



# mithro

## Women's Health

Investor Presentation — VFB

October 2017

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# Management team— Co-founders

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**François Fornieri**  
Chief Executive Officer  
Co-founder

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



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**Jean-Michel Foidart**  
Scientific Committee & Board member  
Co-Founder

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

# Transforming Women's Health through innovation

## **Expert in Women's Health , re-energizing the \$22bn Contraceptive and \$8.6bn Menopause markets**

- Markets characterized by a lack of innovation, which have recently seen a return of interest from Big Pharma
- Unique portfolio based around (1) E4 natural estrogen with improved benefit / risk profile and (2) Complex Therapeutics

### **E4: two potential blockbusters in late-stage development for launch from 2020**

Estelle® - 5th generation oral contraceptive in Phase III;  
Donesta® next-generation HT in Phase II

### **Leveraging know-how in Complex Therapeutics**

Pipeline of complex, polymer-based generics, with international launches of Tibelia® as of 2017 and Myring™ potentially as of 2018

### **Mithra CDMO : fully integrated ecosystem for state-of-the-art research, development & manufacturing**

Develop products from POC to market, for own product portfolio and partners

## **Clear growth strategy: Existing commercial portfolio combined with partnering strategy with leaders in Women's Health at key value inflection points**

- Multiple mid- to near-term catalysts
- Cash flow generative commercial generics portfolio and partnering strategy

# Expert in Women's Health, re-energizing the \$22bn Contraceptive and \$8.6bn Menopause market

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- **Women's Health Market characterized by lack of innovation; recent return of interest from Big Pharma**
  - Total market worth USD 50+bn; CAGR 3%\*
- **Unique Women's Health portfolio of E4-based pipeline and Complex Therapeutics**
  - Highly innovative new approaches based on E4, a native estrogen with improved benefit/risk profile
  - **Complex Therapeutics:** leveraging polymer science & formulation expertise to develop complex generics
  - **Powered by Mithra CDMO** (Contract Development & Manufacturing Organization)



\*Based on Datamonitor 2014; CAGR 2010-2018..

# Advanced pipeline offering multiple mid- to near-term catalysts

	Product	Indication	Ph1	Ph2	Ph3		Next milestone
E4*	Estelle®	Contraception					PhIII results Q3 2018-Q1 2019
	Donesta®	Menopause					PhII results Q1 2018

\*Preclinical: Neuroprotection (ODD in neonatal encephalopathy)

			PK/PD	BioEq	Filing	Market Approval	Next milestone
Complex Therapeutics	Myring™	Contraception					Q4 2017: Filing US MA
	Zoreline®	Cancer					H2 2017: 1 & 3 month PK results
	Tibelia®	Menopause					H2 2017: 36-month shelf life; Add'l launches

# E4 (Estetrol)

# E4 (Estetrol) – Answer from Nature with Unique Potential

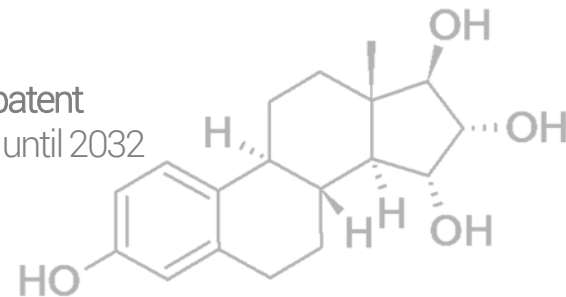


E4: **native estrogen** produced by **human fetus** around week 9

Fetal plasma levels 12x higher than those of mother

E4's broad potential for use in Women's Health validated in **multiple peer-reviewed academic journals**<sup>1-7</sup>

E4-based programs protected by **26 patent families**, including synthesis pathway until 2032



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



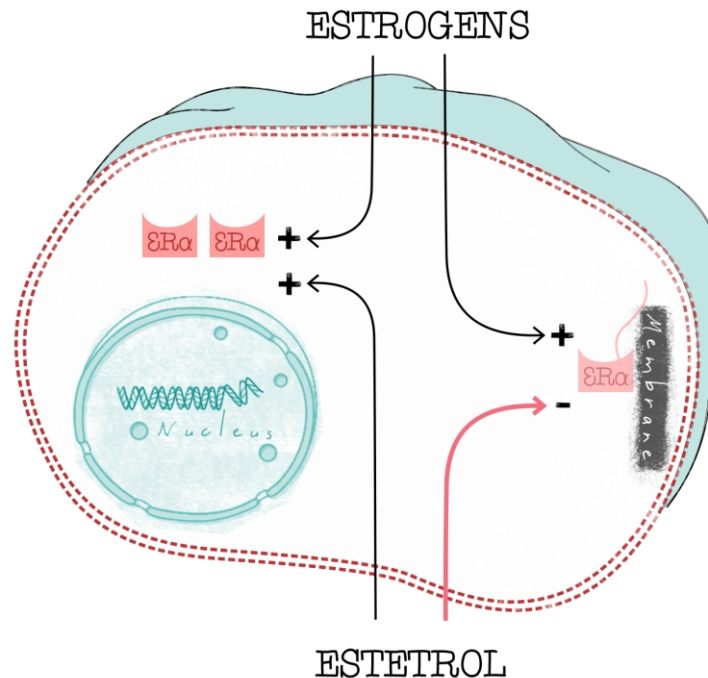
# E4 (Estetrol) – Unique agonist-antagonist mode of action

Cells exhibit 2 types of estrogen receptors (ER $\alpha$ ): membrane and nucleus receptors

Depending on the tissue either the membrane or the nucleus receptor is predominantly active

E4 acts differently compared to other estrogens depending on the tissue:

- *Agonist on nuclear receptor:* E4 acts as an estrogen in bone, vagina, endometrium stability & heart to provide beneficial effects (as other estrogens)
- *Antagonist on the membrane receptor:* E4 blocks the estrogen receptor in breast and has a neutral effect on the liver (unlike other estrogens)



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

## Estrogen's systemic side effects:

- **Heart and liver:** increased risk of Myocardial infarction, Thrombophlebitis
- **Brain:** increased risk of Stroke, Alzheimer's and Dementia
- **Ovary and uterus:** increased risk of Ovarian and 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<sup>1</sup>
- + Favorable drug-drug interaction profile<sup>4</sup>
- + Minimal increase of triglycerides<sup>5</sup>
- + Lower breast pain<sup>6</sup> and lower carcinogenic potential in the presence of E2<sup>\*,2,3</sup>
- + Good user acceptability, body weight control, excellent cycle control, improved spotting and general well-being<sup>6,7,8</sup>

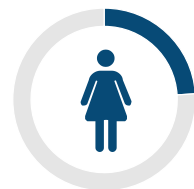
<sup>1</sup> Kluft C et al., *Contraception*. 2016.; <sup>2</sup> Gerard C et al., *Oncotarget*. 2015;6(19):17621-36.; <sup>3</sup> Visser M et al., *Horm Mol Biol Clin Invest*. 2012;9:95-103.; <sup>4</sup> Visser M et al., *Climacteric*. 2008; 11 Suppl 1:64-8.; <sup>5</sup> Mawet M et al., *Eur. J.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

# Estelle®

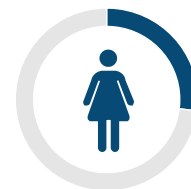
# Estelle® for Contraception, a \$22bn blockbuster market<sup>1</sup>

**Regulators are encouraging new approaches through non-reimbursement, market withdrawal and warnings for existing products**

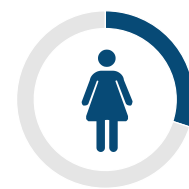
Generation pill	Better user acceptability	Improved safety profile
1st & 2nd generation	✗	✓
3rd & 4th generation (e.g. Yaz family: peak sales €1.2bn; EE + DRSP) <sup>1</sup>	✓	✗
Potential 5th generation (E4 + DRSP)	✓ <b>mithra</b> Women's Health	✓ <b>mithra</b> Women's Health



**24%**  
use alternative  
methods<sup>1</sup>



**27%**  
use no  
contraceptive  
at all<sup>2</sup>



**30%**  
of US women not  
taking pill mainly due  
to safety or  
convenience<sup>4</sup>

<sup>1</sup> Transparency market research 2017. \$22bn is total hormonal contraceptive market. The oral contraceptive market stands at \$9,6bn.

<sup>2</sup> IMS Health Data

<sup>3</sup> In the 8 biggest markets: US, France, Germany, UK, Spain, Italy, Belgium & Netherlands. United Nations, Department of Economic and Social Affairs, World Bank

<sup>4</sup> K. Daniels et al., National Health Statistics report n° 62, 2013

# Estelle® - Phase III program – Results expected Q3 2018 - Q1 2019

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

EU / Russia : June 2016 (Results expected: Q3 2018)			US / Canada : Sept 2016 (Results expected: Q1 2019)		
Contraceptive Efficacy Study	1,577 subjects, 18-50 years	✓	Contraceptive Efficacy Study	2,000 subjects, 16-50 years	
	1,350 subjects, 18-35 years	✓		1,800 subjects, 16-35 years	
Endometrial Safety Substudy	175 subjects, 18-50 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:

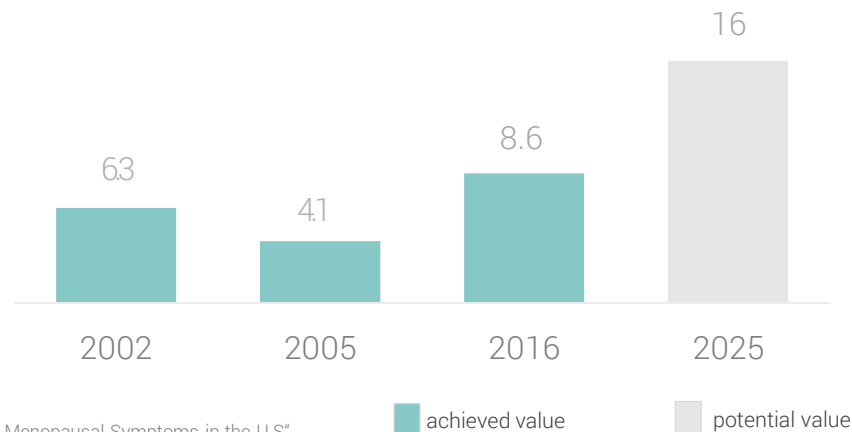
Cycle control – bleeding pattern; Safety – S(AE) reporting; Subject's well being; Population PK substudy (US/CA); Endometrial safety (EU)

# Donesta<sup>®</sup>

# Donesta® for Menopause and HT, a \$8.6bn blockbuster market<sup>1</sup>

- 78%<sup>1</sup> of menopausal women suffer VMS (hot flashes) - only 7.8% receive HT<sup>2</sup>
- 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)
- \$10+ billion potential HT Market in 2025 – VMS potential with safer alternative

Menopause market (in \$bn)<sup>3,4</sup>



Sources: (1) Symphony Health Solutions: "The Hormone Replacement Therapy Market for the Treatment of Menopausal Symptoms in the U.S." Dec 2013; (2) KBC company report Aug 2015 (3) IMS link Q2 2016; (4) Datamonitor 2014; Transparency Market Research 2017

# Donesta® - Phase IIb program – Results expected Q1 2018

## A Multicenter Dose-Finding, Randomized, Double-Blind, Placebo-Controlled Study to Select the Daily Oral Dose of E4 for the Treatment of Vasomotor Symptoms (VMS) in Postmenopausal Women

### Study Design:

- > 260 subjects (recruitment completed)
- > Aged 45 to 65 years
- > Presenting at least 7 moderate to severe hot flushes / day or at least 50 moderate to severe hot flushes / week
- > 4 dose levels of E4 or Placebo up to 13 weeks (2.5 – 5 – 10 – 15 mg)
- > E4 therapy is followed by a Progestin therapy (Dydrogesterone 10 mg) for 2 weeks

### Primary objective:

Minimum effective dose of E4 for vasomotor symptoms (VMS) or hot flushes

### Secondary Endpoints:

- > Genitourinary syndrome of menopause (GSM) or vulvovaginal atrophy (VVA)
- > Vaginal maturation index (MI)
- > Vaginal pH
- > Change in the Menopause Rating Scale (MRS)
- > Lipid and glucose metabolism
- > Hemostatic and bone laboratory variables
- > E4 concentrations at baseline and steady state

### Key safety objectives:

- > Transvaginal ultrasonography (TVUS) change of **endometrial thickness** at each study visit during the E4/placebo treatment period
- > Serious adverse event S(AE) monitoring
- > Electrocardiogram (ECG)
- > Bleeding control



# Complex Therapeutics

# Leveraging know-how of Complex Therapeutics

- Expertise in developing **complex and innovative polymer products**
- Targeting **safer, long-lasting delivery and controlled release** of trusted, established approaches to **contraception, menopause and hormone-dependent cancers**
- Duration ranging from 1 month to 5 years
- One of handful of companies that can deliver **multiple drug delivery strategies** including vaginal rings, implants and intra-uterine systems (IUS)
- To be developed and manufactured in-house at **Mithra's dedicated CDMO** research, development and specialist manufacturing center



# Mithra CDMO: Integrated development & production platform

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## Specialized pharmaceutical ecosystem, to take products from POC to market








### Rationale for CDMO:

- > Keep quality control, IP & expertise in-house
  - > Operate independently from 3rd parties using its own proprietary production technology
  - > Additional source of revenue via production of (partnered) programs
  - > Leverage development expertise through 3rd party production contracts
- 

### 2-Phase construction process:

- > H2 2016: R&D facility and polymeric forms, implants and sterile injectables production line facilities
- > Received **European GMP approval** for Myring™ (May 2017); FDA expected to follow (H1 2018)
- > H1 2019: Production line for tablets to be completed

# Partnering with leaders in Women's Health at key value inflection points

	EU	US	RoW
<b>Estelle®</b>	Intended partnering after Phase III		Partnering ongoing  <b>Libbs</b> Brazil  <b>Fuji Pharma Co., Ltd.</b> Japan & ASEAN
<b>Donesta®</b>	Intended partnering after Phase II		Partnering ongoing  <b>Fuji Pharma Co., Ltd.</b> Japan & ASEAN
<b>Myring™</b>	Partnering discussions ongoing  Austria		Partnering discussions ongoing
<b>Other products (incl. Zoreline® ; Tibelia®)</b>	Partnering discussions ongoing*	Partnering discussions ongoing	Partnering discussions ongoing

\*Tibelia® distribution partners include Gedeon, Mercury, Procure, Campus

# Multiple near-term catalysts

E4

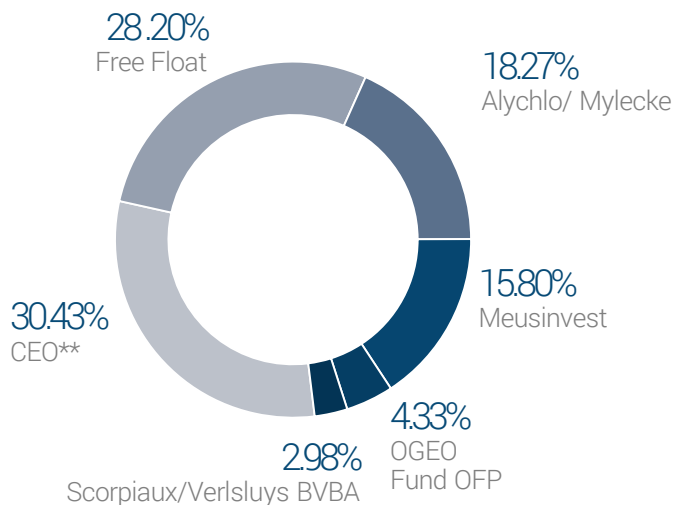
**Complex  
Therapeutics**

**CDMO**

H1 2017	H2 2017	H1 2018	H2 2018	H1 2019
<p>Recruitment Estelle® hemostasis study completed</p> <p>Recruitment Estelle® Phase III study EU/Russia completed</p> <p>ODD in neonatal encephalopathy (EMA)</p> <p>Initiation Estelle® PK ethnobridging study</p> <p>Donesta® contract with Fuji Pharma</p>	<p>Recruitment PK substudy in Estelle® completed</p> <p><b>Estelle® contract with Libbs for Brazil</b></p> <p>Recruitment Donesta® Phase II study completed</p> <p>Estelle® QT evaluation</p> <p>Results PK study for E4 alone</p>	<p>Results Estelle® hemostasis study</p> <p><b>Topline results Donesta® Phase II</b></p> <p>Completion of ovarian function inhibition data Estelle® : 15 mg E4/3mg DRSP</p> <p>Results Estelle® PK ethnobridging study</p>	<p>Q3 2018 (Europe/Russia) – Q1 2019 (US/Canada): Top line results of Estelle® Phase III studies</p>	
<p>European GMP approval Myring™</p> <p>Myring™ contract with Mayne Pharma (US) and Gynial (Austria)</p> <p>Tibelia®: agreement Canada</p>	<p>Myring™ EU MA submitted</p> <p>Tibelia®: 36-month shelf life</p> <p>Zoreline®: month profile &amp; update reformulation 3 month profile</p>	<p>Submission US MA Myring™</p> <p>FDA GMP approval</p> <p>Myring™ US/EU MA expected</p>		
				CDMO Phase II

# Summary Financial Information

## Share capital as of August 2017\*



## IFRS P&L and cash balance (in k€, FY as of 07/30/2017)\*\*

	HY 2016	HY 2017
Revenues	8.4	12.7
R&D Expenses	(16.8)	(25.5)
G&A	(3.8)	(3.9)
Selling expenses	(4.5)	(2.4)
Operating loss	(21.518)	(24.416)

- OTC products Women's Health: EUR 8.8m
- Licensing: EUR 3.9m recognized
  - Donesta®: Fuji Pharma (EUR 1.5m)
  - Myring™: Mayne Pharma (US) and Gynial (EUR 2..4m)

⇒ Cash flow generation thanks to recurring generic business and partnering strategy

⇒ Post-period: Estelle® partnership with Libbs in Brazil (EUR 20m upfront DP)

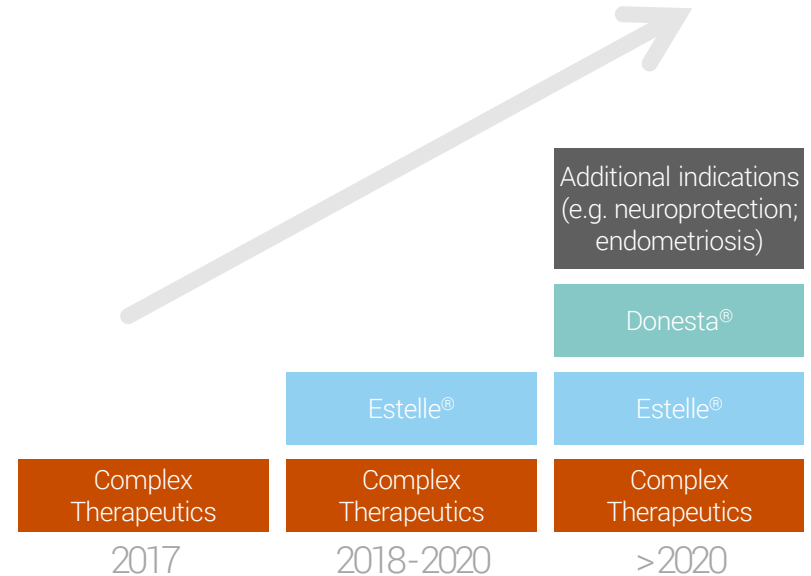
	FY 2016	HY 2017
Cash & Equivalents	45.8	44.7

\* Shareholdership in accordance with transparency declarations received by the company and notified managers' transactions. Market Cap: € 342 m as of September 2017 (Euronext: MITRA)

\*\* CEO (François Fornier) holds warrants for 1,211,100 additional shares of Mithra

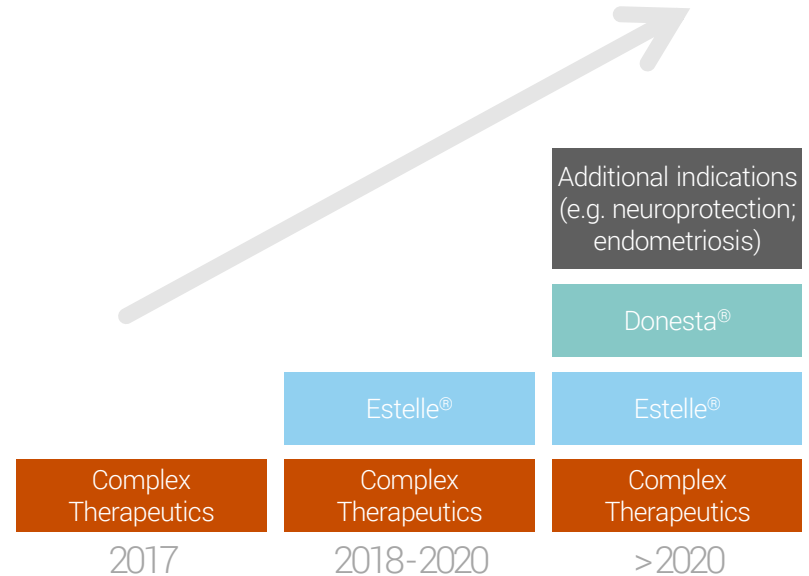
# Building a transformative Women's Health company

- Multiple prospective near- and mid-term milestones and launches to drive long-term growth
- Estelle® and Donesta® – late-stage potential blockbusters built on unique E4 platform
- Acceleration of business development including partnerships for E4-based programs
- Industry partner with specialist research, development and manufacturing capabilities
- Diversified model spreads risk and maximizes product opportunities through collaborations



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# Contact Us

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

François Fornieri  
CEO  
[ffornieri@mithra.com](mailto:ffornieri@mithra.com)

Sofie Van Gijsel  
IR Officer  
[svangijsel@mithra.com](mailto:svangijsel@mithra.com)

Website: [investors.mithra.com](http://investors.mithra.com)



# mithra

## Women's Health

Thank you!

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