mithra
Women's Health

Investor Presentation

June 2022

Mithra

1

2 Innovative E4 platform

3 Complex Therapeutics

4 Mithra CDMO

mithra
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


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

Two complementary innovative platforms powered by a unique CDMO facility

Novel E4-based pipeline

Technology know-how in Complex drug development

Estetrol (E4) Platform

mithracdmo

Complex Therapeutics

Existing hormone-based solutions brought freedom and empowerment to women but with compromises[1,2]

- To date, hormonal-based therapies carry side effects which negatively impact women's quality of life
- Key medical risks and fears associated with current estrogens
- Negative environmental impact, e.g. on marine wildlife
- Need for safer hormone solutions across women's health is high
- **Mithra's E4/Estetrol portfolio offers a solution to unmet needs**

1. Stanczyk FZ *et al. Contraception* 2013.
2. FSRH (Faculty of Sexual and Reproductive Healthcare) Guidelines, 2019.

Diversified pipeline offering multiple near-term catalysts

	Product	Indication	Phase 1	Phase 2	Phase 3	Market Approval
E4	Estelle®	Contraception	**Commercialized in US, Europe & Canada**			
	Donesta®	Menopause				US : H1 2024 EU : H2 2024
		Neuroprotection	Launch Phase 1 H1 2022			
		Wound healing	Pre-clinical development			

	Product	Indication	Formulation / Clinical	Filing	Market Approval
Complex Therapeutics	Myring®	Contraception	EU / RoW		Commercialized
			US		US : H2 2022
	Tibelia®	Menopause			Commercialized
	Zoreline®	Oncology			2025

An innovative E4 platform

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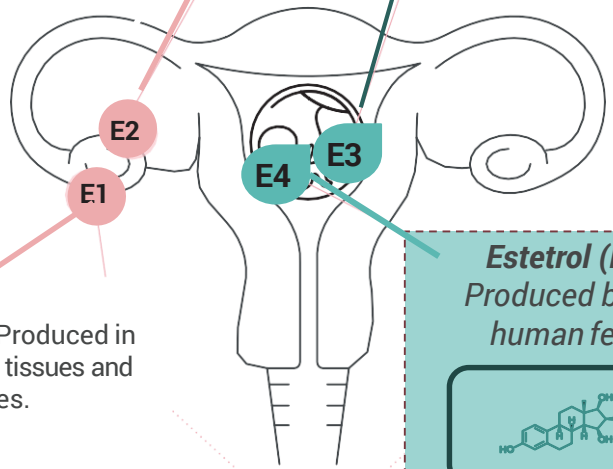
E4 (Estetrol)
a new estrogen with an
improved benefit/risk profile

Estetrol (E4) is the early life native estrogen
Improved Benefit/Risk Profile compared to other Estrogens

Estrogens made by the body

Estradiol (E2): Made in ovaries during reproductive years

Estriol (E3): Produced by the foeto-placental unit



Estrone (E1): Produced in liver, peripheral tissues and ovaries.

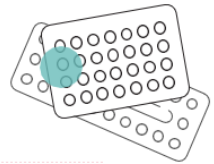
Estetrol (E4): *Produced by the human fetus*

Adult Estrogens

Fetal Estrogens

Estrogens made outside the body

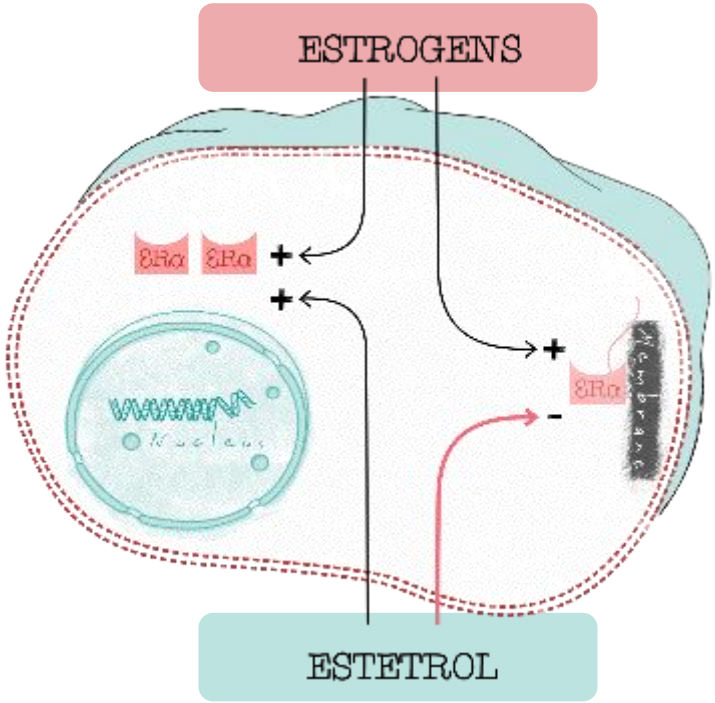
Synthetic Estrogens *(e.g. Ethinyl Estradiol)*	Produced for medical use e.g. in birth control pills
Phytoestrogens	Found in plants, E1 e.g. in soybeans
Xenoestrogens	Pollutants from man-made products that act as endocrine disrupting agents



E4 is a native estrogen with a unique mode of action

AGONIST on the nuclear ERα

- Activates the nuclear estrogen receptor [2-4]
- Important estrogenic activity on **the vagina, endometrium, bone and cardiovascular system** to provide beneficial effects [2-4]

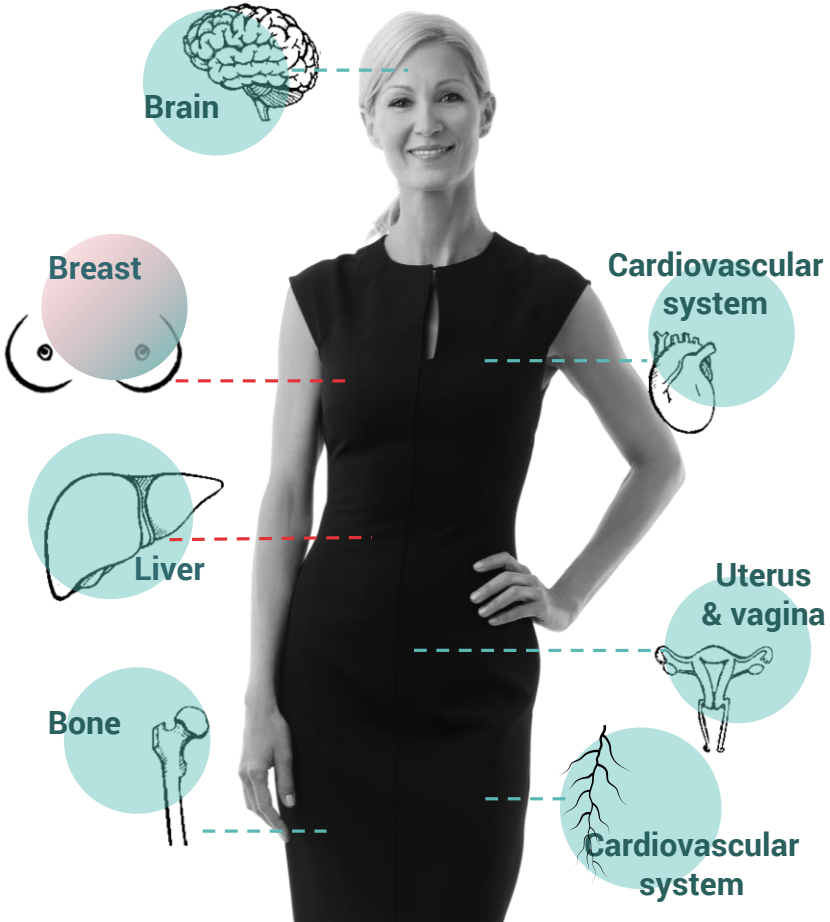


ANTAGONIST on the membrane ERα

- Blocks the membrane estrogen receptor[2-4]
- **Neutral effect on the liver** unlike other oestrogens[2-4]
- **Low impact on normal and malignant breast**[5-8]

1. Abot A *et al. EMBO Mol Med* 2014.2.Foidart JM *et al.* InL Brinton RD et al (eds) 2019, Sex Steroids Effects on Brain, Heart and Vessels. ISGE Series.3.Arnal JF *et al. Physiol Rev* 2017. 4.Giretti MS *et al. Front Endocrinol,* 2014.5.Gerard C et al Endocrinol 2015. 6.Singer CF *et al. Carcinogenesis,* 2014. 7.Visser M *et al. Horm Mol Biol Clin Invest* 2012.

E4 presents a favorable safety profile



- Similar to other estrogens, E4 has also a beneficial and positive impact on the cardiovascular system, brain, bone and endometrium
- Unlike other estrogens, E4 has a limited impact on the liver and breast

Breast: mixed activity on breast cell proliferation, migration and invasion[1], limited impact on breast at therapeutic dose

Liver:

- minimal impact on SHBG[2] synthesis
- minimal impact on synthesis of coagulation factors (lower risk of VTE)
- limited lipid impact (including TGs[3])

1. In presence of Estradiol (E2); 2. Sex Hormone Binding Globulin; 3. Triglycerides

Visser et al. Climacteric 2008 | Mawet et al. Eur J Contracept Reprod Health Care 2015 | Gérard et al. J Endocrinol 2015 | Abot et al. EMBO Mol Med 2014 | Coelingh Bennink et al. Climacteric 2008 | Heegaard et al. Climacteric 2008 | Holinka et al. Biol Reprod. 1980 | Holinka et al. Climacteric 2008 | Pluchino et al. J Steroid Biochem Mol Biol 2014 | Tskitishvili et al. Exp Neurol 2014 | Guivarc'h et al. J Am Heart Assoc 2018 | Kluft et al. Contraception 2017 | Douxfils et al. Contraception 2020 | Klipping et al. Contraception 2021

E4, an environmentally-friendly estrogen

EE (ethynyl estradiol)

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

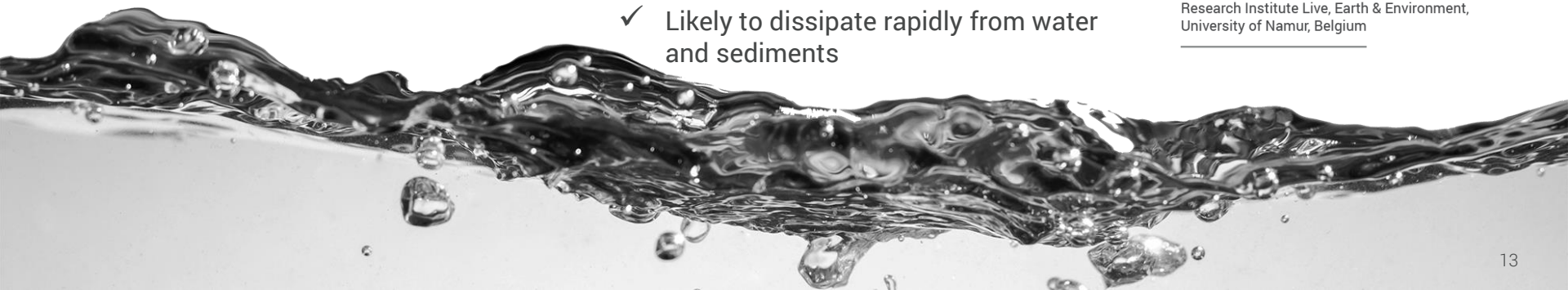
vs

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.”

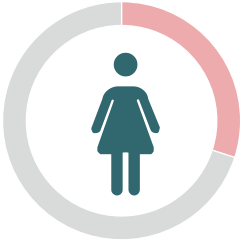
Prof. Patrick Kestemont, President of the Research Institute Live, Earth & Environment, University of Namur, Belgium



Reproductive Years

Estelle® (15mg E4 / 3mg DRSP)

A New Era in Combined Oral Contraception (COC)



30%
of US women do not take the 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"

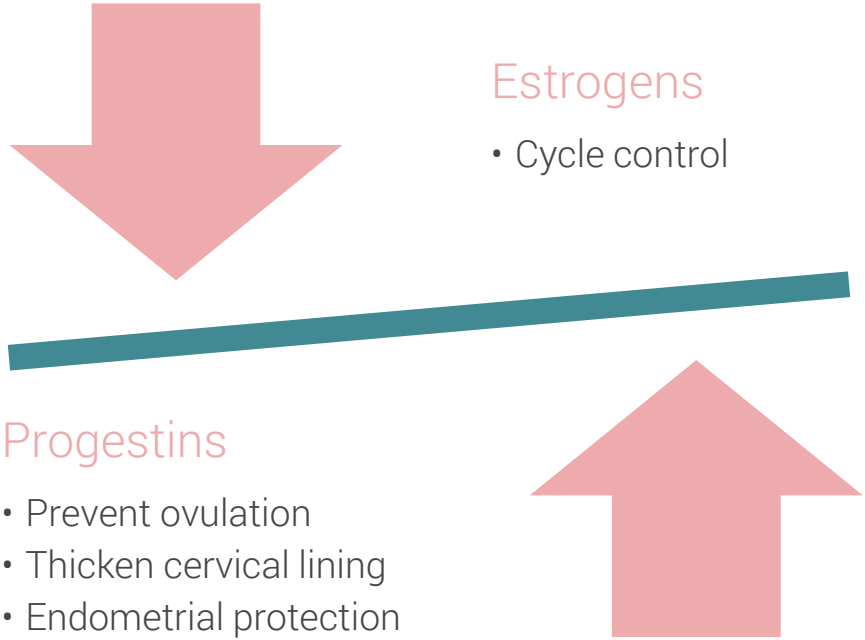
Celmatix Press Release
December 2018

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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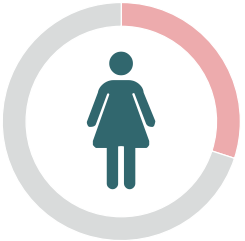
Estelle® addresses women's unmet needs and improves women's contraceptive experience

- Reliable contraceptive efficacy
- Excellent cycle control
- Favorable safety profile in phase 2/3 trials
  - ★ Favourable VTE risk profile with low impact on all markers of coagulation
  - ★ Minimal impact on breast tissue
  - ★ Minimal increase of triglycerides
    - Minimal impact on glucose metabolism
- Neutral impact on body weight (including women with BMI 30-35 kg/m)
- Positive effect on skin
- ★ Low risk of drug-drug interaction
- High user satisfaction with improved quality of life
- ★ Proven superiority in comparison to EE containing COCs



30%

of US women do not take the pill mainly due to safety or convenience

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

Nextstellis® – US highlights end Q1 2022

Product performance[1]

- 20,000 cycles in Q1 22 up 90% from 4Q21 and 9,400 cycles in April 2022
- 3,400 Nextstellis® new writers since launch; averaging 100 new writers / week
- Productivity / writer is increasing with top decile writers averaging 16 cycles / quarter

Market access

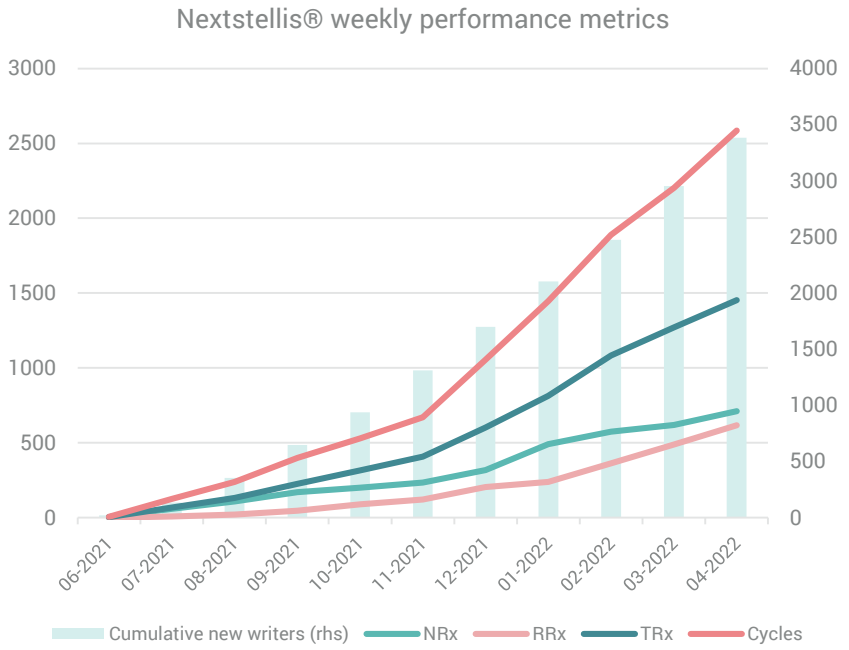
- Commercial coverage[2]: 71% formulary access, 55% unrestricted
- Commercial abandonment rate reduced from >55% in July 2021 to 20% in March 2022[1]

Healthcare Professionals (HCPs)

- Awareness is becoming more prevalent among target HPCs: aided awareness is 79% and unaided awareness is 31% (versus 68% and 15% respectively in August 2021)[3]
- 35% of target prescribers now writing Nextstellis®
- DTC campaign launching over US summer

Source: Mayne Pharma; 1. IQVIA and internal pharmacy partners; 2. Reported by MMIT; 3. Nextstellis® ATU study results February 2022

Nextstellis® – US key performance metrics



	Q3 21	Q4 21	Q1 22	Change Q1 22 vs Q4 21
New writers	627	1,053	1,256	19%
NRx	1,060	3,750	6,100	63%
TRx	1,289	6,002	11,235	87%
Cycles	2,365	10,268	19,652	91%

Currently averaging 100 new writers/week

>85% of HCPs who wrote Nextstellis® in H2 21 have returned in H1 22

Source: Mayne Pharma; IQVIA rapid weekly and internal pharmacy partners

Nextstellis® – US Direct To Consumer campaign

- >50% of women play an active role in choosing their contraceptive method
- >80% of the time brand requests by consumers are granted by HCPs
- Direct to Consumer campaign will be launched in the Summer as we achieved the following milestones:
  - 79% awareness amongst target HCPs[1] (target: >75% awareness)
  - 3400 writers (target: >3,000 writers)
  - 55% unrestricted commercial coverage and 70% formulary access[2] (target: ~60% unrestricted commercial coverage and >70% total coverage

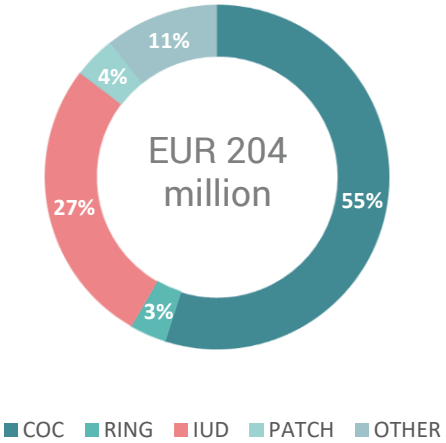
Potential DTC channels

Meta hulu YouTube Google Bing

Source: Mayne Pharma; 1. February ATU report; 2. According to MMIT, which is 5-8% underreported

Nextstellis® – Commercialization in Canada

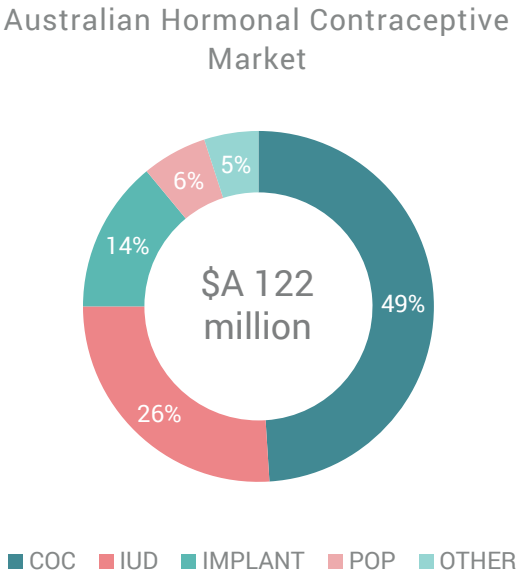
Canadian Hormonal Contraceptive Market



- Launched late August 2021
- Challenging market conditions (limited access to HCPs) have slowed engagement with HCPs & impacted product ramp-up
- Top Tier responsible for > 70 % of COC business visited at least 2 times – Full coverage of targets by end of Q1 2022
- Sample distribution increased by 4-fold to physician offices reaching **22,000 samples – 3,500 women trialing Nextstellis®**
- Reimbursement coverage with private insurers has improved by 80 % **~90% of lives covered by private insurance nationally**
- Looking at recent launches in Canada – launch trajectory by prescription shows promising launch curve for Nextstellis®
- **Direct-to-consumer campaign** will be launched in **H1 2022**

Source: Mayne Pharma; IQVIA MAT Value, Q3 2021

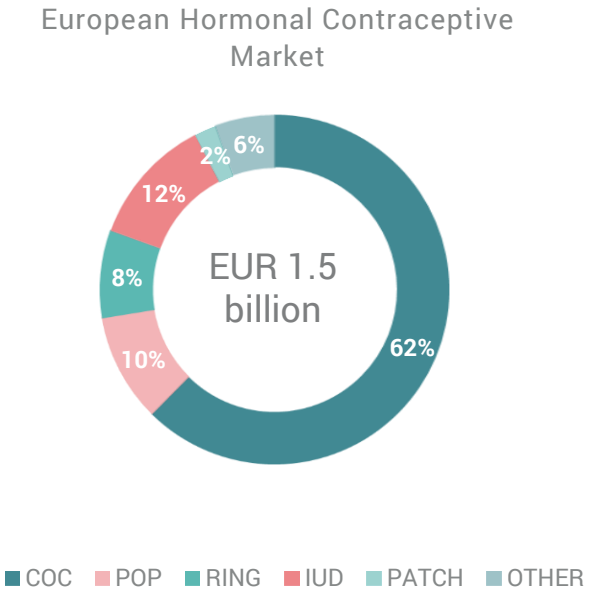
Nextstellis® – Upcoming commercialization in Australia



- TGA approval in November 2021
- **Imminent launch: target in Q3 22**
- Australian contraceptive market size = A$122m
  - Combined oral contraceptives (COCs) = 49% (A$60m)
- 5 year of marketing exclusivity in Australia with potential further patent protection
- Promotion by an expanded national GP/specialist sales team
- Will have active sample program

Source: Mayne Pharma, IQVIA MAT Sales, December 2021

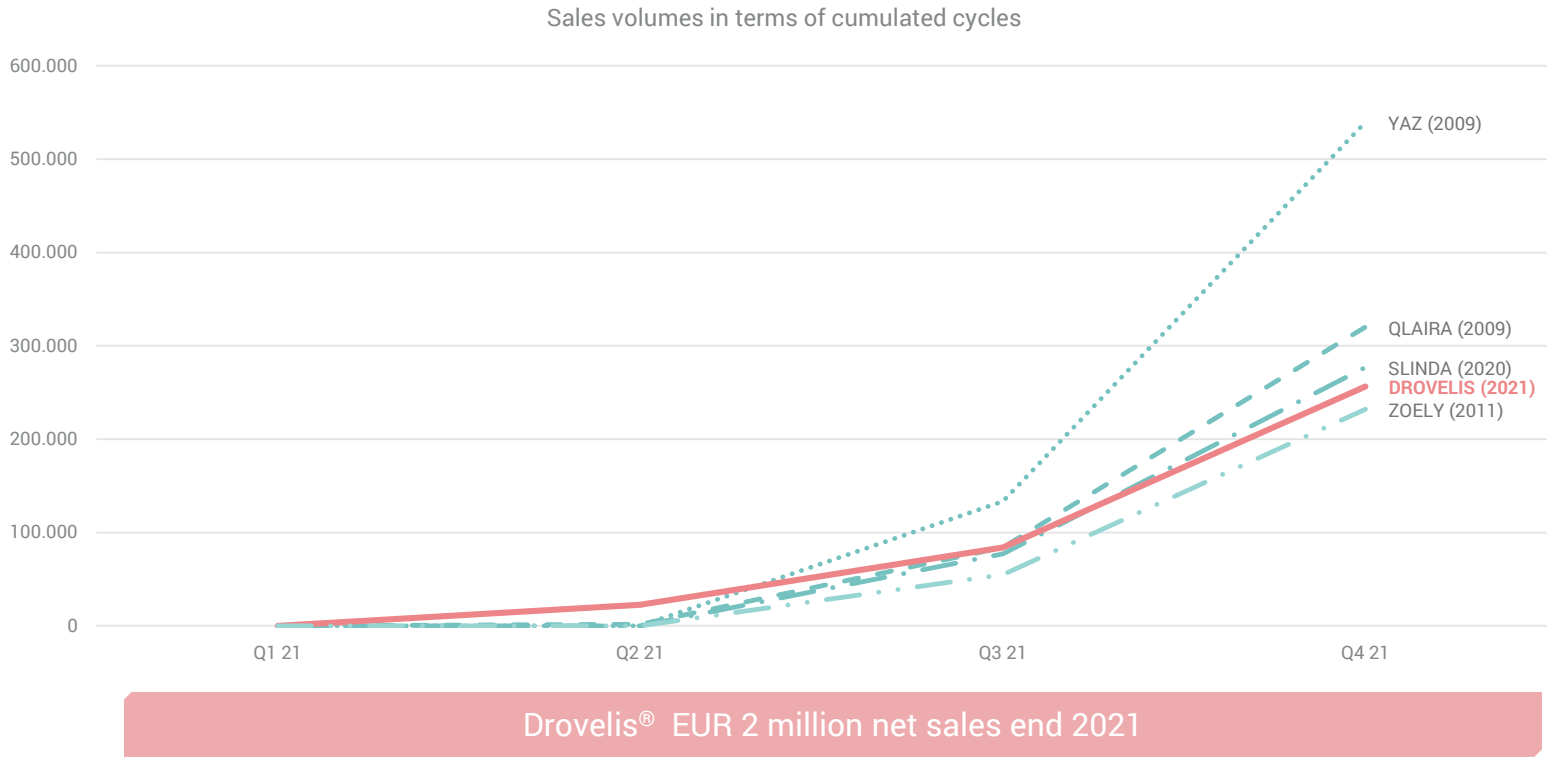
Drovelis® – Commercialization in Europe



- Progressive European roll out since launch in July 2021
- Drovelis® is a new actor in the short acting OC market valued at EUR 1.1 billion
- Impact of Covid-19 – reduced interactions with HCPs
- Global marketing strategy and messaging across Europe with Gedeon Richter HQ and affiliate drive

Source: Mayne Pharma, IQVIA, Value MAT Q3 2021

Drovelis® – Launch curve in EU vs recent launches



Drovelis® EUR 2 million net sales end 2021

Source: IQVIA 2021; Adjusted uptake curves for YAZ, QLAIRA, ZOELY and SLINDA compared to DROVELIS launch date in each country

Drovelis® – Commercial roll out in 2022

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Women's Health

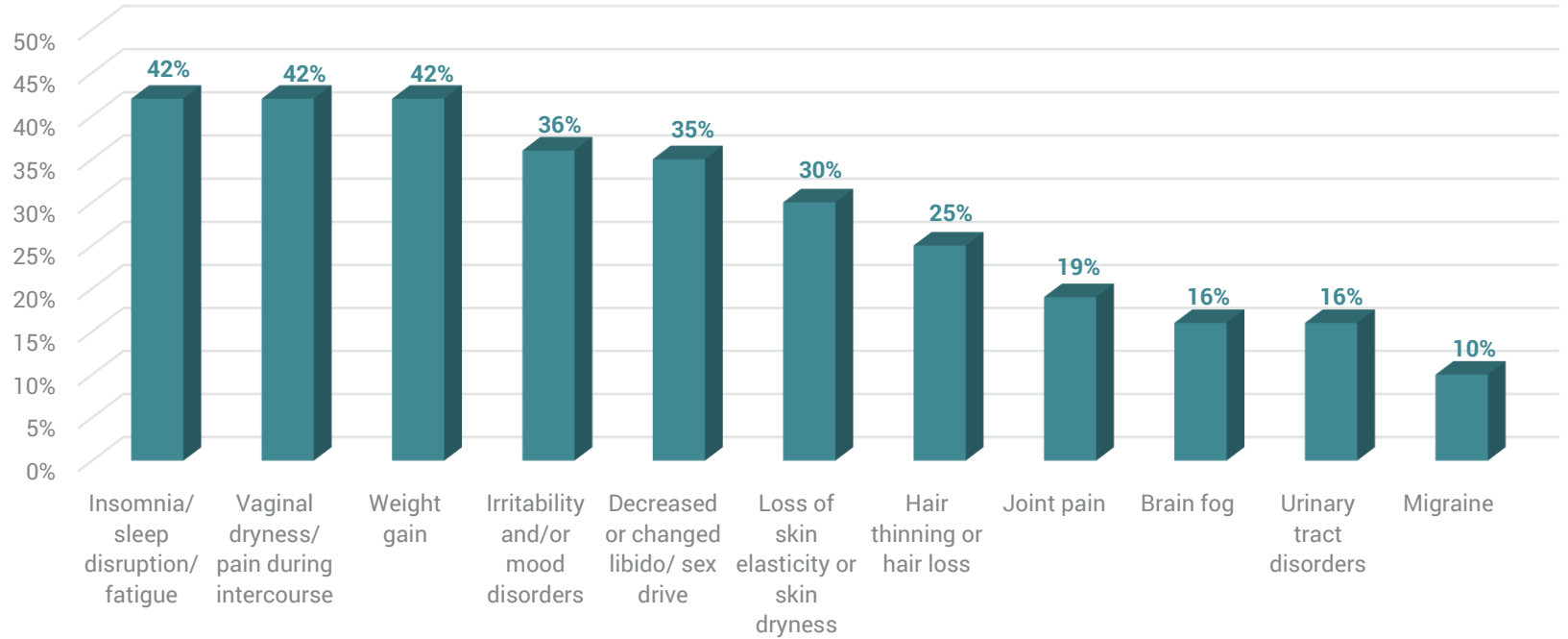
Donesta® (E4 only)

A new era in Hormone Therapy (HT)

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
- Ultimately, all women who reach a certain age – average 51 – will reach menopause. Of these, 75% will get one or multiple troublesome symptoms that deteriorate their quality of life.

Beyond hot flushes, women experience a number of other menopause-related symptoms



Source: IQVIA quantitative market research, 2021

Menopause in figures

There are **significant unmet needs** in the treatment of menopause symptoms primarily **due to the safety concerns** associated with use of **existing hormones**.

Only 1 in 10 women with menopause take Hormone Therapy (HT), despite HT being the most effective therapy for the large majority of women.

Women spend **+/- 40% of their life** time in menopause.
About 25 million women pass through menopause **each year**[1].

By 2030, the world population of menopausal and postmenopausal women is projected to **increase by over 1.2 billion.** Blockbuster market with around **47 million new entrants each year** globally[2].

Source: 1. National Center for Biotechnology Information (NCBI); 2. Maturitas. The demography of menopause. 1996 Mar;23(2):113-27. doi: 10.1016/0378-5122(95)00968-x. Viewed September 21, 2021. https://pubmed.ncbi.nlm.nih.gov/8735350/

Existing and upcoming treatments

- Hormone therapy (HT)

Estro-progestative combination	Estrogen only

- Non-hormonal therapy (NHT)

CNS* derived solutions (NK3)	Anti-depressants	Anti-epileptics

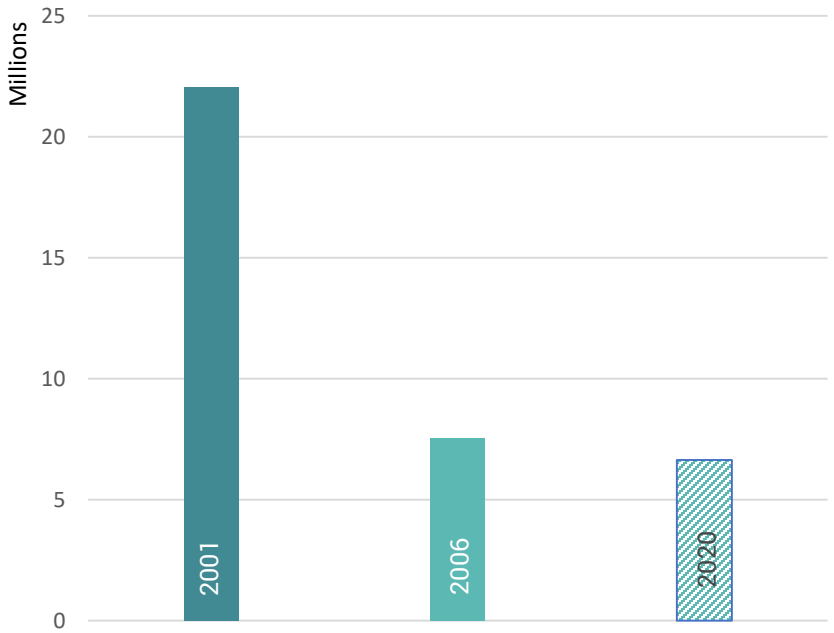
*CNS: Central Nervous System

Hormone Therapy (HT)

- Treatment recommended to **relieve common symptoms of menopause** and to address **long-term biological changes** that result from declining levels of the natural hormones (estrogen and progesterone) during and after menopause.
- HT also helps **to balance estrogen and progesterone** in women around the time of menopause.
- History of HT started **in the 1960s**; first clinical trials on HT and chronic postmenopausal conditions started **in the late 1990s**.
- **Collapsing** of HT's use worldwide after the announcement of the first results of the **Women's Health Initiative (WHI) in 2002**, which indicated that HT could have more detrimental than beneficial effects.

Influence of WHI report – HT use collapsed following publication of initial results

Number of patients with HT in 2001- 2006 - 2020



In 2001, 22 million women treated with HT for menopause symptoms, currently only 7 million despite revised WHI 2006 HT recommendations

- Following publication of WHI report; more than **85% of women in the USA** stopped taking HT and **63% in Europe** due to concerns of risk of breast cancer and cardiovascular disease.
- **In 2006, WHI** updated analysis confirmed no increased risk of breast cancer with estrogen-alone HT, however **the market has not recovered**.
- There have been **few innovations** to treat menopause symptoms since publishing of the WHI.

Source: IQVIA primary and secondary market research, 2021

Donesta® - Phase 3 (E4 Comfort)

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

C302 [1]		
Study part	VMS Efficacy	Safety
Target population	Post-menopausal H and NH* 40-65 years	Post-menopausal H and NH* 40-65 years
Trial Size	600 subjects	400 subjects
Dosing	15 / 20 mg E4**	20 mg E4
Duration	12 weeks (efficacy) + 40 weeks safety	52 weeks

C301 [2]		
Study part	VMS Efficacy	Safety
Target population	Post-menopausal H and NH* 40-65 years	Post-menopausal NH [4] 40-65 years
Trial Size	600 subjects	600 subjects
Dosing	15 / 20 mg E4**	20 mg E4 + 100 mg P4
Duration	12 weeks	52 weeks

Primary endpoint:

Efficacy - to measure the effect of treatment with 15mg and 20mg of E4 compared to placebo on the frequency and severity of VMS at weeks 4 and 12 (C301 & C302)

Safety - to evaluate the general safety of treatment with E4 (C302) and the endometrial protection when combined with P4 (C301)

Secondary Endpoints:

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

[1] US, Canada [2] EU, Russia, Latam (+US, Canada) *H: Hysterectomized & NH: Non-Hysterectomized ** vs. placebo

Phase 3 trials: top line efficacy results

- Donesta® demonstrates a **statistically significant** and **meaningful reduction** in the frequency and severity of moderate to severe VMS from baseline and compared to placebo[1] in C-301 and C-302 trials:

- All co-primary endpoints were met statistically in both studies (all $p < 0.05$).

- Both **frequency and severity** of hot flushes showed a **continued decrease** week after week until week 12 (end of efficacy study) where:
  - ➔ VMS frequency declined by up to 80% compared to baseline with Donesta®.
  - ➔ VMS severity was reduced by up to 56% compared to baseline with Donesta®.

- Determination of **effective dose** is a regulatory discussion and cannot be disclosed in order to avoid any bias with the ongoing Donesta® trial.

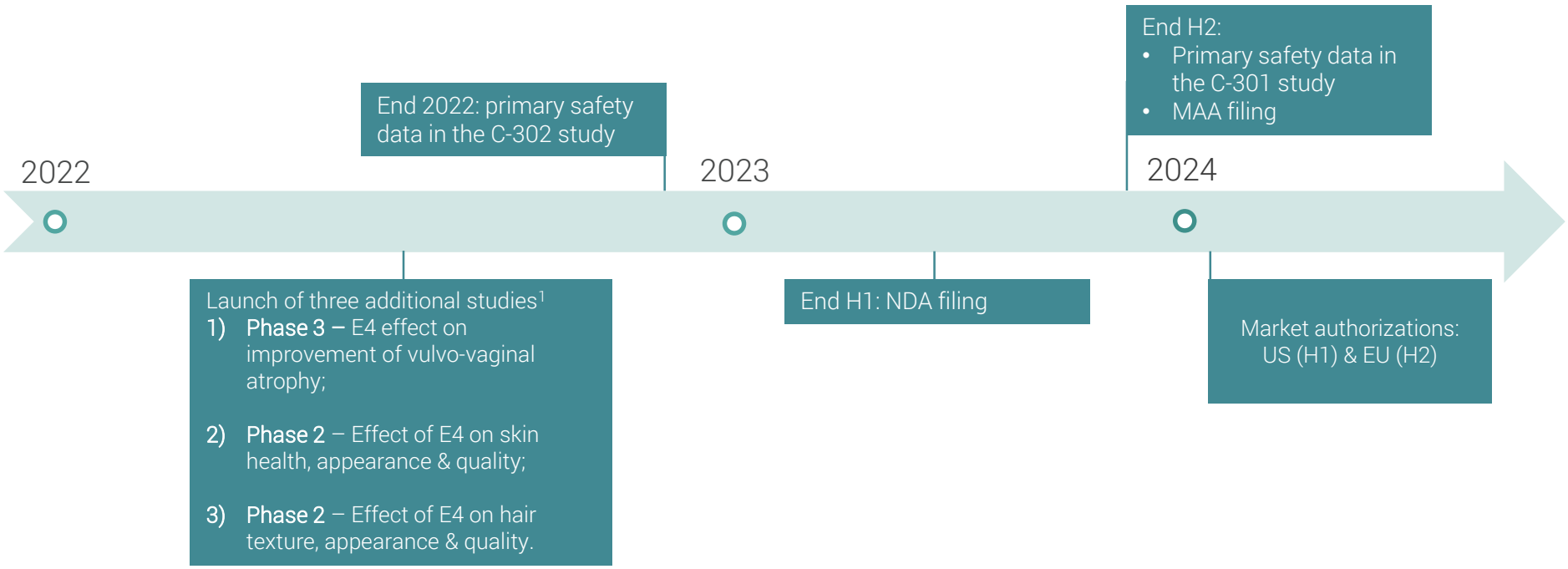
- **Positive impact of Donesta® on the quality of life** based on secondary endpoints evaluated at 3 months in the C301 study (hot flushes, mood swings, anxiety, sleep, joint pain, skin & hair quality, libido,…). For C302 study, results for secondary endpoints at 3 months and 12 months are expected end 2022.

Donesta® has the potential to target menopausal symptoms beyond VMS – additional clinical studies

Clinical Phase	Primary Endpoint	Secondary Endpoint
Phase 3	E4 effect on reducing Vaso-Motor Symptom frequency / severity, H & NH* women	Effect on lipids, glucose metabolism, hemostasis parameters, breast density endometrial safety, health-related quality of life, treatment satisfaction and vulvar and vulvo-vaginal atrophy
Phase 3	E4 effect on improvement of vulvo-Vaginal Atrophy	Effect on various aspects of Female Sexual and Urogenital Functions
Phase 2	Effect of E4 on skin health, quality and appearance	Effect of E4 on quality of life and various skin-related endpoints
Phase 2	Effect of E4 on hair texture, quality and appearance	Effect of E4 on quality of life and various hair-related endpoints

*Hysterectomized and non-hysterectomized

Donesta® : expected timeline

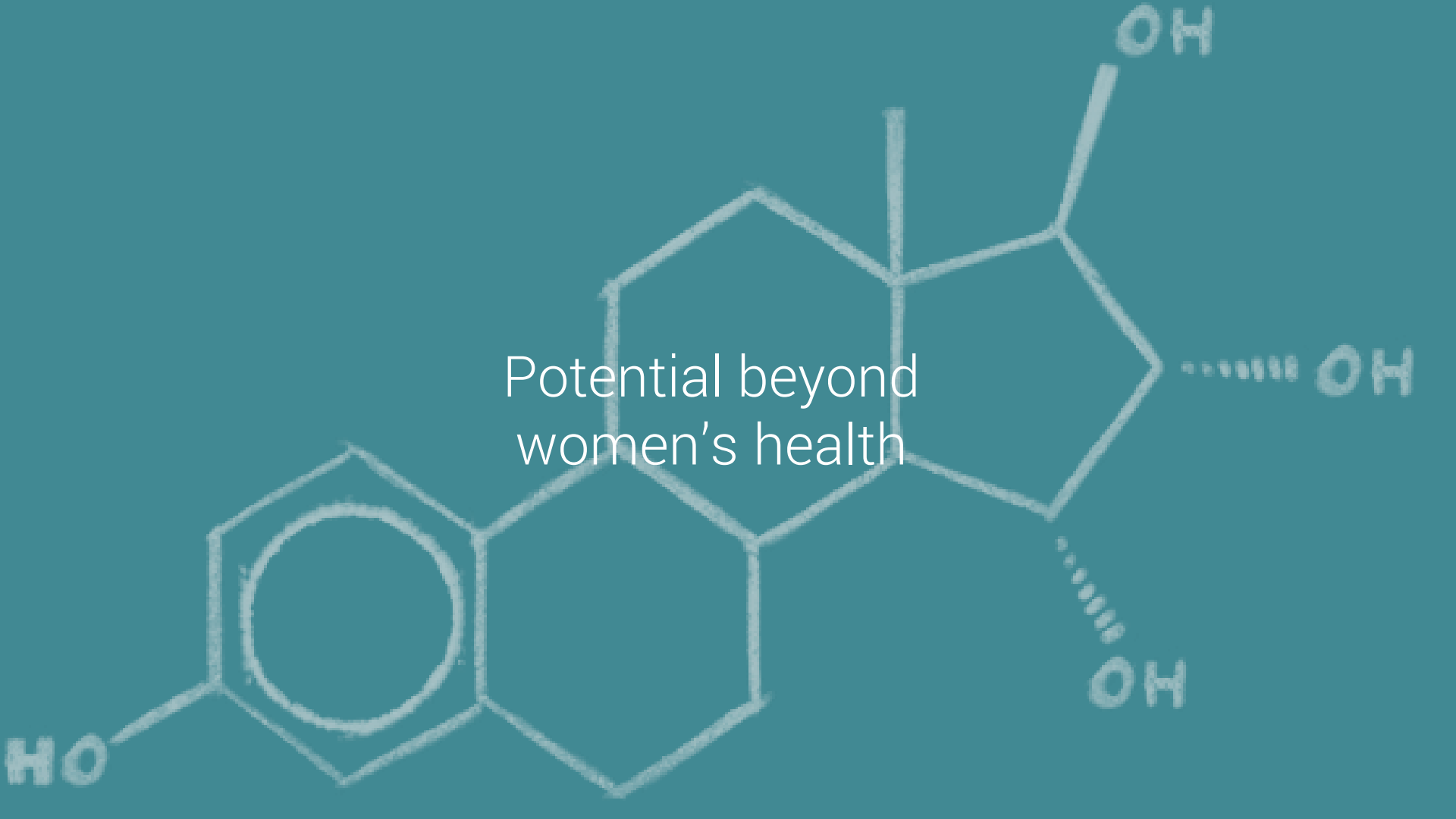


1. Depending on regulatory agencies' feedback

Donesta®'s potential

- Positive impact of Donesta® on women's quality of life (hot flushes, mood swings, anxiety, sleep, joint pain, skin & hair quality, libido,…).

- If approved, Donesta® should disrupt the menopause market being the first native hormone therapy for menopausal women with:
    - Improved benefit/risk profile compared to other estrogens;
    - Potential to address the broad range menopause symptoms in both hysterectomized and non-hysterectomized (NH) menopausal women;
    - Oral once per day;
    - Potential for treating symptoms through the duration of menopause.



Potential beyond women's health

E4 in neuroprotection and wound healing

Additional promising solutions beyond women's health

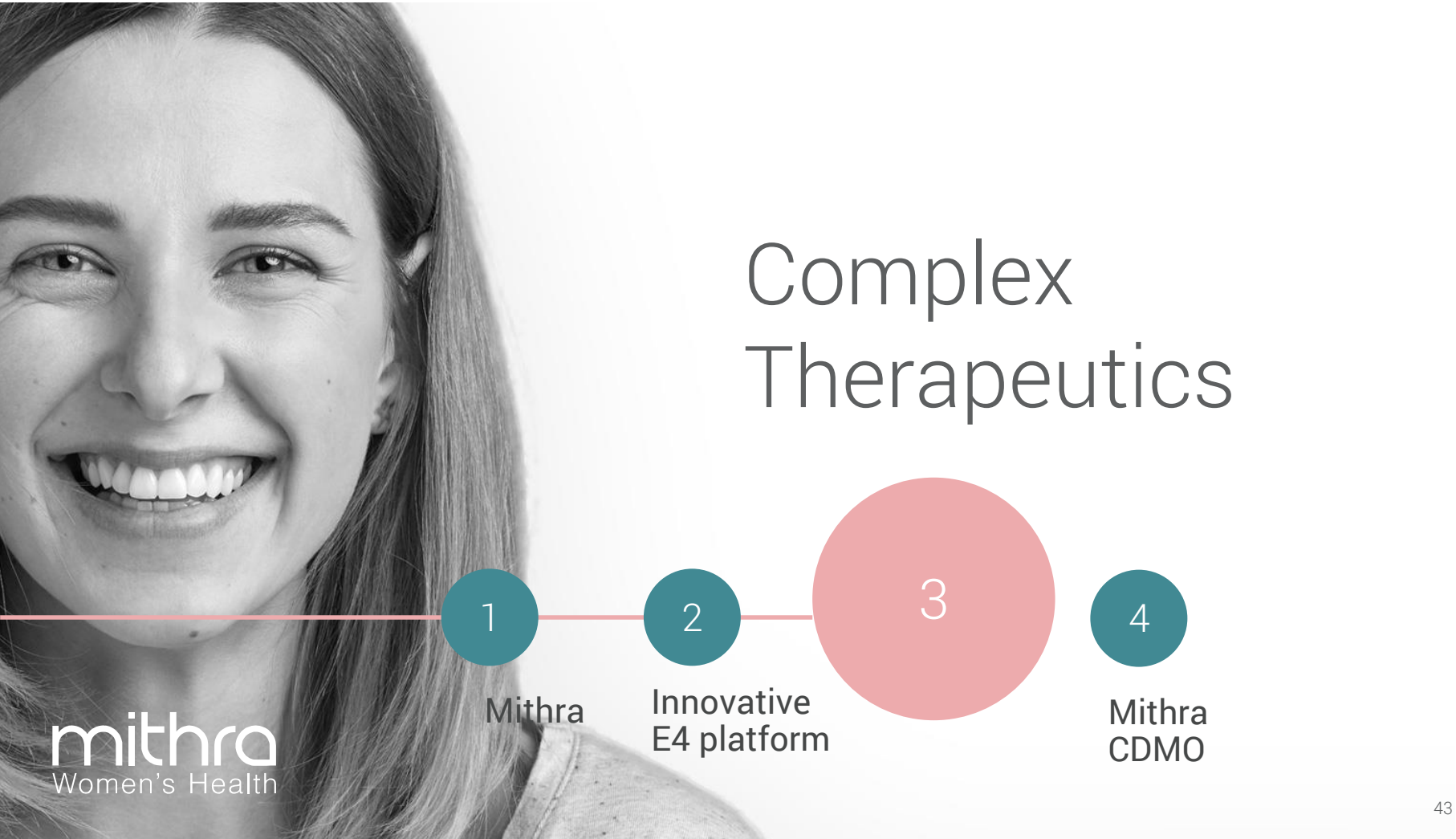
	Neonatal Encephalopathy (NE)	Wound Healing
Key Value Proposition	Add-on therapy to hypothermia to reduce the incidence of death or neurodevelopmental impairment at 24 months of age	1st E4 treatment for wound healing to promote faster and more effective healing
Affected Population	Newborns (> 36 weeks)	Adult males and females
Status	Preclinical stage EMA & FDA ODD granted	Pre clinical + formulation

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 in 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: PK in healthy adult population should start in H1 2022 – results expected end 2022

E4 for wound healing

- Current SoC entails compression, wound dressings and invasive treatment
- No EMA-approved drugs for advanced wound healing
- Mithra is developing an E4-based product enabling faster and more effective healing
- Programme starting with clinical PoC 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 as market extension
- Status: Non-clinical investigations and formulation development to be finalized before moving to clinical trial



Complex Therapeutics

1 Mithra

2 Innovative E4 platform

3

4 Mithra CDMO

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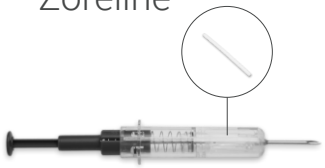
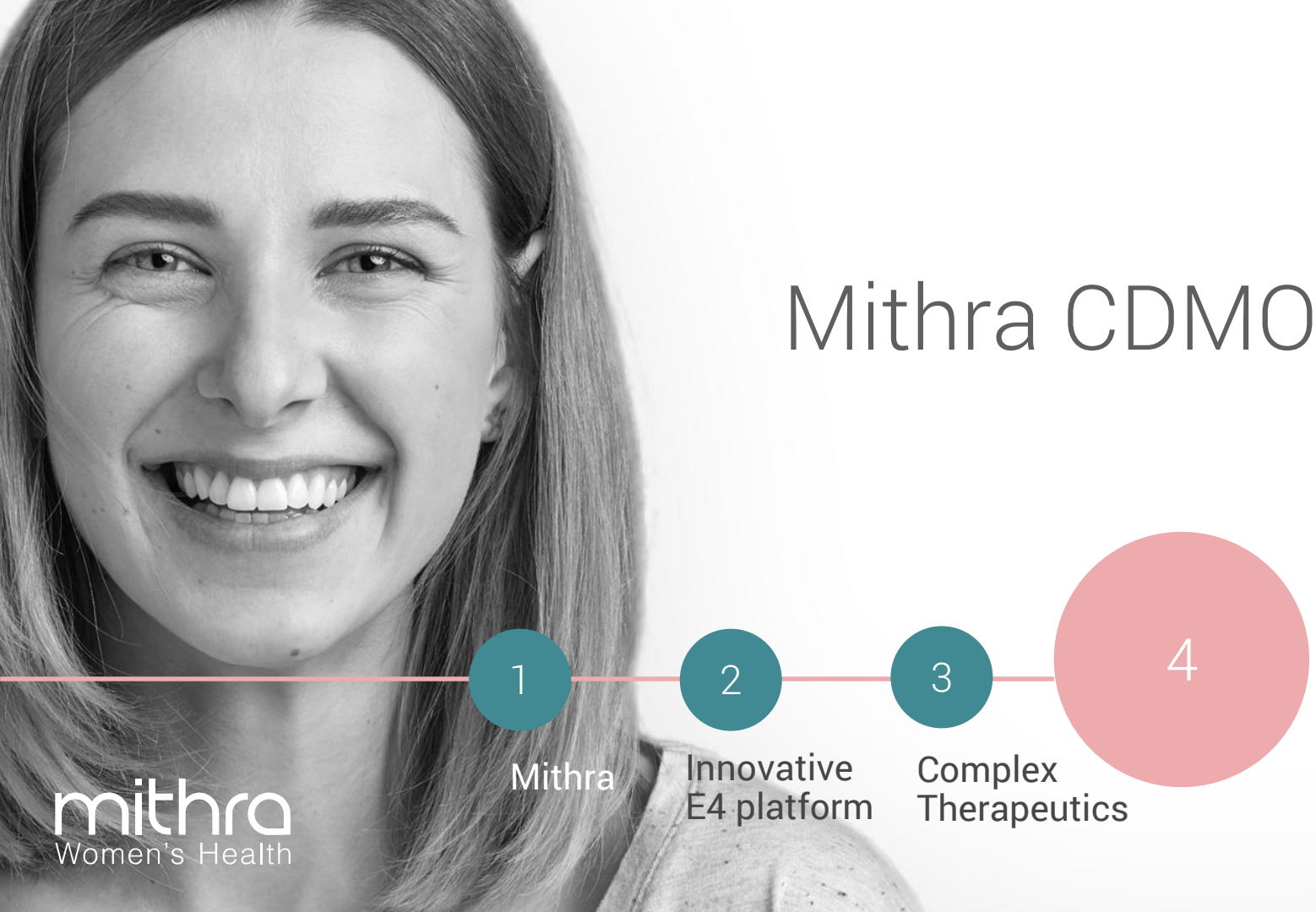
Women's Health

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 : H2 2022
Zoreline® 	Biodegradable SQ implant (goserelin)	For prostate & breast cancer and benign gynecological indications	Circa $700m Original product: Zoladex® from AstraZeneca	New formulations are being assessed on animals
Tibelia® 	Therapeutic solution for HT Composed of tibolone (synthetic steroid)	Menopause	Circa $126m Original product: Livial® from Merck	Launched



Mithra CDMO

1 Mithra

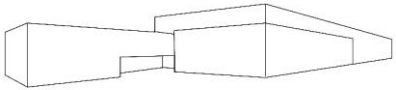
2 Innovative E4 platform

3 Complex Therapeutics

4

mithra 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
- Ability to handle high potent and complex developments

Contact us

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