.6)
Selling Epenses	(2.0)	(1.4)
Other Operating Income	23.9	14.9
EBITDA	38.3	40.7

	FY 2018	FY 2019
Total Equity	150.9	163.3
Cash & Equivalents	119.0	49.7

- Strong revenue generation driven by Mayne Pharma deal for the commercialization of Estelle in US
  - IFRS15 allows for recognition of revenue from contracts with customers issued
- R&D spend increased mainly due to Ph3 start of Donesta
- EBITDA +6% over last year reaching new record high
- Total Equity strengthened thanks to partial conversion of earnouts into equity
- Continued good cash management
- Significant reduction of effective tax rate thanks to PID ruling

Partnering strategy with leaders in Women's Health

Commercial Agreements in 100+ countries

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

UC DAVIS UNIVERSITY OF CALIFORNIA
UNIVERSITÀ DI PISA
BOSTON UNIVERSITY
THE UNIVERSITY OF CHICAGO 1890
Université de Toulouse
NORTHWESTERN UNIVERSITY
UNIVERSITE DE RENNES 1
CHU de Liège
Universität Basel
Maastricht University
Karolinska Institutet
Newcastle University
UNIVERSITY OF LONDON
KU LEUVEN
ULB
UNIVERSITEIT GENT
UNIVERSITÉ PARIS SORBONNE PARIS IV
European Commission
OREGON HEALTH & SCIENCE UNIVERSITY
NYU
CHU Saint-Pierre UMC Sint-Pieter
UNIVERSITY OF COPENHAGEN
University of Colorado Denver
OYS OULU UNIVERSITY HOSPITAL
UCL Université catholique de Louvain
UNIVERSITE D'ORLEANS

- [1]Non-exhaustive list

Expected newsflow 2020

- Estelle® submission EMA/FDA
  - MA expected in early 2021
  - Order ramp-up from commercial partners to begin
- PeriNesta™ clinical trial start
- Donesta® Ph3, last patient in
- Myring approval FDA
- Pre-clinical POC in new indications

Belgian Biotech dedicated to Women's Health for 20 years

Why invest in Mithra?

5

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

1

Breakthrough innovation
with the unique hormone : Estetrol (E4)

4

Expertise in polymers and formulation
(Myring US to be launched shortly)

6

Additional indications based on E4 outside of women's health

2

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

3

3 late-stage
potential blockbusters

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Thank you

Appendix: Data

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*

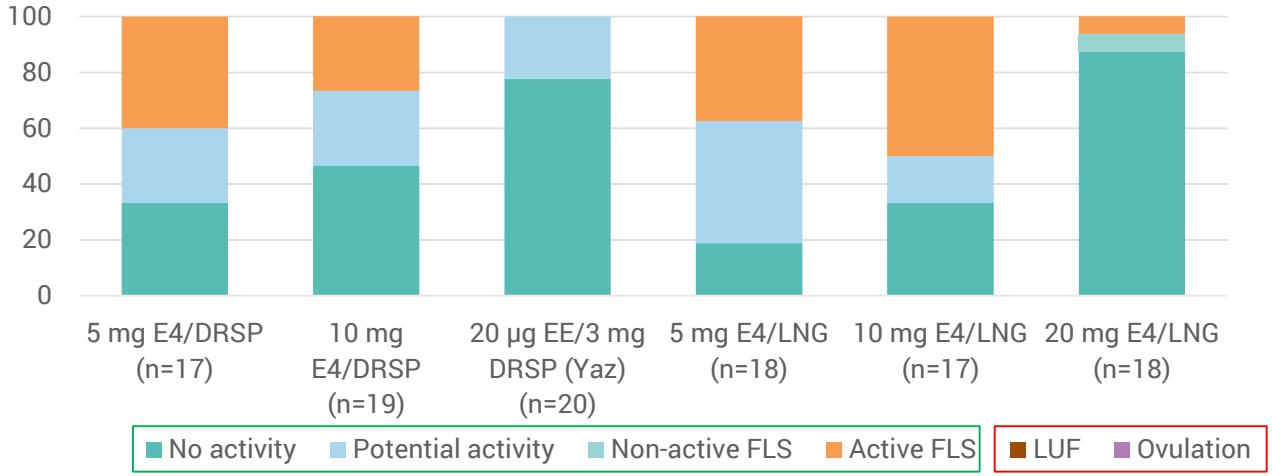
Estelle®

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

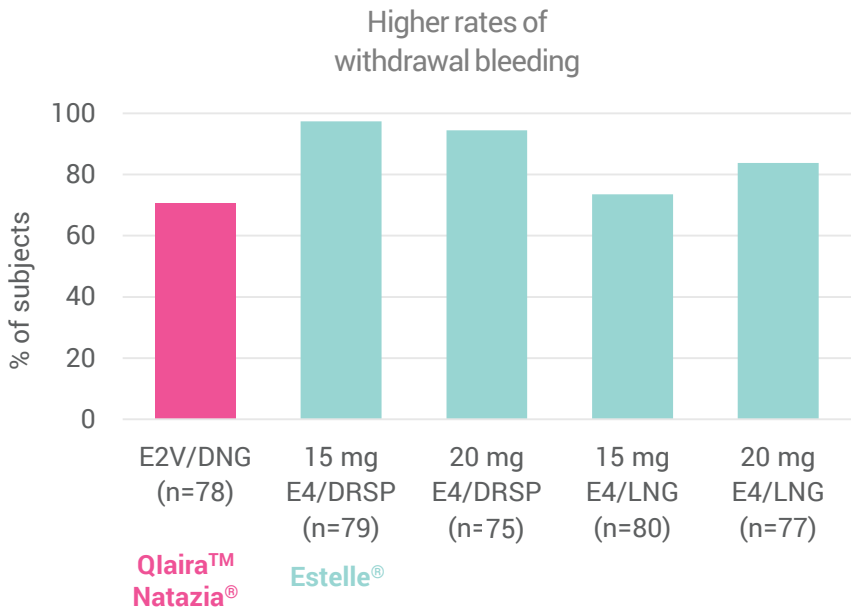
Evaluation of ovulation inhibition: % of patients scored according to Hoogland score (treatment cycle 3; n= 109 healthy premenopausal women of child bearing age)[1]

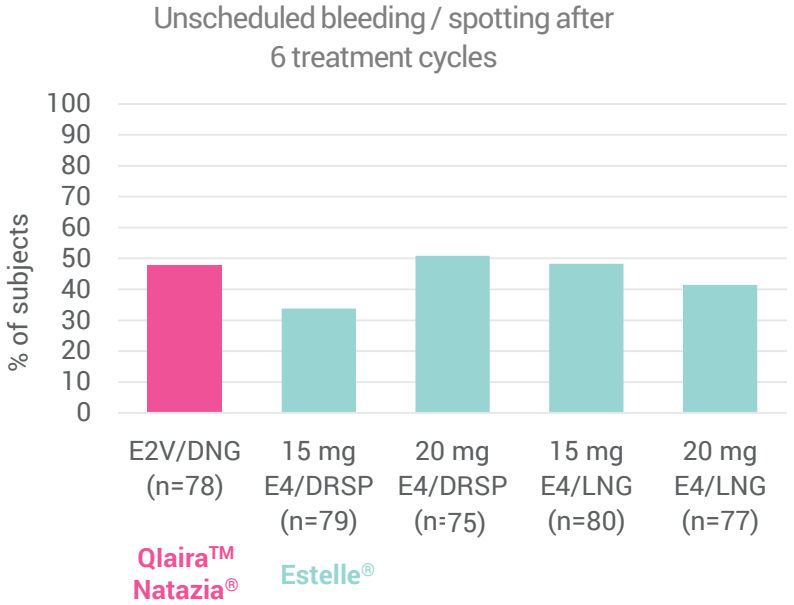


E4 inhibits ovulation in association with a progestin and **allows rapid & complete return to fertility**

- *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*

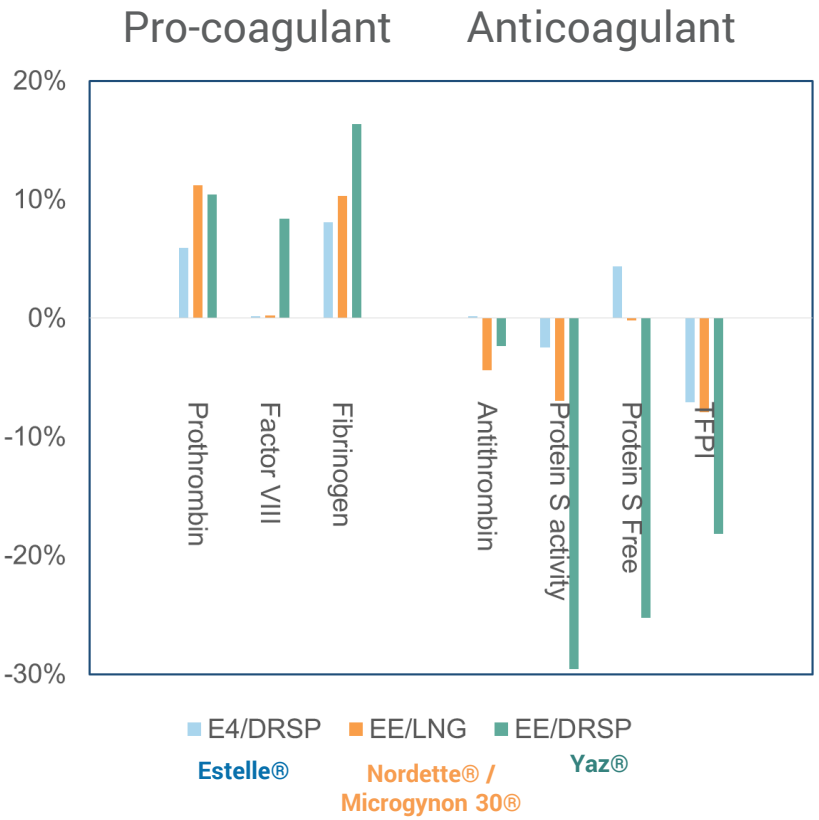
Estelle® Phase 2b: Dose-finding study shows well-controlled bleeding pattern[1]





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

Estelle® Phase 2 substudy: Reduced VTE* risk profile



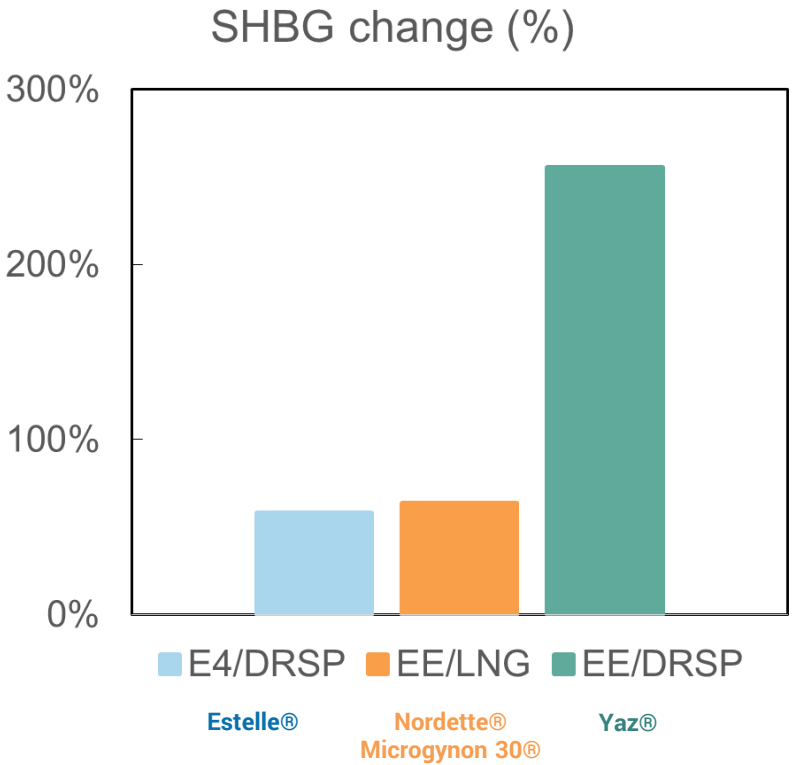
Effect of COCs on VTE Risk Factors

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® - Phase III (E4Comfort) program design

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

US / Canada October 2019		
Study	VMS Efficacy Study	Safety Study
Target population	Post-menopause H and NH* 40-65 years	Post-menopause H* 40-65 years
Trial Size	600 subjects	400 subjects
Dosing	15 / 20mg E4	20mg E4
Follow-up	12 & 52 weeks	52 weeks

EU / Russia / Latam December 2019		
Study	VMS Efficacy Study	Safety Study
Target population	Post-menopause H and NH* 40-65 years	Post-menopause NH* 40-65 years
Trial Size	600 subjects	600 subjects
Dosing	15 / 20mg E4	20mg E4 + 100mg 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, health-related quality of life and treatment satisfaction)

* Hysterectomized and Non-Hysterectomized

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)

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