A new class of oral GnRH antagonists for the treatment of endometriosis and uterine leiomyomas

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- Dosing
- Safety considerations
- Addressing the contraception during tx
- Long-term treatment considerations
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Overview

Discoveries of GnRH production of the brain

The Nobel Prize in Physiology or Medicine 1977

"for their discoveries concerning the peptide hormone production of the brain"

"for the development of radioimmunoassays of peptide hormones"

Roger Guillemin

1/4 of the prize

USA

The Salk Institute
San Diego, CA, USA

b. 1924
(in Dijon, France)

Andrew V. Schally

1/4 of the prize

USA

Veterans Administration Hospital
New Orleans, LA, USA

b. 1926
(in Wilno, Poland)

Rosalyn Yalow

1/2 of the prize

USA

Veterans Administration Hospital
Bronx, NY, USA

b. 1921

Hypothalamus-pituitary-gonadal axis

Box 1 | Applications of HPG axis hormone analogues

Gonadal function
- Female and male contraception
- Female and male infertility induction of ovulation for IVF
- Delayed puberty
- Precocious puberty
- Hypothalamic amenorrhoea

Sex steroid-dependent reproductive diseases

Male
- Prostate cancer
- Benign prostatic hyperplasia

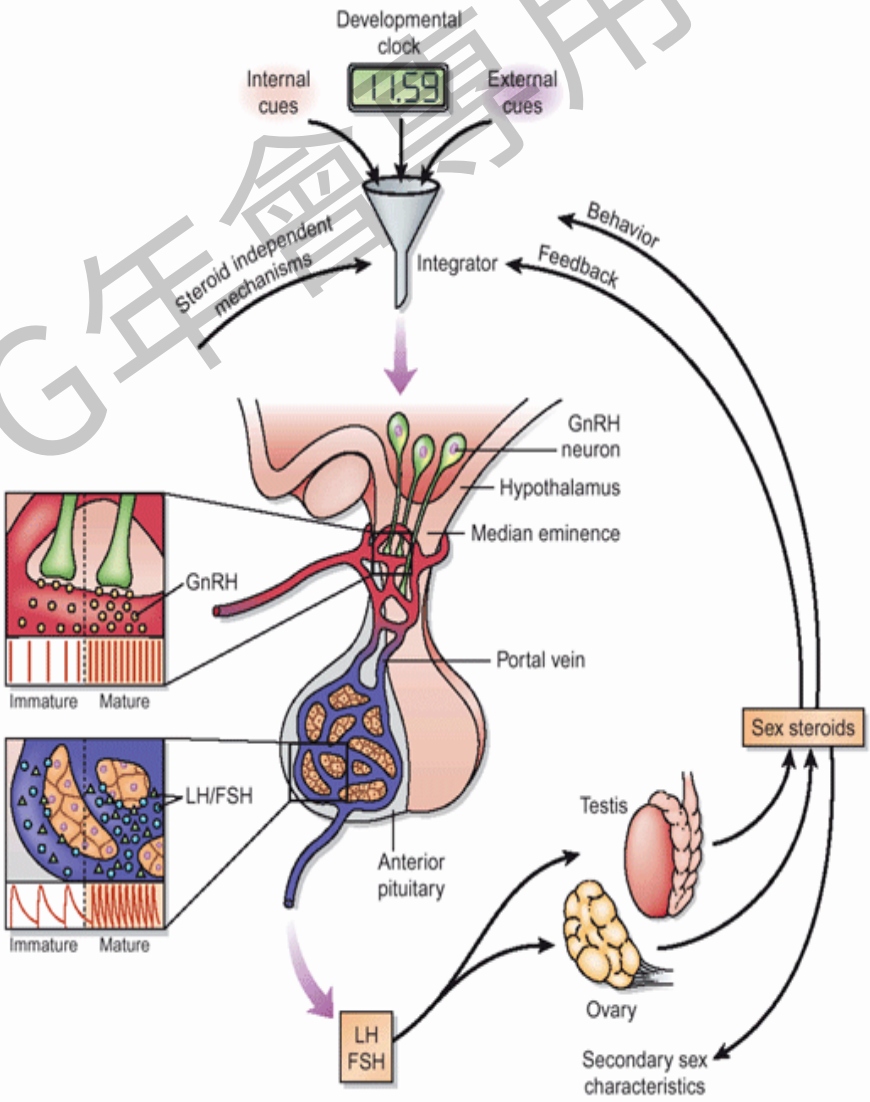
Female
- Endometriosis
- Uterine fibroids
- Polycystic ovary syndrome
- Breast cancer
- Ovarian cancer

Muscle and bone
- Bone loss (osteoporosis)
- Muscle loss in ageing and catabolic states

Brain
- Cognitive function
- Senile dementia and Alzheimer disease

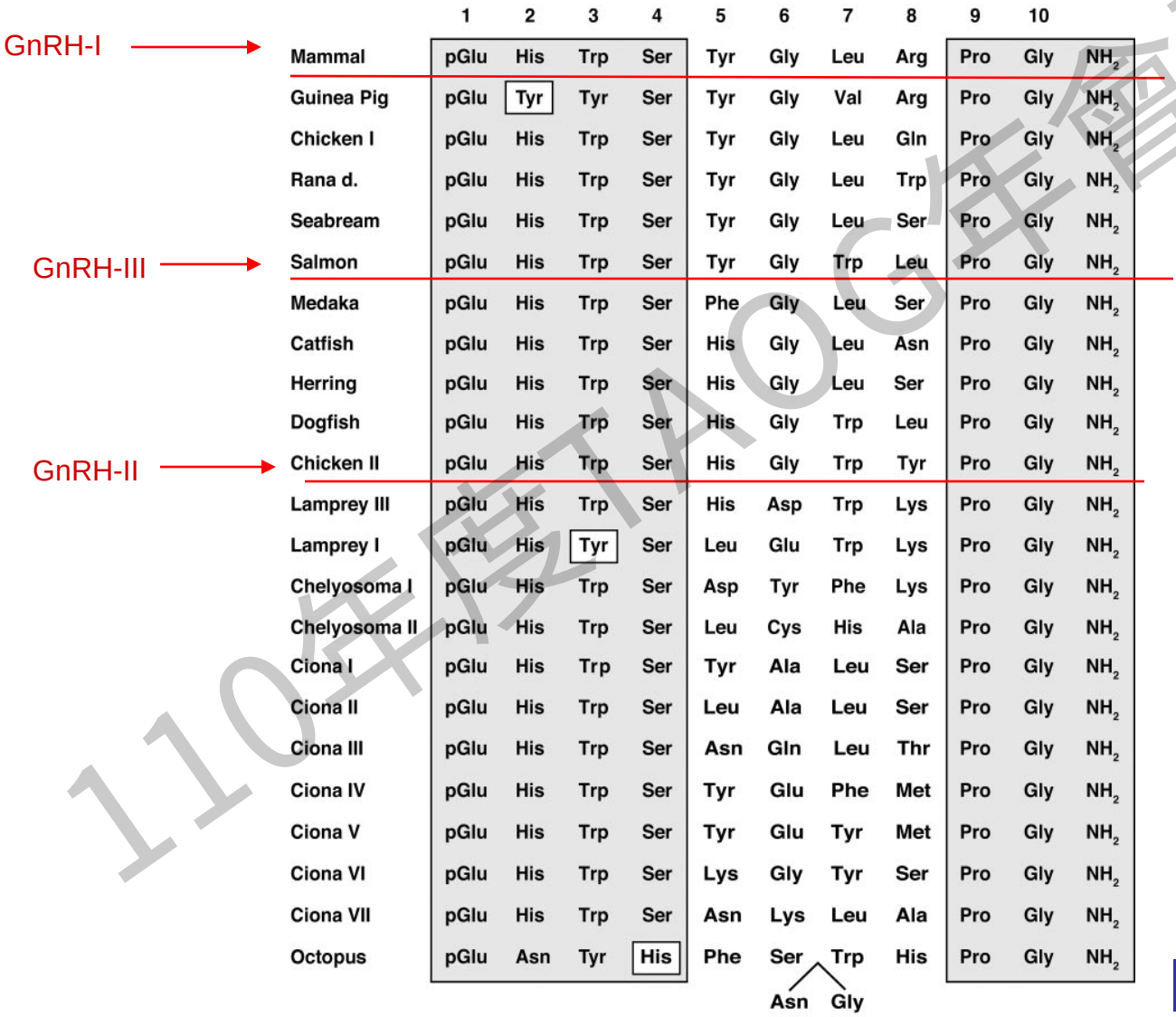
Metabolism
- Obesity
- Hypogonadism in diabetes mellitus
- Reduced lean body mass in ageing

Abbreviations: HPG, hypothalamic–pituitary–gonadal; IVF, *in vitro* fertilization.



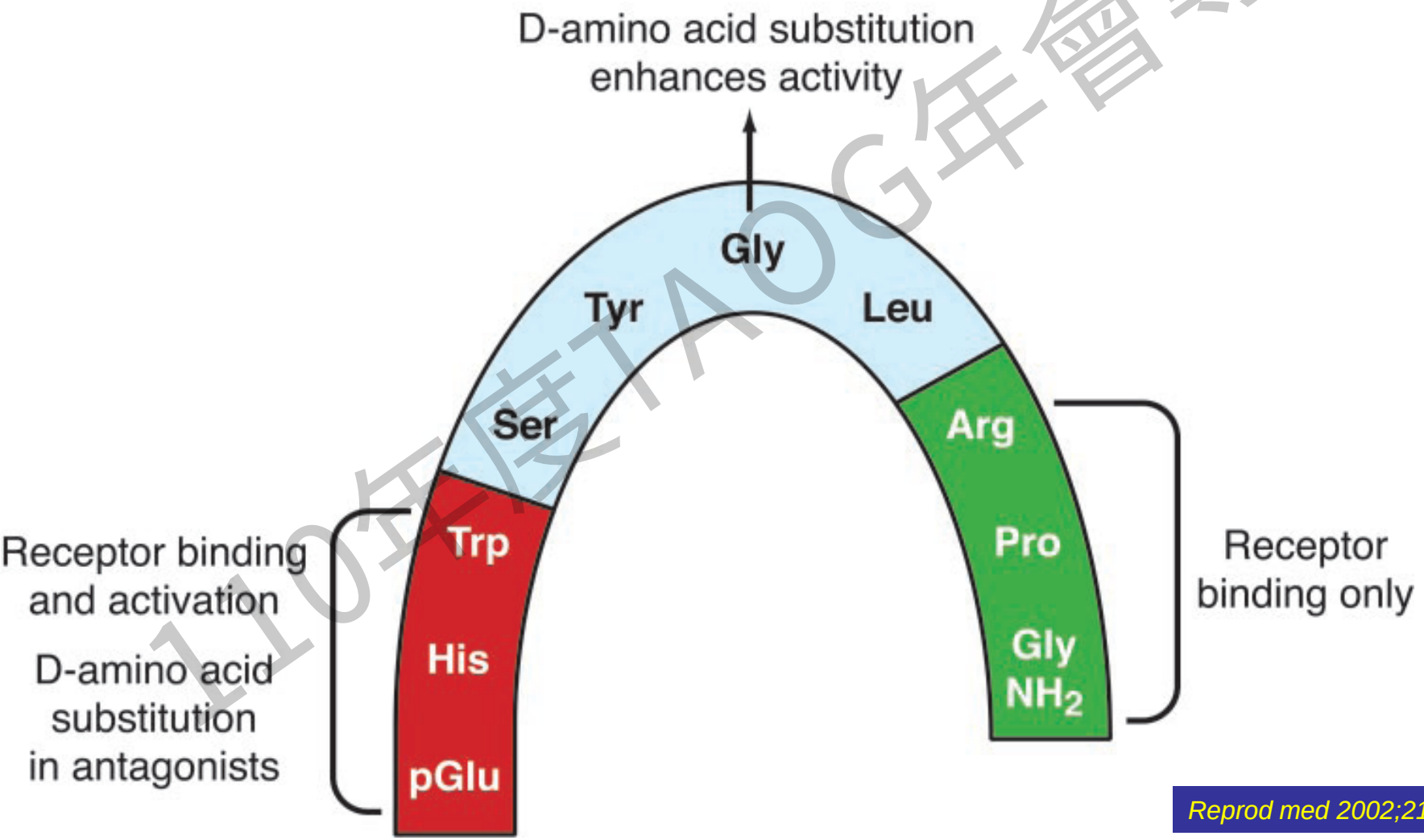
Endocr Rev 2004;25:235-275

Amino acid sequences of natural GnRH



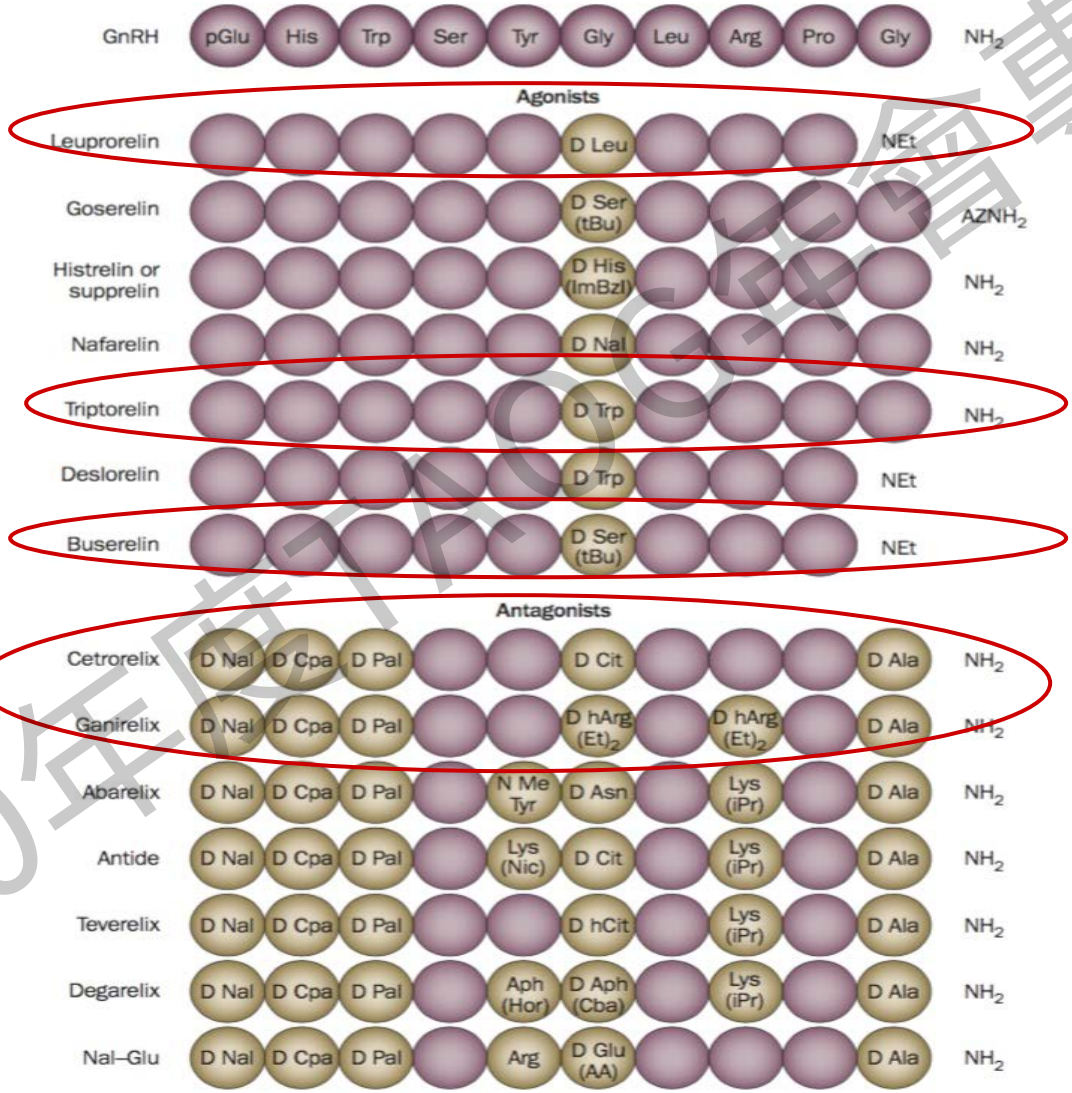
Endocr Rev 2004;25:235-275

The folded conformation of GnRH



Reprod med 2002;21:199-224

GnRH analogs



Endocr Rev 2004;25:235-275

Nonpeptide GnRH antagonists

First nonpeptide GnRH antagonist

J Med Chem. 1998 Oct 22;41(22):4190-5. doi: 10.1021/jm9803673.

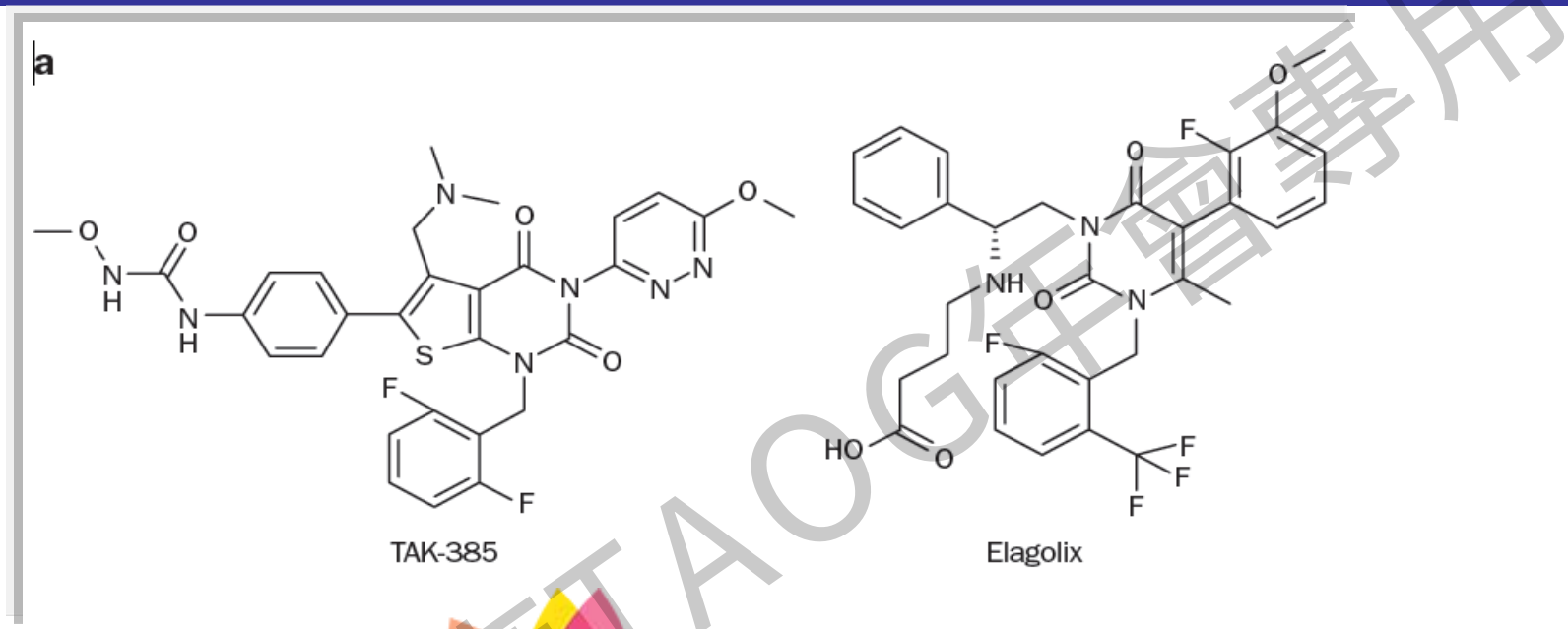
Discovery of a novel, potent, and orally active nonpeptide antagonist of the human luteinizing hormone-releasing hormone (LHRH) receptor

N Cho [1], M Harada, T Imaeda, T Imada, H Matsumoto, Y Hayase, S Sasaki, S Furuya, N Suzuki, S Okubo, K Ogi, S Endo, H Onda, M Fujino

Affiliations + expand

PMID: 9784092 DOI: 10.1021/jm9803673

Nonpeptide GnRH antagonist



Orilissa™

elagolix tablets 150 mg 200 mg

Nonpeptide GnRH antagonists

- Overcome the requirement of **injection** of peptide antagonists.
- Provide the potential for titrating the dose to accomplish **partial inhibition** of sex steroid hormones, which cannot be achieved with injectable peptide antagonists.

Drugs (2018) 78:1501–1508

Nonpeptide GnRH antagonists

- **Partial inhibition** is desirable in certain hormone-dependent diseases, such as **endometriosis** and **benign prostatic hyperplasia**, to ameliorate the pathology without inducing the unwanted adverse effects resulting from total gonadal steroid inhibition, such as **bone loss and hot flushes.**

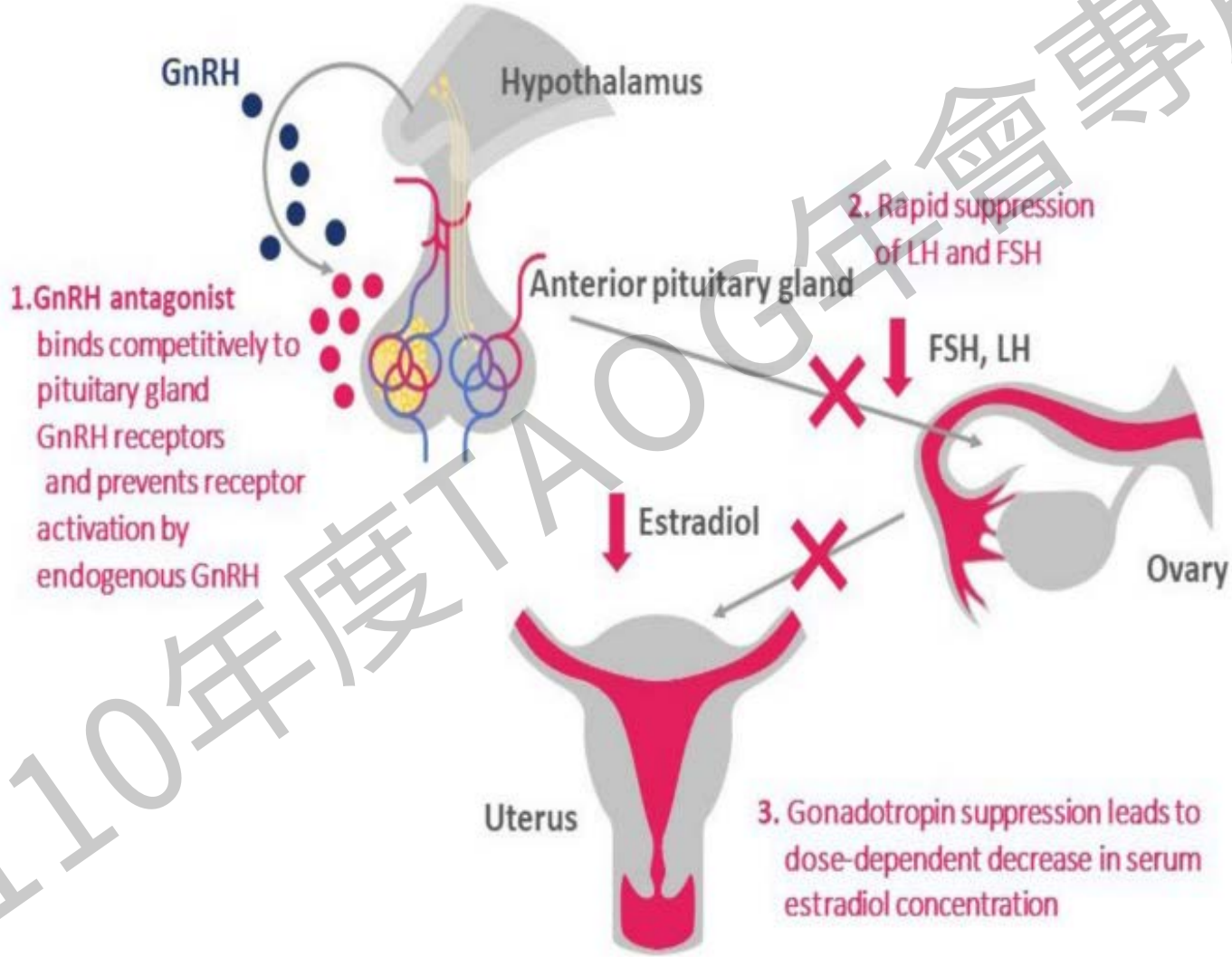
Drugs (2018) 78:1501–1508

Pharmacodynamics

- Maximum E2 suppression was achieved with regimen starting from 200 mg twice daily or higher
- LH suppression was more noticeable than FSH in all groups except for the 150 mg once daily group
- Upon discontinuation, LH, FSH, and E2 levels rise within 24 h (future fertility)

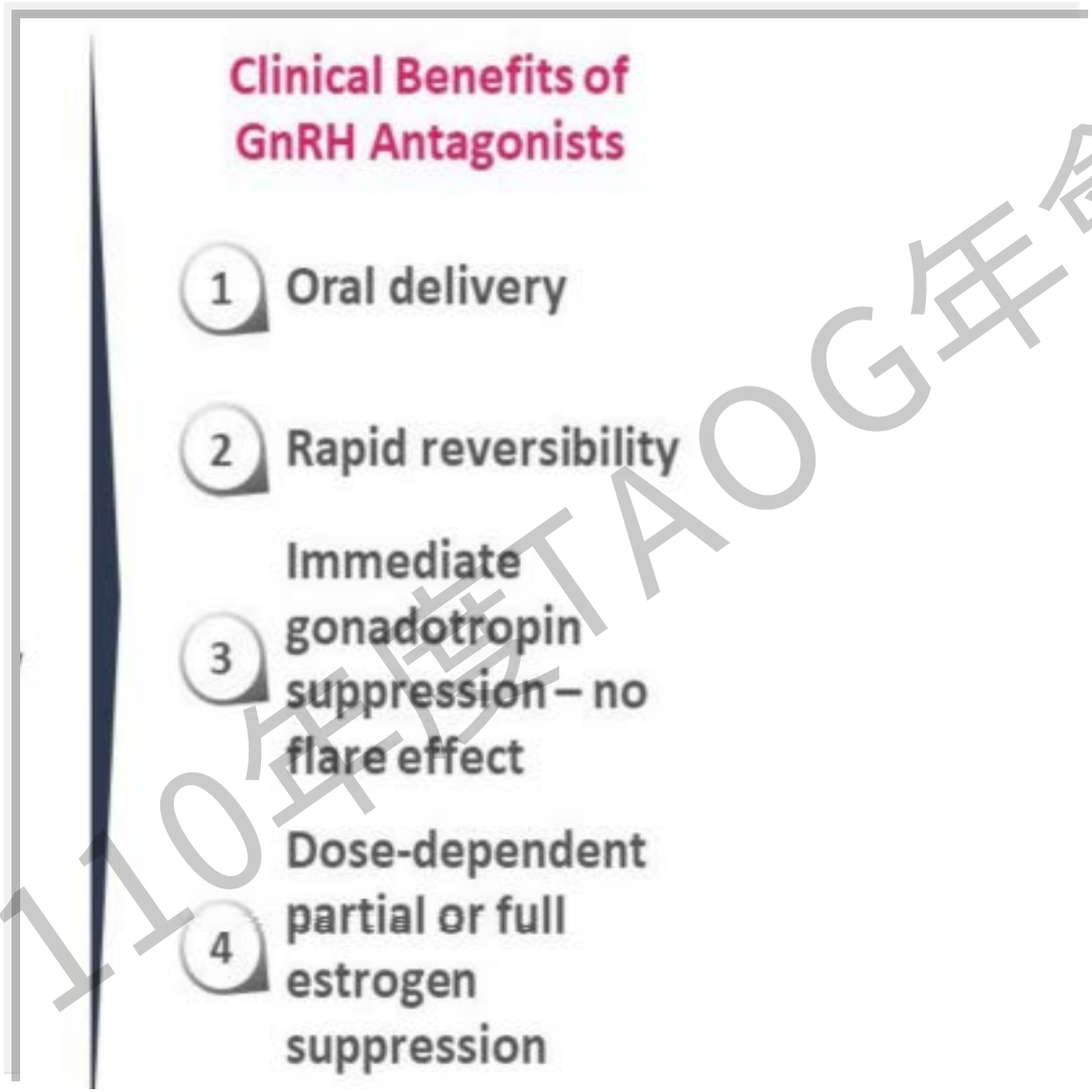
Drugs (2018) 78:1501–1508

GnRH antagonist mechanism of action



J. Clin. Med. 2021, 10, 1085

Clinical benefits of oral nonpeptide GnRH derivatives



J. Clin. Med. 2021, 10, 1085

Expected estradiol (E2) levels

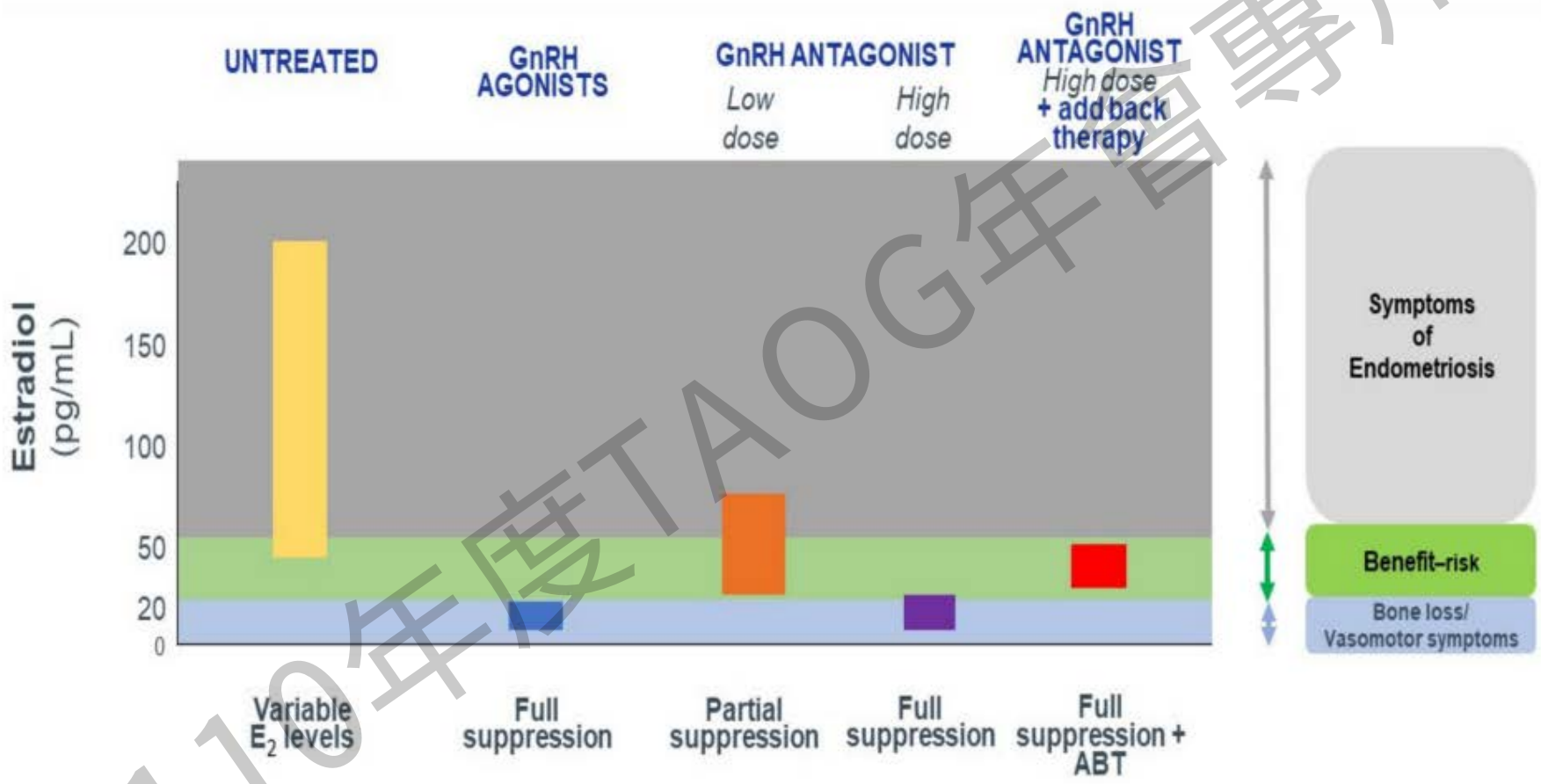
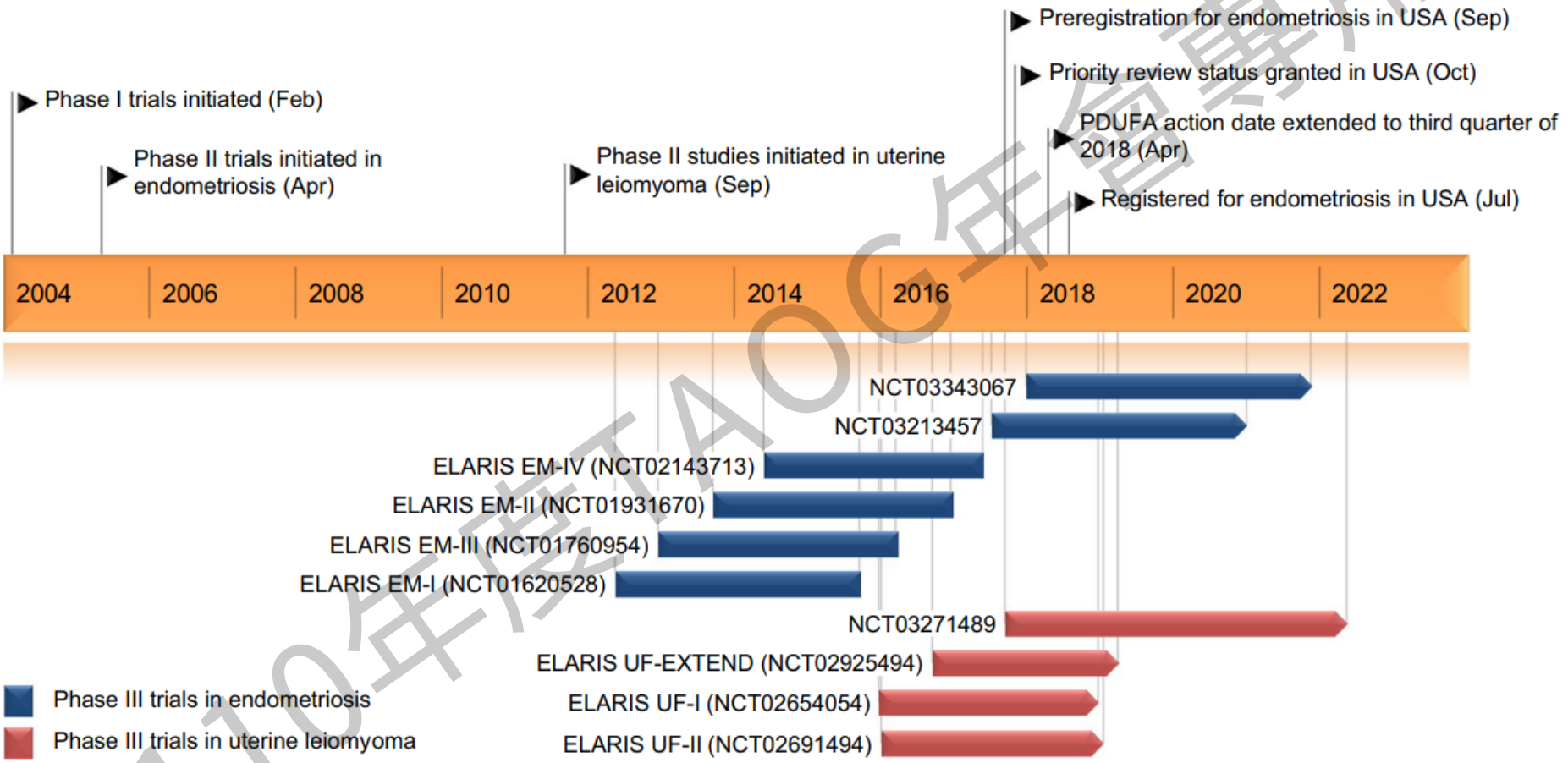


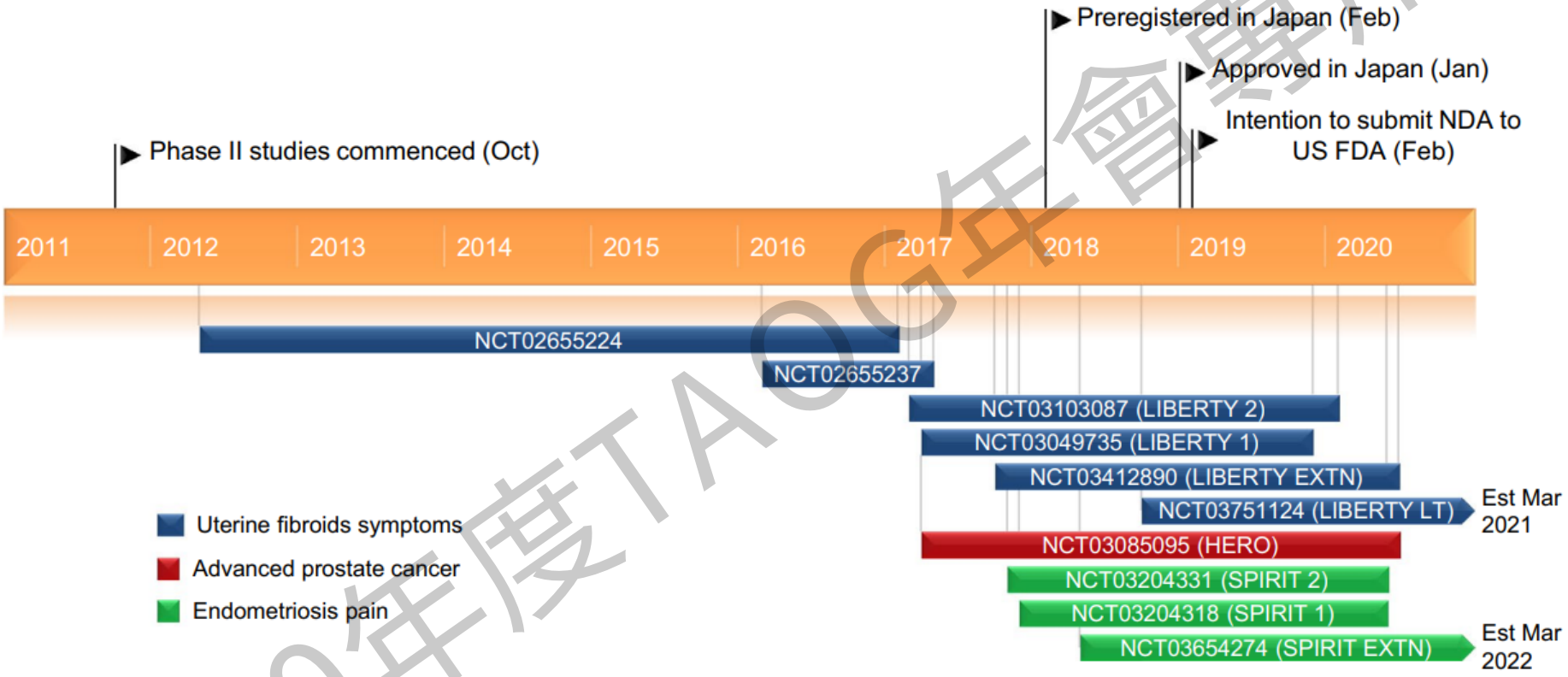
Figure 2. Expected estradiol (E2) levels during the menstrual cycle, under GnRH agonist and under GnRH antagonist therapy without and with add-back therapy (ABT).

Key milestones in the development of oral nonpeptide GnRH derivatives



Key milestones in the development of elagolix, leading to its first global approval in endometriosis. *PDUFA* Prescription Drug User Fee Act

Key milestones in the development of relugolix



Key milestones in the development of relugolix for the treatment symptoms associated with uterine fibroids, with the focus on phase III studies. *EXTN* extension, *LT* long-term, *NDA* new drug application

Drugs (2019) 79:675–679

Current indications and applications on oral nonpeptide GnRH derivatives

Table 4

Current indications and applications on oral non-peptide GnRH derivatives.

Regimen	Indications	Reference
Elagolix	Moderate to severe pain related to endometriosis.	1. Lamb (2018)
	Management of abnormal uterine bleeding related to uterine fibroids.	2. Schlaff et al. (2020)
Relugolix	Treatment of pain symptoms associated with uterine fibroids.	1. Osuga et al. (2019)
	Heavy menstrual bleeding associated with uterine fibroids	2. Osuga et al. (2019)
Linzagolix	Management of heavy menstrual bleeding related to uterine fibroids.	Pohl et al. (2020)
	Treatment of endometriosis-associated pain.	

Front Neuroendocrinol. 2021 Jan;60:100876.

Pharmacokinetics of elagolix

Table 1. Pharmacokinetic properties of elagolix in healthy subjects.

Absorption	
T_{max} (h)	1.5(1.0–4.0)
Effect of Food	
High-fat meal (826kcal, 52% fat, relative to fasting)	AUC: ↓25%, C_{max}: ↓36%
Distribution	
% Bound to human plasma proteins	80
Blood-to-plasma ratio	0.6
Metabolism	CYP3A (major)Minor pathways include: CYP2D6, CYP2C8, and uridine glucuronosyl transferases (UGTs)
Elimination	
Major route of elimination	Hepatic metabolism
Terminal phase elimination half-life ($t_{1/2}$) (h)	5.9 ± 2.1
% of dose excreted in urine	<3
% of dose excreted in feces	90

Expert Rev Clin Pharmacol. 2021 Apr;14(4):427-437

Pharmacokinetics of relugolix

Features and properties of relugolix	
Alternative names	Relumina, RVT 601, TAK-385
Class	Analgesics, antineoplastics, fluorobenzenes, ketones, pyridazines, pyrimidines, small molecules, thiophenes, urea compounds
Mechanism of action	LHRH receptor antagonists
Route of administration	PO
Pharmacodynamics	GnRH receptor antagonist (IC_{50} of 0.12 nmol/L against GnRH agonist ^{125}I-leuprorelin acetate)
Pharmacokinetics	C_{max} 29.05 ng/mL, t_{max} 1.5 h $AUC_{0-\infty}$ 139.1 ng·h/mL, and $t_{½}$ 45.42 h after a single 40 mg oral dose
Adverse events	
Most frequent	Metrorrhagia, hot flush, viral upper respiratory tract infection, menorrhagia headache, bone density decreased/bone resorption increased
Occasional	Hyperhidrosis, dizziness, malaise, arthralgia, somnolence, genital haemorrhage
Rare	
ATC codes	
WHO ATC code	H01C-C (antigonadotropin-releasing hormones), L02 (endocrine therapy), N02B (other analgesics and antipyretics)
EphMRA ATC code	H1C3 (antigonadotropin-releasing hormones), L2 (cytostatic hormone therapy), N2 (analgesics)
Chemical name	1-[4-[1-(2,6-Difluorobenzyl)-5-[(dimethylamino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-6-yl]phenyl)-3-methoxyurea

Drugs (2019) 79:675–679

Candidates for treatment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist

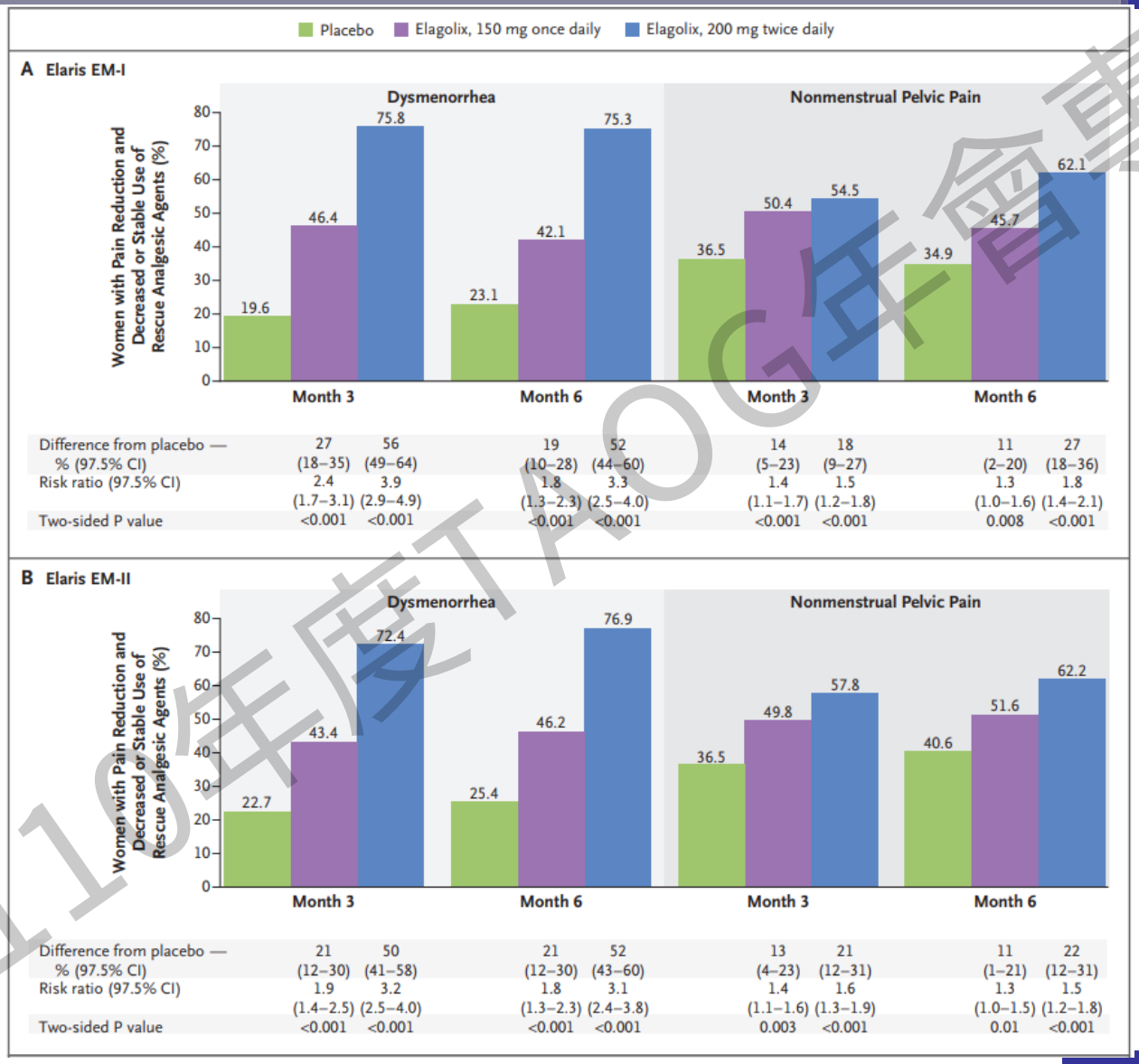
H.S. Taylor, L.C. Giudice, B.A. Lessey, M.S. Abrao, J. Kotarski, D.F. Archer, M.P. Diamond, E. Surrey, N.P. Johnson, N.B. Watts, J.C. Gallagher, J.A. Simon, B.R. Carr, W.P. Dmowski, N. Leyland, J.P. Rowan, W.R. Duan, J. Ng, B. Schwefel, J.W. Thomas, R.I. Jain, and K. Chwalisz

Objective: Multicenter, double□blind, randomized, placebo-controlled, phase 3 trials (Elaris Endometriosis I and II [EM-I and EM-II]) of 6-month treatment with elagolix at two doses in women with moderate or severe endometriosis-associated pain.

BACKGROUND

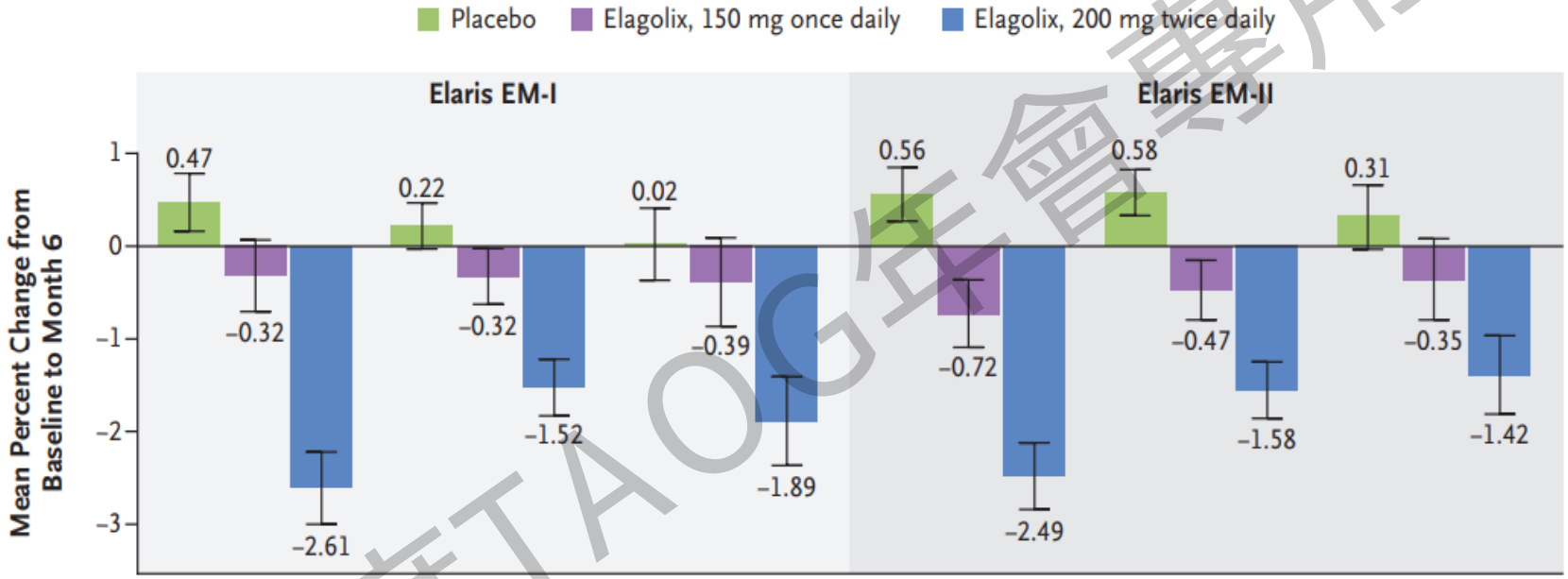
Interventions :To evaluate the effects of two doses of elagolix — 150 mg once daily (lower-dose group) and 200 mg twice daily (higher-dose group) — as compared with placebo in women with surgically diagnosed endometriosis and moderate or severe endometriosis-associated pain at 6 months.

Reduction in dysmenorrhea and nonmenstrual pelvic pain



N Engl J Med 2017;377:28

Mean change from baseline to month 6 in BMD



	Lumbar Spine			Total Hip			Femoral Neck			Lumbar Spine			Total Hip			Femoral Neck		
	**	***		**	***		NS	***		***	***		***	***		*	***	
Difference from placebo (%)	−0.79	−3.08		−0.54	−1.74		−0.41	−1.91		−1.28	−3.04		−1.05	−2.16		−0.66	−1.73	
95% CI, lower boundary	−1.29	−3.58		−0.93	−2.13		−1.02	−2.53		−1.75	−3.51		−1.46	−2.57		−1.23	−2.28	
95% CI, upper boundary	−0.30	−2.59		−0.15	−1.35		0.20	−1.29		−0.80	−2.58		−0.64	−1.76		−0.10	−1.17	
No. of women	282	186	182	280	185	182	280	185	182	271	174	183	271	172	182	271	172	182

Figure 2. Mean Percent Change from Baseline to Month 6 in Bone Mineral Density.

At 6 months, all the percent differences in bone mineral density between the elagolix groups and the placebo group were significant, except for the between-group difference at the femoral neck in Elaris EM-I. One asterisk indicates P<0.05, two asterisks P<0.01, three asterisks P<0.001, and NS not significant. The I bars indicate 95% confidence intervals.

N Engl J Med 2017;377:28

Conclusions

- Both higher and lower doses of elagolix were **effective** in improving dysmenorrhea and nonmenstrual pelvic pain during a 6-month period in women with endometriosis-associated pain.
- The two doses of elagolix were associated with **hypoestrogenic** adverse effects.

Relugolix, an oral gonadotropin-releasing hormone receptor antagonist, reduces endometriosis-associated pain in a dose–response manner: a randomized, double-blind, placebo-controlled study

Yutaka Osuga, M.D., Ph.D.,[a] Yoshifumi Seki, M.Sc.,[b] Masataka Tanimoto, B.Pharm.,[b] Takeru Kusumoto, M.Sc.,[b] Kentarou Kudou, M.Sc.,[b] and Naoki Terakawa, M.D., Ph.D.[c]

Objective: To evaluate the efficacy and safety of three dose levels of relugolix compared with placebo and leuprorelin in women with endometriosis-associated pain.

Interventions :During a 12-week treatment period, patients received relugolix 10 mg (n = 103), 20 mg (n = 100), or 40 mg (n =103) as a daily oral dose; placebo (n =97) as a daily oral dose; or leuprorelin 3.75 mg (n = 80) as a monthly subcutaneous injection.

Intervention(s): During a 12-week treatment period, patients received relugolix 10 mg (n = 103), 20 mg (n = 100), or 40 mg (n = 103)

TABLE 1

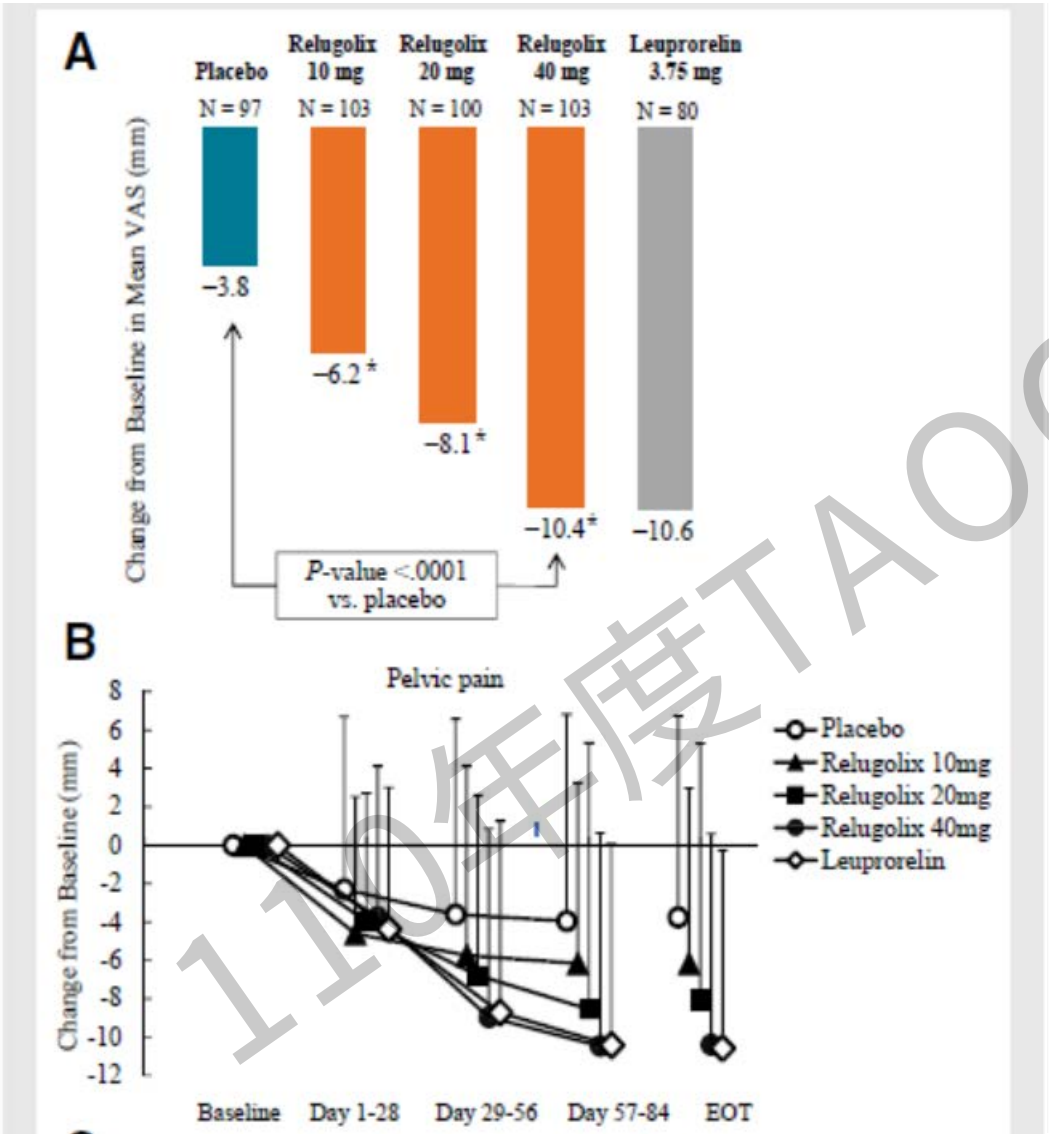
Demographic and baseline characteristics.

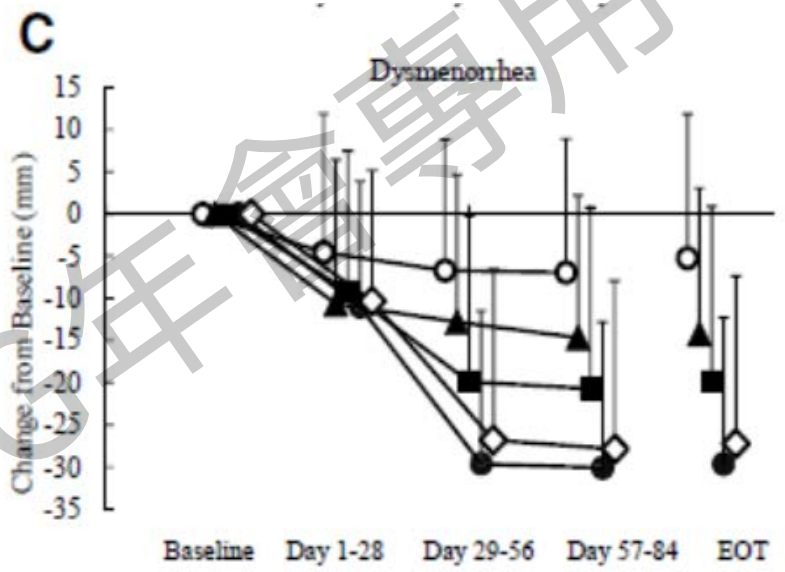
Characteristic	Relugolix 10 mg (n = 103)	Relugolix 20 mg (n = 100)	Relugolix 40 mg (n = 103)	Leuprorelin 3.75 mg (n = 82)	Placebo (n = 99)
Age (y)	35.3 (6.2)	35.1 (6.8)	35.6 (6.0)	36.1 (6.1)	35.7 (6.1)
BMI, kg/m^2	103	100	103	81	97
	21.5 (3.3)	20.4 (2.5)	21.6 (3.1)	21.8 (3.4)	21.1 (3.0)
Disease duration (y)	3.8 (5.0)	3.2 (3.8)	4.3 (5.5)	2.9 (3.8)	3.9 (4.7)
VAS score, mm					
Pelvic pain	103	100	103	81	97
	14.6 (12.0)	15.6 (15.1)	15.3 (12.0)	15.2 (15.1)	15.6 (14.3)
Dysmenorrhea	103	100	103	81	97
	28.2 (17.6)	27.7 (18.9)	30.4 (17.0)	27.1 (19. 8)	28.4 (16.6)
Dyspareunia	46	47	44	26	41
	8.8 (14.2)	12.5 (16.5)	9.4 (15.4)	9.5 (10.7)	11.0 (14.2)
M-B&B score					
Pelvic pain	103	100	103	81	97
	0.66 (0.46)	0.63 (0.47)	0.65 (0.44)	0.68 (0.55)	0.65 (0.45)
Dysmenorrhea	103	100	103	81	97
	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	1.2 (0.4)
Deep dyspareunia	46	47	44	26	41
	0.56 (0.60)	0.64 (0.55)	0.55 (0.48)	0.60 (0.45)	0.55 (0.45)
EHP-30 score	103	100	103	81	97
Pain	28.6 (21.8)	26.7 (18.6)	28.9 (20.1)	26.5 (19.6)	24.8 (20.0)
Control and powerlessness	27.4 (23.0)	28.6 (22.5)	25.9 (21.2)	27.8 (22.9)	25.8 (20.8)
Emotional well-being	21.8 (20.1)	23.8 (19.3)	20.4 (17.5)	21.2 (19.1)	23.0 (20.0)
Social support	16.5 (17.7)	20.0 (20.6)	15.7 (18.7)	17.1 (20.3)	17.7 (20.0)
Self-image	15.9 (16.7)	15.7 (18.1)	15.0 (18.7)	16.3 (21.9)	19.4 (22.2)
Proportion of days with analgesic use (%)	103	100	103	81	97
	12.5 (12.3)	13.3 (16.4)	12.0 (14.5)	11.6 (13.8)	10.0 (11.5)
Amount score of bleeding	103	100	103	81	97
	2.3 (0.5)	2.3 (0.6)	2.4 (0.5)	2.4 (0.6)	2.3 (0.5)

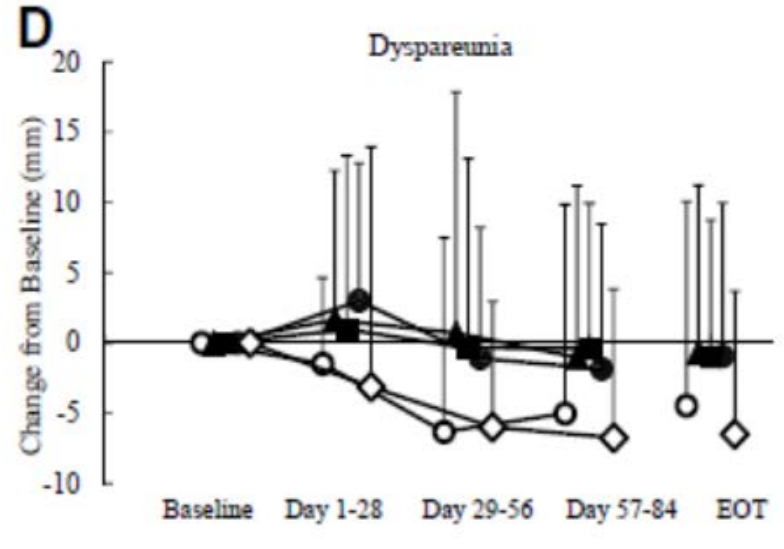
Note: Data presented as mean (standard deviation) or n, unless stated otherwise. BMI = body mass index; EHP-30 = Endometriosis Health Profile-30; M-B&B score = Modified Biberoglu and Behrman score; VAS = visual analog scale.

Osuga. Relugolix for endometriosis pain. Fertil Steril 2020.

Mean change from baseline in the visual analog scale score







Fertility and Sterility 2021 Vol. 115, No. 2, 0015-0282

Treatment-emergent adverse events

TABLE 2

Summary of treatment-emergent adverse events.

Variable	Relugolix 10 mg (n = 103)	Relugolix 20 mg (n = 100)	Relugolix 40 mg (n = 103)	Leuprorelin 3.75 mg (n = 80)	Placebo (n = 97)
TEAEs	205	232	280	238	165
Patients with any TEAEs	82 (79.6)	89 (89.0)	97 (94.2)	73 (91.3)	69 (71.1)
Patients with drug-related TEAEs	64 (62.1)	82 (82.0)	88 (85.4)	67 (83.8)	36 (37.1)
Intensity of TEAEs					
Mild	78 (75.7)	80 (80.0)	88 (85.4)	63 (78.8)	63 (64.9)
Moderate	4 (3.9)	9 (9.0)	9 (8.7)	10 (12.5)	5 (5.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
TEAEs leading to study drug discontinuation	1 (1.0)	5 (5.0)	1 (1.0)	3 (3.8)	1 (1.0)
Serious TEAEs	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	3 (3.1)
TEAEs occurring in ≥10% of patients in any treatment group					
Nasopharyngitis	21 (20.4)	19 (19.0)	22 (21.4)	15 (18.8)	21 (21.6)
Headache	4 (3.9)	11 (11.0)	6 (5.8)	8 (10.0)	9 (9.3)
Metrorrhagia	26 (25.2)	30 (30.0)	25 (24.3)	32 (40.0)	4 (4.1)
Menorrhagia	7 (6.8)	14 (14.0)	13 (12.6)	9 (11.3)	4 (4.1)
Irregular menstruation	16 (15.5)	19 (19.0)	3 (2.9)	5 (6.3)	4 (4.1)
Genital hemorrhage	3 (2.9)	4 (4.0)	5 (4.9)	8 (10.0)	1 (1.0)
Hyperhidrosis	3 (2.9)	10 (10.0)	10 (9.7)	7 (8.8)	1 (1.0)
Hot flush	9 (8.7)	19 (19.0)	54 (52.4)	33 (41.3)	8 (8.2)

Note: Data present as n or n (%), unless stated otherwise. TEAE = treatment-emergent adverse event.

Osuga. Relugolix for endometriosis pain. Fertil Steril 2020.

Conclusions

- Oral administration of relugolix alleviated **endometriosis-associated pain** in a dose–response manner.
- Relugolix 40 mg demonstrated efficacy and safety comparable with those of leuprorelin.

GYNECOLOGY

Predictors of response for elagolix with add-back therapy in women with heavy menstrual bleeding associated with uterine fibroids

Ayman Al-Hendy, MD, PhD; Linda Bradley, MD; Charlotte D. Owens, MD; Hui Wang, PhD; Kurt T. Barnhart, MD; Eve Feinberg, MD; William D. Schlaff, MD; Elizabeth E. Puscheck, MD; Alice Wang, MA; Veronica Gillispie, MD; Sandra Hurtado, MD; Ozgul Muneyyirci-Delale, MD; David F. Archer, MD; Bruce R. Carr, MD; James A. Simon, MD; Elizabeth A. Stewart, MD

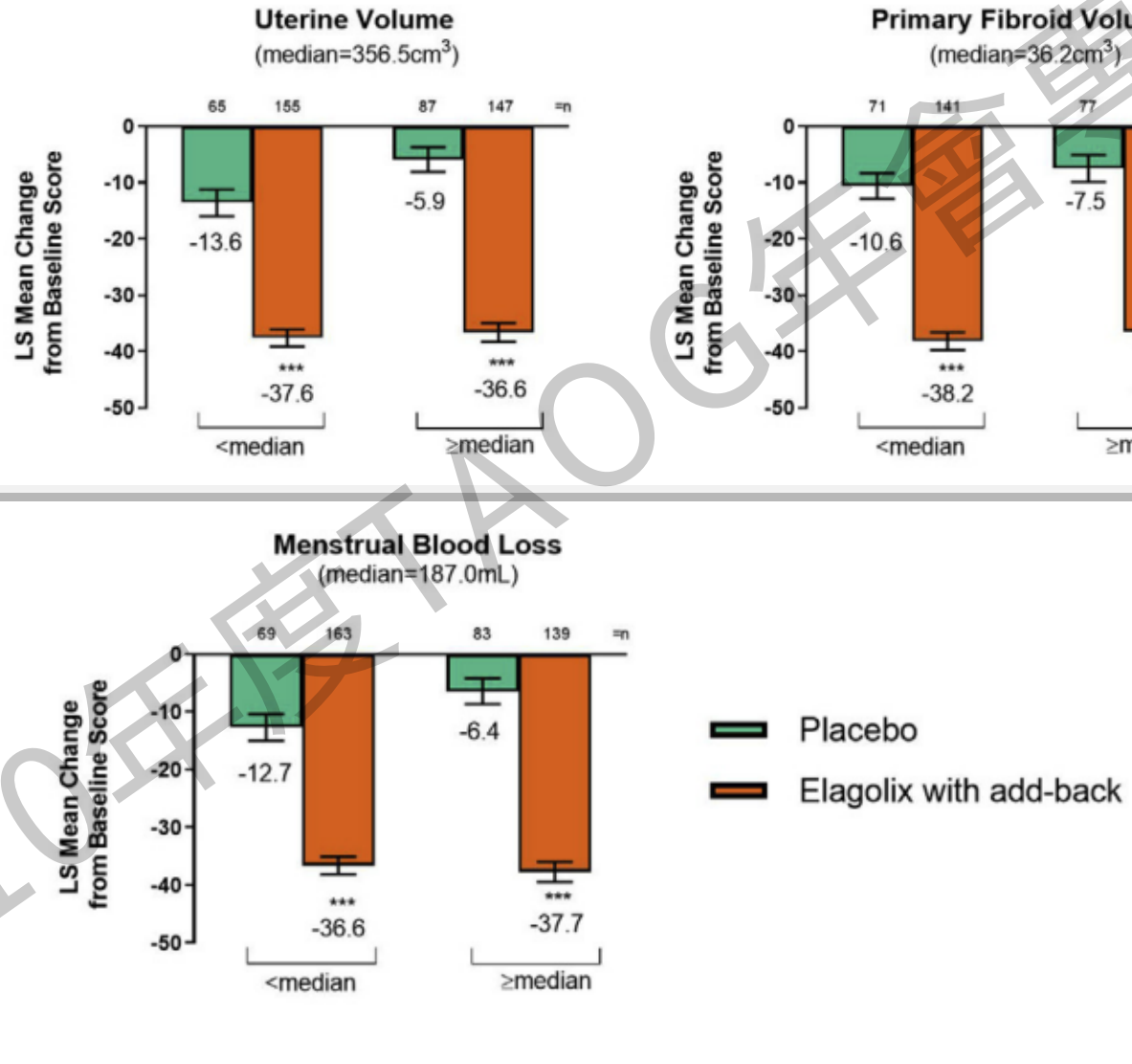
BACKGROUND: Uterine fibroids are one of the most common neoplasms found among women globally, with a prevalence of approximately 11 million women in the United States alone. The morbidity of this common disease is significant because it is the leading cause of hysterectomy and causes significant functional impairment for women of reproductive age.

menstrual blood loss during the final month and ≥50% menstrual blood loss reduction from baseline to final month. Secondary and other efficacy endpoints included mean change in menstrual blood loss from baseline to final month, amenorrhea, symptom severity, and health-related quality of life. Adverse events and other safety endpoints were monitored.

Objective: To evaluate the safety and efficacy of elagolix (300 mg twice a day) with add-back therapy (1 mg estradiol/0.5 mg norethindrone acetate once a day) in reducing heavy menstrual bleeding associated with uterine fibroids over 6 months of treatment.

Am J Obstet Gynecol 2021;224:72.e1-50

Mean changes in UFS-QOL scores



Am J Obstet Gynecol 2021;224:72.e1-50

Conclusions

- Elagolix with hormonal add-back therapy was effectiv in reducing heavy **AUB associated with uterine fibroid** independent of age, body mass index, race, ethnicity, baseline menstrual blood loss, fibroid location, and uterine and primary fibroid volume.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Uterine Fibroid Symptoms with Relugolix Combination Therapy

Ayman Al-Hendy, M.D., Ph.D., Andrea S. Lukes, M.D., Alfred N. Poindexter III, M.D., Roberta Venturella, M.D., Ph.D., Claudio Villarroel, M.D., Hilary O.D. Critchley, M.D., Yulan Li, Ph.D., Laura McKain, M.D., Juan C. Arjona Ferreira, M.D., Andria G.M. Langenberg, M.D., Rachel B. Wagman, M.D., and Elizabeth A. Stewart, M.D.

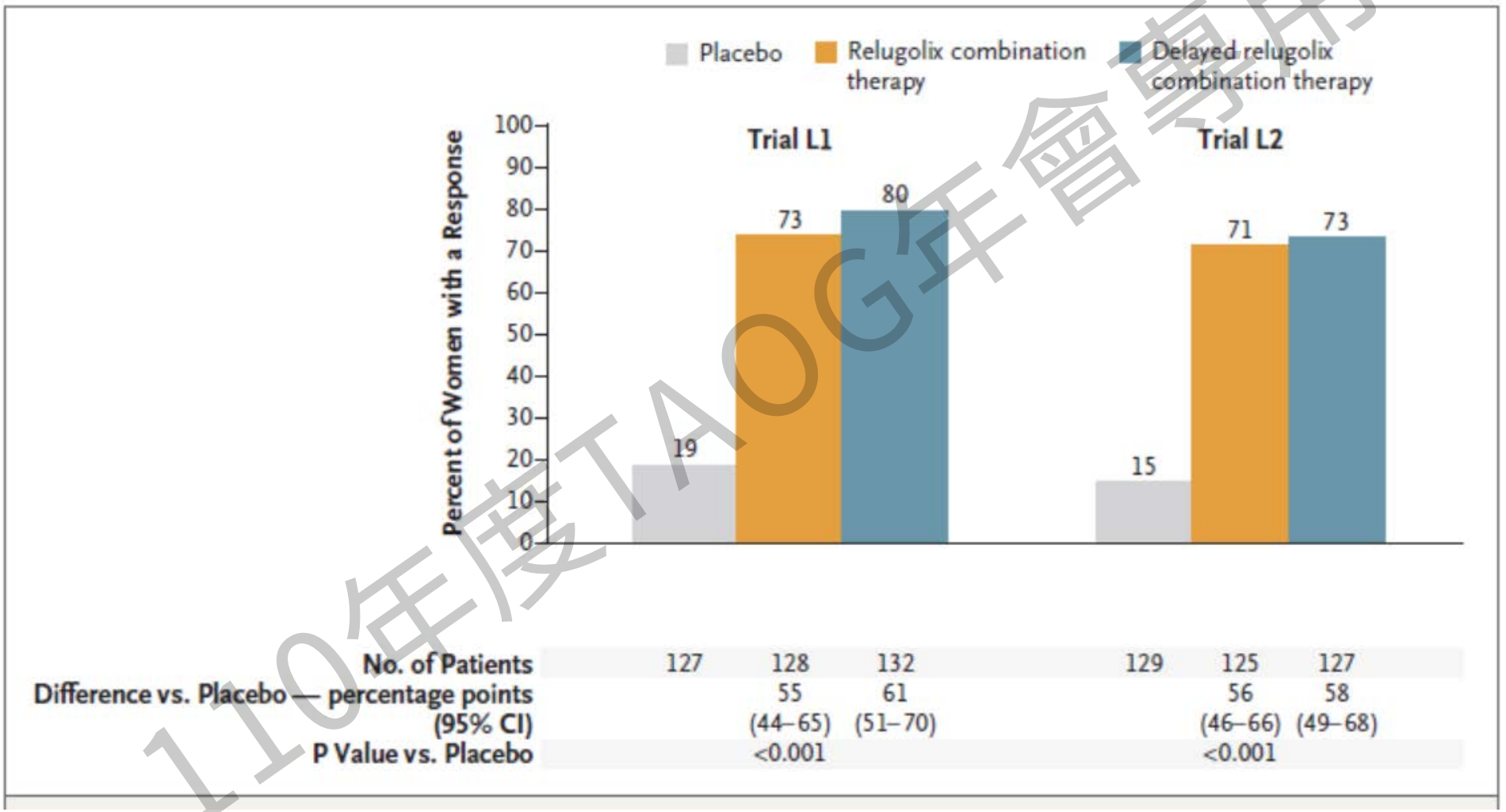
Objective: The combination of relugolix, estradiol, and norethindrone acetate, may have efficacy in women with uterine fibroids and heavy bleeding while avoiding hypoestrogenic effects.

Interventions :Double-blind, 24-week, phase 3 trials involving women with fibroid-associated heavy menstrual bleeding. Participants were randomly assigned in a 1:1:1 ratio to receive once-daily placebo, relugolix combination therapy (40 mg of relugolix, 1 mg of estradiol, and 0.5 mg of norethindrone acetate), or delayed relugolix combination therapy (40 mg of relugolix monotherapy, followed by relugolix combination therapy, each for 12 weeks).

avoiding hypoestrogenic effects.

N Engl J Med 2021;384:630-42

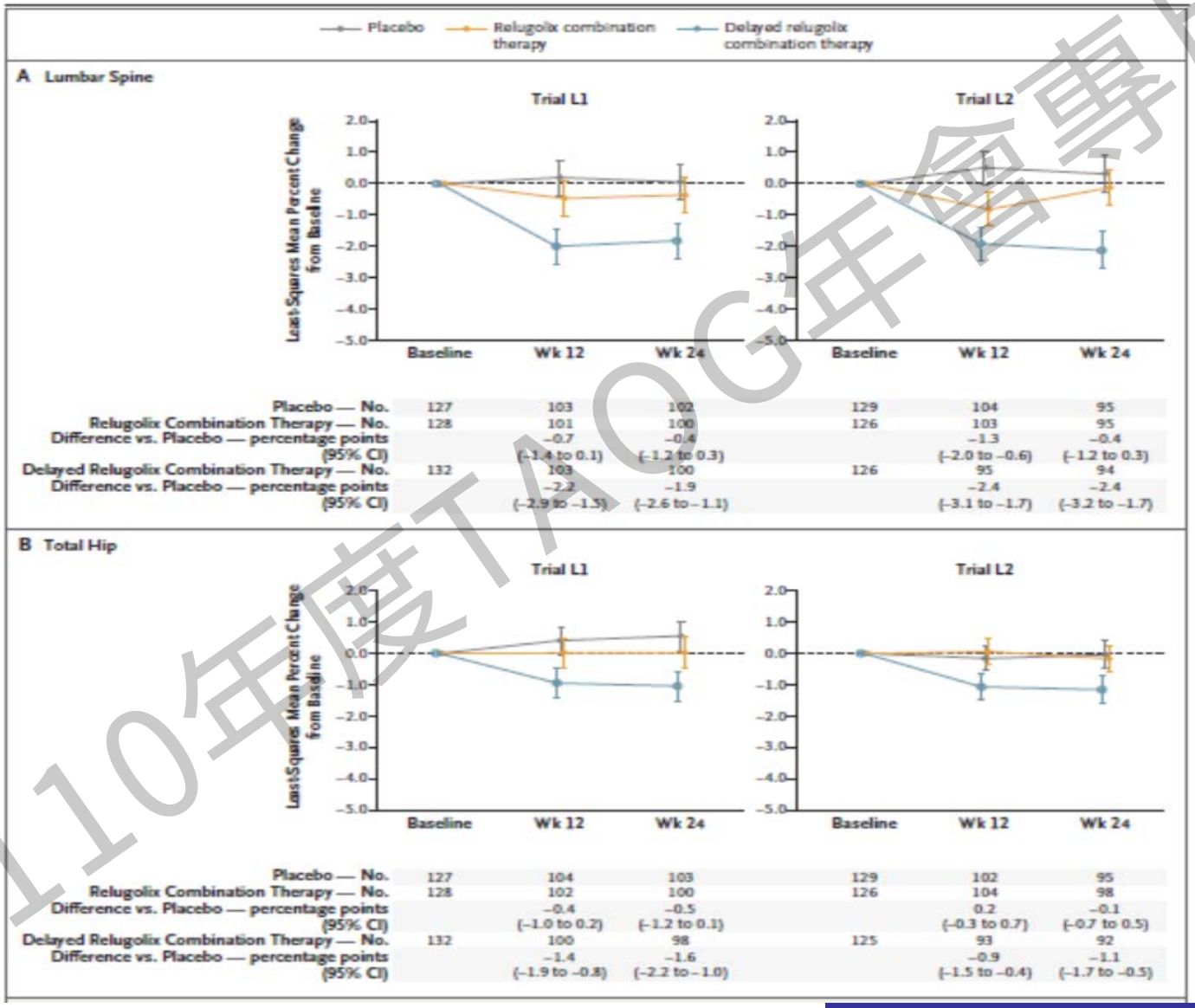
Participants with reduction in heavy menstrual bleeding



No. of Patients	127	128	132	129	125	127
Difference vs. Placebo — percentage points (95% CI)		55 (44–65)	61 (51–70)		56 (46–66)	58 (49–68)
P Value vs. Placebo		<0.001			<0.001	

N Engl J Med 2021;384:630-42

Change in bone mineral density



Placebo — No.	127	103	102	129	104	95
Relugolix Combination Therapy — No.	128	101	100	126	103	95
Difference vs. Placebo — percentage points (95% CI)		−0.7 (−1.4 to 0.1)	−0.4 (−1.2 to 0.3)		−1.3 (−2.0 to −0.6)	−0.4 (−1.2 to 0.3)
Delayed Relugolix Combination Therapy — No.	132	103	100	126	95	94
Difference vs. Placebo — percentage points (95% CI)		−2.2 (−2.9 to −1.5)	−1.9 (−2.6 to −1.1)		−2.4 (−3.1 to −1.7)	−2.4 (−3.2 to −1.7)

Placebo — No.	127	104	103	129	102	95
Relugolix Combination Therapy — No.	128	102	100	126	104	98
Difference vs. Placebo — percentage points (95% CI)		−0.4 (−1.0 to 0.2)	−0.5 (−1.2 to 0.1)		0.2 (−0.3 to 0.7)	−0.1 (−0.7 to 0.5)
Delayed Relugolix Combination Therapy — No.	132	100	98	125	93	92
Difference vs. Placebo — percentage points (95% CI)		−1.4 (−1.9 to −0.8)	−1.6 (−2.2 to −1.0)		−0.9 (−1.5 to −0.4)	−1.1 (−1.7 to −0.5)

N Engl J Med 2021;384:630-42

Conclusions

- Once-daily relugolix combination therapy resulted in a significant **reduction in menstrual bleeding**, as compared with placebo.
- And preserved **bone mineral density** in women with uterine fibroids.

Patients may benefit from oral nonpeptide GnRH derivatives

- **Premenopausal women with surgically or clinically diagnosed endometriosis-associated pain.**
- **Premenopausal women with surgically or clinically diagnosed uterine leiomyoma-associated AUB.**

N Engl J Med 2017;377:28

Fertility and Sterility 2021 Vol. 115, No. 2, 0015-0282

Am J Obstet Gynecol 2021;224:72.e1-50

N Engl J Med 2021;384:630-42

J Womens Health. 2021 Apr;30(4):569-578.

Contraindications

Contraindications
Pregnancy
Known osteoporosis
Severe hepatic impairment (Child-Pugh C)
Concomitant use of strong OATP1B1 inhibitors (*e.g.*, cyclosporine and gemfibrozil)

J Womens Health. 2021 Apr;30(4):569-578.

Oral GnRH antagonist dosing

Elagolix dosing

150mg QD ➢ The lowest effective starting dose

200mg BID ➢ Initiating therapy: for patients in whom dyspareunia is the main symptom and pain severe enough to require opioid analgesics

Elagolix dose: are **not influenced by body weight/BMI** or by presence of **renal impairment, end-stage renal disease, or mild hepatic impairment** (child-Pugh A)

Child-Pugh B: limited to 6 months of elagolix 150 mg once daily
Child-Pugh C: contraindicated

J Womens Health. 2021 Apr;30(4):569-578.
Obstet Gynecol 2018;132:147–160.
N Engl J Med 2017;377:28–40.

Safety considerations

Safety considerations

Hot flush

- 24% in Elagolix 150 mg QD, 48% in Elagolix 200 mg BID.

Taylor HS, et al. N Engl J Med 2017

Decrease in BMD

Dose- and duration-dependent

- After 6 months of treatment, changes in lumbar spine BMD :
  -0.3% to -0.7% with elagolix 150mg QD
  -2.5% to -2.6% with elagolix 200mg BID.
- Partial recovery of BMD at 6 and 12 months post treatmer in long term follow up

Elagolix is contraindicated in patients with osteoporosis.
(T-score of <-2.5)

Surrey E, et al. Obstet Gynecol 2018

Safety considerations

Change in lipid profile

dose-dependent increases in cholesterol, HDL, LDL, TG

- Lipid increases in **first 1–2 months of treatment** and remained stable thereafter
- **A return to the baseline occurred within 1 month of discontinuing treatment**

Surrey E, et al. Obstet Gynecol 2018

Orilissa (elagolix) tablets [prescribing information]. North Chicago, IL: AbbVie, Inc., 2018

Others

- Headache, insomnia, mood swings, night sweats, arthralgia, amenorrhea
- Asymptomatic increase in ALT > 3 times the upper limit of normal

Orilissa (elagolix) tablets [prescribing information]. North Chicago, IL: AbbVie, Inc., 2018
Fertility and Sterility 2021 Vol. 115, No. 2, 0015-0282

Addressing the contraception during tx

Addressing the contraception during Elagolix use

- **Pregnancy should be discouraged in women taking elagolix**
  - **Few congenital malformations report**
- **Use contraception during treatment and for 1 week after completing treatment**
- **Estrogen-containing contraceptives: higher exogenous estrogen may lower treatment efficacy**
- **Progestin-releasing IUD: provide contraception and treatment of endometriosis**
- **Immediately discontinue Elagolix if pregnant**

Orilissa (elagolix) tablets [prescribing information]. North Chicago, IL: AbbVie, Inc., 2018
Clin Pharmacokinet. 2021 Aug;60(8):1003-1013

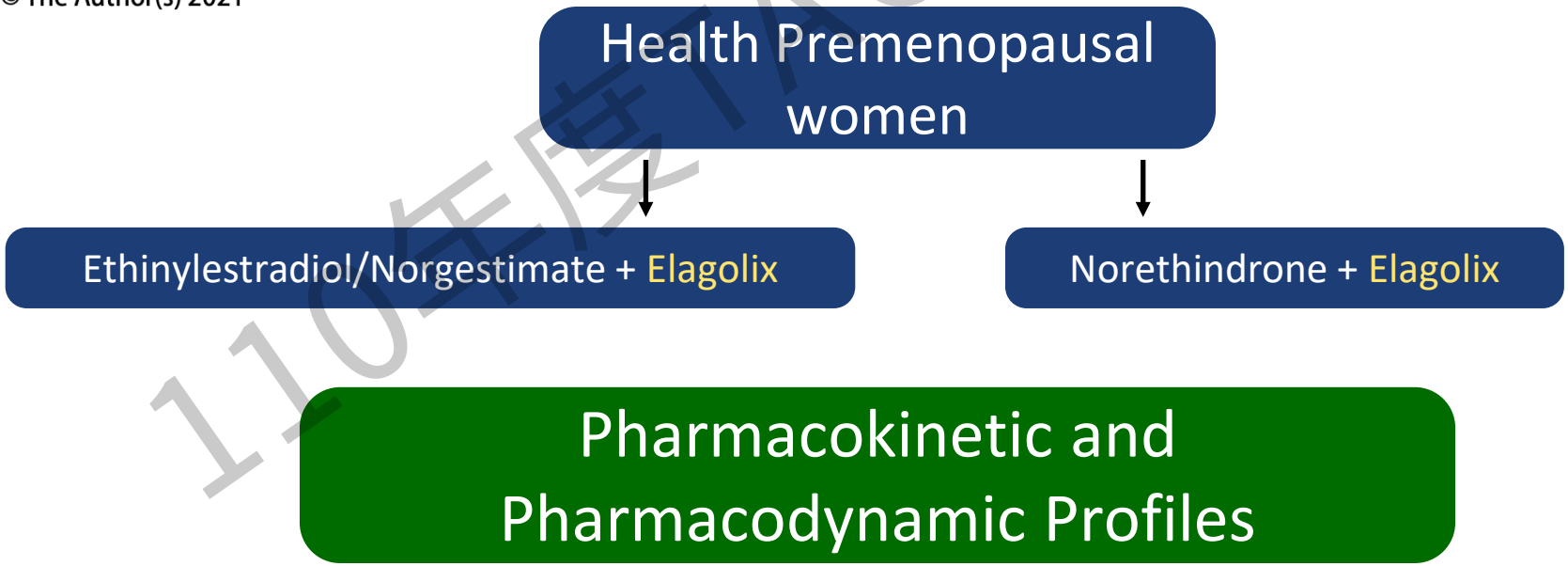
Clinical Pharmacokinetics
https://doi.org/10.1007/s40262-021-00989-0

ORIGINAL RESEARCH ARTICLE

Pharmacokinetic and Pharmacodynamic Profiles of Ethinylestradiol/Norgestimate Combination or Norethindrone upon Coadministration with Elagolix 150 mg Once Daily in Healthy Premenopausal Women

Robert A. Feldman[1] · Yi-Lin Chiu[2] · Cheri E. Klein[3] · Juki Ng[4]

Accepted: 16 January 2021



Pharmacokinetic

Pharmacokinetic parameters (units)	Regimens	
	Period 1, day 21 (ethinylestradiol/norgestimate 0.035 mg/0.25 mg QD alone) [$n = 21$]	Period 2, day 77 (estradiol/norgestimate 0.035 mg/0.25 mg QD + elagolix 150 mg QD) [$n = 21$]
Ethinylestradiol		
C_{max} (ng/mL)	0.168 ± 0.061	0.195 ± 0.076[c]
T_{max} (h)	1.5 ± 0.5	1.9 ± 2.4
AUC_{24} (ng·h/mL)	1.27 ± 0.56	1.65 ± 0.72[c]
$t_{½}$[a,b] (h)	15.4 ± 5.7	14.2 ± 4.9
NGMN		
C_{max} (ng/mL)	2.29 ± 0.60	2.00 ± 0.51[c]
T_{max} (h)	1.4 ± 0.3	1.4 ± 0.3
AUC_{24} (ng·h/mL)	18.3 ± 4.8	15.5 ± 4.3[c]
$t_{½}$[a] (h)	22.8 ± 7.3	20.9 ± 6.8
NG		
C_{max} (ng/mL)	3.02 ± 1.91	2.72 ± 1.54
T_{max} (h)	2.7 ± 4.9	2.2 ± 2.5
AUC_{24} (ng·h/mL)	51.6 ± 32.9	49.0 ± 30.8
$t_{½}$[a,d] (h)	43.5 ± 24.6	43.5 ± 24.8
Elagolix		
C_{max} (ng/mL)	–	504.4 ± 179.3
T_{max} (h)	–	1.1 ± 0.4
AUC_{24} (ng·h/mL)	–	1100.9 ± 392.6
$t_{½}$[a,d] (h)	–	3.7 ± 1.7

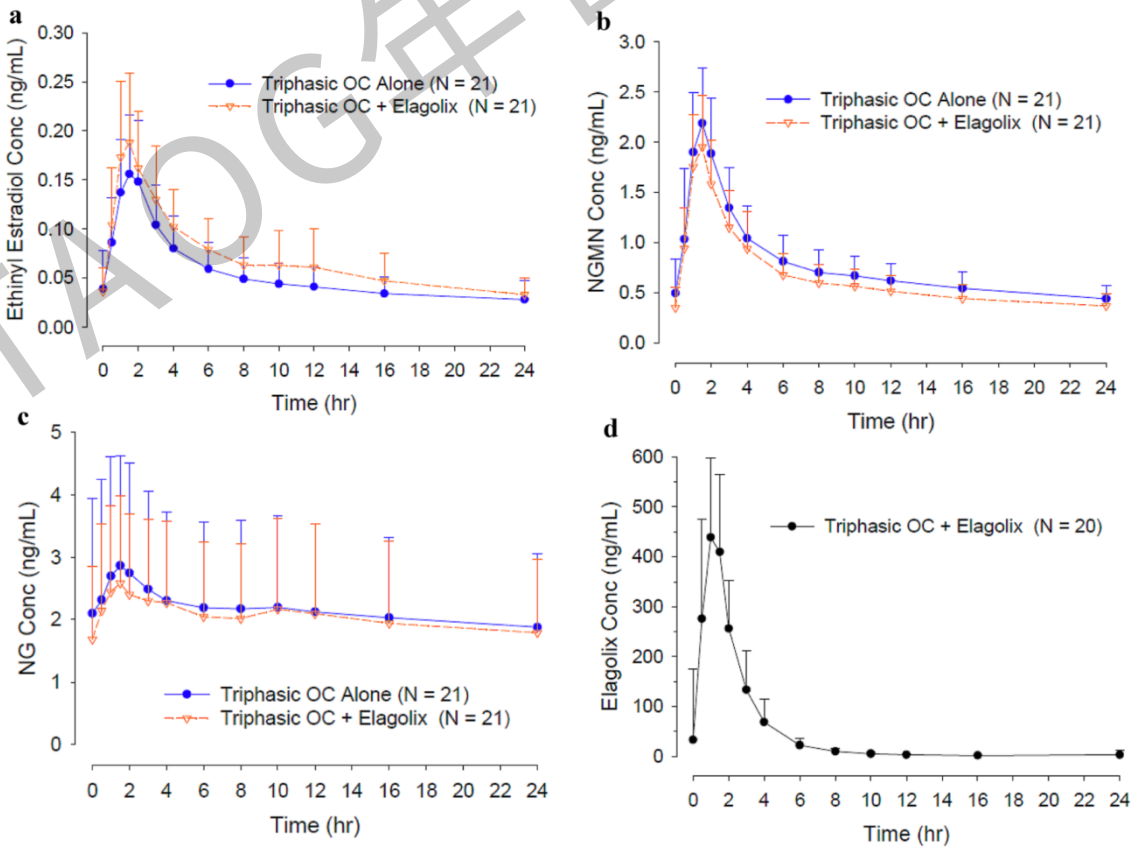


Fig. 2 Pharmacokinetic profiles mean + standard deviat
nylestradiol; **b** NGMN; **c** NG; and **d** Elagolix ($n = 20$). OC oral contraceptive, NGMN norgestrel, NG norgestrel

Clin Pharmacokinet. 2021 Aug;60(8):1003-1013

Pharmacodynamic

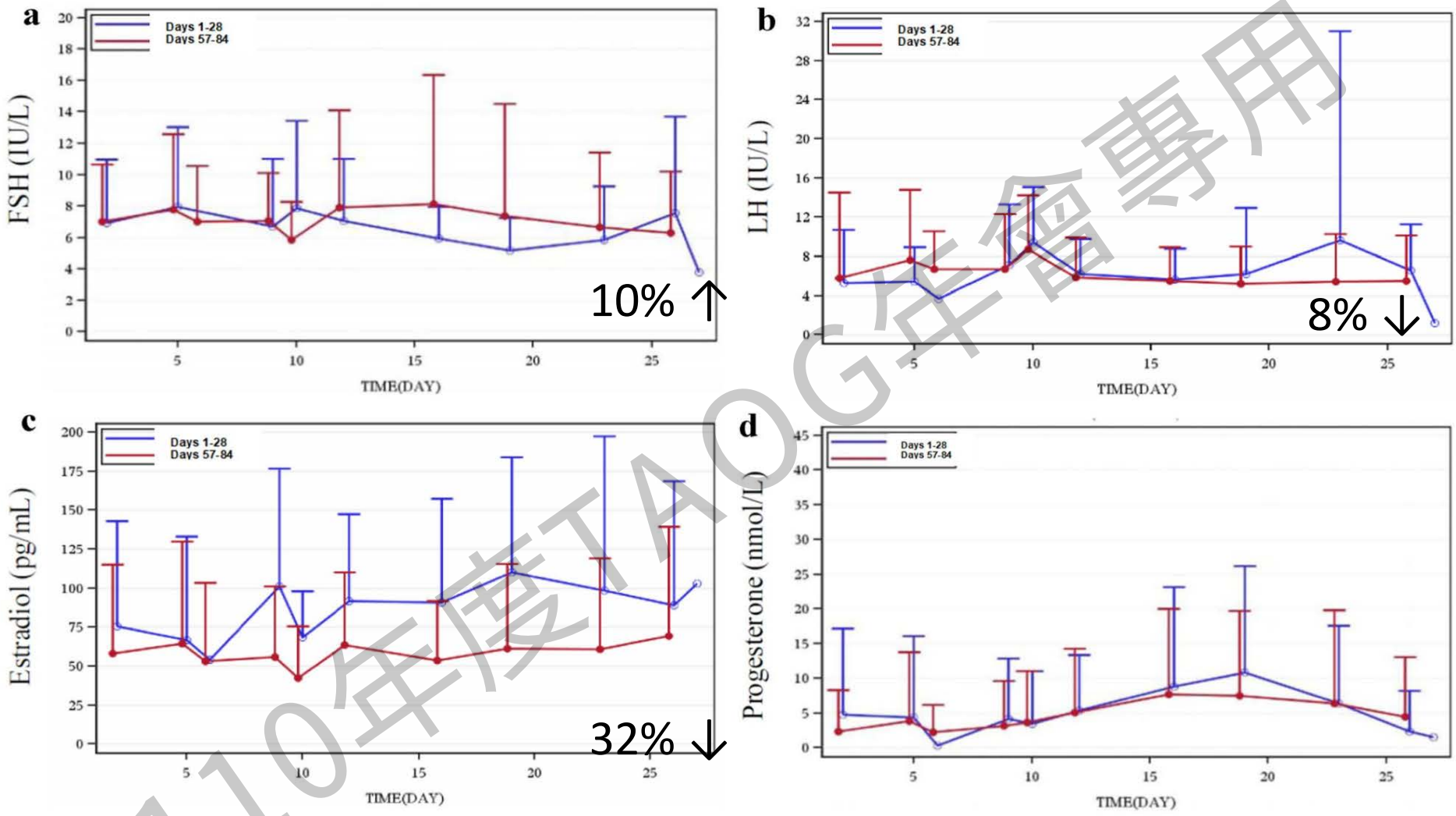


Fig. 5. Mean ± standard deviation concentration–time profiles after administration of norethindrone alone and norethindrone with elagolix in study 2 (linear scale, $n = 26$). Days 1–28, norethindrone alone; days 57–84, norethindrone with elagolix. **a** FSH; **b** LH; **c** estradiol; **d** progesterone. *FSH* follicle-stimulating hormone, *LH* luteinizing hormone

Clin Pharmacokinet. 2021 Aug;60(8):1003-1013

Conclusion

- **Coadministration of elagolix with orally administered norethindrone or combination hormonal contraceptives (EE and norgestimate)**
- **Small changes in the PK of oral hormonal contraceptive components; Elagolix PK not affected**
- **Hormonal PD effects of oral contraceptives: not negatively impacted**

Clin Pharmacokinet. 2021 Aug;60(8):1003-1013

Long-term treatment considerations

Managing endometriosis as a chronic disease

- Patients with normal liver function
  150 mg QD: continue for up to **24** months
  200 mg BID: continue for up to **6** months

Cost to benefit ratio is favorable

- Use of elagolix provides clinical benefit relative to no active treatment.
- Both elagolix treatment regimens were more **cost effective** than leuprolide acetate

Wang ST, et al. J Comp Eff Res 2019

Orilissa (elagolix) tablets [prescribing information]. North Chicago, IL: AbbVie, Inc., 2018

Institute for Clinical and Economic Review. Elagolix for treating endometriosis: Final evidence report., 2018

Managing endometriosis as a chronic disease

- **Add-back therapy**:
  continuous estradiol 0.5 mg/norethindrone acetate 0.1 mg or
  continuous estradiol 1mg and cyclical progestogen 200 mg
- **decreased the occurrence of hot flushes and lessened the effect of elagolix on the lipid profile**

TABLE 3. CLINICAL TRIAL OF ELAGOLIX WITH ADD-BACK THERAPY

Phase 3, randomized, double-blind placebo-controlled study
Enrollment: 680 adult women with moderate-to-severe endometriosis-associated pain
Treatment arms:
- Elagolix 200 mg BID + low-dose estradiol/norethindrone acetate
- Elagolix 200 mg BID
- Placebo

Duration: 12 months
Primary outcome measures:
- Proportion of responders based on dysmenorrhea at month 6
- Proportion of responders based on NMPP at month 6

Secondary outcome measures:
- Change from baseline in dysmenorrhea (months 3, 6, and 12)
- Change from baseline in dyspareunia (months 3, 6, and 12)
- Change from baseline in numeric rating scale (months 3, 6, and 12)
- Change from baseline in NMPP (months 3, 6, and 12)

ClinicalTrials.gov identifier: NCT03213457.
BID, twice daily; NMPP, nonmenstrual pelvic pain.

Archer DF et al, . Fertil Steril 2017

The future role in IVF through suppressing ovulation and HPO axis

Elagolix Suppresses Ovulation in a Dose-Dependent Manner: Results From a 3-Month, Randomized Study in Ovulatory Women

David F. Archer,[1] Juki Ng,[2] Kristof Chwalisz,[3] Yi-Lin Chiu,[4] Eve C. Feinberg,[5] Charles E. Miller,[6] Robert A. Feldman,[7] and Cheri E. Klein[2]

[1]Department of Obstetrics & Gynecology, Eastern Virginia Medical School, Norfolk, Virginia, 23507; [2]Clinical Pharmacology and Pharmacometrics, AbbVie Inc., North Chicago, Illinois, 60064; [3]General Medicine, AbbVie Inc., North Chicago, Illinois, 60064; [4]Data and Statistical Sciences, AbbVie Inc., North Chicago, Illinois, 60064; [5]Northwestern University Feinberg School of Medicine, Chicago, Illinois, 60611; [6]The Advanced IVF Institute, Naperville, Illinois, 60540; and [7]Baptist Health Medical Group, Miami, Florida, 33173

Objective: The objective was to evaluate the effects of elagolix on ovulation and ovarian sex hormones.

Interventions Elagolix was administered orally for 3 continuous 28-day dosing intervals at 100 to 200 mg once daily (QD), 100 to 300 mg twice daily (BID), and 300 mg BID plus estradiol/norethindrone acetate (E2/NETA) 1/0.5 mg QD.

J Clin Endocrinol Metab, March 2020, 105(3):821–832

Ovulation rates across all elagolix dosing

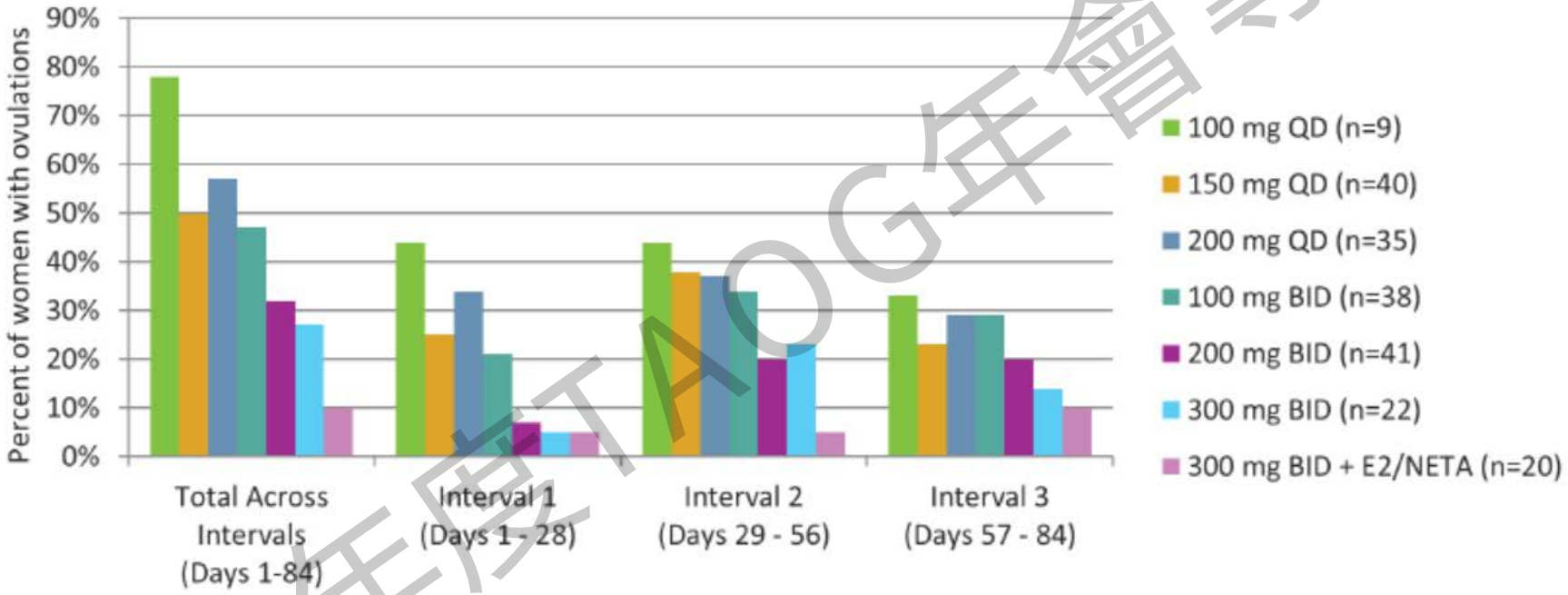


Figure 2. Ovulation rates across all elagolix dosing intervals (total) and during each individual dosing interval.

J Clin Endocrinol Metab, March 2020, 105(3):821–832

Median hormone concentrations

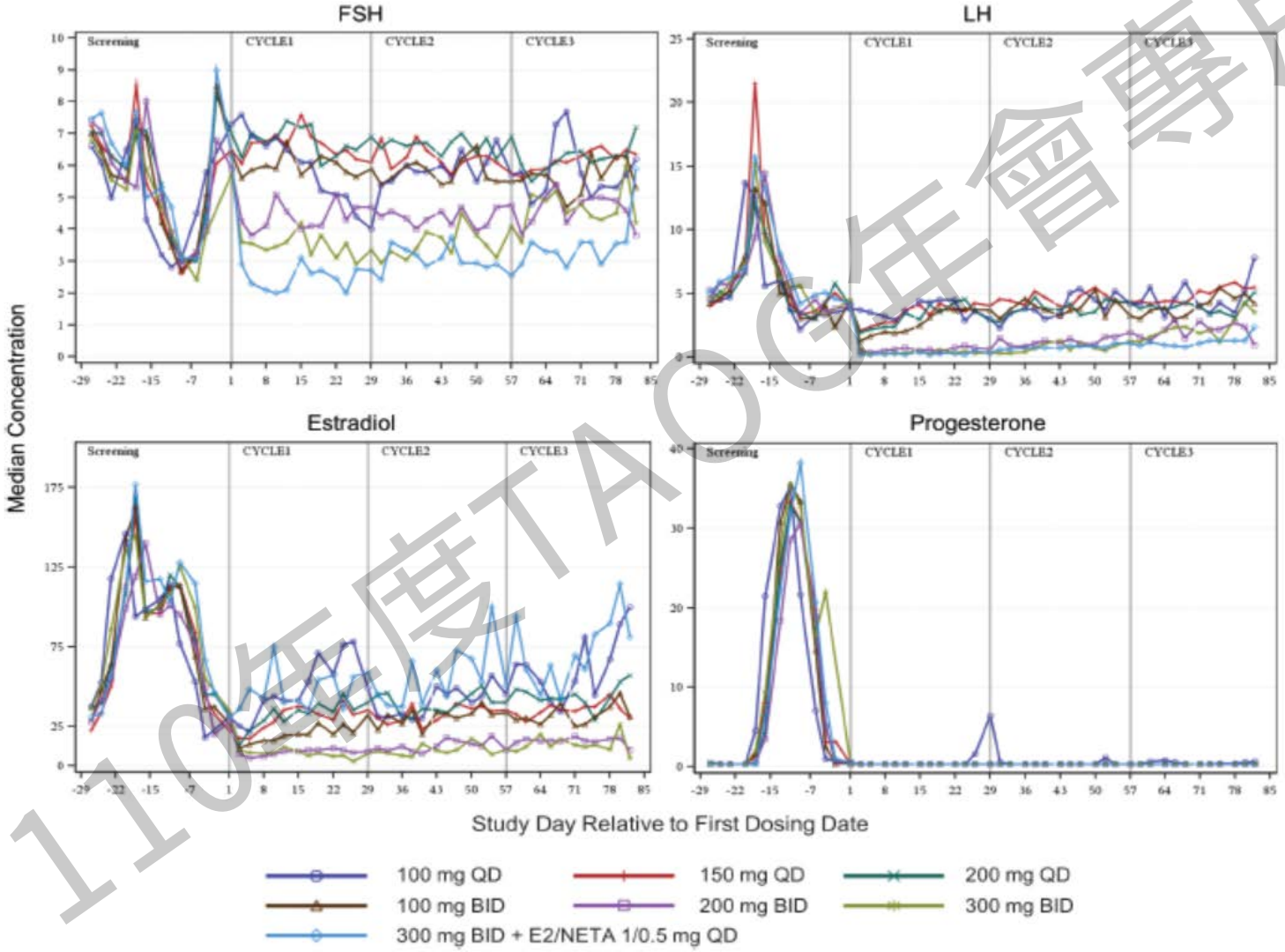


Figure 3. Median hormone concentrations during screening and 3 sequential 28-day intervals of dosing with elagolix.

J Clin Endocrinol Metab, March 2020, 105(3):821–832

Ovarian Reserve

Table 5. Ovarian Reserve as Measured by Anti-Mullerian Hormone (AMH) Serum Concentrations

	AMH (ng/mL)[a]						
	Elagolix Dose Group						
Time period	100 mg QD N = 9	150 mg QD N = 40	200 mg QD N = 35	100 mg BID N = 38	200 mg BID N = 41	300 mg BID N = 22	300 mg BID + E2/NETA 1/0.5 mg QD N = 20
Screening	2.73 ± 1.80	2.79 ± 2.72	2.32 ± 1.75	2.26 ± 1.32	2.44 ± 2.12	2.41 ± 1.33	2.92 ± 2.22
Interval 1 (Day 28)	0.31 ± 1.64	–0.17 ± 1.65	0.73 ± 1.89	0.06 ±1.09	0.89 ± 1.48	0.94 ± 1.16	0.51 ± 0.91
Interval 2 (Day 56)	–0.39 ± 1.14	0.22 ± 2.01	0.44 ± 1.22	0.53 ± 1.28	0.32 ± 1.61	0.38 ± 1.03	–0.07 ± 1.37
Interval 3 (Day 84)	–0.20 ± 1.38	0.24 ± 1.62	0.54 ± 1.47	0.18 ± 0.68	–0.09 ± 1.43	0.04 ± 0.99	–0.44 ± 1.29

Abbreviations: BID, twice daily; E2/NETA, estradiol/norethindrone acetate; QD, once daily.
[a]Mean change from baseline ± SD, except Screening represents mean ± SD

J Clin Endocrinol Metab, March 2020, 105(3):821–832

Mean endometrial thickness profiles

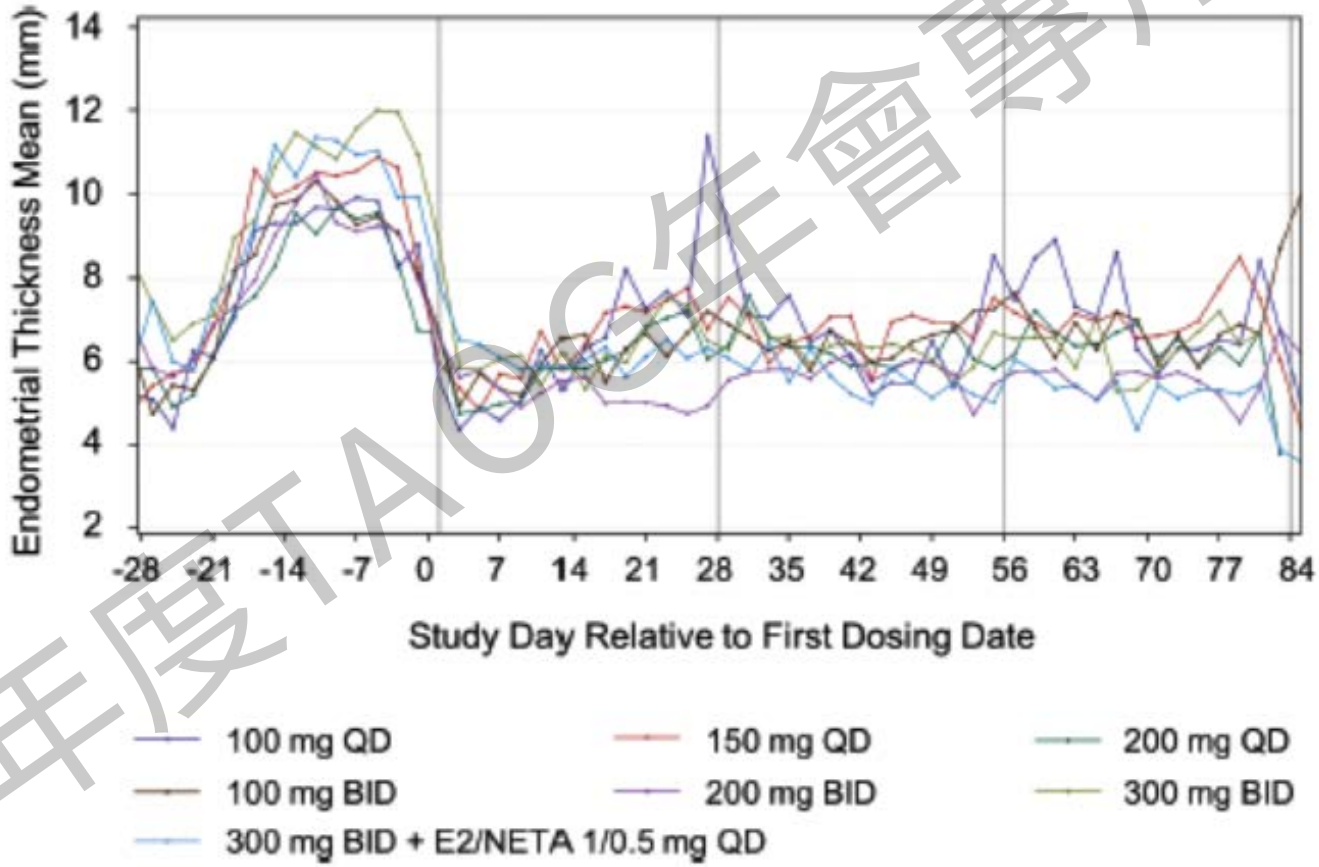


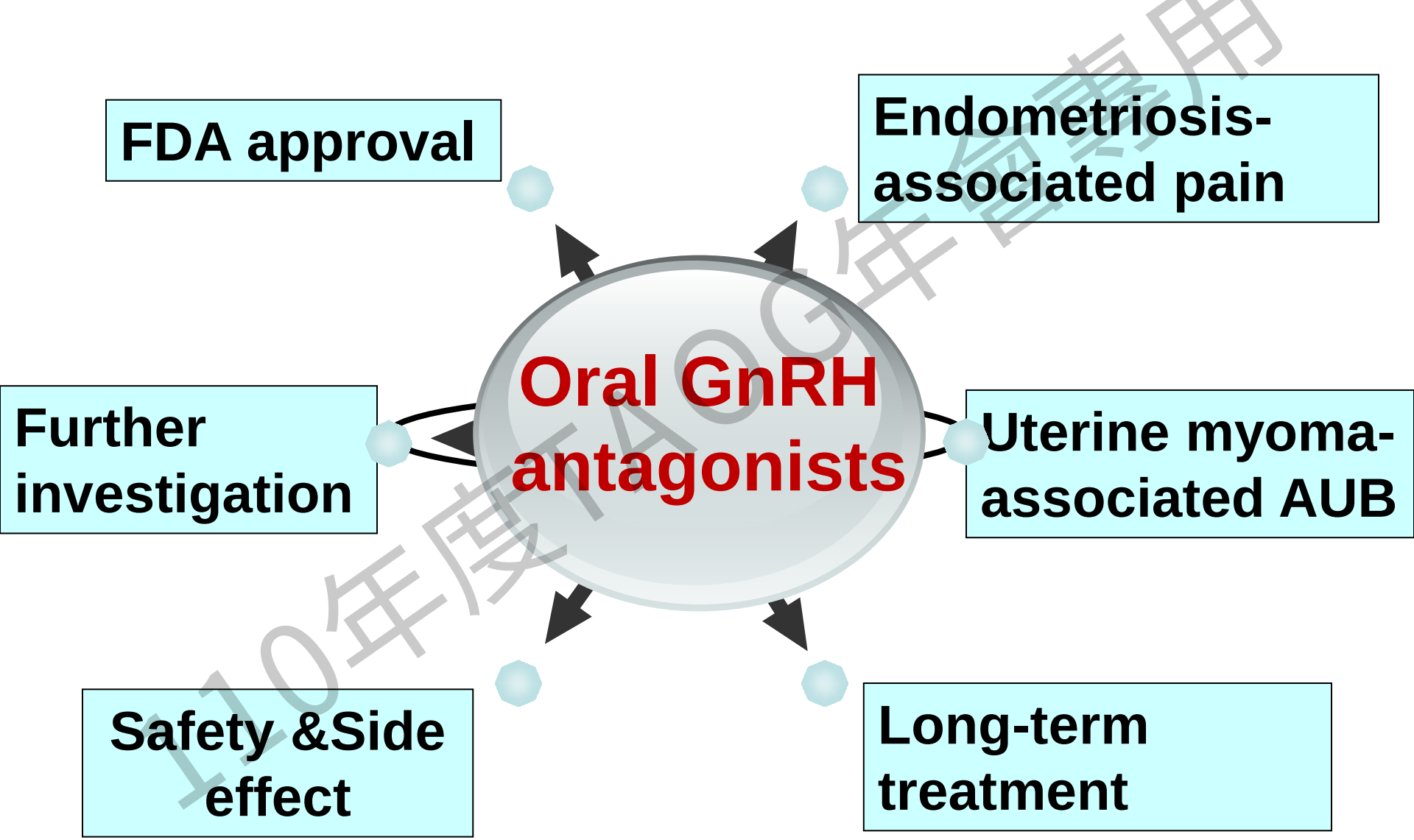
Figure 4. Mean endometrial thickness profiles during screening and 3 sequential 28-day intervals of dosing with elagolix.

J Clin Endocrinol Metab, March 2020, 105(3):821–832

Conclusions

- Elagolix suppresses **ovulation** and pituitary and ovarian hormones in a dose-dependent manner.
- No effect on **AMH**
- Reduces **endometrial thickness** at doses being targeted for endometriosis-associated pain and AUB associated with uterine fibroids.

Summary



Acknowledgement

-- Reproductive center, CGMH

Thank you