

POZICIONIRANJE MEDIKAMENTNOG LIJEČENJA MIOMA

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Zagreb

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MIOMI - SIMPTOMATOLOGIJA

esmya® 5mg
Ulipristal acetate

IZBOR LIJEČENJA

CILJ LIJEČENJA



Smanjenje/ prestanak simptoma

Kvaliteta života

Plodnost

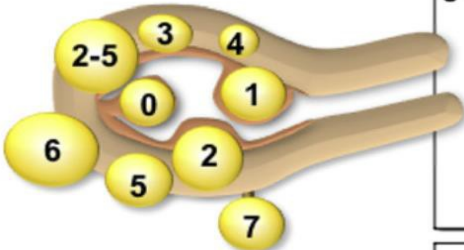
Kirurško liječenje?



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Laparoskopska miomektomija: rizik se povećava s veličinom i brojem mioma

- **Penetracija mioma u miometriju**
- **Udio endometralne sluznice koji je deformiran bazom mioma**
- **Promjer mioma**
- **Smještaj mioma**

Leiomyoma Subclassification System 		SM- Submucosal	0	Pedunculated Intracavitary
		O - Other	1	<50% Intramural
			2	≥50% Intramural
			3	Contacts endometrium; 100% Intramural
			4	Intramural
			5	Subserosal ≥50% Intramural
			6	Subserosal <50% Intramural
			7	Subserosal Pedunculated
			8	Other (specify e.g. cervical, parasitic)
Hybrid Leiomyomas (impact both endometrium and serosa)		Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below		
		2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.	

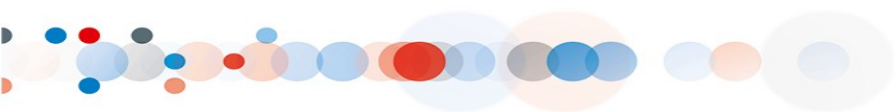


LPSC / HYSC – kako učiniti zahvat sigurnim i lakšim



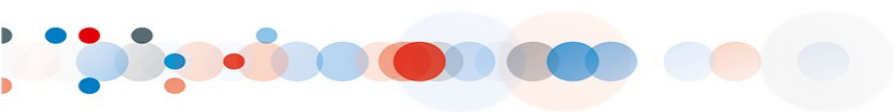
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- **Kontrola krvarenja**
- **Značajno smanjenje volumena mioma**
- **Kirurško liječenje se može izbjeći uz značajno smanjenje volumena mioma i ako nema deformacije endometrija, simptomi se povlače**



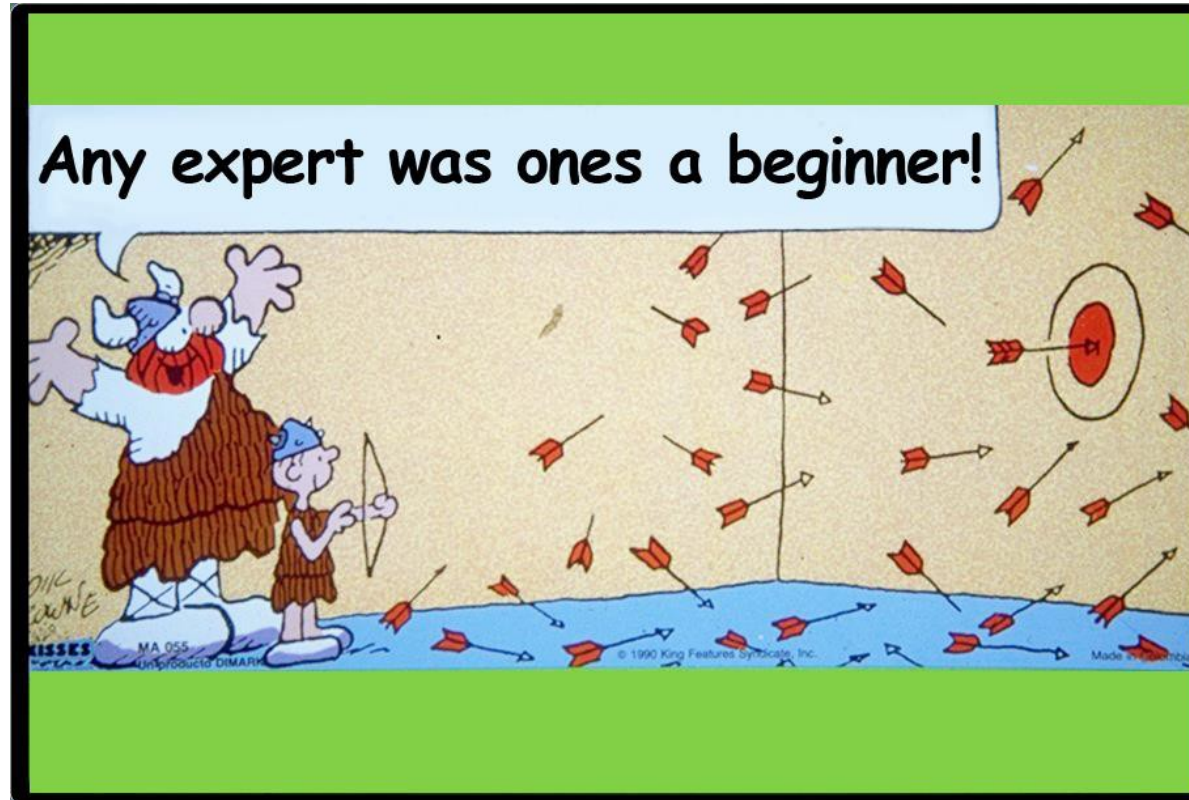
Histeroskopska miomektomija - ciljevi

- E nukleacija mioma u cijelosti
- Očuvanje cjelovitosti stijenke maternice



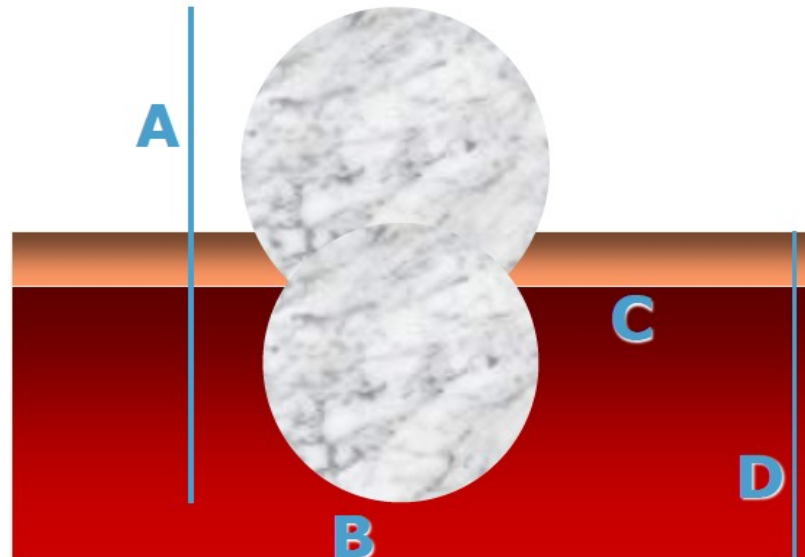
Histeroskopska miomektomija - OGRANIČENJA

- Iskustvo kirurga



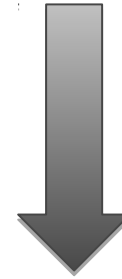
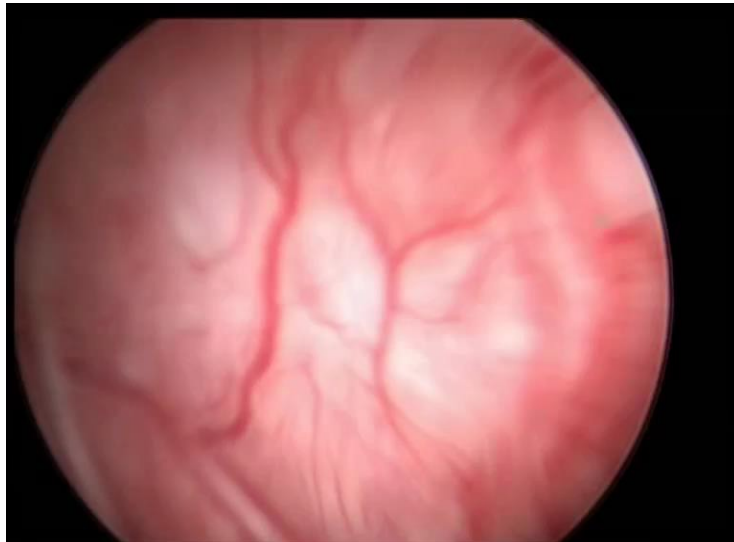
Histeroskopska miomektomija - OGRANIČENJA

- Patologija mioma :
 - A. Veličina mioma
 - B. Slobodni rubovi miometrija
 - C. Intramuralni udio mioma
 - D. Debljina stijenke maternice

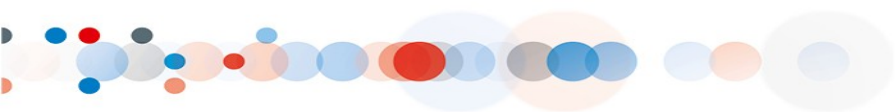


Histeroskopska miomektomija - OGRANIČENJA

- Patologija mioma : > 3 cm
tip 2 (1-2)
hipervaskularizacija



UPA 5mg 3 mjeseca



Histeroskopska miomektomija - OGRANIČENJA

- operacijske tehnike i instrumentarij i oprema



Histeroskopska miomektomija - OGRANIČENJA

- operacijske tehnike i instrumentarij i oprema
- Monopolarna – bipolarna tehnologija
- G1, G2 – 1 step procedure
2 step procedure

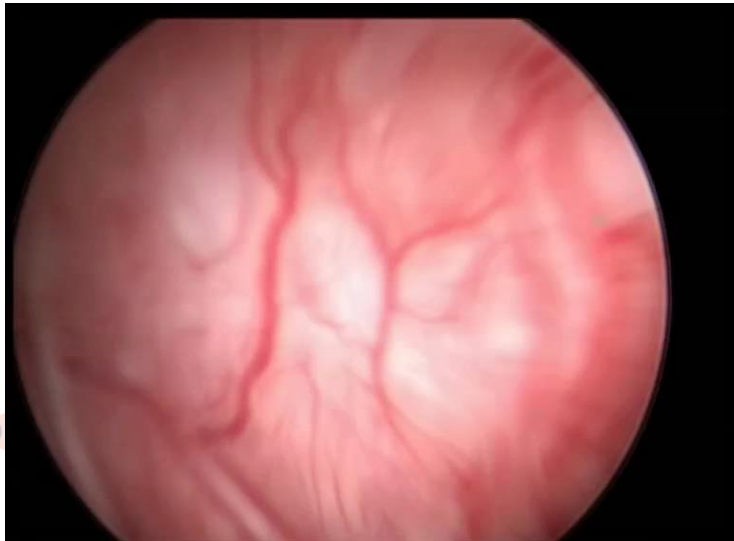


- Histeroskopska miomektomija - OGRANIČENJA

Hysteroscopic Treatment of Submucous Myomas

PAUL D. INDMAN, MD

Gynecology and Obstetrics, Stanford University, Stanford, Good Samaritan Hospital, San Jose, California, and Los Gatos Surgical Center, Los Gatos, California

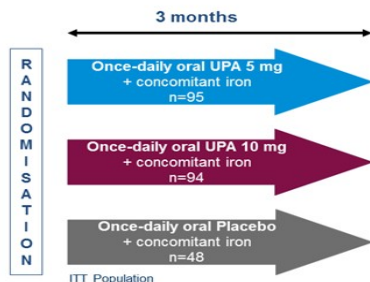


SUMMARY

Hysteroscopic resection allows minimally invasive treatment of many, but not all, submucous myomas. Proper patient evaluation and selection is crucial to the achievement of good results. Understanding the instrumentation, electrosurgical principles, fluid considerations, and the anatomic orientation of the myomas to the uterus will decrease the risk of complications. Hysteroscopic resection of myomas can challenge the skill of even the most experienced endoscopic surgeon and, consequently, many cases should only be done by surgeons with extensive experience in hysteroscopic surgery.

Ulipristal Acetate versus Placebo for Fibroid Treatment before Surgery

Jacques Donnez, M.D., Ph.D., Tetyana F. Tataruchuk, M.D., Ph.D.,
Philippe Bouchard, M.D., Lucian Puscasiu, M.D., Ph.D.,
Nataliya F. Zakharenko, M.D., Ph.D., Tatiana Ivanova, M.D., Ph.D.,
Gyula Ugocsai, M.D., Ph.D., Michal Mara, M.D., Ph.D., Manju P. Jilla, M.B., B.S., M.D.,
Elke Bestel, M.D., Paul Terrill, Ph.D., Ian Osterloh, M.R.C.P.,
and Ernest Loumaye, M.D., Ph.D., for the PEARL I Study Group*

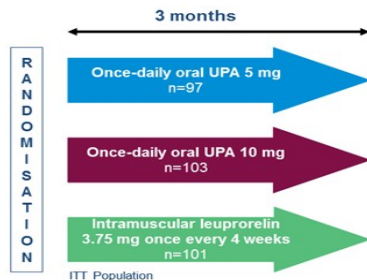


N ENGL J MED 366:5 NEJM.ORG FEBRUARY 2, 2012

ulipristal acetate

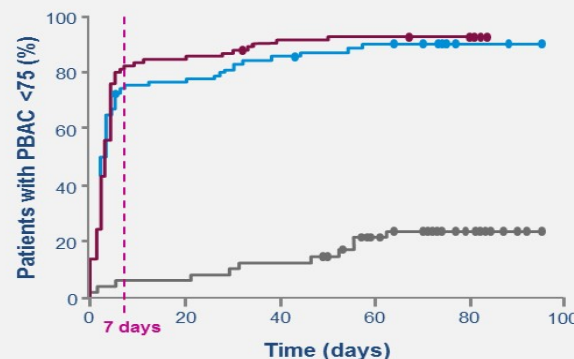
Ulipristal Acetate versus Leuprolide Acetate for Uterine Fibroids

Jacques Donnez, M.D., Ph.D., Janusz Tomaszewski, M.D., Ph.D.,
Francisco Vázquez, M.D., Ph.D., Philippe Bouchard, M.D.,
Bogusław Lemieśczuk, M.D., Francesco Baró, M.D., Ph.D., Kazem Nouri, M.D.,
Luigi Selvaggi, M.D., Krzysztof Sadowski, M.D., Elke Bestel, M.D.,
Paul Terrill, Ph.D., Ian Osterloh, M.R.C.P., and Ernest Loumaye, M.D., Ph.D.,
for the PEARL II Study Group*

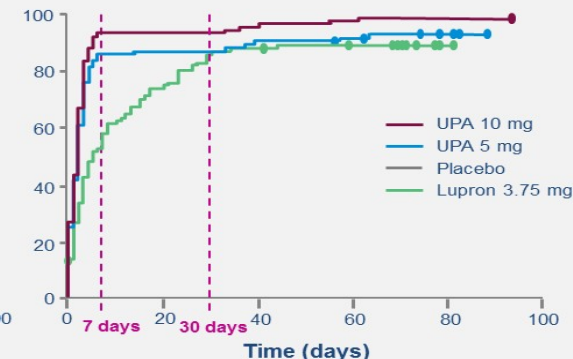


TIME TO CONTROL OF BLEEDING (PBAC <75)

PEARL I



PEARL II



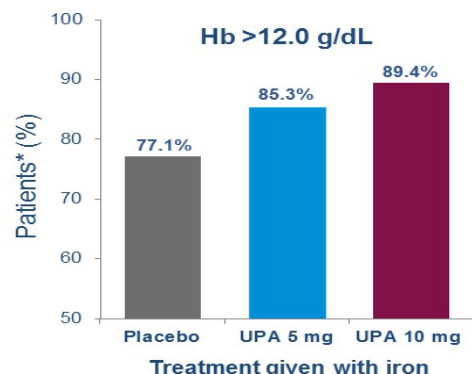
PBAC, Pictorial Bleeding Assessment Chart
UPA, ulipristal acetate

Donnez J, et al. N Engl J Med 2012;366:409-20
Donnez J, et al. N Engl J Med 2012;366:421-32

ulipristal acetate

HIGHER NUMBER OF PATIENTS WITH CORRECTED ANAEMIA IN UPA GROUPS

ANAEMIA CORRECTION AT WEEK 13



*Inc. Criteria: All patients to have Hb ≤10.2 g/dL at screening

UPA, ulipristal acetate

Donnez J, et al. N Engl J Med 2012;366:409-20

ulipristal acetate

Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study

Khalid M Musallam, Hani M Tamin, Toby Richards, Donat R Spahn, Fikri R Rosendahl, Aida Habbal, Mohammed Khreis, Fadi S Dabbas, Kalwan Khayat

Data from 227,425 non-cardiac surgical patients, of whom 30% had preoperative anaemia

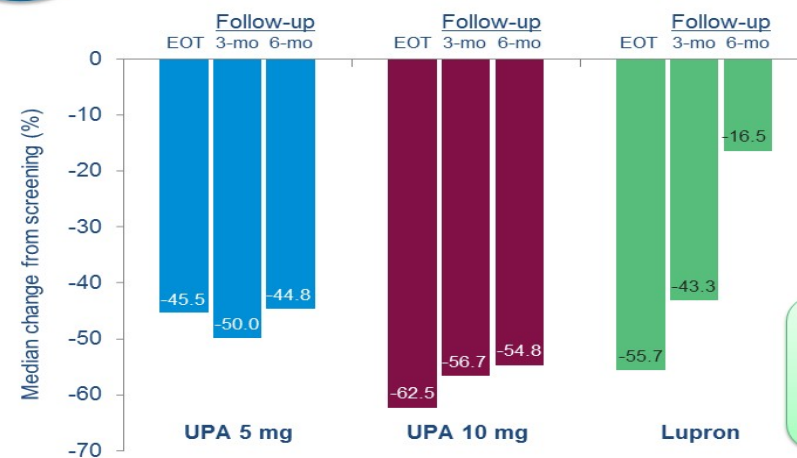
“Interpretation Preoperative anaemia, even to a mild degree, is independently associated with an increased risk of 30-day morbidity and mortality in patients undergoing major non-cardiac surgery.”

Interpretation Preoperative anaemia, even to a mild degree, is independently associated with an increased risk of 30-day morbidity and mortality in patients undergoing major non-cardiac surgery.

Funding Vifor Pharma.

Musallam KM, et al. Lancet 2011;378:1396-407

VOLUME REDUCTION IN 3 LARGEST FIBROIDS AT END OF TREATMENT (EOT) AND FOLLOW-UP



Subpopulation of subjects where no surgery/UAE was performed

Change from EOT to 6-month follow-up for UPA 5 mg and UPA 10 mg vs Lupron: p<0.05

EOT, end of 3-months' treatment; mo, months; UAE, uterine artery embolisation
UPA, ulipristal acetate

Donnez J, et al. N Engl J Med 2012;366:421-32

ulipristal acetate

PEARL III

UPA 10 mg

PEARL IV

UPA 5 mg & UPA 10 mg

Long-term treatment of uterine fibroids with ulipristal acetate[☆]

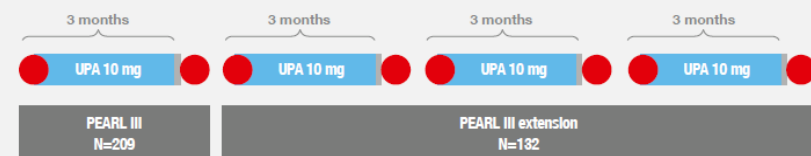
Jacques Donnez, M.D.,^a Francisco Vázquez, M.D.,^b Janusz Tomaszewski, M.D.,^c Kazem Nouri, M.D.,^d Philippe Bouchard, M.D.,^e Bart C. J. M. Fauser, M.D.,^f David H. Barlow, F.R.C.O.G.,^g Santiago Palacios, M.D.,^h Olivier Donnez, M.D.,ⁱ Elke Bestel, M.D.,^j Ian Osterloh, M.R.C.P.,^k and Ernest Loumaye, M.D.,^l for the PEARL III and PEARL III Extension Study Group

^a Société de Recherche pour l'Infertilité, Brussels, Belgium; ^b Centro de Estudios de Obstetricia y Ginecología Asociado, Lugo, Spain; ^c Prywatna Klinika Polozniczo-Ginekologiczna, Bialystok, Poland; ^d Department of Gynecological Endocrinology and Reproductive Medicine, Medical School of Vienna, Vienna, Austria; ^e Endocrinology Unit, AP-HP Hospital Saint-Antoine, Paris, France; ^f Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, Utrecht, the Netherlands; ^g College of Medical, Veterinary, and Life Sciences, University of Glasgow, Glasgow, Scotland; ^h Palacios' Institute of Women's Health, Madrid, Spain; ⁱ Centre Hospitalier Universitaire Université Catholique de Louvain Mont-Godinne Dinant, Yvoir, Belgium; ^j PregLem S.A., Geneva, Switzerland; ^k OsterMed Ltd., Birmingham, United Kingdom; and ^l ObsEva S.A., Geneva, Switzerland

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1565



Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids

Jacques Donnez, M.D.,^a Robert Hudecek, M.D.,^b Olivier Donnez, M.D.,^c Dace Matule, M.D.,^d Hans-Joachim Arhendt, M.D.,^e Janos Zatik, M.D.,^f Zaneta Kasilovskiene, M.D.,^g Mihai Cristian Dumitrascu, M.D.,^h Hervé Fernandez, M.D.,ⁱ David H. Barlow, F.R.C.O.G.,^j Philippe Bouchard, M.D.,^k Bart C. J. M. Fauser, M.D.,^l Elke Bestel, M.D.,^m Paul Terrill, Ph.D.,ⁿ Ian Osterloh, M.R.C.P.,^o and Ernest Loumaye, M.D.^p

Objective: To investigate the efficacy and safety of repeated 12-week courses of 5 or 10 mg daily of ulipristal acetate for intermittent treatment of symptomatic uterine fibroids.

Design: Double-blind, randomized administration of two 12-week courses of ulipristal acetate.

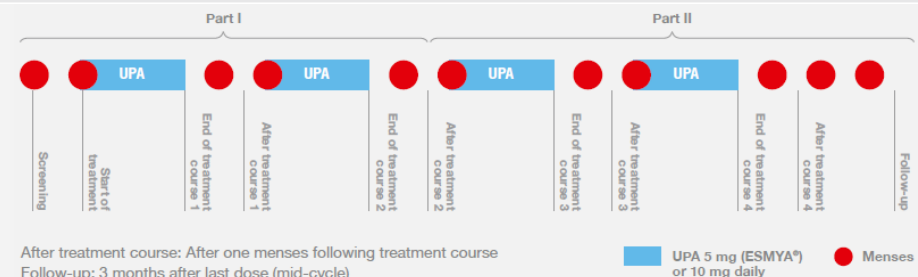
Setting: Gynecology centers.

Patient(s): A total of 451 patients with symptomatic uterine fibroid(s) and heavy bleeding.

Intervention(s): Two repeated 12-week treatment courses of daily 5 or 10 mg of ulipristal acetate.

Main Outcome Measure(s): Amenorrhea, controlled bleeding, fibroid volume, quality of life (QoL), pain.

Result(s): In the 5- and 10-mg treatment groups (62% and 73% of patients, respectively) achieved amenorrhea during both treatment courses. Proportions of patients achieving controlled bleeding during two treatment courses were >80%. Menstruation resumed after each treatment course and was diminished compared with baseline. After the second treatment course, median reductions from baseline in fibroid volume were 54% and 58% for the patients receiving 5 and 10 mg of ulipristal acetate, respectively. Pain and QoL improved in both groups. Ulipristal acetate was well tolerated with less than 5% of patients discontinuing treatment due to adverse events.

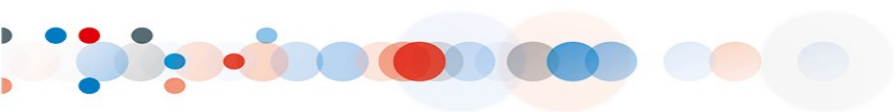


Cilj studija bio je istražiti kliničku efikasnost i sigurnost dugotrajne intermitentne primjene UPA-e u liječenju simptomatskih mioma.

PEARL IV

Faza III kliničkog ispitivanja, multicentrična, randomizirana, dvostrukoslijepa klinička studija s ciljem istraživanja učinkovitosti i sigurnosti 12-tjedne ponavljajuće, dugotrajne, cikličke primjene UPA 5 mg i UPA 10 mg dnevno u liječenju simptomatskih mioma maternice

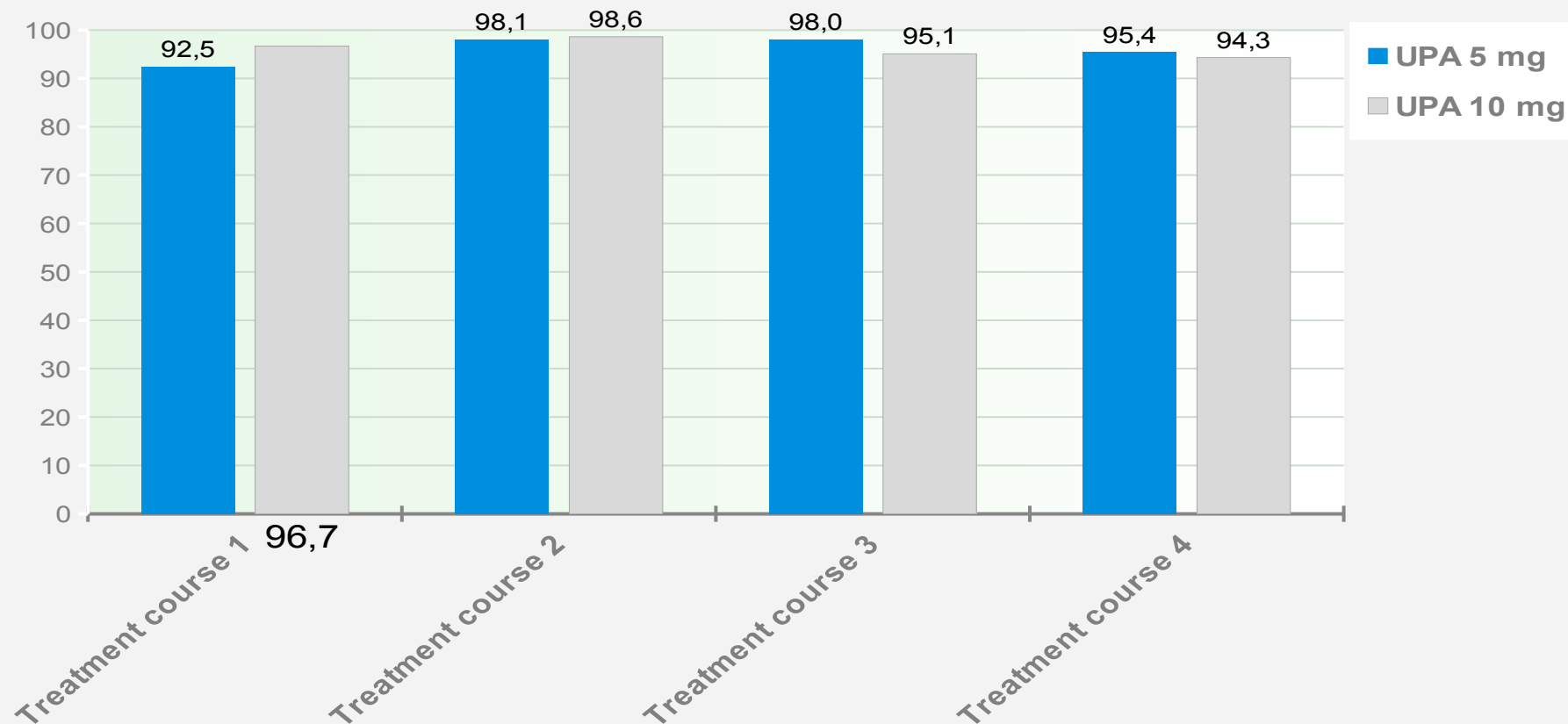
Drugo kliničko ispitivanje faze III u indikaciji intermitentno liječenje ulipristal acetatom



ESMYA: Ponovljena primjena maksimizira korist terapije

- više pacijentica postiže kontrolu krverenja ponavljanjem ciklusa liječenja

PEARL IV



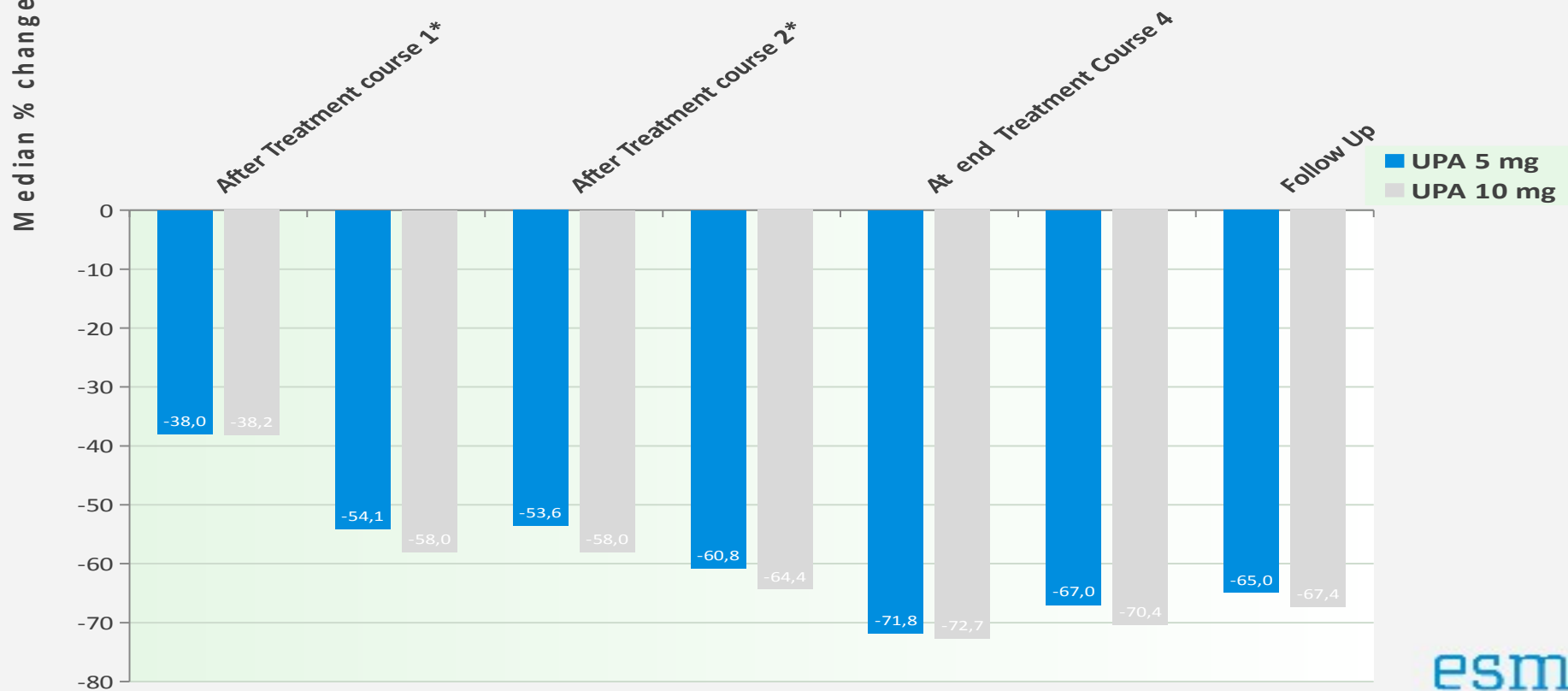
- Većina pacijentica za vrijeme terapije je amenoroična

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Ulipristal acetate

ESMYA: Ponovljena primjena maksimizira korist terapije

- **veće smanjenje volumena mioma ponovljanjem ciklusa liječenja**

PEARL IV



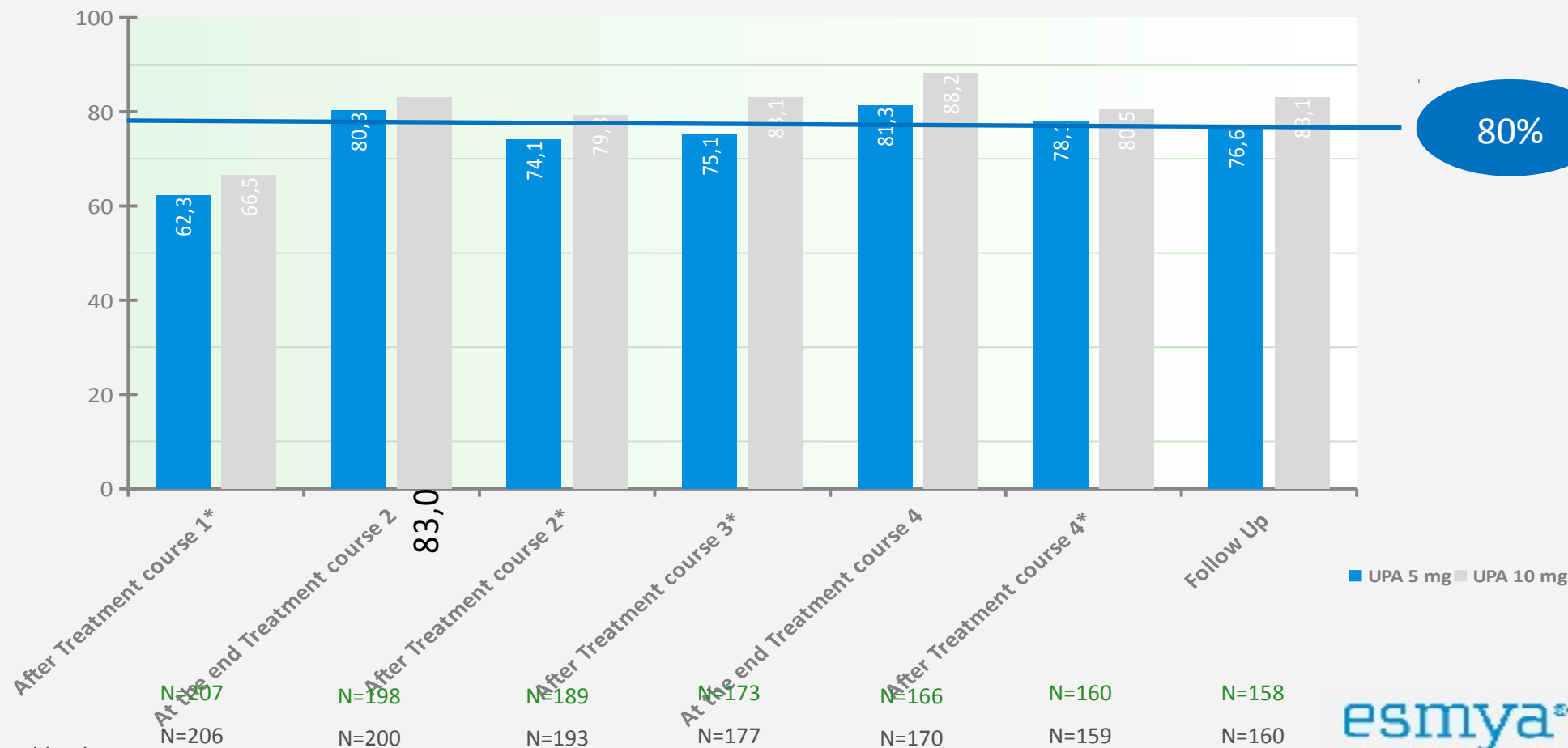
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Učinkovitost: klinički značajno smanjenje volumena mioma

Patients with clinically significant reduction in fibroid volume^a ($\geq 25\%$) [FAS1]

PEARL IV

Percentage of patients



80%

■ UPA 5 mg ■ UPA 10 mg

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^aVolume of 3 largest fibroids combined

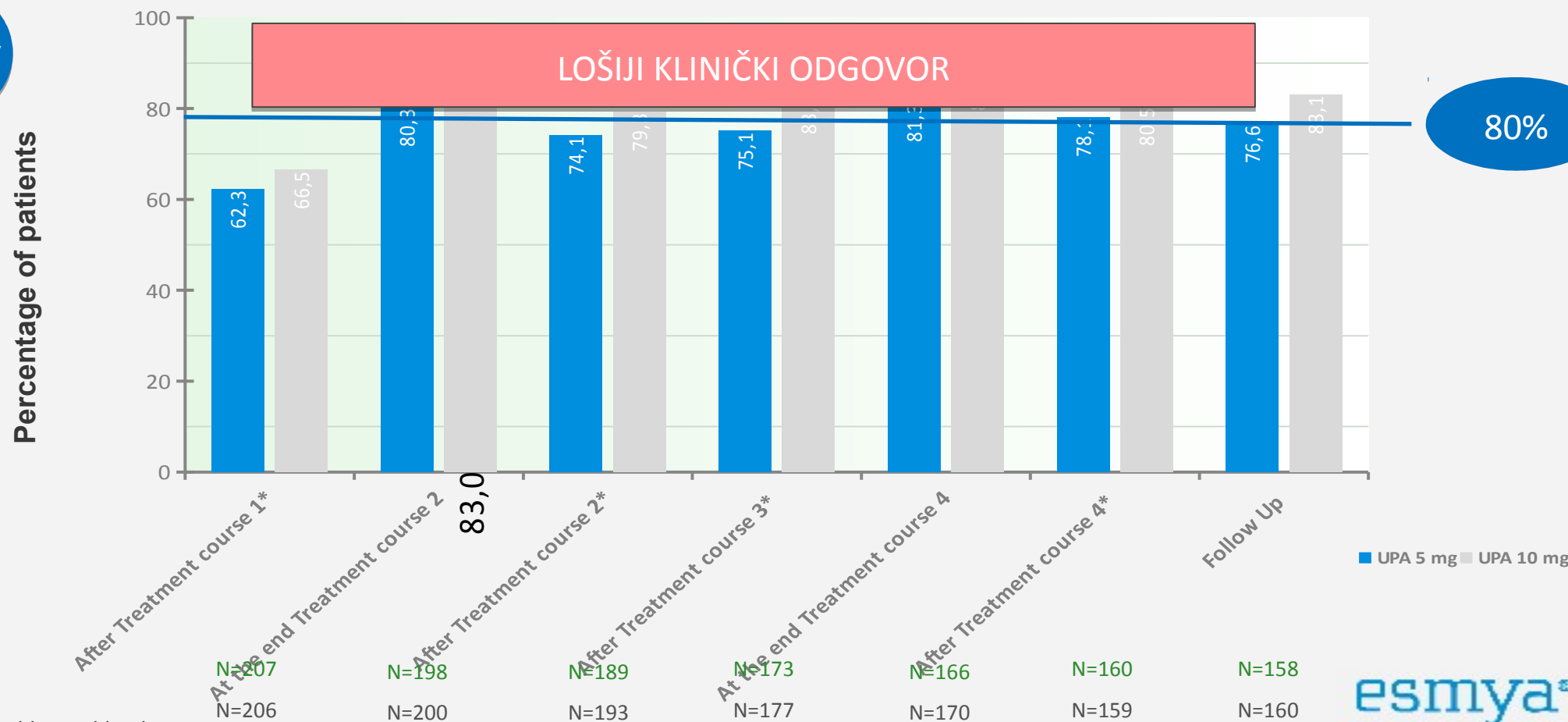
* After treatment course + 1 bleed

N, number of patients with non-missing assessments; UPA, ulipristal acetate

Učinkovitost: klinički značajno smanjenje volumena mioma

Patients with clinically significant reduction in fibroid volume^a ($\geq 25\%$) [FAS1]

PEARL IV



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Ulipristal acetate

^aVolume of 3 largest fibroids combined

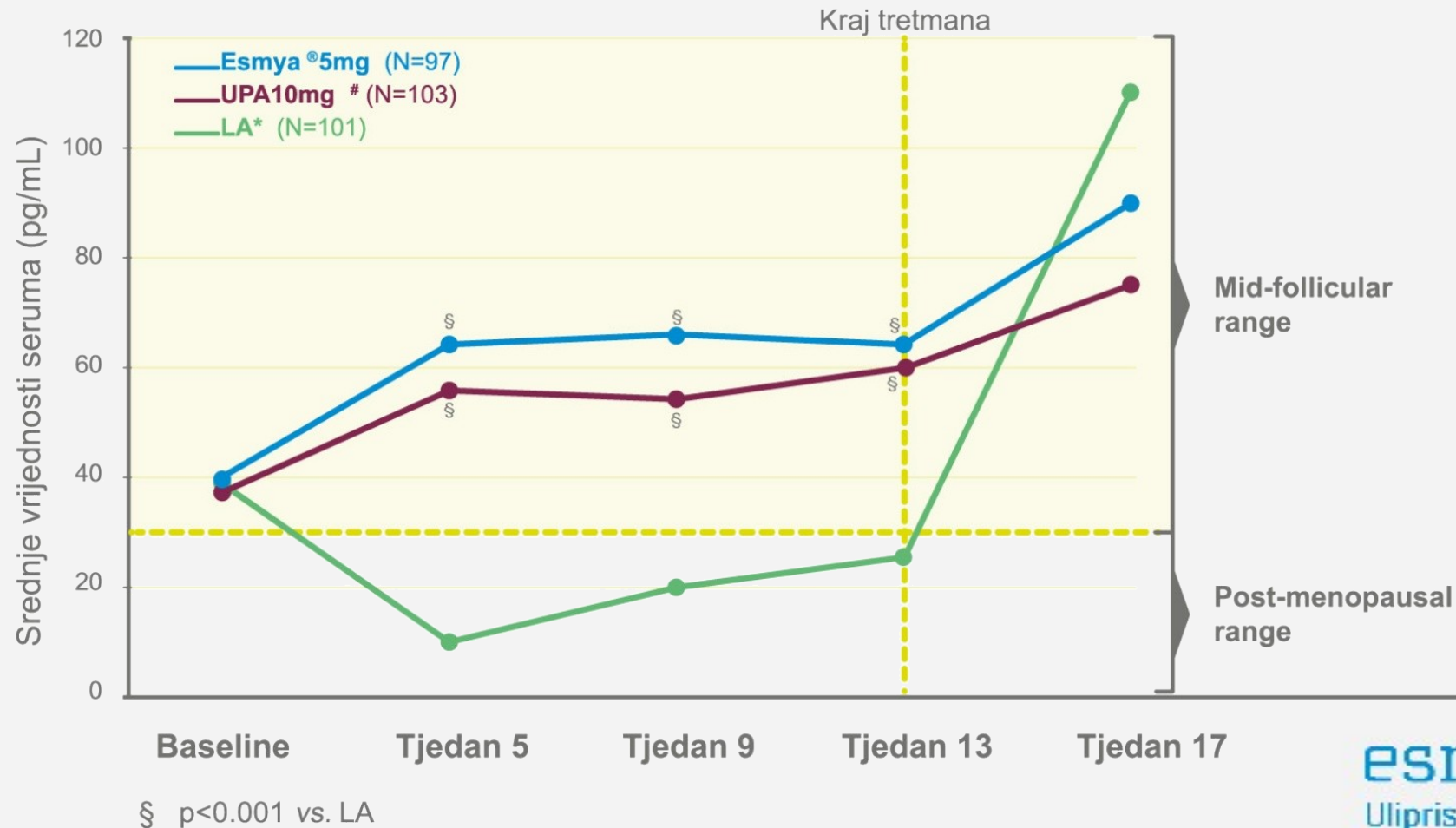
* After treatment course + 1 bleed

N, number of patients with non-missing assessments; UPA, ulipristal acetate

ESMYA: Niska incidencija klimakteričnih tegoba

- Razine estradiola ostaju na razini sredine folikularne faze menstruacijskog ciklusa²

PEARL II





ESMYA: Dobro podnošljiva

Najčešće prijavljena nuspojava u kliničkim ispitivanjima bila je amenoreja koja se smatra poželjnim ishodom liječenja.

I u ponovljenim ciklusima liječenja sigurnosni profil lijeka je očuvan!

PEARL IV:

AE, No. of patients (%)	Treatment course 1		Treatment course 2		Treatment course 3		Treatment course 4	
	UPA 5 mg (N=230)	UPA 10 mg (N=221)	UPA 5 mg (N=215)	UPA 10 mg (N=205)	UPA 5 mg (N=193)	UPA 10 mg (N=188)	UPA 5 mg (N=180)	UPA 10 mg (N=174)
Patients with ≥1 AE	47 (20.4)	43 (19.5)	28 (13.0)	22 (10.7)	9 (4.7)	12 (6.4)	11 (6.1)	14 (8.0)
Glavobolja	10 (4.3)	10 (4.5)	6 (2.8)	0	3 (1.6)	2 (1.1)	1 (0.6)	2 (1.1)
Valovi vrućine	12 (5.2)	14 (6.3)	8 (3.7)	6 (2.9)	3 (1.6)	5 (2.7)	5 (2.8)	7 (4.0)
Slabost / umor	2 (0.9)	5 (2.3)	2 (0.9)	1 (0.5)	0	1 (0.5)	0	1 (0.6)
Akne	4 (1.7)	4 (1.8)	2 (0.9)	1 (0.5)	1 (0.5)	0	0	0

PROMJENE ENDOMETRIJA I SIGURNOST

- Benigne i reverzibilne promjene endometrija, okarakterizirane kao PAEC** zapažene su u 60% pacijentica liječenih sa UPA kroz 3 mjeseca
- Ponavljanjem ciklusa liječenja udio pacijentica sa PAEC-om se smanjuje
- Ove promjene ne smiju se zamijeniti s hiperplazijom endometrija
- Tijekom kliničkih ispitivanja nisu zabilježeni slučajevi kompleksne hiperplazije endometrija i maligniteta



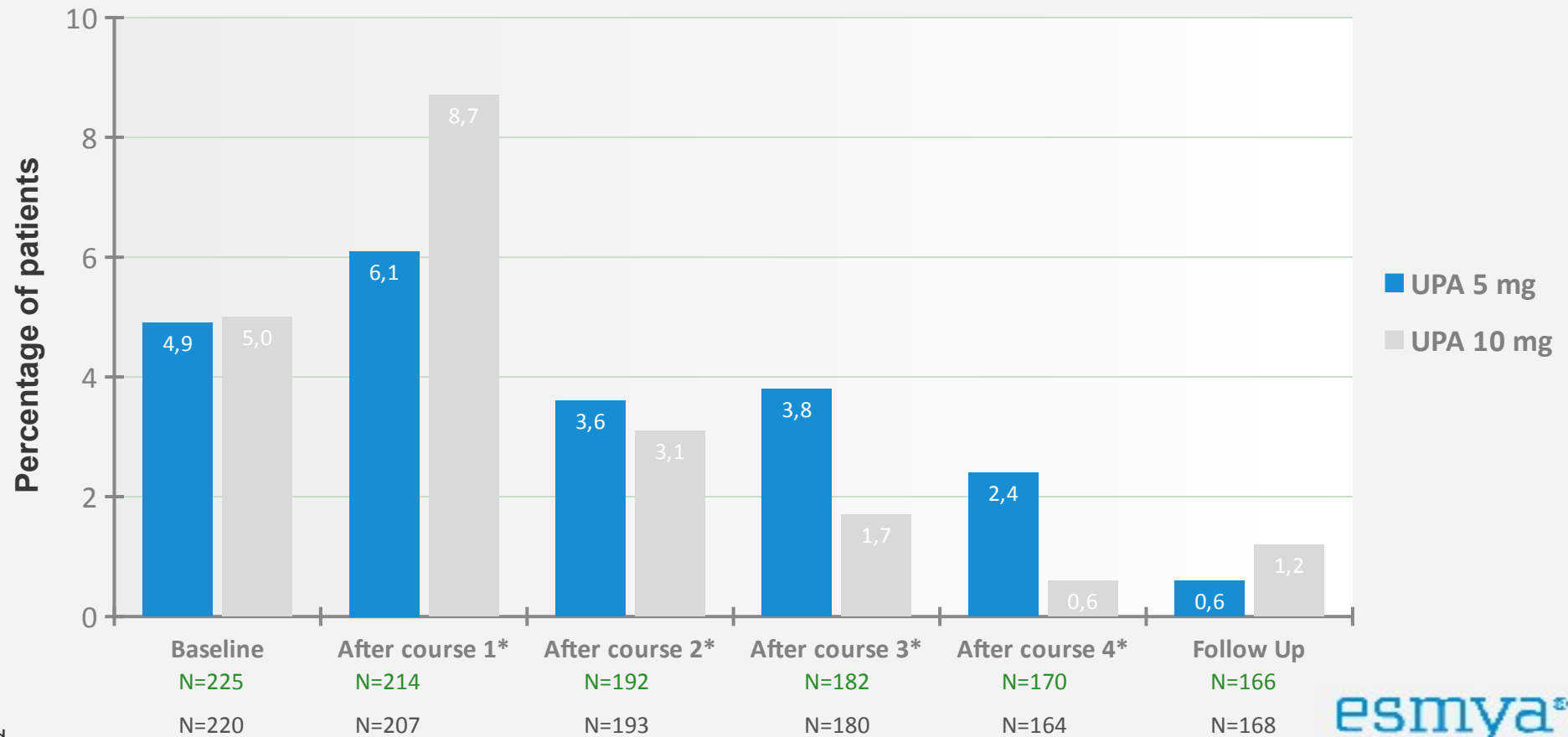
PEARL IV REZULTATI, 4 CIKLUSA LIJEČENJA	Screening		After treatment course 2		After treatment course 4		Follow Up	
Histology, n (%)	UPA 5 mg (N=230)	UPA 10 mg (N=221)	UPA 5 mg (N=230)	UPA 10 mg (N=221)	UPA 5 mg (N=230)	UPA 10 mg (N=221)	UPA 5 mg (N=230)	UPA 10 mg (N=221)
Number of diagnoses	219	203	178	182	148	145	144	142
Non- physiological changes	17 (7.8)	17 (8.4)	29 (16.3)	35 (19.2)	24 (16.2)	15 (10.3)	13 (9.0)	9 (6.3)
*REZULTATI USPOREDIVI SA POČETNIM NALAZIMA !								

* PRM – progesterone receptor modulators
 ** PAEC, PRM-associated endometrial change;

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ZADEBLJENJE ENDOMETRIJA (>16 mm)

Patients with endometrium thickness >16 mm (Safety population)



* After treatment course + 1 bleed

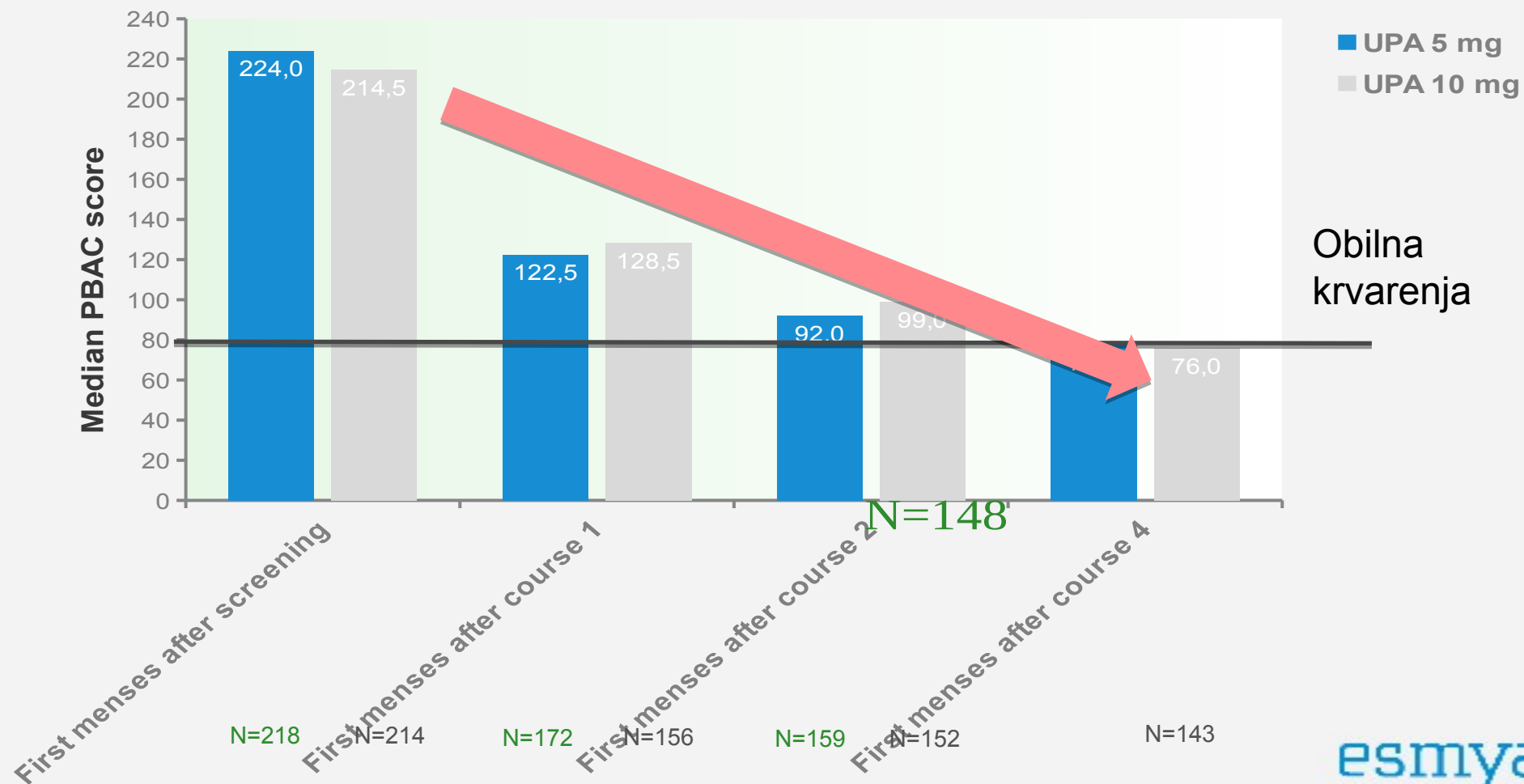
N, number of patients in whom endometrial thickness was measured

UPA, ulipristal acetate

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Ulipristal acetate

Procjena jačine krvarenja u pauzi uzimanja (PBAC score)

PEARL IV

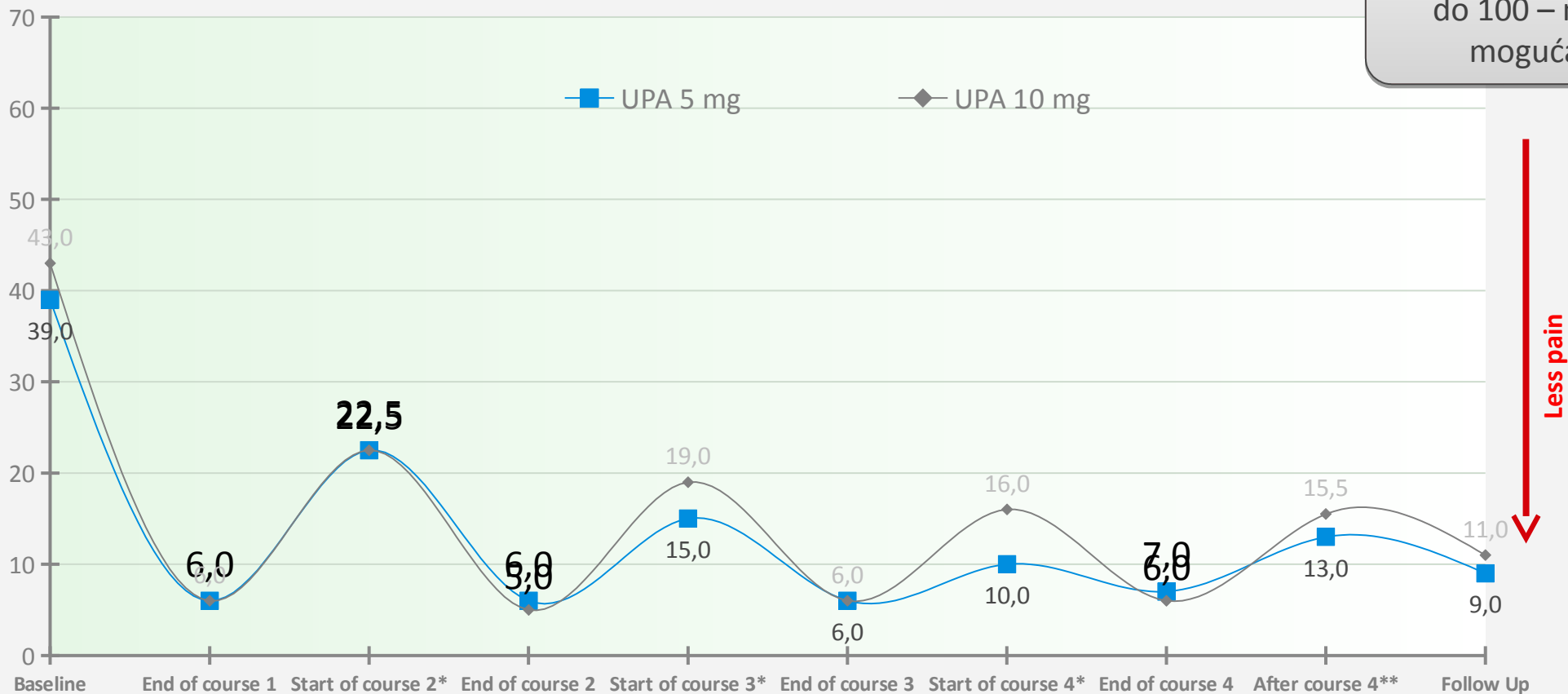


^aOnly the first 8 days of menses are included in the total PBAC score
PBAC, Pictorial Bleeding Assessment Chart; UPA, ulipristal acetate

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ESMYA: Smanjenje boli ponavljanjem ciklusa je veće

PAIN (VAS): Median VAS score (FAS1)



* During menses

** at the start of the second menses after treatment course 4

N, number of patients with non-missing assessments;

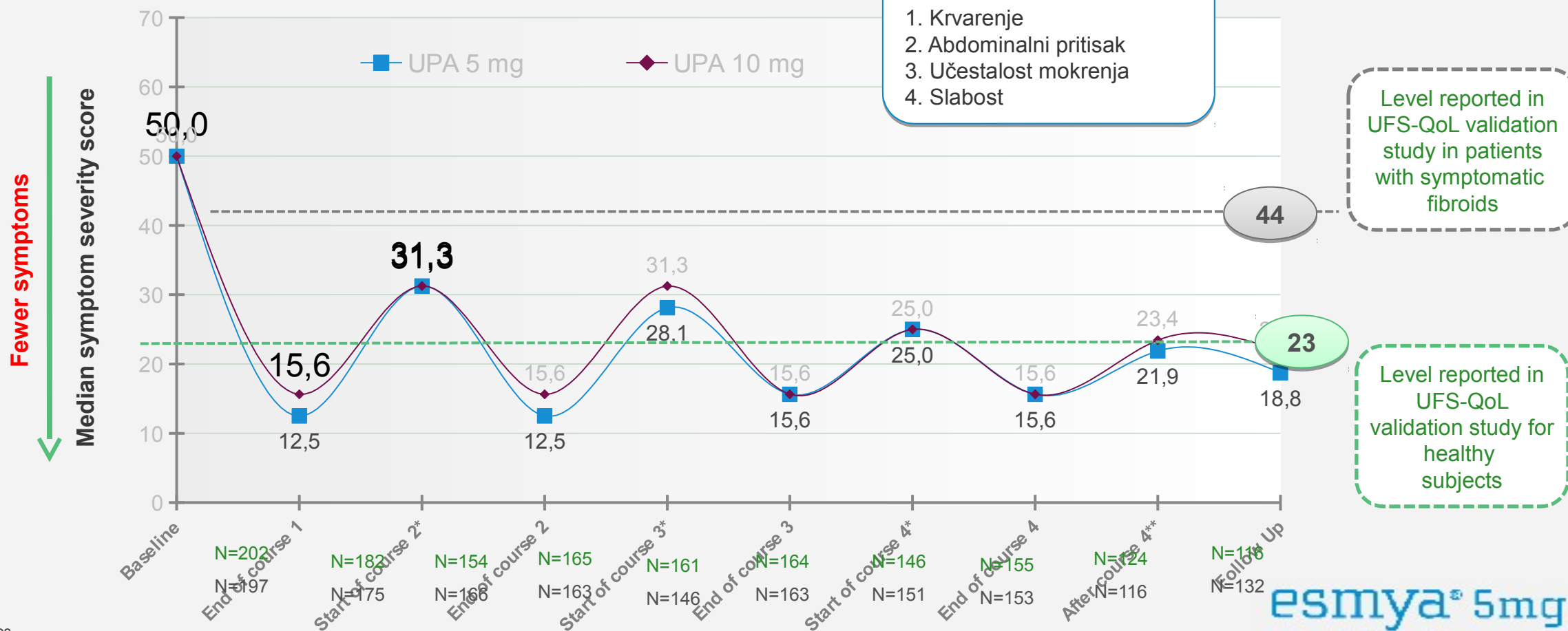
VAS, visual analogue scale UPA, ulipristal acetate;

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ESMYA: Kvaliteta života vraća se na razinu one kod zdravih žena

UFS-QoL: Median symptom severity score (FAS1)

PEARL IV



* During menses

** at the start of the second menses after treatment course 4

N, number of patients with non-missing assessments;

UFS-QoL, Uterine Fibroid Symptom and Quality of Life questionnaire; UPA, ulipristal acetate

1. Spies JB, et al. Obstet Gynecol 2002;99:290–300

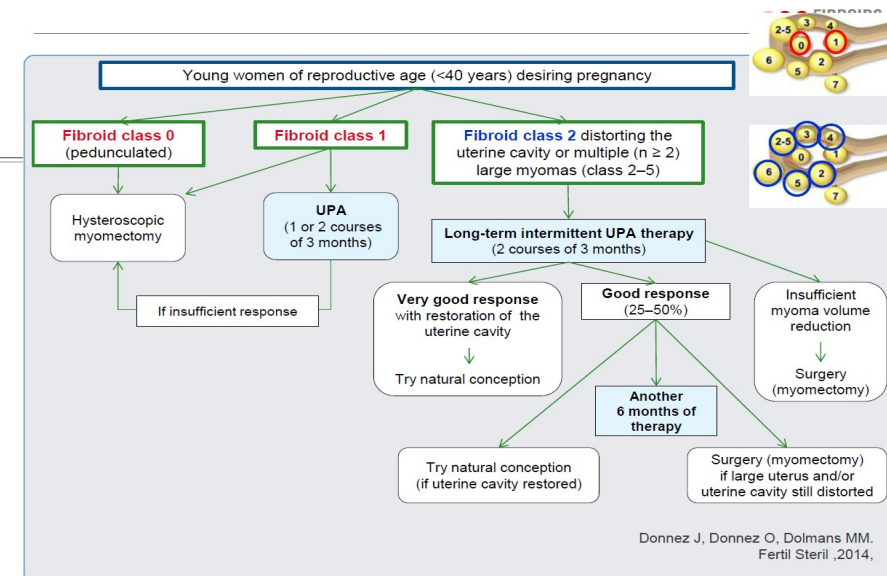
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Predloženi algoritam za pacijentice < 40 g sa simptomatskim miomima i željom za trudnoćom

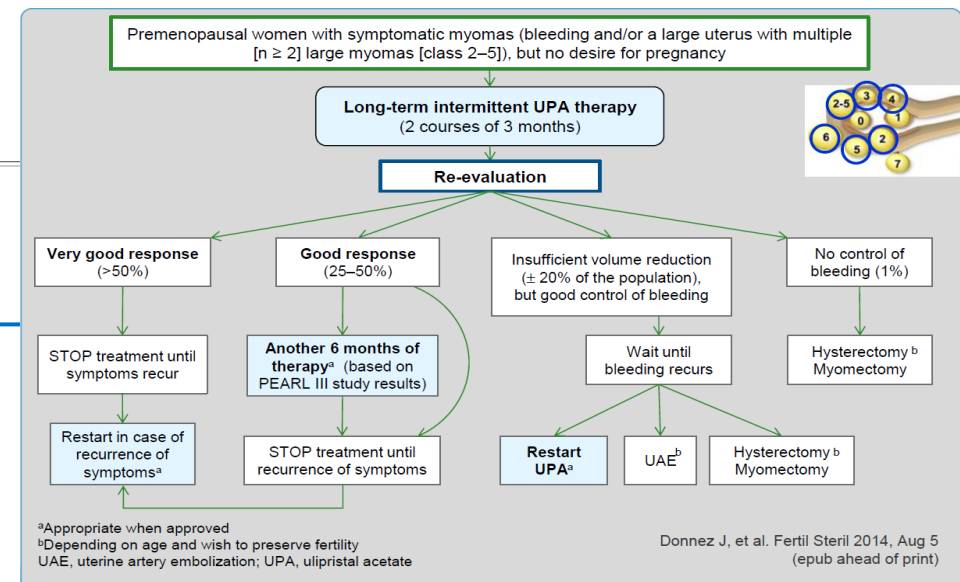
Miomi tip 0 (i 1?) – histeroskopska miomektomija

Miomi tip 2-5 - 2 ciklusa UPA (2 x 3 mjeseca) pa reevaluacija:

- vrlo dobar odgovor (nema deformacije kavuma)– koncepcija ili IVF
- dobar odgovor na terapiju – **koncepcija** ako nema deformacije kavuma ili još **3+3 mj UPA** ili **miomektomija**
- bez zadovoljavajućeg odgovora na terapiju - **miomektomija**



Predloženi algoritam za pacijentice sa simptomatskim miomima koje ne žele trudnoću, ali žele zadržati maternicu



Miomi tip 2-5 - 2 ciklusa UPA (2 x 3 mjeseca) pa reevaluacija:

- vrlo dobar odgovor – čekati do povrata simptoma pa ponoviti liječenje 3+3 UPA
- dobar odgovor na terapiju - još 3+3 mj UPA
- bez značajnog smanjenja volumena ali kontrola krvarenja – KONTROLA SIMPTOMA (cilj liječenja?)
nastaviti UPA ili Histerektomija/Miomektomija –
- Potpuni izostanak odgovora na terapiju – Histerektomija/ Miomektomija

Otvvaraju se nove
mogućnosti
liječenja za žene s
simptomatskim
miomima maternice

