New approaches in the treatment of OAB

assist.mr.sci.Dejan Bratuš, MD

University Medical Center Maribor
Slovenia

The symposium is sponsored by Astellas Pharma

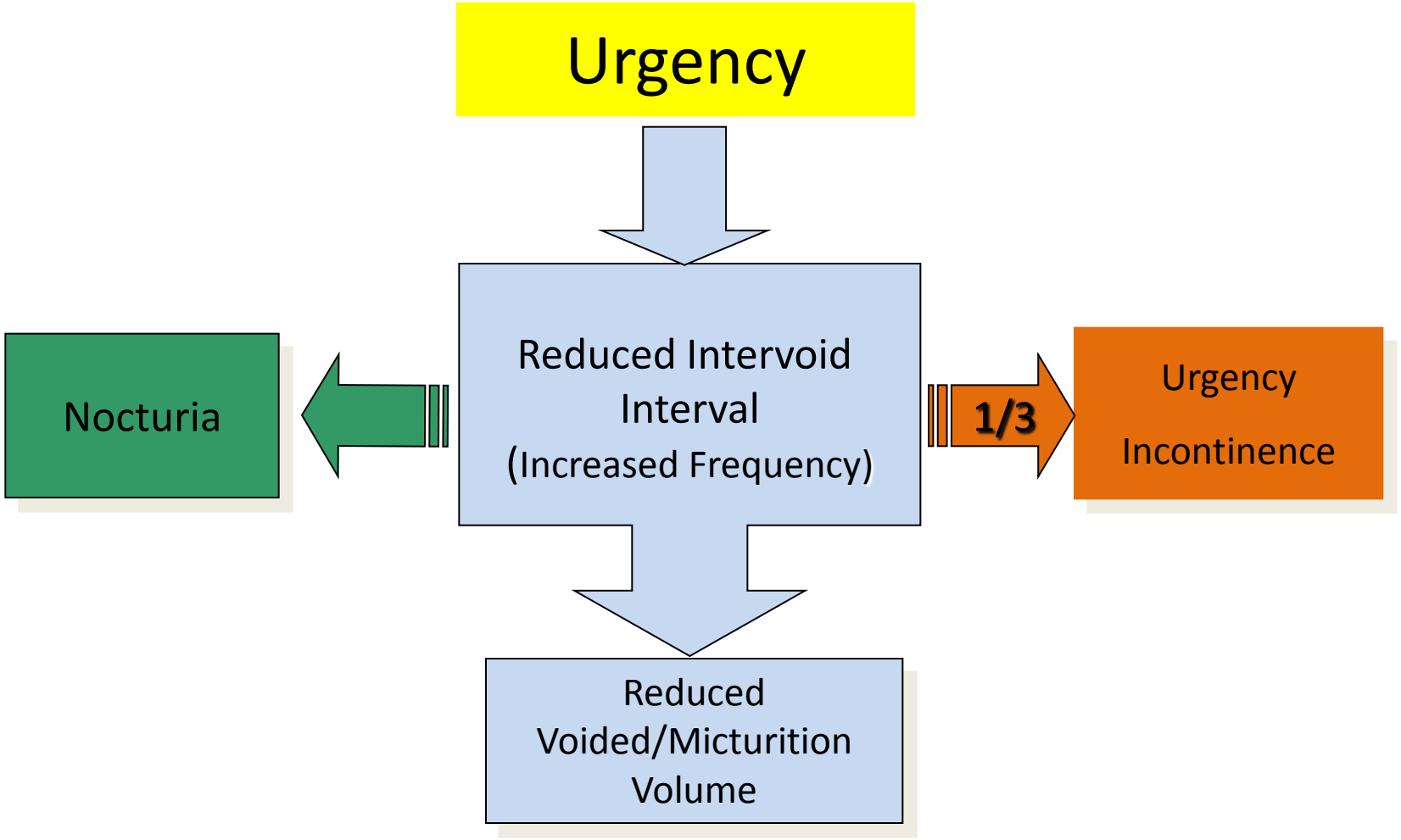
ICS Definition: Overactive Bladder

- OAB is defined as urgency, with or without urgency incontinence, usually with frequency and nocturia

ICS = International Continence Society.

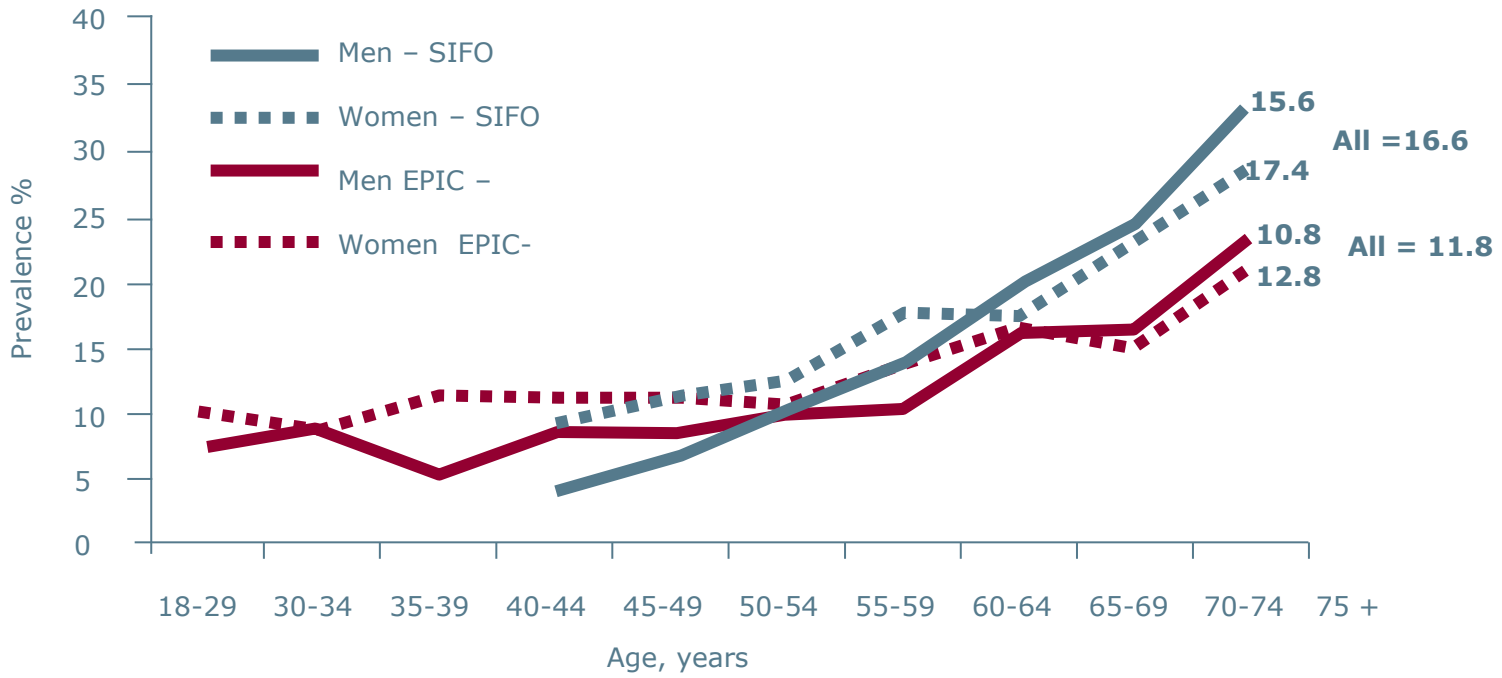
Abrams P et al. *Urology.* 2003;61:37-49.

OAB Syndrome: A symptomatic sequence



Chapple CR, et al. BJU Int 2005;95:335–40

Age and prevalence of OAB[1, 2]



SIFO conducted in 6 European countries (n=16,776)

EPIC conducted in 4 European countries and Canada (n=19,165)

1. Milsom I, et al. BJU Int 2001; 87: 760–766.
2. Milsom I, Irwin DE. Eur Urol Suppl 2007; 6: 4–9.

Impact of OAB on patients QoL

Emotional effects

- Embarrassment
- Shame
- Social withdrawn

Disruption of activities of daily life

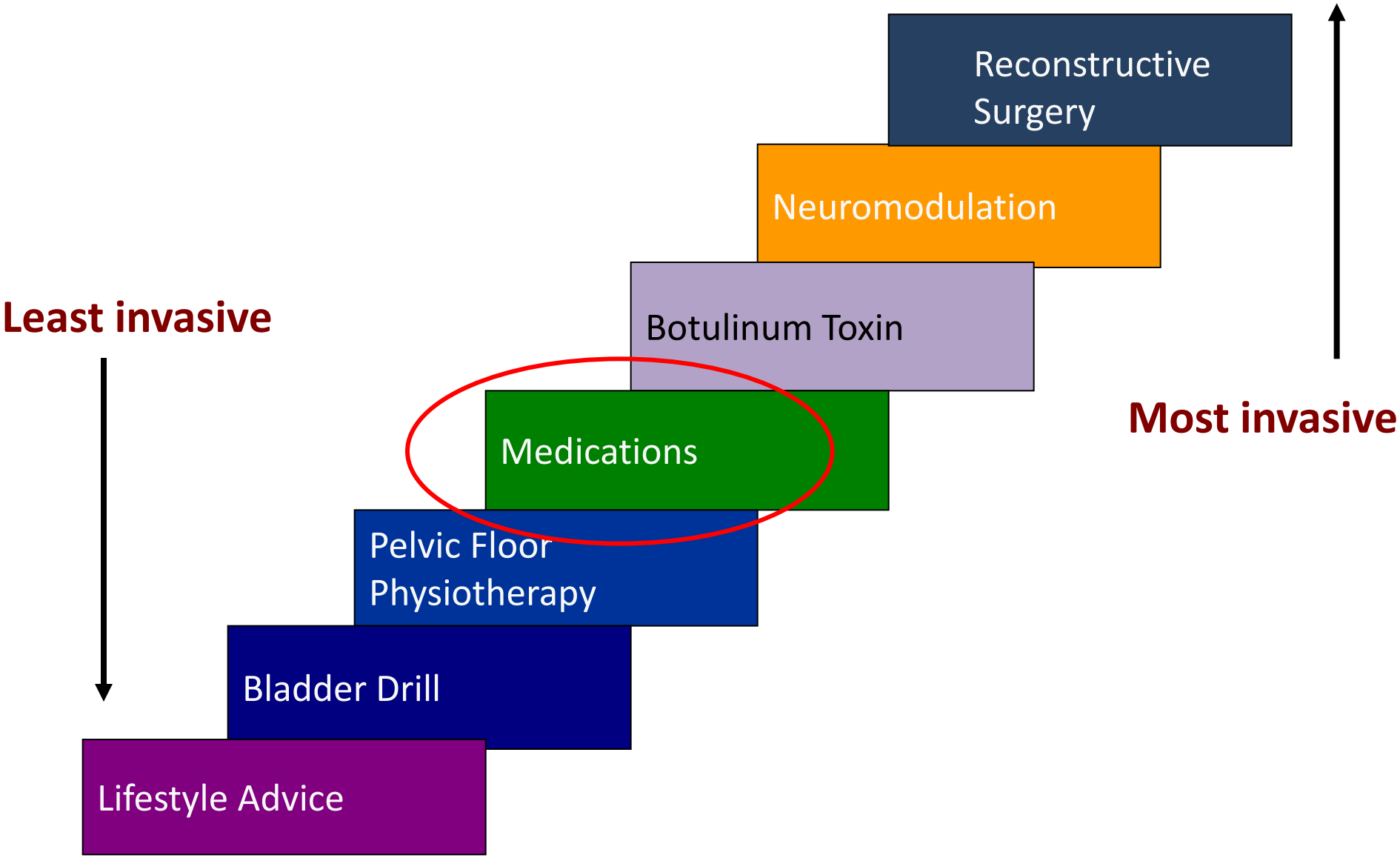
- Proximity to toilets is important
- Reduced fluid intake
- Avoidance of sexual intimacy
- Loss of independence

Quality of life

Economic burden

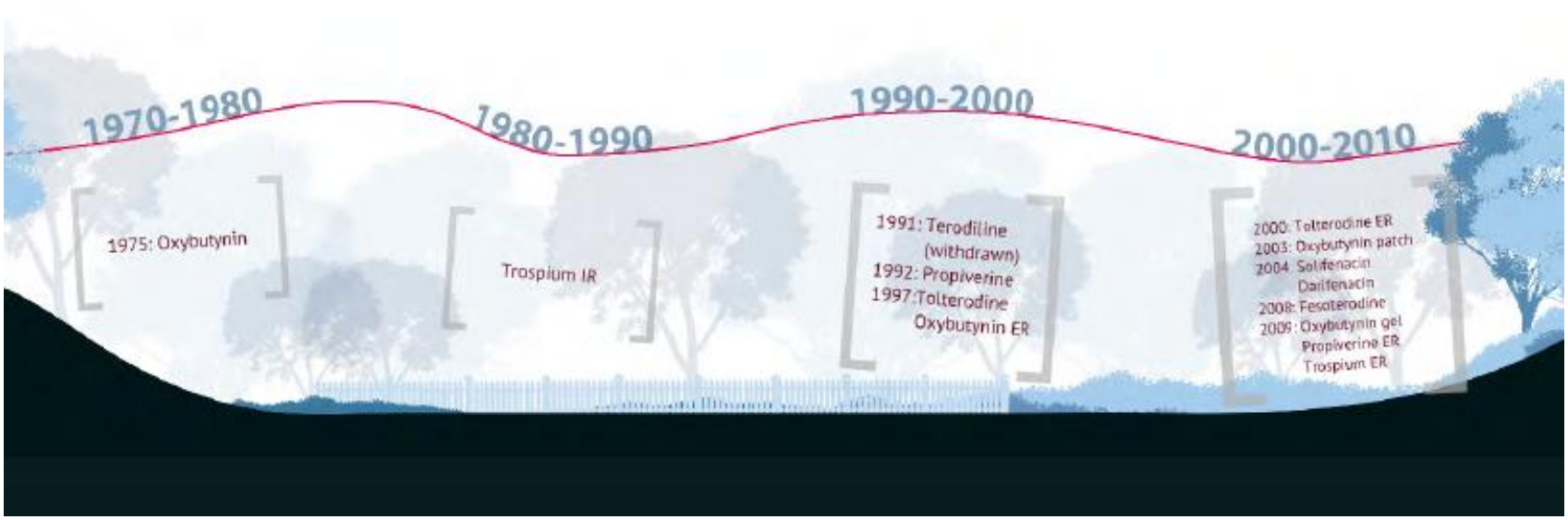
- Money spent on incontinence pads
- Loss of employment
- Direct costs of laundry

Spectrum of treatments in overactive bladder



For the past 30 years….

….antimuscarinics were the only option for majority of patients suffering from OAB ….



Vesicare


STAY IN LANE
FUTURE
PAST

The new class of drugs in treatment of OAB was discovered ...the first articles were published almost 10 years ago…

KJU
Korean Journal of Urology
www.kjurology.org
DOI:10.4111/kju.2010.51.12.811

Review Article

Beta3-Adrenoceptor Agonists: Possible Role in the Treatment of Overactive Bladder

Yasuhiko Igawa, Naoki Aizawa, Yukio Homma[1]

Department of Continence Medicine, University of Tokyo Graduate School of Medicine, [1]Department of Urology, University Graduate School of Medicine, Tokyo, Japan

EXPERT OPINION

1. Introduction
2. Materials and methods

Drug Discovery Case History

Discovery history and clinical development of mirabegron for treatment of overactive and urinary incontinence

MIRABEGRON FOR THE TREATMENT OF OVERACTIVE BLADDER

Curr Urol Rep
DOI 10.1007/s11934-013-0335-8

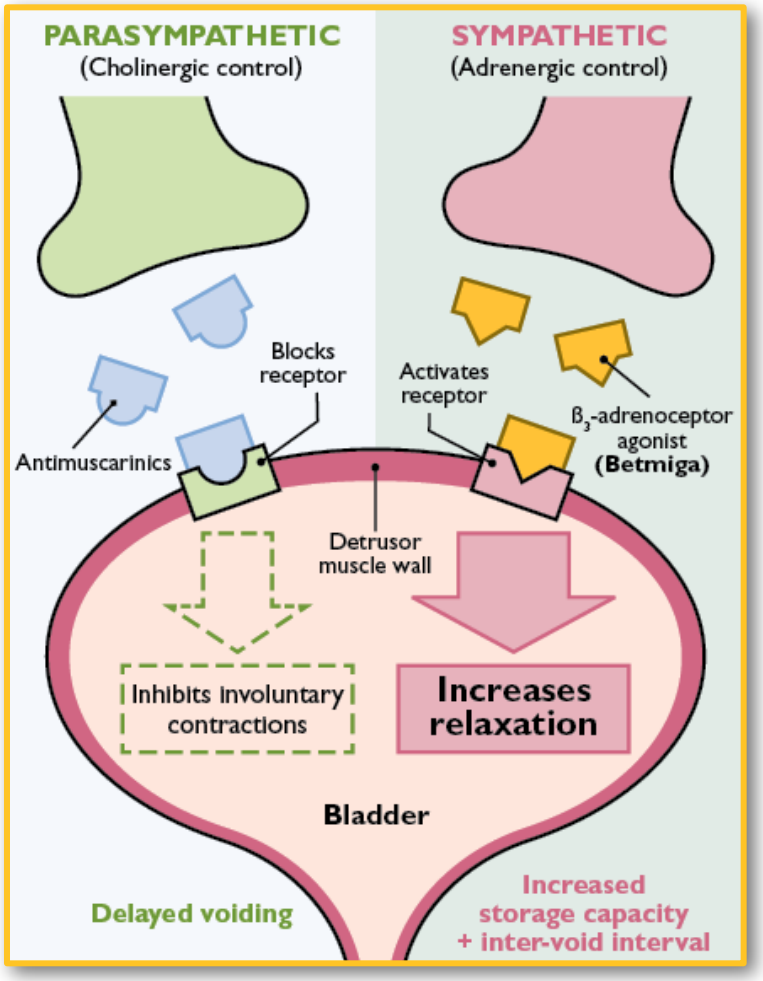
LOWER URINARY TRACT SYMPTOMS AND VOIDING DYSFUNCTION (G BADLANI AND H GOLDMAN, SECTION EDITORS)

β_3-Receptor Agonists for Overactive Bladder—New Frontier or More of the Same?

Karl-Erik Andersson

Antimuscarinics and beta-3 agonists in OAB – Mode of Action

Mode of action of OAB treatments



Adapted from Chu FM, Dmochowski R. Am J Med 2006;119(3 Suppl 1):3–8.

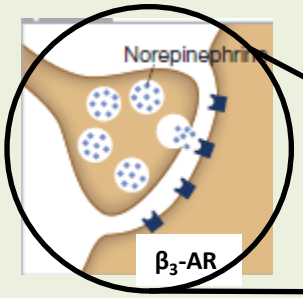
Mirabegron promotes urine storage through potent and selective agonism of the β_3-AR

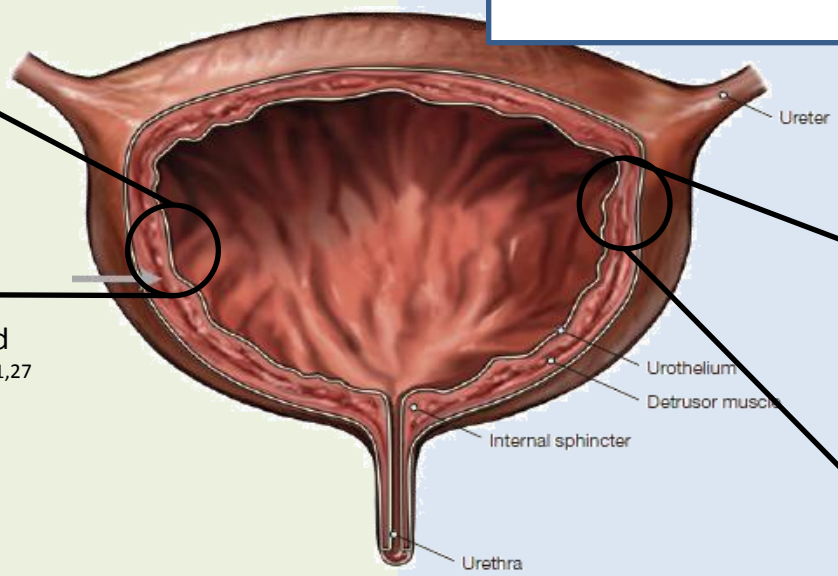
- Mirabegron is a potent full agonist for the β_3-AR[1,25,26]
- Mirabegron is highly selective for the β_3-AR subtype over the β_1- and β_2-ARs[26]
  - 105-fold greater affinity for β_3- vs β_1-AR
  - 33-fold greater affinity for β_3- vs β_2-AR

Binding affinity (K_i) of mirabegron for human ARs[26]

Receptor subtype	Mirabegron K_i, nmol/L*
β_1-AR	4,200 ± 900
β_2-AR	1,300 ± 300
β_3-AR	40 ± 20.2

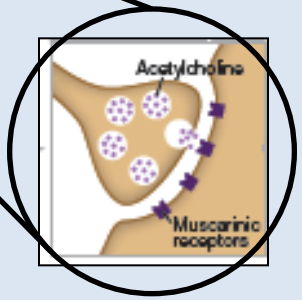
Activation of the β_3-AR by mirabegron stimulates detrusor relaxation to promote urine storage[1,27]





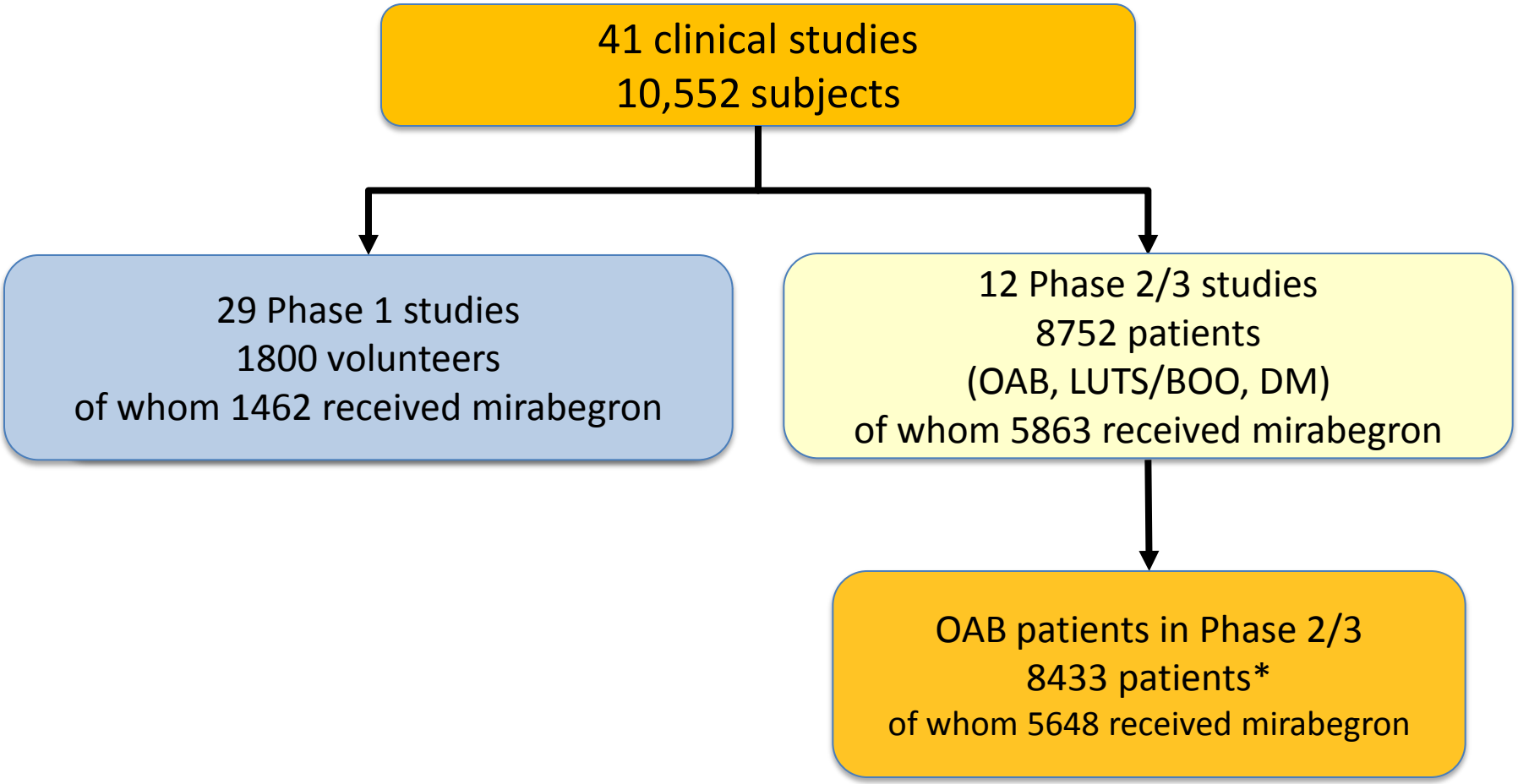
→increased bladder capacity and increased duration between voids[1,27]

In contrast, mirabegron has no effect on parasympathetic stimulation of detrusor contraction and bladder emptying[1,25]



→may reduce the risk of acute urinary retention compared with antimuscarinics[1,25,28]

Mirabegron



*622 OAB patients received mirabegron ≥1 year

Primary and key secondary endpoints:

Phase 3 (Europe, Australia, USA and Canada)

Co-Primary Efficacy Variables

- Change from baseline to Final Visit (end of treatment) in mean number of
  - Incontinence episodes/24h*
  - Micturitions/24h*

Key Secondary Efficacy Variables

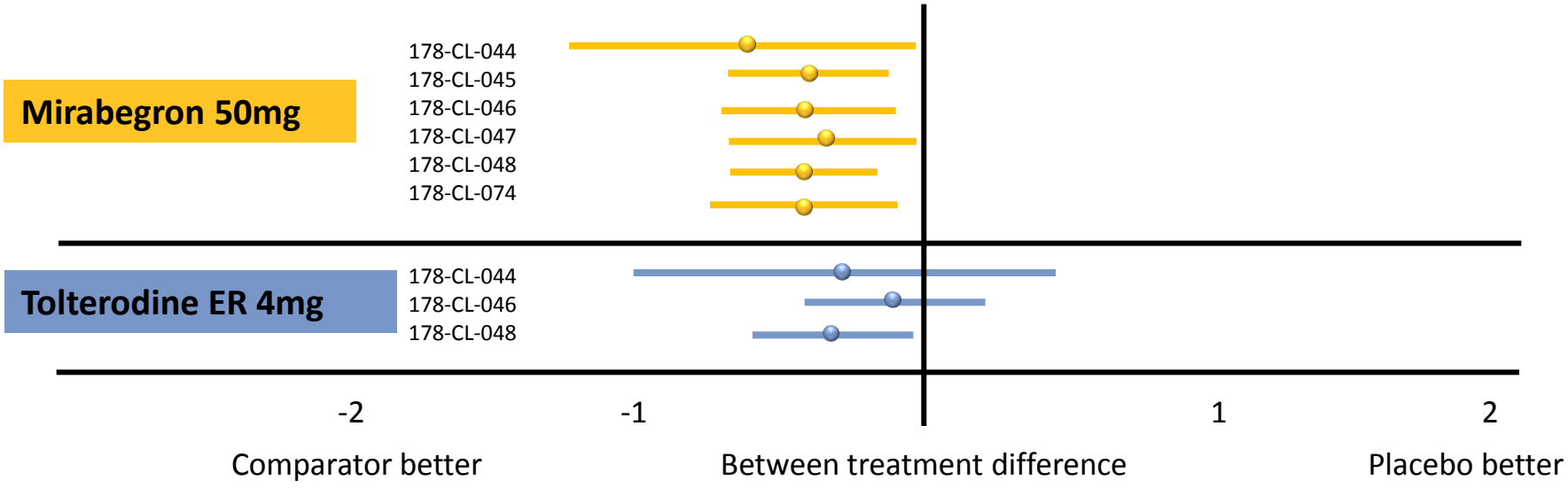
- Change from baseline to Final Visit (end of treatment) in mean voided/micturition volume
- Change from baseline to Week 4 in mean number of
  - Incontinence episodes/24h*
  - Micturitions/24h*

*Based on 3-day diary
EU, Europe; NA, North America (USA and Canada)

1. Khullar V, et al. *Eur Urol* 2013;63(2):283-95. 2. Nitti V, et al. *J Urol* 2012. pii: S0022-5347(12)05216-0.
3. Herschorn S et al. Urology 2013;82(2):313-320

Mean number of incontinence episodes/24 hrs in primary studies

- Consistent response across studies including those with tolterodine ER 4mg as an active control

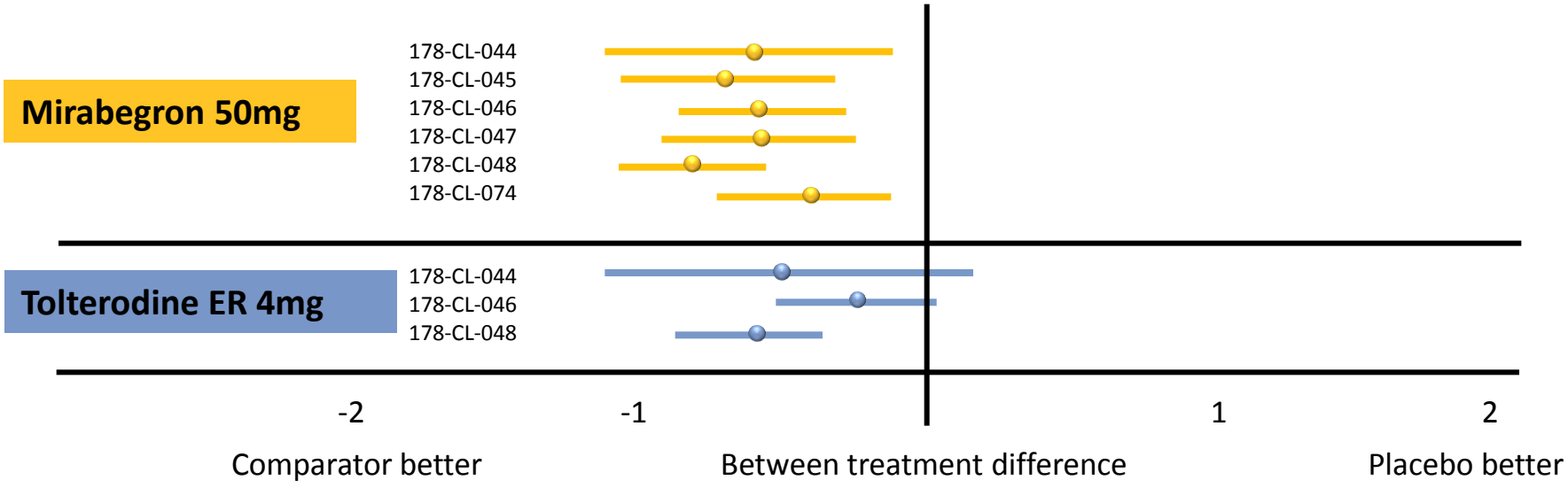


Astellas Data on File MIR/13/0004/EU

BET/13/0136/EU

Mean number of micturitions/24 hrs in primary studies

- Consistent response across studies including those with tolterodine ER 4mg as an active control



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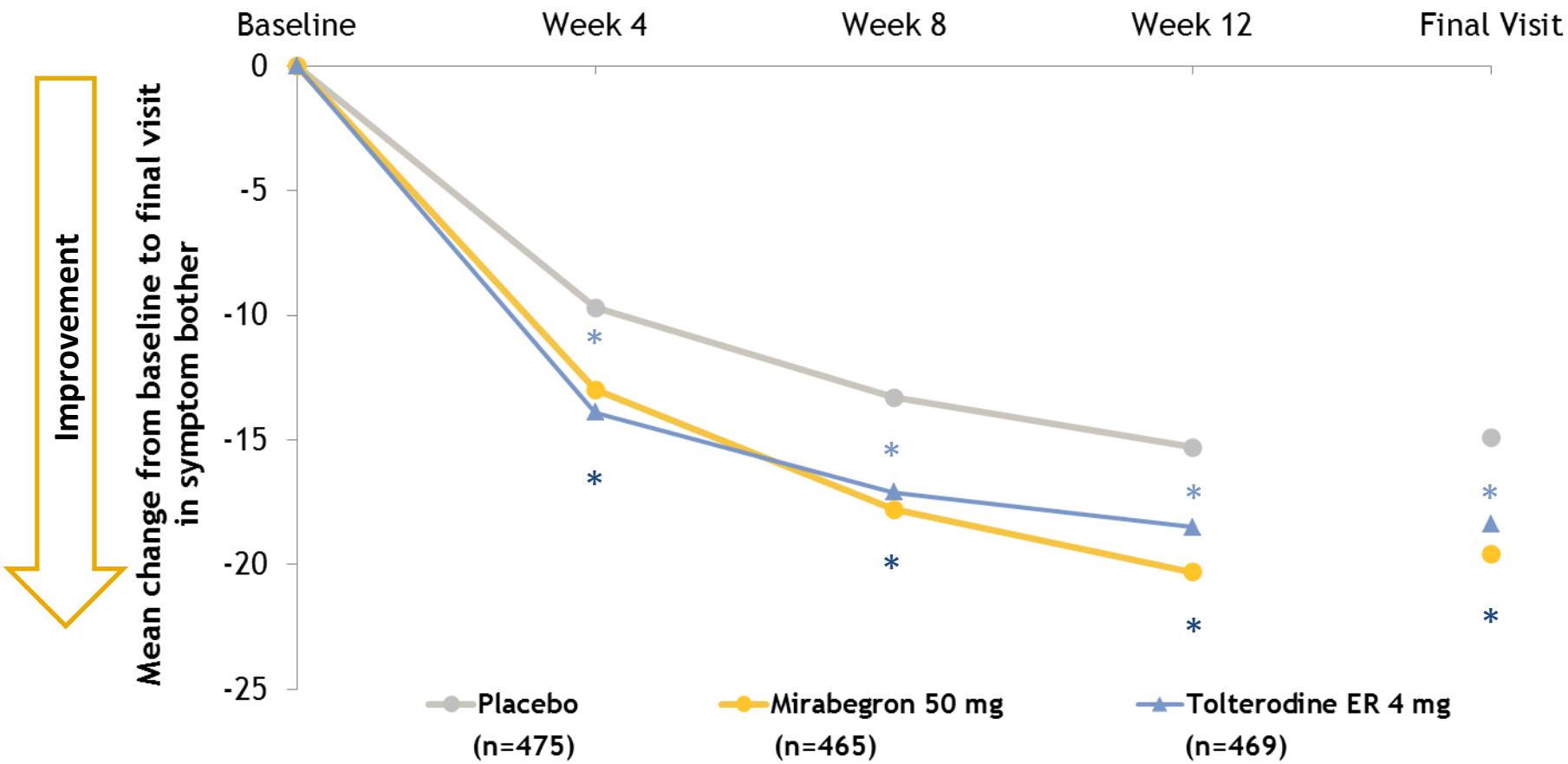
Quality of life

Mirabegron significantly improved symptom bother (OAB-q) at each visit (FAS): 046



FAS, Full Analysis Set
OAB-q, overactive bladder questionnaire

* Statistically significant improvement versus placebo at 0.05 level

1. Adapted from Khullar V, et al. *Eur Urol* 2013;63(2):283–95.

BET/13/0136/EU

Tolerability and safety profile

Study 046-Common treatment-emergent adverse events (≥2% in any treatment group)

Adverse events n (%)	Placebo (n=494)	Mirabegron 50mg (n=493)	Tolterodine ER 4mg (n=495)
Hypertension	38 (7.7 %)	29 (5.9%)	40 (8.1%)
Nasopharyngitis	8 (1.6%)	14 (2.8%)	14 (2.8%)
Dry Mouth	**13 (2.6%)**	**14 (2.8%)**	**50 (10.1%)**
Headache	14 (2.8%)	18 (3.7%)	18 (3.6%)
Influenza	8 (1.6%)	11 (2.2%)	7 (1.4%)
Urinary tract infection	7 (1.4%)	7 (1.4%)	10 (2.0%)
Constipation	**7 (1.4%)**	**8 (1.6%)**	**10 (2.0%)**

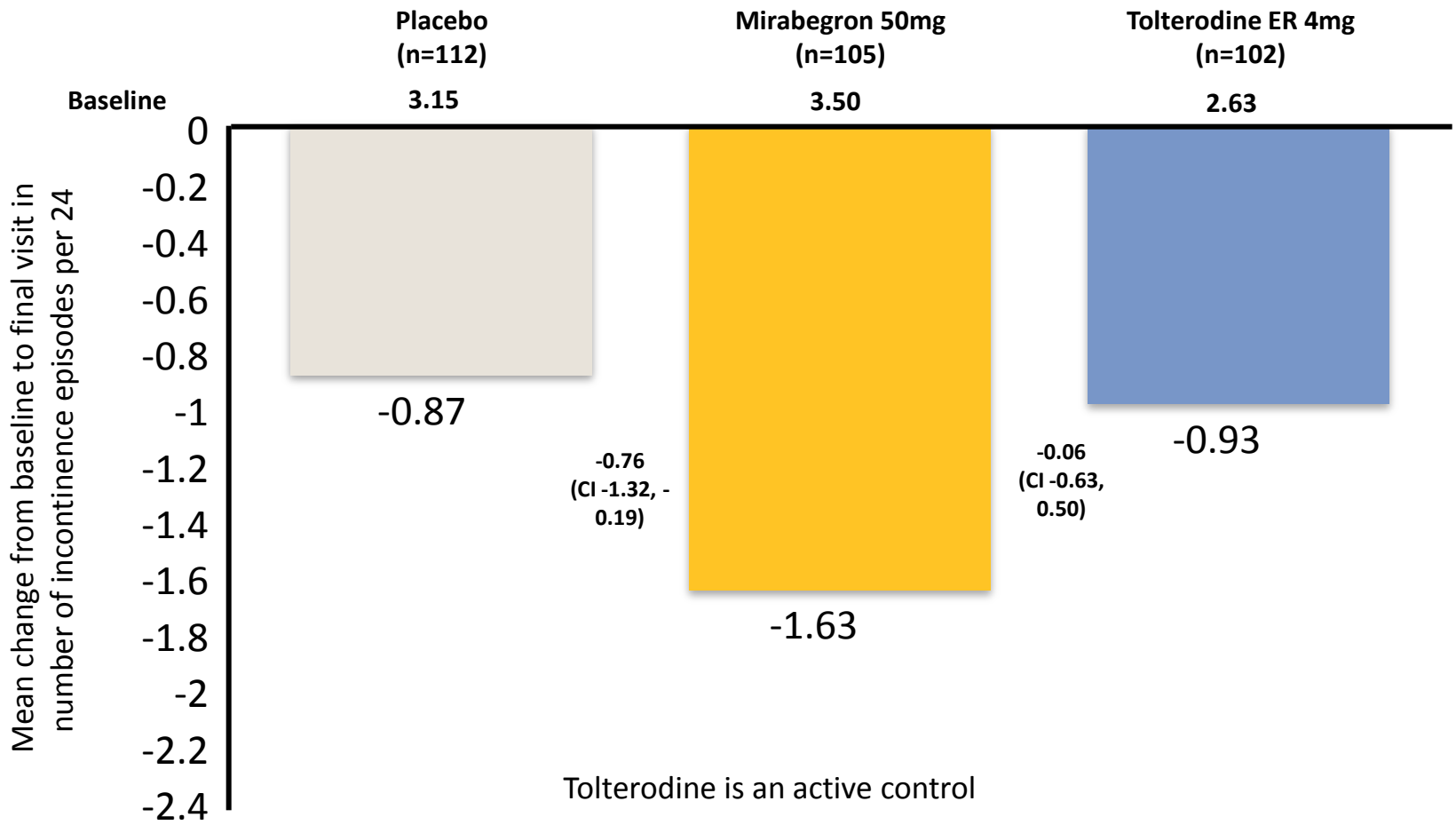
Data are for the safety analysis set. Adverse events, defined according to the Medical Dictionary for the Regulatory Activities (MedDRA version 9.1)

BET/13/0136/EU

Adapted from Khullar V, et al. *Eur Urol* 2013; 63: 283-95

Post-hoc analysis (study 046)

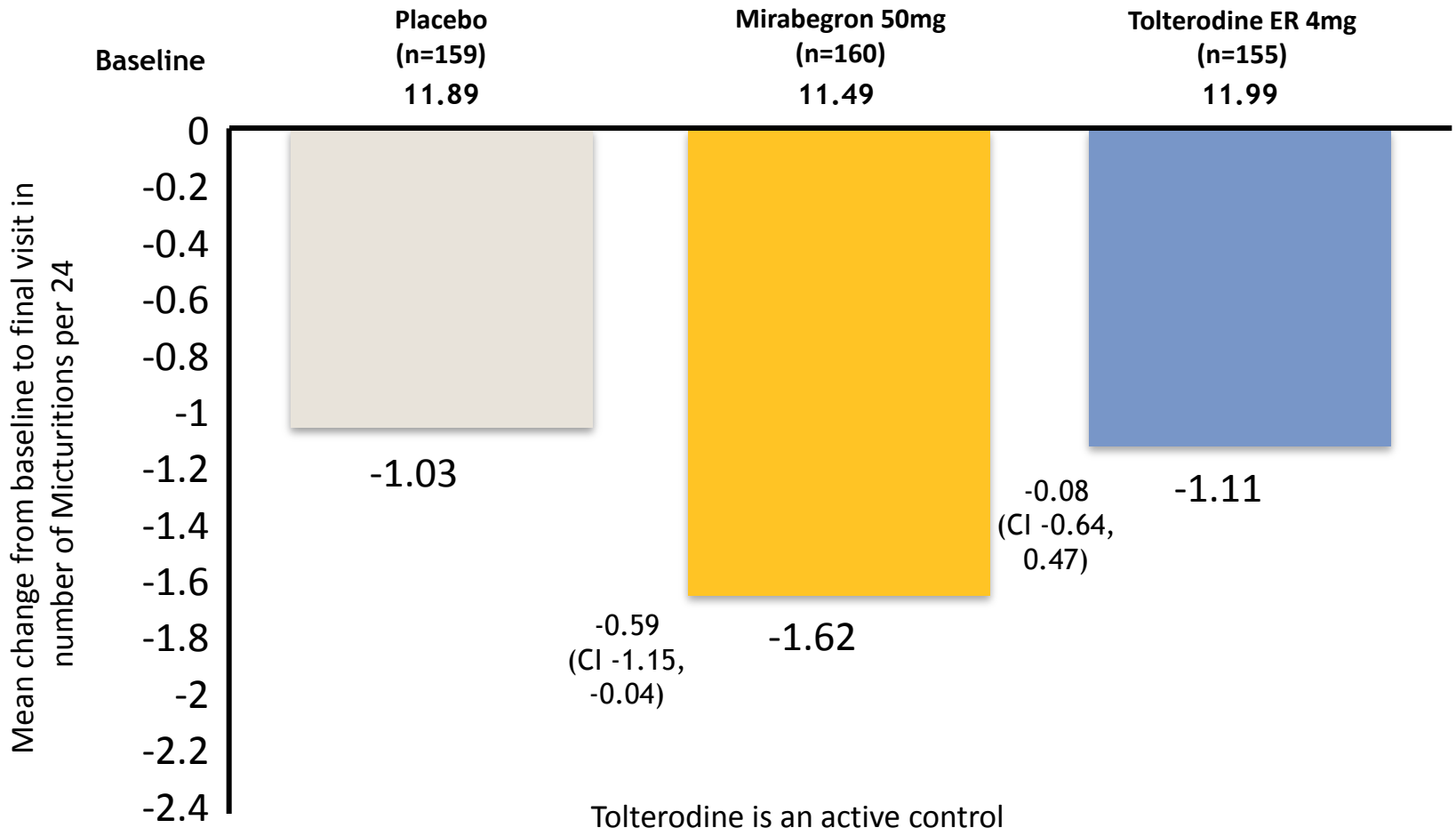
Post-hoc analysis (Study 046): Incontinence
Prior OAB medication with insufficient efficacy



Adapted from Khullar V et al. BMC Urology 2013,13:4.doi:10,1186/1471-2490/13/45

BET/13/0136/EU

Post-hoc analysis (Study 046): Micturitions Prior OAB medication with insufficient efficacy



Adapted from Khullar V et al. BMC Urology 2013,13:4.doi:10,1186/1471-2490/13/45


Welcome To
The Future

Best friends in treatment of OAB

Combination Treatment with Mirabegron and Solifenacin in Patients with Overactive Bladder: Efficacy and Safety Results from a Randomised, Double-blind, Dose-ranging, Phase 2 Study (Symphony)

- Combining the β3-adrenoceptor agonist mirabegron and the antimuscarinic (AM) agent solifenacin may improve efficacy in the treatment of overactive bladder (OAB) while reducing the AM side effects.
- The primary objective was to evaluate the efficacy of combinations of solifenacin/mirabegron compared with solifenacin 5mg monotherapy. The secondary objective was to explore the dose-response relationship and the safety/tolerability compared with placebo and monotherapy.

Abrams P, Kelleher C, Staskin D, Rechberger T, Kay R, Martina R, Newgreen D, Paireddy A, van Maanen R, Ridder A. Eur Urol. 2014 Feb 19. [Epub ahead of print]

Conclusions

- Combination therapy with solifenacin/mirabegron significantly improved MVV, micturition frequency, and urgency compared with solifenacin 5 mg monotherapy. All combinations were well tolerated, with no important additional safety findings compared to monotherapy or placebo.

- **The best balance between efficacy and tolerabilty was achieved by combination mirabegron 50 mg + solifenacin 5mg.**

Abrams P *Eur Urol* 2014 pii:S0302 – 2838 (14)00131-6 doi: 10.1016/j.eururo.2014.02.012;

BESIDE study

Efficacy and safety of mirabegron add-on treatment to solifenacin in incontinent OAB subjects with an inadequate response to initial 4-week solifenacin monotherapy

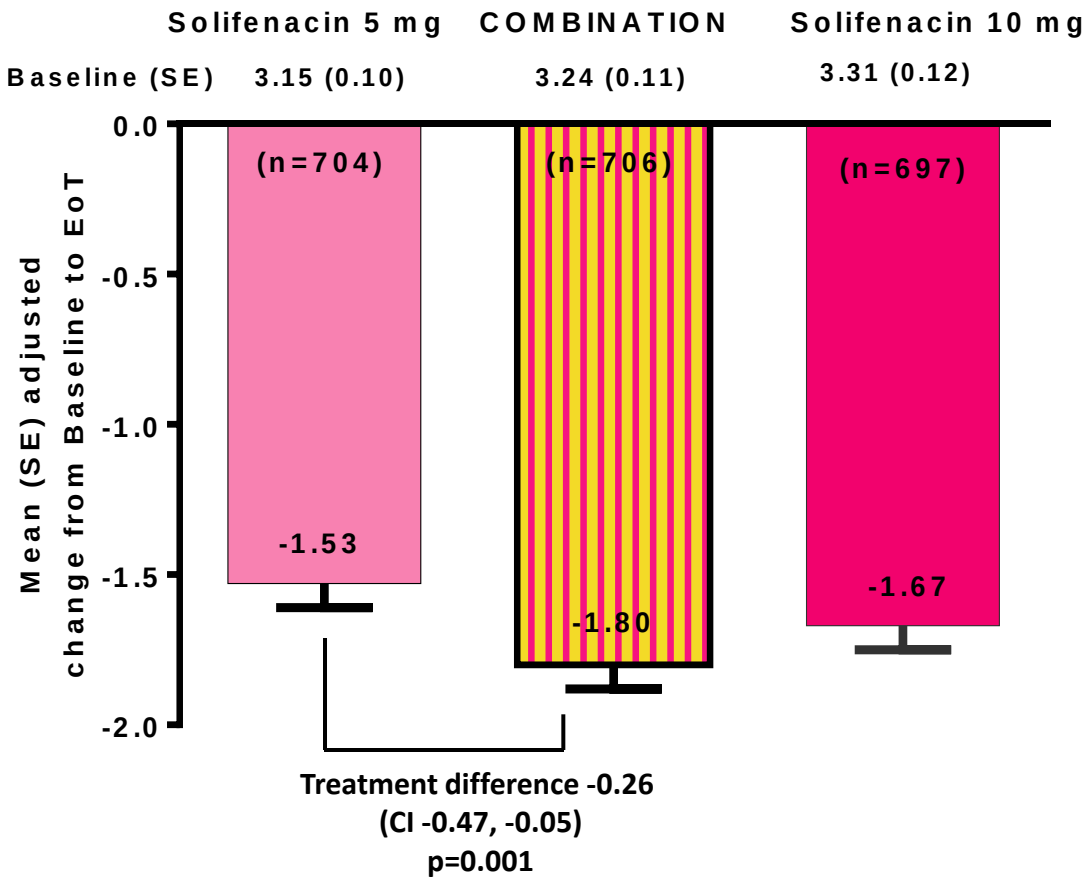
Drake M. J Urol 2015;193(4 Suppl):e498-e499(abs.PII-LBA9)

Study design and results

- 2172 patients randomised into study – pts who required additional relief of their OAB following solifenacin 5mg monotherapy – they`ve received combination therapy (mirabegron 25mg-50mg* + solifenacin 5mg)
- Objectives:
  - Improved efficacy with add-on therapy versus monotherapy
  - Primary endpoint: # of incontinence episodes
  - Superiority study
- Results:

  At EoT, reductions in the mean number of incontinence episodes/24 h, the mean number of micturitions/24 h, and incontinence episodes during a 3-day diary, were statistically significantly greater in the COMBN group vs SOLI 5 mg.

Primary efficacy endpoint: change from baseline to EoT in mean number of incontinence episodes/24 h

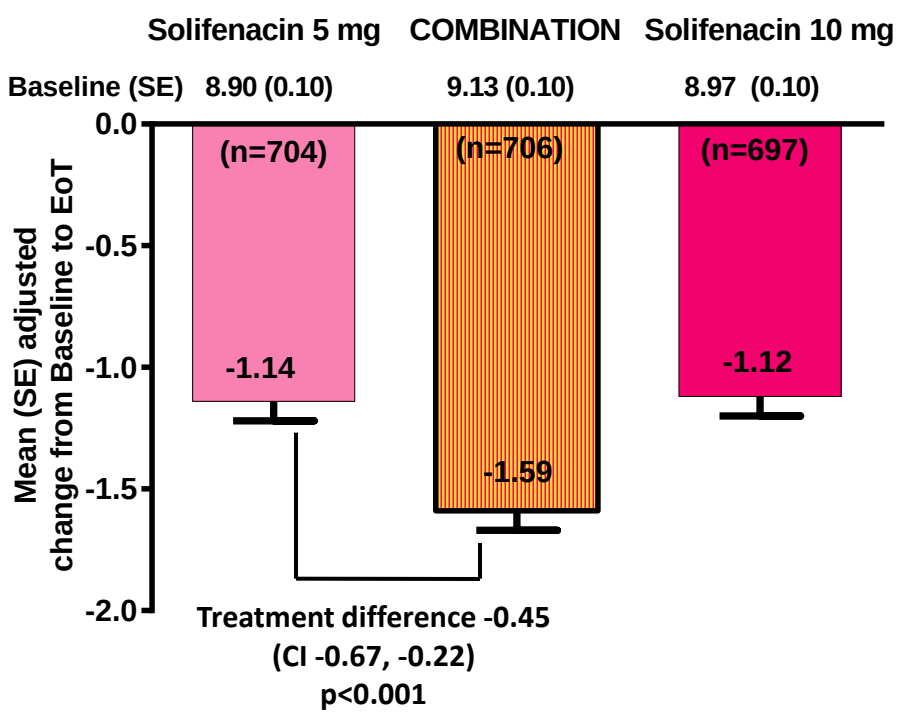


Adjusted change from Baseline and 95% CIs for pair-wise comparisons were derived from an ANCOVA model with treatment group, sex, age group (<65, ≥65 years), geographic region and 4 week incontinence episode reduction group (<50%, ≥ 50%) as fixed factors and mean number of incontinence episodes/24h at Baseline as covariate. P-values for pair-wise comparisons are from a separate stratified rank ANCOVA model. P<0.05 indicates superiority in favour of treatment group with the largest improvement. Full Analysis Set (FAS): randomized subjects who took ≥1 dose of study treatment, reported ≥ 1 micturition at baseline and post-baseline, and ≥ 1 incontinence episode at baseline. EoT=end of treatment. CI=95% confidence interval. SE=standard error

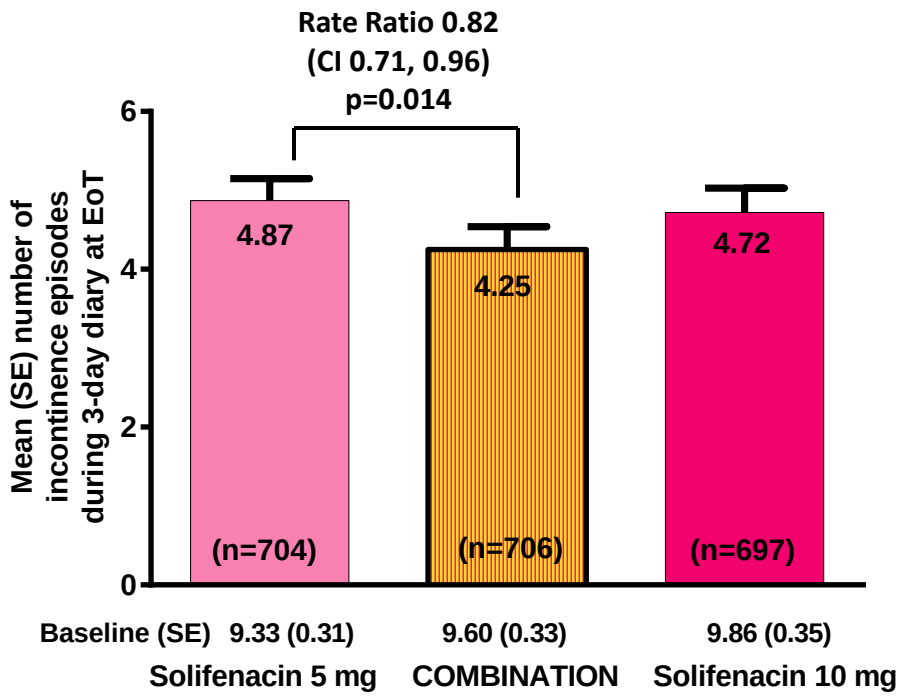
Drake M. J Urol 2015;193(4 Suppl):e498-e499(abs.PII-LBA9)

Key secondary efficacy endpoints

1. Change from baseline to EoT in mean number of micturitions/24 h



2. Number of incontinence episodes reported during 3-day diary at EoT



1. Adjusted change from Baseline, 95% CIs and p-values for pair-wise comparisons were derived from an ANCOVA model with treatment group, sex, age group (<65, ≥65 years), geographic region and 4 week incontinence episode reduction group (<50%, ≥ 50%) as fixed factors and Baseline value as a covariate
2. Results are from a Poisson regression model including treatment group, sex, age group (<65, ≥65 years), geographic region, 4-week incontinence episode reduction group as factors, log (number of incontinence episodes/number of valid diary days) at Baseline as covariate and log (number of valid diary days) as the offset variable.CI=95% confidence interval; EoT=end of treatment; SE=standard error

Drake M. J Urol 2015;193(4 Suppl):e498-e499(abs.PII-LBA9)

Conclusion

- In incontinent OAB patients with an insufficient response to solifenacin 5 mg, add-on treatment with mirabegron provides additional benefit compared to solifenacin 5 mg monotherapy or an increase to solifenacin 10 mg and is well tolerated

Drake M. J Urol 2015;193(4 Suppl):e498-e499(abs.PII-LBA9)

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