ELECTRONIC SUPPLEMENTARY MATERIAL

Cost Effectiveness of Mirabegron Compared with Tolterodine Extended Release for the Treatment of Adults with Overactive Bladder in the United Kingdom

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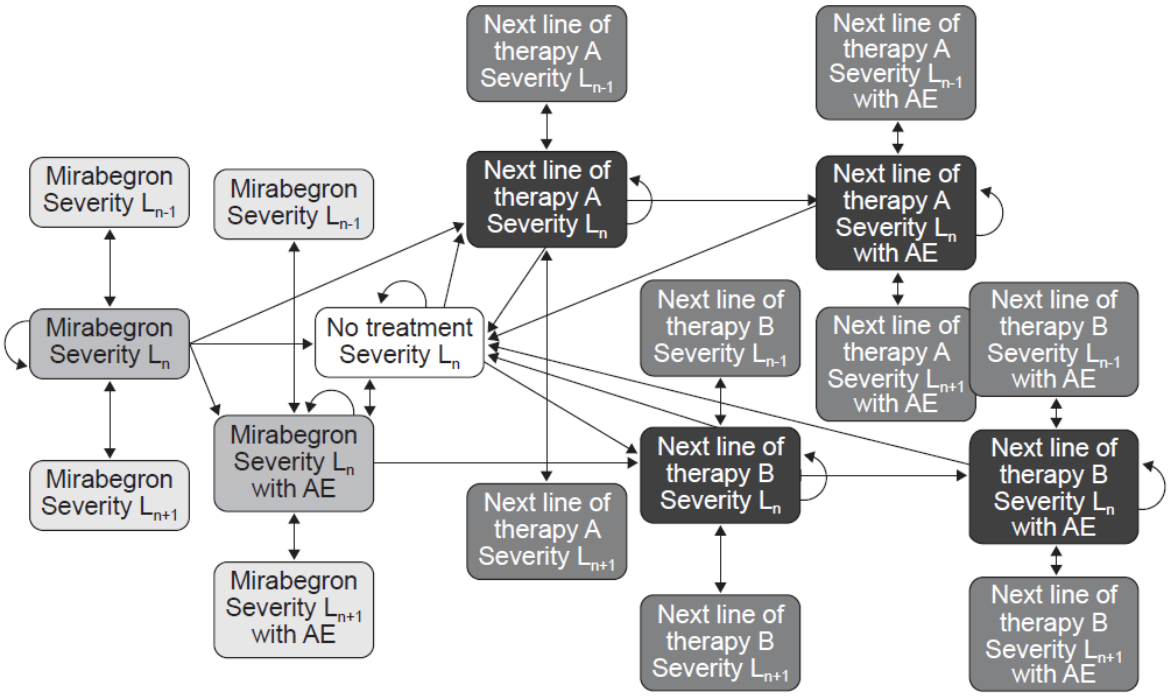
Model structure for the general OAB population

Supplementary Figure 1. Transitions for the general population before BTX initiation



The model simulates in parallel the evolution of two symptom types: micturitions and incontinence. For each of these symptoms, five levels of severity are defined.

Input parameters

Supplementary Table 1. Input parameters for base case model: general OAB population - mirabegron 50 mg vs tolterodine ER 4 mg

Parameter	Base case value	DSA values	PSA	Source
Statistical distributions for proportions of patients by severity level at baseline - General OAB population				
Micturition 1	6.30%	0% - 0%	Dirichlet distribution[1] (α1, α2, α3, α4, α5)=(120,585,518,371,312)	Base case / PSA: SCORPIO based on pooled data from the 3 treatment arms at baseline DSA: assumption
Micturition 2	30.69%	100% - 0%		
Micturition 3	27.18%	0% - 0%		
Micturition 4	19.46%	0% - 0%		
Micturition 5	16.37%	0% - 100%		
Incontinence 1	38.87%	100% - 0%	Dirichlet distribution (α1, α2, α3, α4, α5)=(741,359,279,175,352)	
Incontinence 2	18.84%	0% - 0%		
Incontinence 3	14.64%	0% - 0%		
Incontinence 4	9.18%	0% - 0%		
Incontinence 5	18.47%	0% - 100%		
Probabilities of transition between different severity levels, by treatment - for Mirabegron 50 mg, Tolterodine ER 4 mg, Solifenacin 5 mg				
Beta coefficients for Mirabegron 50 mg				
Micturition 1 (5 as reference)	0.6037	0.2239 – 0.9835	Normal distribution[2] (μ , σ)=(0.6037,0.1938)	Base case / PSA: SCORPIO DSA: 95% CI assuming normal distribution
Micturition 2 (5 as reference)	0.3803	0.0295 – 0.7311	Normal distribution (μ , σ)=(0.3803,0.1790)	
Micturition 3 (5 as reference)	0.1454	-0.1876 – 0.4784	Normal distribution (μ , σ)=(0.1454,0.1699)	
Micturition 4 (5 as reference)	0.0665	-0.2738 – 0.4068	Normal distribution (μ , σ)=(0.0665,0.1736)	
Incontinence 1 (5 as reference)	0.3617	0.0054 – 0.7180	Normal distribution (μ , σ)=(0.3617,0.1818)	
Incontinence 2 (5 as reference)	0.4634	0.1043 – 0.8225	Normal distribution (μ , σ)=(0.4634,0.1832)	
Incontinence 3 (5 as reference)	-0.0251	-0.4042 – 0.3540	Normal distribution (μ , σ)=(-0.0251,0.1934)	
Incontinence 4 (5 as reference)	0.2040	-0.2119 – 0.6199	Normal distribution (μ , σ)=(0.2040,0.2122)	
Beta coefficients for Tolterodine ER 4 mg				
Micturition 1 (5 as reference)	0.3667	-0.0073 – 0.7407	Normal distribution (μ , σ)=(0.3667,0.1908)	Base case / PSA: SCORPIO DSA: 95% CI assuming normal distribution
Micturition 2 (5 as reference)	0.1826	-0.1610 – 0.5262	Normal distribution (μ , σ)=(0.1826,0.1753)	
Micturition 3 (5 as reference)	-0.0609	-0.3867 – 0.2649	Normal distribution (μ , σ)=(-0.0609,0.1662)	
Micturition 4 (5 as reference)	0.0550	-0.2739 – 0.3839	Normal distribution (μ , σ)=(0.0550,0.1678)	

[1] Dirichlet distributions were used to model uncertainty of proportions with >2 categories as it is a multivariate generalisation of the beta distribution. [Briggs 2006]
[2] Normal distributions were the natural choice for coefficients obtained by regression, with the mean and standard deviation as parameters.

Supplementary Table 1. Input parameters for base case model: general OAB population - mirabegron 50 mg vs tolterodine ER 4 mg				
Parameter	**Base case value**	**DSA values**	**PSA**	**Source**
Incontinence 1 (5 as reference)	0.1431	-0.2028 – 0.4890	Normal distribution (μ , σ)=(0.1431,0.1765)	
Incontinence 2 (5 as reference)	0.1768	-0.1735 – 0.5271	Normal distribution (μ , σ)=(0.1768,0.1787)	
Incontinence 3 (5 as reference)	-0.3271	-0.7009 – 0.0467	Normal distribution (μ , σ)=(-0.3271,0.1907)	
Incontinence 4 (5 as reference)	-0.0298	-0.4385 – 0.3789	Normal distribution (μ , σ)=(-0.0298,0.2085)	
Beta coefficients for Solifenacin 5 mg				
Micturition 1 (5 as reference)	0,9977	0,6237 – 1.3717	Normal distribution (μ , σ)=(0,9977,0,1908)	MTC based on SCORPIO and calibration method (calibration following the seven-step approach defined by Vanni, 2011) Initial betas for the calibration were those for mirabegron 50 mg
Micturition 2 (5 as reference)	0,4933	0,1497 – 0.8639	Normal distribution (μ , σ)=(0,4933,0,1753)	
Micturition 3 (5 as reference)	0,0384	0,3641 - -0.2874	Normal distribution (μ , σ)=(0,0384,0,1662)	
Micturition 4 (5 as reference)	-0,0729	0,2560 - -0.4017	Normal distribution (μ , σ)=(-0,0729,0,1678)	
Incontinence 1 (5 as reference)	1,1403	0,7944 – 1.4863	Normal distribution (μ , σ)=(1,1403,0,1765)	
Incontinence 2 (5 as reference)	0,7343	0,3840 – 1.0845	Normal distribution (μ , σ)=(0,7343,0,1787)	
Incontinence 3 (5 as reference)	0,0347	0,4084 - -0.3391	Normal distribution (μ , σ)=(0,0347,0,1907)	
Incontinence 4 (5 as reference)	0,1136	0,5223 - -0.2950	Normal distribution (μ , σ)=(0,1136,0,2085)	
Probability of having a dry mouth AE				
Mirabegron 50 mg	2.80%	2.1% - 3.5%	Beta distribution[3] (α,ß) =(47.60,1652.40)	Base case / PSA: SCORPIO DSA: 95% CI
Tolterodine 4 mg	10.10%	8.7% - 11.5%	Beta distribution (α,ß)=(113.12,1006.86)	
No treatment	0%	NA	NA	Assumption
Probability of having a constipation AE				
Mirabegron 50 mg	1.60%	1% - 2.20%	NA	Base case / PSA: SCORPIO DSA: 95% CI
Tolterodine 4 mg	2%	1.40% - 2.60%	NA	
No treatment	0%	NA	NA	Assumption
Probability of success of botulinum toxin (all patients)				
	79%	60% - 92%	NA	Wu et al, 2009
Utilities according to symptom severity – EQ-5D (coefficients of regression equation)				
Micturition 1 (5 as reference)	0.0632	0.0453 – 0.0811	Normal distribution (μ , σ)=(0.0632,0.0091)	Base case/PSA: SCORPIO
Micturition 2 (5 as reference)	0.0422	0.0258 – 0.0587	Normal distribution (μ , σ)=(0.0422,0.0084)	

[3] Beta distribution were used to model uncertainty of event probabilities as it represents the distribution for a probability of a binomial process and is characterised by two parameters (α,ß) corresponding to the number of events and the number of non-events. [Briggs 2006]

Supplementary Table 1. Input parameters for base case model: general OAB population - mirabegron 50 mg vs tolterodine ER 4 mg

Parameter	Base case value	DSA values	PSA	Source
Micturition 3 (5 as reference)	0.0204	0.0045 – 0.0363	Normal distribution (μ , σ)=(0.0204,0.0081)	DSA: 95% CI assuming normal distribution
Micturition 4 (5 as reference)	0.0104	-0.0054 – 0.0262	Normal distribution (μ , σ)=(0.0104,0.0081)	
Incontinence 1 (5 as reference)	0.0586	0.0422 – 0.0749	Normal distribution (μ , σ)=(0.0586,0.0083)	
Incontinence 2 (5 as reference)	0.0437	0.0271 – 0.0602	Normal distribution (μ , σ)=(0.0437,0.0084)	
Incontinence 3 (5 as reference)	0.0314	0.0142 – 0.0486	Normal distribution (μ , σ)=(0.0314,0.0088)	
Incontinence 4 (5 as reference)	0.0128	-0.0056 – 0.0313	Normal distribution (μ , σ)=(0.0128,0.0094)	
Utilities according to symptom severity – OAB-5D (coefficients of regression equation)				
Micturition 1 (5 as reference)	0.0988	0.0919 – 0.1057	Normal distribution (μ , σ)=(0.0988,0.0035)	Base case/PSA: SCORPIO DSA: 95% CI assuming normal distribution
Micturition 2 (5 as reference)	0.0620	0.0556 – 0.0683	Normal distribution (μ , σ)=(0.0620,0.0033)	
Micturition 3 (5 as reference)	0.0353	0.0292 – 0.0415	Normal distribution (μ , σ)=(0.0353,0.0031)	
Micturition 4 (5 as reference)	0.0185	0.0123 – 0.0246	Normal distribution (μ , σ)=(0.0185,0.0031)	
Incontinence 1 (5 as reference)	0.0777	0.0714 – 0.0840	Normal distribution (μ , σ)=(0.0777,0.0032)	
Incontinence 2 (5 as reference)	0.0511	0.0447 – 0.0575	Normal distribution (μ , σ)=(0.0511,0.0033)	
Incontinence 3 (5 as reference)	0.0246	0.0179 – 0.0313	Normal distribution (μ , σ)=(0.0246,0.0034)	
Incontinence 4 (5 as reference)	0.0094	0.0022 – 0.0166	Normal distribution (μ , σ)=(0.0094,0.0037)	
Utility decrement associated with AE				
All AE	-0.0357	0 - -0.1	NA	Base case: SCORPIO SA: Assumption
Pad use per day by level of incontinence (coefficients of linear regression equation)				
Incontinence 1	0.17	0.150 – 0.198	NA	Base case: SCORPIO SA: 95% CI assuming normal distribution
Incontinence 2	0.75	0.687 – 0.817	NA	
Incontinence 3	1.38	1.282 – 1.486	NA	
Incontinence 4	1.89	1.745 – 2.039	NA	
Incontinence 5	3.34	3.167 – 3.511	NA	
Monthly probability of discontinuation of OAB therapy				
Without AEs	6.40%	3.0% - 14.5%	NA	Base case: 28.2% of patients on tolterodine ER persistent at 12 months (Wagg et al. 2012), N=1,758; 24% of discontinuations are due to AEs (Sánchez-Ballester et al. 2014) SA: Estimate based on mean duration of treatment with

Supplementary Table 1. Input parameters for base case model: general OAB population - mirabegron 50 mg vs tolterodine ER 4 mg

Parameter	Base case value	DSA values	PSA	Source
				tolterodine (156.7 days) instead of persistence rate at 12 months (Wagg et al, 2012) SA: Assumption
With AEs	90%	50% - 100%	Beta distribution (α,ß)=(6.92,0.77)	Base case and SA: Assumption
Monthly probability of switch after discontinuation of OAB therapy				
Probability of switch, among all patients discontinuing OAB treatment	26.06%	15.32% - 50%	Beta distribution	Base case: Odeyemi et al, 2006
				SA: D'Souza et al, 2008 / Assumption
Monthly probabilities of restarting OAB therapy among patients without treatment				
Monthly probability of restarting treatment	10%	0.05% - 20%	Beta distribution (α,ß)=(1.74,15.63)	Base case and SA: Assumption
Split between different medications, for general OAB population*				
- Initial treatment (mirabegron or tolterodine)	33.33%	0% - 50%	NA	Base case and SA: Assumption
- Next line A	33.33%	0% - 50%	NA	Base case and SA: Assumption
- Next line B	33.33%	0% - 50%	NA	Base case and SA: Assumption
Monthly probability of transition to botulinum toxin				
Monthly probability of having botulinum toxin injection in the general OAB population	0.01%	0% - 0.05%	Beta distribution (α,ß)= (0.70,834.78)	Base case and SA: Assumption
Resource utilisation (physician visits and botulinum toxin reinjections)				
Number of GP consultations	1 visit at the start and at every switch	0 - 2	Lognormal distribution (μ , σ)[4]=(1,0.20)	Base case: Cardozo 2010 SA: Assumption
Number of specialist consultations	1.5 visits at the start and at every switch	1 - 3	Lognormal distribution (μ , σ)=(1.5,0.95)	Base case: Cardozo 2010 SA: Assumption
Number of Botulinum toxin reinjections, following success of first injection	0.17 per month	0	NA	Base case: Expert opinion (Once every 6 months) SA: Assumption
Model inputs: Monthly OAB medication costs				
Mirabegron 50 mg	£29.40	NA	NA	BNF 2011/12
Tolterodine 4 mg ER	£28.01	NA	NA	BNF 2011/12

[4] Lognormal distributions were used to model uncertainty of quantities that have a distribution skewed to the right (number of GP and specialist visits) [Briggs 2012]

Supplementary Table 1. Input parameters for base case model: general OAB population - mirabegron 50 mg vs tolterodine ER 4 mg					
Parameter	**Base case value**	**DSA values**		**PSA**	**Source**
Solifenacin 5 mg	£28.00	NA		NA	BNF 2011/12
Model inputs: unit costs of health care resources					
GP consultation	£36	NA		NA	PSSRU 2011
Specialist visit: Follow-up visit	£96	NA		NA	NHS Payment 2010-2011
Botulinum toxin injection: Initial / Reinjections	£1158 / £964	NA		NA	http://www.nottinghamurologygroup.co.uk/treatments/bladder-botulinum toxin-injections
Incontinence pad (per pad)	£0.16	NA		NA	Age UK incontinence
Discount rates					
Costs Outcomes (QALYs)	3.5% 3.5%	0% 0%	6% 6%	NA NA	NICE guidelines

References not included in main manuscript

Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation. Oxford University Press, 2006.

Briggs AH, Weinstein MC, Fenwick EAL, Karnon J, Sculpher MJ, Paltiel AD. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM modeling good research practices task force-6. Value Health 2012;1:835-42.

Vanni T, Karnon J, Madan J, White RG, Edmunds WJ, Foss AM et al. Calibrating models in economic evaluation: a seven-step approach. Pharmacoeconomics 2011;29:35-49.

Transitions between severity levels: logistic regression

Probabilities of transition between severity levels for each symptom were obtained from a multinomial logistic regression model based on CL-046 clinical trial data. The probability of being at symptom level *j* at month (*t*+1) was expressed as a function of treatment, symptom severity in previous month (*t*), sex and age:

$$Prob(Severity_{t+1} = j \mid x) = \frac{e^{\beta_0^j + \beta_1^j.Treatment + \beta_2^j.Severity_t + \beta_3^j.Sex + \beta_4^j.Age + \beta_5^j.Treatment*Severity_t}}{1 + \sum_{k=1}^{J-1} e^{\beta_0^k + \beta_1^k.Treatment + \beta_2^k.Severity_t + \beta_3^k.Sex + \beta_4^k.Age + \beta_5^k.Treatment*Severity_t}}$$

The log odds of being at a symptom level lower than *j* rather than greater than *j* are as following:

$$Log\left(\frac{Prob(Severity_{t+1} \leq j \mid x)}{Prob(Severity_{t+1} > j \mid x)}\right) = \beta_0^j + \beta_1^j.Treatment + \beta_2^j.Severity_t + \beta_3^j.Sex + \beta_4^j.Age + \beta_5^j.Treatment * Severity_t$$

If the test of the proportional odds assumption is not rejected, an ordinal logistic regression can be used. This assumption is that the effects of any explanatory variables (here treatment, severity in previous month, sex and age) are consistent across different pairs of symptom levels. In other words, that the explanatory variables have the same effect on the odds regardless of the cut-off level:

$$Log\left(\frac{Prob(Severity_{t+1} \leq j \mid x)}{Prob(Severity_{t+1} > j \mid x)}\right) = \beta_0^j + \beta_1 .Treatment + \beta_2 .Severity_t + \beta_3 .Sex + \beta_4 .Age + \beta_5 .Treatment * Severity_t$$

In the defined model, the null hypothesis of the proportional odds assumption was rejected, so the Ordinal Logistic Regression was not used.

The interaction between the treatment and the severity was also tested and appeared not significant.

Consequently the final equation to compute the transition probabilities was:

$$Prob(Severity_{t+1} = j \mid x) = \frac{e^{\beta_0^j + \beta_1^j.Treatment + \beta_2^j.Severity_t + \beta_3^j.Sex + \beta_4^j.Age}}{1 + \sum_{k=1}^{J-1} e^{\beta_0^k + \beta_1^k.Treatment + \beta_2^k.Severity_t + \beta_3^k.Sex + \beta_4^k.Age}}$$

Using the multinomial logistic regression model described above, we produced three transition matrices (5x5) for each type of symptom, one for the transition between baseline and the first month, one between the first month and the second month, and finally one between the second month and the third month (Supplementary Tables 1 and 2). For patients staying on treatment beyond 3 months, the transition matrix from 2 to 3 months was reapplied for the cycle from 3 to 4 months and subsequent monthly cycles until discontinuation.

Supplementary Table 2. Transition probabilities between micturition severity levels for the general OAB population based on logistic regression analysis of SCORPIO data					
	Transition severity level				
Starting severity level	1	2	3	4	5
Mirabegron 50 mg: baseline to month 1					
1	0.805	0.180	0.013	0.002	0.000
2	0.408	0.465	0.113	0.012	0.002
3	0.160	0.387	0.343	0.084	0.026
4	0.055	0.202	0.368	0.251	0.124
5	0.030	0.074	0.156	0.241	0.500
Mirabegron 50 mg: month 1 to month 2					
1	0.761	0.213	0.021	0.004	0.001
2	0.334	0.476	0.162	0.023	0.004
3	0.107	0.321	0.399	0.132	0.040
4	0.030	0.138	0.352	0.323	0.157
5	0.014	0.043	0.128	0.268	0.546
Mirabegron 50 mg: month 2 to month 3					
1	0.734	0.237	0.024	0.004	0.001
2	0.302	0.497	0.175	0.021	0.005
3	0.094	0.326	0.420	0.115	0.046
4	0.027	0.140	0.372	0.282	0.179
5	0.012	0.042	0.129	0.223	0.594
Tolterodine 4 mg ER: baseline to month 1					
1	0.799	0.186	0.013	0.002	0.000
2	0.397	0.472	0.113	0.015	0.003

Supplementary Table 2. Transition probabilities between micturition severity levels for the general OAB population based on logistic regression analysis of SCORPIO data					
3	0.152	0.381	0.335	0.100	0.031
4	0.050	0.188	0.340	0.281	0.141
5	0.025	0.064	0.133	0.251	0.527
Tolterodine 4 mg ER: month 1 to month 2					
1	0.754	0.219	0.021	0.005	0.001
2	0.324	0.480	0.162	0.028	0.005
3	0.100	0.312	0.385	0.155	0.048
4	0.027	0.126	0.319	0.355	0.175
5	0.011	0.037	0.109	0.275	0.568
Tolterodine 4 mg ER: month 2 to month 3					
1	0.726	0.243	0.024	0.005	0.001
2	0.293	0.501	0.175	0.025	0.006
3	0.088	0.317	0.405	0.135	0.055
4	0.024	0.128	0.337	0.311	0.200
5	0.004	0.020	0.086	0.243	0.646
No treatment: n months to (n+1) months					
1	0.063	0.307	0.272	0.195	0.164
2	0.063	0.307	0.272	0.195	0.164
3	0.063	0.307	0.272	0.195	0.164
4	0.063	0.307	0.272	0.195	0.164
5	0.063	0.307	0.272	0.195	0.164

Supplementary Table 3. Transition probabilities between incontinence severity levels for the general OAB population based on logistic regression analysis of SCORPIO data					
	Transition severity level				
Starting severity level	1	2	3	4	5
Mirabegron 50 mg: baseline to month 1					
1	0.879	0.100	0.012	0.005	0.005
2	0.518	0.364	0.078	0.022	0.018
3	0.348	0.354	0.184	0.076	0.037
4	0.209	0.290	0.219	0.158	0.125
5	0.123	0.134	0.135	0.144	0.463
Mirabegron 50 mg: month 1 to month 2					
1	0.866	0.105	0.015	0.007	0.007
2	0.484	0.361	0.096	0.033	0.026
3	0.305	0.329	0.212	0.105	0.050
4	0.168	0.247	0.231	0.199	0.154
5	0.089	0.103	0.129	0.164	0.515
Mirabegron 50 mg: month 2 to month 3					
1	0.850	0.120	0.015	0.008	0.008
2	0.454	0.394	0.091	0.034	0.026
3	0.284	0.357	0.201	0.109	0.050
4	0.156	0.267	0.218	0.206	0.152
5	0.083	0.112	0.122	0.170	0.512
Tolterodine 4 mg ER: baseline to month 1					
1	0.884	0.094	0.011	0.005	0.006
2	0.532	0.349	0.074	0.022	0.023

Supplementary Table 3. Transition probabilities between incontinence severity levels for the general OAB population based on logistic regression analysis of SCORPIO data					
3	0.359	0.341	0.175	0.077	0.048
4	0.211	0.273	0.203	0.157	0.157
5	0.113	0.115	0.114	0.130	0.528
Tolterodine 4 mg ER: month 1 to month 2					
1	0.871	0.098	0.014	0.007	0.009
2	0.497	0.346	0.091	0.033	0.033
3	0.313	0.316	0.201	0.106	0.064
4	0.168	0.231	0.213	0.196	0.192
5	0.080	0.087	0.107	0.146	0.580
Tolterodine 4 mg ER: month 2 to month 3					
1	0.871	0.098	0.014	0.007	0.009
2	0.497	0.346	0.091	0.033	0.033
3	0.313	0.316	0.201	0.106	0.064
4	0.168	0.231	0.213	0.196	0.192
5	0.080	0.087	0.107	0.146	0.580
No treatment: n months to (n+1) months					
1	0.856	0.113	0.014	0.008	0.010
2	0.467	0.379	0.086	0.035	0.033
3	0.293	0.343	0.190	0.110	0.064
4	0.156	0.250	0.201	0.203	0.190
5	0.052	0.070	0.093	0.167	0.618

Health state utilities according to symptom severity

Utility values according to symptom severity were derived from EQ-5D index scores, based on the UK time trade-off tariff, collected in the SCORPIO trial. A linear regression model was estimated, with adjustments for age, sex, and country (as a random effect), accounting for repeated measures by patient:

$$Utility = \beta_0 + \beta_1 ClassMict + \beta_2 ClassInco + \beta_3 Age + \beta_4 Sex + \varepsilon_{patient} + \varepsilon_{country}$$

The model was estimated from all treatment arms of SCORPIO. We verified that there was no significant treatment effect independent of symptom severity. Supplementary Table 3 shows the parameter estimates for the general OAB population. For example, the coefficient for micturitions at level 1 is 0.06321: this means that the utility of patients with micturitions at level 1 is higher than the utility of patients with micturitions at level 5 by 0.0321. Health utilities according to symptom severity for subgroups were obtained in the same way.

Supplementary Table 4. Regression model of EQ-5D utilities

Effect	Class/level	Estimates	Sensitivity analyses (95% CIs)
Intercept		0.7838	
Age		–0.00041	
Micturition severity level	1	0.06321	0.0453, 0.0811
	2	0.04224	0.0258, 0.0587
	3	0.02042	0.0045, 0.0363
	4	0.01039	–0.0316
	5	0	
Incontinence severity level	1	0.05859	0.0422, 0.0749
	2	0.04367	0.0271, 0.0602
	3	0.03141	0.0142, 0.0486
	4	0.01282	–0.0369
	5	0	
Sex	F	–0.04412	
	M	0	