REVIEW ARTICLE

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Solifenacin in Overactive Bladder Syndrome

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Contents

Abstract

Overactive bladder (OAB) syndrome is a prevalent condition, increasingly recognised as a cause of reduced quality of life that places a substantial economic burden on healthcare provision. While antimuscarinic agents are the therapy of choice for OAB, their use is associated with a number of drawbacks, not least of which is the high rate of adverse events, which is intimately linked with poor compliance with treatment.

Solifenacin succinate is a novel antimuscarinic agent approved in Europe and the US for the treatment of men and women with OAB. The recommended starting dose of solifenacin is 5mg once daily and, if needed, the dose may be increased to 10mg once daily. In multiple clinical trials, solifenacin treatment has been associated with statistically significant reductions in all key symptoms of OAB (notably frequency, urgency and incontinence) as well as increases in volume voided. Solifenacin has been shown to be well tolerated, producing few adverse effects, which are usually mild in nature. Furthermore, possibly because of this favourable efficacy and tolerability, solifenacin treatment has been associated with a high rate of patient persistence with therapy, with 81% of 1802 patients who completed 12-week, double-blind trials enrolling in and completing a 40-week open-label extension study. Solifenacin has been shown to display

selectivity for bladder versus salivary tissue *in vitro*, and studies in healthy men have shown that absorption is slow but extensive with an absolute bioavailability of 88%.

Solifenacin is a well tolerated and efficacious agent for the treatment of OAB, significantly reducing symptoms and improving patients' quality of life.

Overactive bladder (OAB) syndrome is defined by the International Continence Society as urgency (a sudden desire to pass urine which is hard to defer) with or without urge incontinence (involuntary leakage of urine accompanied or preceded by urgency), usually with frequency (increased voiding) and nocturia (waking at night to void).[1] OAB is not purely a bladder condition, but may also involve pelvic floor muscle dysfunction and behavioural issues. No drug can ever correct all facets of this multifactorial disorder. Nevertheless, antimuscarinic medications, aimed at blocking cholinergic receptor activity in the bladder, are the primary pharmacotherapeutic option for OAB in practice. These drugs are widely used and their efficacy over placebo has been reported in many randomised clinical trials. However, antimuscarinics are associated with adverse effects that impact on both compliance and persistence with long-term treatment. In fact, the clinical utility of currently available antimuscarinic agents has been questioned recently in a systematic literature review comprising 32 clinical trials.[2] The authors concluded that "for many of the outcomes studied, the observed difference between anticholinergics and placebo may be of questionable clinical significance".[2] While this conclusion could be considered to be highly subjective, it highlights the need for improved pharmacological options to treat OAB as well as for outcome measures that capture clinically relevant changes in urinary symptoms. This need for better understanding of patient acceptance of drug therapy is further emphasised by evidence of poor patient compliance and persistence with traditional antimuscarinic agents.[3] Moreover, in a recently reported prescription tracking analysis including newer antimuscarinics, <15% of patients treated with antimuscarinic agents remained on therapy at 1 year.[4] Several factors probably contribute to the lack of patient persistence, including the high cost of newer medications, inadequate counselling and adjuvant therapy, and poor initial patient selection, but the critical factor is likely to be the ratio of efficacy to tolerability offered by a compound.

None of the currently available OAB medications are ideal, i.e. both efficacious and free of anticholinergic and other adverse effects.[5] However, there is hope that new and emerging agents may improve the balance of efficacy and tolerability. Solifenacin succinate is a once-daily oral antimuscarinic approved for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with OAB.

This review describes the preclinical characteristics and pharmacology of solifenacin, along with efficacy, safety and tolerability outcomes from clinical trials in patients with OAB symptoms. To identify pertinent articles for this review, a MEDLINE search was undertaken for publications since 1990 using the key words 'OAB', 'solifenacin', 'Vesicare' and 'YM905'. In addition, this article includes some congress abstracts and data from studies performed to meet regulatory requirements, but where possible, peer-reviewed data were used. This was done for the sake of completeness, but the author acknowledges that these data have not been subject to the rigorous peer-review process of a journal publication and, as such, should be viewed with caution. In some instances, p-values that were not statistically significant were not provided in published articles. In these instances, the author entered into dialogue with the company biostatisticians to obtain these data.

1. Preclinical Characteristics

Antimuscarinic therapy is associated with a number of adverse effects caused by blockade of the

cholinergic system. These include dry mouth, blurred vision and constipation. Findings from *in vitro* and *in vivo* studies using animal models have demonstrated the relative selectivity of solifenacin for bladder tissue over salivary gland.[6-8] Solifenacin inhibited carbachol-induced intracellular calcium mobilisation *in vitro* more potently in bladder smooth muscle cells than in submandibular gland cells.[6] A second *in vitro* study evaluated carbachol-induced intracellular calcium mobilisation in bladder smooth muscle and submandibular gland cells from rats and monkeys. The inhibitory effects of solifenacin were statistically significantly greater ($p < 0.01$) for bladder smooth muscle cells versus submandibular gland cells from rat tissues. When a 'selectivity index' was calculated (using the ratio of the affinity constant for binding to salivary gland cells to the affinity constant for binding to bladder cells), solifenacin demonstrated the greatest relative bladder selectivity among the agents tested (tolterodine, oxybutynin and darifenacin) with both rat and monkey preparations, but the difference was only statistically significant in monkey cells (selectivity index gland/bladder for solifenacin 2.1 ± 0.38 [$p < 0.01$] compared with 0.51 ± 0.076 for oxybutynin [not significant for selectivity]).[7]

Another preclinical analysis of tissue specificity utilised an *in vivo* model in which changes in intravesical pressure and salivary secretion were evaluated in mice and rats. In both systems, solifenacin inhibited carbachol-induced pressure elevations of the bladder at a lower dose than was observed for the inhibition of salivary secretion. The functional selectivity measured with solifenacin treatment (based on a ratio of salivary inhibition and intravesicular pressure change) was high and compared favourably with that seen with the other agents tested (tolterodine, oxybutynin and darifenacin).[8] A review by Kershen and Hsieh[9] suggested that solifenacin has the highest degree of bladder selectivity *in vitro* and *in vivo* compared with tolterodine, oxybutynin and darifenacin in animal studies.[9]

These preclinical observations suggest that solifenacin might be expected to have a relatively potent effect on the muscarinic receptors in the bladder and a relatively weaker effect on the muscarinic receptors in the salivary glands in humans. No selectivity studies of this nature have been carried out on human tissue, so the clinical relevance of the animal data cannot be assured.

2. Solifenacin Clinical Pharmacology

A total of 17 studies have been carried out on the clinical pharmacology of solifenacin to date and eight of these have been published as abstracts. Studies included healthy individuals and patients with renal or hepatic impairment.

In healthy men, solifenacin was found to be slowly but extensively absorbed after oral administration, with a mean absolute bioavailability of 88%.[10] Peak plasma concentrations were reached on average within 5 hours postdose, with a range between 3 and 8 hours. Plasma concentrations tended to be constant over several hours as a result of the slow absorption and disposition of solifenacin (figure 1).[10] The rate of absorption and bioavailability were unaffected by prior ingestion of food; maximum plasma concentration (C_{max}), time to C_{max} (t_{max}) and area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}) were unaltered.[10] Therefore, solifenacin may be taken with or without food.

Solifenacin is extensively distributed to tissues; the volume of distribution at steady state is approximately 600L after a single intravenous infusion of 5mg.[10] A study in healthy volunteers showed that solifenacin is highly protein bound (98%) in plasma, and *in vitro* findings indicated that solifenacin is

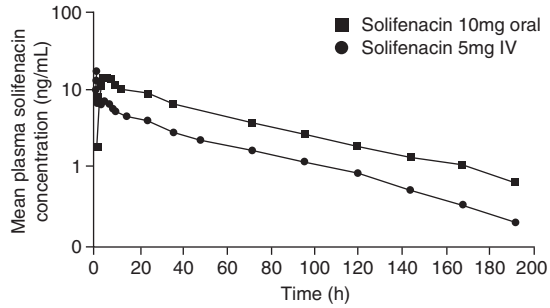

Fig. 1. Solifenacin plasma concentrations vs time after a single intravenous (IV) or oral dose in healthy male volunteers.[10]

primarily bound to α_1-acid glycoprotein. After a single intravenous 5mg dose of solifenacin, the mean clearance was approximately 10 L/h in healthy volunteers.[10] Renal clearance accounts for a small fraction of total clearance, at an estimated 0.67 L/h. In a mass balance study in healthy volunteers, a single oral 10mg dose of ^{14}C-solifenacin was found to be extensively metabolised: 70% of a 10mg oral dose was excreted in the urine, of which only 11% was unchanged parent compound.[11]

Findings from *in vitro* studies indicated that the metabolism of solifenacin occurs primarily via cytochrome P450 (CYP) 3A4; however, other isoenzymes also have the ability to metabolise solifenacin, including CYP2C19, CYP3A5, CYP2C8, CYP2D6 and CYP1A1, albeit to a lesser extent.[12] Solifenacin is also subject to direct glucuronidation. Four major metabolites have been identified in human plasma and urine: M2 (solifenacin N-oxide, which is the predominant metabolite in urine), M3 (4R-hydroxy solifenacin, which is the only metabolite that has appreciable affinity for the M3 muscarinic receptor but constitutes 5–8% of total solifenacin concentration), M4 (4R-hydroxy solifenacin N-oxide) and M5 (N-glucuronide of solifenacin).

The large volume of distribution and low clearance associated with solifenacin translate into a long terminal elimination half-life ($t_{1/2}$) of approximately 50 hours in healthy adults, which, along with other pharmacokinetic properties, provides extended coverage with once-daily dose administration.[10] In studies evaluating dose proportionality, the values of C_{max} and AUC were found to increase in proportion to dose. In addition, dose proportionality with solifenacin was confirmed at steady state over a dose range of 5–20mg, and $t_{1/2}$ was independent of dose. During multiple dose administration studies, there were no major changes observed in the pharmacokinetics of solifenacin.[13,14]

2.1 Special Populations

Differences in pharmacokinetics between elderly and young subjects in one study were small.[15] The mean AUC_{24} was statistically significantly increased by 20% in the elderly, and C_{max} occurred approximately 1 hour later. C_{max} was not statistically significantly changed by age. The mean $t_{1/2}$ was also increased in the elderly, to 64.8–75.2 hours from 50.6–59.4 hours in the young.[15] These differences in pharmacokinetic parameters between young and elderly subjects were not considered clinically significant.

To determine the potential effects of renal impairment on the pharmacokinetics of solifenacin, the safety and tolerability of a single oral 10mg dose of solifenacin were evaluated in patients with mild, moderate and severe renal impairment.[16] In the mild and moderate renal impairment cohort, clearance of solifenacin following oral administration was decreased by 20–25% and the $t_{1/2}$ was increased by approximately 30%. In the severe impairment cohort, clearance was statistically significantly lower than in healthy individuals. Increases of approximately 30% were observed for C_{max}, >100% for AUC_∞ and >60% for $t_{1/2}$. On the basis of these results, no dose adjustment is necessary for patients with mild to moderate renal impairment (creatinine clearance >30 mL/min). Patients with severe renal impairment (creatinine clearance ≤30 mL/min) should be treated with caution and receive no more than 5mg once daily.[16]

The potential effect of hepatic impairment on the pharmacokinetics of solifenacin was also investigated.[17] A single 10mg dose of solifenacin was administered to patients with moderate liver impairment and to healthy volunteers. Both groups were followed at an inpatient clinic for 8 days postdose, and additional blood and urine samples were collected on days 9, 11, 13 and 15 after discharge. A post-study assessment, completed 1–2 weeks after the final sampling visit, involved full safety testing. In patients with hepatic impairment, mean C_{max} was unaffected; however, AUC_∞ was increased by 60% and $t_{1/2}$ was doubled compared with the healthy volunteers (106 vs 50 hours). Clearance of solifenacin following oral administration was also lower in patients with hepatic impairment versus healthy volunteers. Nevertheless, a single dose of solifenacin was well tolerated in these study partici-

pants and no dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate hepatic impairment (Child-Pugh category B[18]) should be treated with caution and receive no more than 5mg once daily.[11] The use of solifenacin in patients with severe hepatic impairment is not recommended.

Other pharmacokinetic studies showed that most pharmacokinetic parameters were similar in men and women, and the pharmacokinetics of solifenacin do not appear to be affected by race, although the number of subjects studied is not adequate to draw any formal conclusions.[11,19]

2.2 Drug-Drug Interactions

In vitro data suggested a low potential for solifenacin to inhibit CYP enzymes and P-glycoprotein (P-gp)-mediated transport. Nevertheless, drug-drug interaction studies were conducted to evaluate the effects of solifenacin on relevant medications that may be prescribed concomitantly in patients with OAB. Because solifenacin is largely metabolised by CYP3A4, a study of potential drug-drug interactions with warfarin, a substrate for CYP3A4, was carried out. In addition, preclinical data demonstrated that solifenacin is a weak inhibitor of P-gp.[20] Because the bioavailability and renal clearance of digoxin are dependent on the activity of the transport protein P-gp,[21,22] steady-state pharmacokinetics of digoxin were evaluated in the presence of solifenacin. Interaction studies have determined that solifenacin does not interact with warfarin and digoxin, indicating that solifenacin can be coadministered with these agents.[11] Ethinylestradiol and levonorgestrel, components of commonly prescribed combined oral contraceptives, are substrates of CYP3A4. Solifenacin demonstrated no statistically significant interference with the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel, and the combination of ethinylestradiol and levonorgestrel with solifenacin was well tolerated.[23]

Ketoconazole is a known potent inhibitor of CYP3A4, and is the standard drug used to evaluate the effects of CYP3A4 inhibition on the pharmacokinetics of CYP3A4 substrates (e.g. selected antidepressants, antifungals, benzodiazepines, calcium channel antagonists, HMG-CoA reductase inhibitors [statins], macrolides and corticosteroids). When administered concomitantly with ketoconazole 200mg once daily (therapeutic dose), the C_{max} of solifenacin increased 1.4-fold and AUC_{∞} increased 2-fold in healthy volunteers, while ketoconazole administered at a dosage of 400 mg/day resulted in a 3-fold increase of the AUC of solifenacin;[11,24] these are relatively modest increases in C_{max} and AUC_{∞} considering the potency of ketoconazole. Despite this, the maximum dose of solifenacin should be limited to 5mg when administered simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors (e.g. ritonavir, nelfinavir or itraconazole).

3. Clinical Trial Data

3.1 Phase I Studies

Results from phase I studies conducted in healthy volunteers indicated that the maximum tolerated dosage of solifenacin was 20 mg/day.[14] Age, sex and food had no apparent effect on the pharmacokinetics of solifenacin.[14,19,25] Adverse events in the phase I studies were primarily related to expected anticholinergic adverse effects, such as dry mouth and constipation.[14,19,25]

3.2 Phase II Studies

Two randomised, double-blind, placebo-controlled, parallel-group studies were conducted, one each in the US and Europe, to determine the dose administration, efficacy and safety of solifenacin.[26-29] Men and women with OAB were enrolled and administered once-daily solifenacin doses ranging from 2.5 to 20mg. In both studies, eligible subjects were adults with a mean of eight or more micturitions per 24 hours, and at least one incontinence episode per 24 hours or one urgency episode per 24 hours, as recorded in a 3-day patient diary.

In the European phase II dose-ranging study, a total of 225 patients aged 21–83 years were

randomised, and 85% (192) completed the study.[26] Patients received once-daily doses of solifenacin 2.5, 5, 10 or 20mg, tolterodine 2mg twice daily or placebo for 28 days. The primary efficacy endpoint was baseline to endpoint change in micturition frequency (number of micturitions per 24 hours). Secondary efficacy endpoints were based on number of episodes of urgency, and incontinence and volume voided. Safety and tolerability were also assessed.

Table I summarises the statistically significant reduction from baseline to study endpoint in micturition frequency. This reduction occurred rapidly with the 5, 10 and 20 mg/day dosages of solifenacin compared with placebo, with an effect on the volume voided per micturition being seen at 2 weeks.[26] In comparison, the reduction in micturition frequency with tolterodine 2mg twice daily did not reach statistical significance.[26,27] A dose-response relationship was observed for reductions in micturition frequency with solifenacin, although this was not statistically significant. In contrast, no dose-response effect was noted for urgency or urge incontinence. Volume voided was statistically significantly increased from baseline to study endpoint with solifenacin 5, 10 and 20 mg/day compared with placebo, and a dose-response relationship was observed for this efficacy parameter as well. Adverse effects observed were primarily anticholinergic in nature, including dry mouth, constipation and blurred vision. Dry mouth was the most common adverse effect, affecting 14% of patients in the solifenacin 5 and 10mg group and 38% of patients receiving solifenacin 20 mg/day. The majority of adverse effects were mild in nature and the percentage of study subjects discontinuing with adverse effects as the primary reason was 2%, 3%, 9% and 14% for the solifenacin 2.5, 5, 10 and 20mg groups, respectively. In the tolterodine group, dry mouth was also the most common adverse effect, affecting 24% of patients. There was one discontinuation due to adverse effects reported in the tolterodine group.

In the US phase II study,[28,29] 265 patients 30–86 years of age were randomised to a solifenacin 2.5, 5, 10 or 20mg single oral daily dose or placebo for 28 days (239 patients completed treatment), with no active comparator arm. The primary and secondary efficacy endpoints, i.e. mean change from baseline, were the same as in the European study. The US results showed less consistency in the dose-response relationship compared with the European study, but an overall favourable trend for the drug was seen. The onset of action was rapid, with statistically significant reductions in micturition frequency being realised with solifenacin 10 mg/day after only 2 weeks of treatment. Micturition frequency was statistically significantly reduced with solifenacin 10 and 20 mg/day at study end. Statistically significant increases in volume voided were seen at the 5, 10 and 20 mg/day dosage levels at study end. Statistically significant differences from placebo were observed in volume voided with the solifenacin 5 and 20 mg/day dosages at the earliest timepoint evaluated (1 week). A statistically significant reduction in incontinence episodes was also observed with solifenacin 10 mg/day, beginning by day 14 of treatment. As with the European dose-ranging study, the expected anticholinergic adverse effects, specifically constipation and dry mouth, were observed and dry mouth was dose-related. No serious adverse effects related to treatment occurred in either study. On the basis of the results from these studies, subsequent phase III trials were designed to evaluate the efficacy and safety of solifenacin 5 and 10mg once daily.

3.3 Phase III Studies

To date, two of the four 12-week international, randomised, double-blind, placebo-controlled, multicentre phase III studies have been fully published.[30,31] These studies demonstrate the efficacy, safety and tolerability of solifenacin in men and women who had been experiencing symptoms of OAB (defined as including urinary frequency with urgency and/or urge incontinence) for ≥3 months. To be eligible for randomisation in these studies patients had to report micturition frequency ≥8 times per 24 hours, and at least three episodes of urgency and/or urinary incontinence during a 3-day micturition diary period.[30,31] The studies had similar designs with common definitions for the key efficacy

Table I. Mean change from baseline to endpoint in efficacy variables of a phase II evaluation of solifenacin[26]

Efficacy outcome	Placebo (n = 36)	Solifenacin 2.5mg od (n = 40)	Solifenacin 5mg od (n = 37)	Solifenacin 10mg od (n = 33)	Solifenacin 20mg od (n = 34)	Tolterodine 2mg bid (n = 37)
Number of urgency episodes/24h						
Mean change/baseline	−1.03/5.2	−1.07/5.9	−2.35/5.6	−2.46/5.3	−2.24/5.2	−1.62/5.7
Mean percentage change	−20%	−18%	−42%	−46%	−43%	−28%
p-Value[a]		NS	NS	NS	0.150	0.461
Number of incontinence episodes/24h						
Mean change/baseline	−0.29/1.7	−0.66/1.6	−0.83/1.5	−0.79/1.7	−0.58/1.0	−0.41/1.5
Mean percentage change	−17%	−41%	−55%	−46%	−58%	−27%
p-Value[a]		NS	NS	NS	0.380	0.666
Number of micturitions/24h						
Mean change/baseline	−1.03/11.1	−1.45/11.9	−2.21/11.5	−2.47/11.4	−2.75/11.7	−1.79/12.1
Mean percentage change	−9%	−12%	−18%	−21%	−23%	−15%
p-Value[a]		0.364	<0.05	<0.01	<0.005	0.131
Volume voided/micturition (mL)						
Mean change/baseline	9.7/134.7	19.9/147.6	38.0/161.9	43.2/152.8	64.7/152.1	14.7/159.9
Mean percentage change	14%	20%	28%	35%	45%	14%
p-Value[a]		0.296	<0.005	<0.001	<0.001	0.636

a Compared with placebo.

bid = twice daily; **NS** = a p-value that is not statistically significant based on the hierarchical test procedure, where the p-value for the next highest dose was found to be nonsignificant (p-value >0.05); **od** = once daily.

Table II. Change from baseline to endpoint in efficacy variables of a phase III evaluation of solifenacin[30]

Efficacy outcome	Placebo	Solifenacin 5mg od	Solifenacin 10mg od	Tolterodine 2mg bid
Number of urgency episodes/24h				
Number of patients	248	264	261	250
Adjusted mean change/baseline	−1.39/5.30	−2.83/5.77	−3.06/5.82	−2.04/5.45
p-Value[a]		0.0001	0.0001	0.0511
Mean percentage change	−33%	−52%	−55%	−38%
Median percentage change	−44%	−67%	−67%	−57%
Number of incontinence episodes/24h (n)				
Number of patients	153	141	158	157
Adjusted mean change/baseline	−0.75/2.71	−1.41/2.64	−1.45/2.59	−1.14/2.32
p-Value[a]		0.008	0.0038	0.1122
Mean percentage change	−29%	−59%	−47%	−59%
Median percentage change	−67%	−100%	−100%	−94%
Number of micturitions/24h				
Number of patients	253	266	264	250
Adjusted mean change/baseline	−1.20/12.20	−2.18/12.08	−2.61/12.32	−1.87/12.08
p-Value[a]		0.0003	0.0001	0.0145
Mean percentage change	−8%	−17%	−20%	−15%
Median percentage change	−8%	−17%	−21%	−17%
Volume voided/micturition (mL)				
Number of patients	253	266	264	250
Adjusted mean change/baseline	7.63/143.8	33.0/149.6	39.4/147.2	24.6/147.0
p-Value[a]		0.0001	0.0001	0.0001
Mean percentage change	9%	25%	29%	20%
Median percentage change	3%	19%	22%	14%

a p-Values are compared with placebo, and based on ANOVA model with treatment and centre as terms.

bid = twice daily; **od** = once daily.

variables and included a 2-week placebo run-in followed by a 12-week active treatment period. In both studies, baseline demographics were comparable between all treatment groups. Efficacy was assessed by patient recordings in 3-day micturition diaries, which were completed four times (at baseline and prior to each monthly visit). For both studies, mean reduction from baseline in urinary frequency (the number of micturitions per 24 hours) was the primary efficacy variable. Secondary efficacy variables included the mean reductions from baseline in the number of urgency episodes, number of incontinence episodes and number of nocturia episodes, and the increase in the mean volume voided per micturition. The studies also examined the impact on quality of life using the King's Health Questionnaire (KHQ).[32] Safety was evaluated on the basis of adverse effects, clinical laboratory values, vital signs, physical examination findings and ECG findings.

Two additional phase III studies evaluating solifenacin 10 mg/day versus placebo support the safety and efficacy profile of this compound, and pooled data from these two additional studies have been presented as congress abstracts only.[33,34] These data are reviewed briefly in sections 3.3.1 and 3.3.2.

3.3.1 Efficacy

The two published studies included treatment arms of solifenacin 5mg once daily, solifenacin 10mg once daily and placebo. One study[30] also included tolterodine 2mg twice daily as an active treatment arm. These studies were powered to make comparisons between each active treatment group and placebo, but not between active treatment

groups; therefore, outcomes with solifenacin treatment are the focus of this review. Specifically, the studies were designed to detect a difference of one micturition frequency per 24 hours between solifenacin and placebo, with 90% of power by using a two-sided test with a significance level of 0.05.

In the first study, a total of 1281 patients were enrolled, 1081 were randomised and 1077 were treated; 1033 patients were eligible for the efficacy evaluation. The results are presented in table II.[30] Treatment with solifenacin 5 and 10 mg/day statistically significantly reduced all the symptoms of OAB, including frequency, urgency and incontinence; improvement with tolterodine only reached significance for frequency. Both solifenacin and tolterodine statistically significantly increased mean volume voided per micturition. In addition, the majority of the treatment effect on micturition frequency was observed by the first treatment visit at week 4, with incremental efficacy observed by week 12.[30]

Table III. Change from baseline to endpoint in efficacy variables of a phase III evaluation of solifenacin[31]

Efficacy outcome	Placebo	Solifenacin 5mg od	Solifenacin 10mg od
Number of urgency episodes/24h			
Number of patients	278	284	289
Adjusted mean change/baseline	−1.98/5.62	−2.84/6.04	−2.90/5.52
p-Value[a]		0.003	0.002
Mean percentage change	−33%	−51%	−52%
Median percentage change	−51%	−65%	−73%
Number of incontinence episodes/24h			
Number of patients	153	173	165
Adjusted mean change/baseline	−1.08/3.21	−1.73/2.65	−1.58/2.82
p-Value[a]		0.002[b]	0.016[b]
Mean percentage change	−28%	−61%	−52%
Median percentage change	−63%	−100%	−95%
Number of micturitions/24h			
Number of patients	281	286	290
Adjusted mean change/baseline	−1.59/12.31	−2.37/12.05	−2.81/12.12
p-Value[a]		0.0018	0.0001
Mean percentage change	−13%	−20%	−22%
Median percentage change	−14%	−21%	−23%
Volume voided/micturition (mL)			
Number of patients	281	286	290
Adjusted mean change/baseline	10.7/147.2	30.8/148.5	36.0/145.9
p-Value[a]		0.0001	0.0001
Mean percentage change	11%	25%	30%
Median percentage change	5%	20%	25%
Number of nocturia episodes/24h			
Number of patients	240	254	259
Adjusted mean change/baseline	−0.52/2.05	−0.58/1.96	−0.71/1.89
p-Value[a]		0.26	0.036
Mean percentage change	−16%	−25%	−39%
Median percentage change	−25%	−36%	−44%

a p-Values are based on ANOVA model with treatment and centre as terms.

b Using analysis with baseline as a covariate because of baseline variations.

od = once daily.

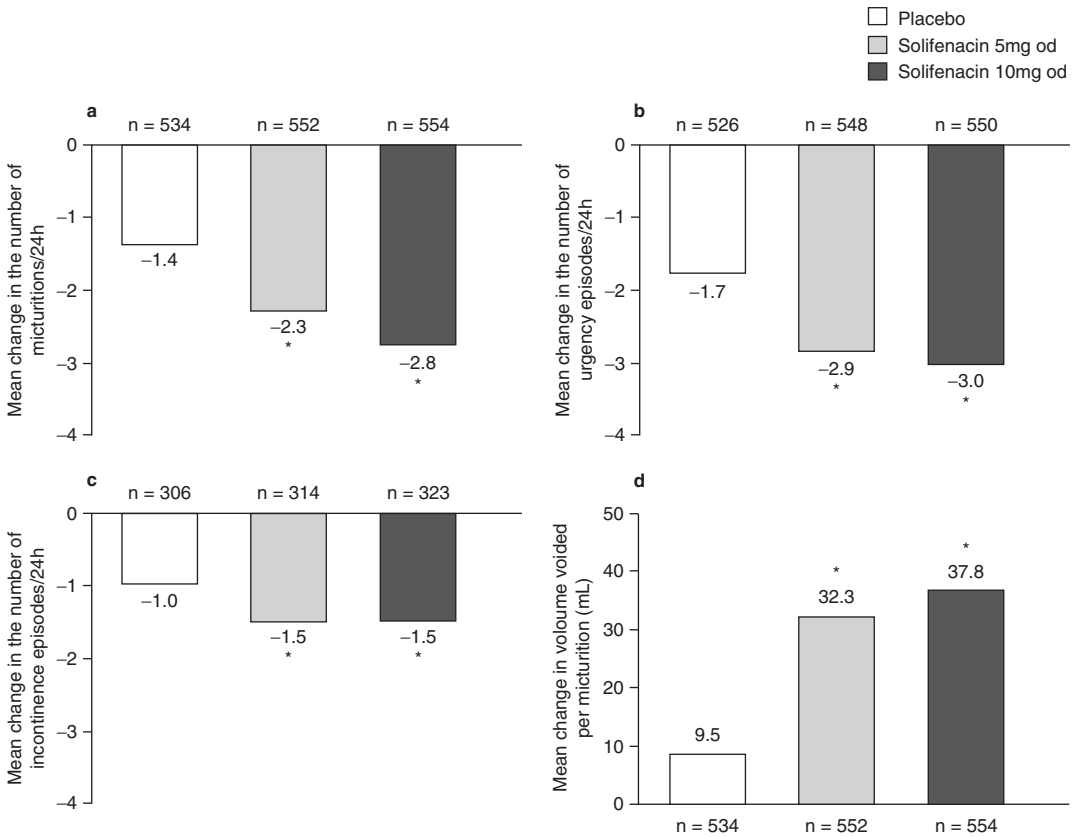

Fig. 2. Pooled efficacy data[11] from two phase III clinical trials.[30,31] Mean change from baseline to endpoint in: (**a**) the number of micturitions per 24 hours; (**b**) the number of urgency episodes per 24 hours; (**c**) the number of incontinence episodes per 24 hours; and (**d**) volume voided per micturition for solifenacin and placebo; ANCOVA with baseline as a covariate analysis. p-Values are based on ANCOVA with centre and treatment as terms and baseline as a covariate. **od** = once daily; * $p < 0.001$ vs placebo.

In the second study,[31] a total of 1091 patients were enrolled, 911 were randomised, 907 were treated and 857 were eligible for the efficacy analysis. Results again demonstrated that solifenacin 5 and 10 mg/day produced statistically significant reductions in frequency, urgency and incontinence, and statistically significantly increased mean volume voided. Nocturia was also statistically significantly reduced with solifenacin 10 mg/day (table III). Of the patients who reported incontinence in baseline voiding diaries, 51% and 50% of patients treated with either solifenacin 5 or 10 mg/day, respectively, in the two studies pooled[30,31] experienced no incontinence at endpoint, compared with 38% of placebo-treated patients.[30,31,35] In the two solifenacin 10 mg/day studies, 53% of solifenacin-treated patients became continent at endpoint compared with 31% of placebo-treated patients.[36] It must be noted that there is no standard definition for 'continence' in clinical trials. In this study 'continent' was defined as no incontinence episodes during the final 3-day diary. These results cannot be compared with other studies using different definitions.

Patient baseline demographics were comparable between the two[30,31] solifenacin 5 and 10 mg/day studies; hence, data pooling was accepted by the US FDA and also the European Agency for the Evaluation of Medicinal Products. Pooled efficacy data from these two studies are illustrated in figure 2.[11]

3.3.2 Safety

Similar protocols were used for the phase III studies and, as such, safety data were pooled from the two published trials.[30,31] Overall, solifenacin was well tolerated. The rates of anticholinergic adverse effects, including dry mouth, constipation and blurred vision, were higher with solifenacin than with placebo and were dose related. Table IV displays the pooled treatment-emergent adverse effects data.[30,31] Discontinuation rates due to dry mouth based on pooled data were similar between solifenacin 5mg once daily (0.5%) and placebo (0.4%). The discontinuation rate was higher with solifenacin 10mg once daily but still remained low (1.2%).[30,31] No deaths related to solifenacin treatment occurred, and solifenacin caused no clinically relevant changes in laboratory parameters, ECG parameters or vital signs. Looking at the safety data from these two phase III studies separately, dry mouth remained the most common adverse effect. In the first study, dry mouth was experienced by 14.0% and 21.3% of patients treated with solifenacin 5 and 10 mg/day, respectively, compared with 4.9% in the placebo group.[30] The second study reported the incidence of dry mouth as 7.5% and 23.1% in the solifenacin 5 and 10mg groups, respectively, compared with 2.3% in the placebo group.[31]

The two solifenacin 10 mg/day studies showed rates of adverse effects to be 74% in solifenacin-treated patients and 61% in placebo recipients; all of the adverse effects reported were mild to moderate in nature, with dry mouth being the most commonly reported.[36]

3.3.3 Quality of Life

Quality-of-life data were collected in three multinational, randomised, double-blind, multicentre studies (one phase II, two phase III) involving men and women with OAB.

The phase II study used the Contilife™ Quality of Life Assessment Concerning Urinary Incontinence Questionnaire, which contains five domains (daily activities, effort, self-image, emotional consequences and sexuality) assessing disease-specific impact on quality of life.[27] In this study patients treated with solifenacin (all doses tested individually) reported statistically significant baseline to endpoint improvements in four of the five domains for solifenacin 10 mg/day and two of the five domains for solifenacin 5 mg/day, as compared with placebo; mean baseline to endpoint changes for combined solifenacin groups in the effort domain were numerically greater than placebo, although not statistically significant.[27]

The European phase III studies[30,31] used the KHQ.[32] Analysis of the combined data from the two phase III trials showed statistically significant improvements from baseline compared with placebo for solifenacin 5 and 10 mg/day in nine of the ten survey domains of the KHQ, including general health perception, incontinence impact, role limitations, physical limitations, social limitations, emotions, sleep/energy, severity measures and symptom severity.[37] Kelleher et al.[38] have suggested that a change from baseline of ≥5 points on the KHQ domains is an indication of a meaningful clinical effect, although it has also been suggested that smaller changes in the KHQ domains could be im-

Table IV. Pooled treatment-emergent adverse effects and rates of discontinuation from two phase III studies of solifenacin[30,31][a]

Adverse effect	Pooled phase III studies (%)		
	placebo (n = 568)	solifenacin 5mg od (n = 578)	solifenacin 10mg od (n = 575)
Dry mouth (% discontinuation)	3.5 (0.4)	11 (0.5)	22 (1.2)
Constipation (% discontinuation)	1.9 (0.4)	5.4 (0.2)	8.5 (0.7)
Blurred vision (% discontinuation)	2.5 (0.2)	3.8 (0.2)	5.9 (0.2)
Discontinuation due to *all* adverse effects[b] (%)	3.5	2.8	3.3

a Tolterodine data are only from one study and so they have not been included in this pooled data table.

b Primary reason for discontinuation.

bid = twice daily; **od** = once daily.

Table V. Changes in efficacy parameters (mean and median) for patients treated with solifenacin during double-blind and extension studies for up to 52 weeks (reproduced from Haab et al.[40] © 2005, with permission from the European Urology Association)

Efficacy outcome	Baseline from original double-blind studies	Extension study endpoint (after 52 weeks)	Overall change from original baseline to extension study endpoint[a]
Urgency episodes/24h			
Number of patients	925	925	925
Mean[b]	5.76 (4.46)	2.28 (3.59)	−3.48 [−63%]
Median	4.33	1.00	−2.67 [−82%]
Incontinence episodes/24h			
Number of patients	535	535	535
Mean[b]	2.66 (2.51)	0.93 (2.06)	−1.74 [−66%]
Median	2.00	0.00	−1.33 [−100%]
Number of micturitions/24h			
Number of patients	931	931	931
Mean[b]	12.16 (3.79)	9.18 (3.33)	−2.97 [−23%]
Median	11.33	8.33	−3.00 [−26%]
Volume voided/micturition (mL)			
Number of patients	931	930	930
Mean[b]	147.6 (53.8)	187.4 (75.4)	39.8 [31%]
Median	138.8	177.5	34.0 [24%]
Nocturia episodes/24h			
Number of patients	841	838	838
Mean[b]	1.95 (1.22)	1.25 (1.26)	−0.70 [−32%]
Median	1.67	1.00	−0.67 [−50%]

a Mean and median percentage change over 52 weeks in brackets.

b Data presented as mean (standard deviation).

portant to patients. Based on the ≥5 cut-point, solifenacin treatment at either dose resulted in a clinically meaningful reduction in eight of the ten domains of the KHQ. These findings strongly suggest that treatment with solifenacin produces a meaningful improvement in patients' ability to perform daily activities.

3.4 Long-Term, Open-Label Extension Study

Patients who completed the two 12-week phase III trials were invited to enter a 40-week open-label extension study designed to evaluate the long-term efficacy, safety and tolerability of solifenacin 5 and 10mg once daily.[39] Since this was an open-label study with no placebo or comparator arm, only descriptive statistics were reported for safety and efficacy. A total of 1637 (91%) of the 1802 patients who completed the 12-week double-blind trials enrolled in the extension study; 81% (n = 1329) of them completed the additional 40 weeks of solifenacin treatment. All patients received solifenacin 5mg once daily for the initial 4 weeks of this study, followed by 36 weeks during which the solifenacin dosage could be changed (either from 5 to 10 mg/day or from 10 to 5 mg/day), remain the same or discontinued at any of three study visits (weeks 4, 16 and 28 from the start of the open-label extension) based on patient satisfaction with therapy. A total of 685 patients (42%) received solifenacin 5 mg/day only throughout the extension study, while the dosage for 840 patients (51%) was increased to, and remained at, 10 mg/day to the end of the open-label extension, and the dosage for 108 patients (6.6%) was increased to 10 mg/day but was returned to 5 mg/day by the end of the open-label extension.[39] Efficacy variables were the same as in the 12-week studies.

The improvements in OAB symptoms achieved with solifenacin in the initial double-blind treatment phase were maintained throughout the extension study period (mean and median changes are presented in table V). Patients treated with solifenacin for up to 52 weeks experienced a mean change in episodes of urgency of −3.48 (−63%) and a mean change in episodes of incontinence of −1.74 (−66%). In this same cohort, micturition frequency was changed by a mean of −2.97 daily voids (−23%) and mean volume voided per micturition was changed by 39.8mL (31%). Finally, a mean change of −0.70 (−32%) episodes of nocturia was reported by patients treated with solifenacin for up to 52 weeks.[39]

For patients reporting incontinence at double-blind study entry who were randomised to receive solifenacin during the double-blind studies, and who continued to receive solifenacin during the open-label extension study, the continence rate increased from 52% at the end of the double-blind period (week 12) to 58% at endpoint of the open-label extension. The proportion of patients reporting no urgency increased from 31% at the end of the double-blind period (week 12) to 40% at endpoint of the extension study, and the proportion of patients reporting normalised micturition frequency (<8 micturitions per 24 hours) increased from 34% at the end of the double-blind period (week 12) to 39% at endpoint of the extension study.[39]

Quality-of-life scores from the KHQ confirmed that additional improvements occurred in most domains with long-term solifenacin treatment. In addition, when asked to assess the tolerability of solifenacin as 'satisfactory', 'acceptable' or 'unsatisfactory', 98% of patients rated solifenacin as either 'satisfactory' or 'acceptable' at week 40. The extension study established that treatment with solifenacin at both the 5 and 10mg once-daily doses had sustained long-term safety and efficacy, and patients enjoyed a high degree of satisfaction with treatment.[40]

3.5 Phase IIIb Data

A European phase IIIb study (STAR [Solifenacin and Tolterodine as an Active comparator in a Randomized study]) recruited 1355 men and women with OAB.[41] Eligibility and outcome criteria were parallel to those used in the phase III trials discussed in section 3.3 The study employed a pragmatic design in which patients were randomised to either solifenacin 5 mg/day or extended-release tolterodine 4 mg/day. At the end of 4 weeks, study subjects were offered the opportunity to elect for a higher dose if they were not satisfied with the efficacy during the initial period. Solifenacin recipients were then given 10 mg/day, but as there is no higher approved dose of tolterodine, this group remained on the same 4 mg/day dose. There was no option to reduce the dose after initial escalation. All solifenacin recipients were combined and compared against all tolterodine recipients.

The primary outcome measure was change in micturition frequency. Solifenacin decreased micturition frequency by 2.45 per day compared with 2.24 for tolterodine ($p = 0.004$ for non-inferiority of solifenacin compared with tolterodine). The combined solifenacin arm showed superior efficacy to tolterodine in many of the secondary endpoints (table VI). In addition to the objective improvements, the subjective measure of patient perception of bladder condition also improved to a significantly greater extent in the solifenacin group compared with the tolterodine group (−1.51 vs −1.33 on a 6-point scale; $p < 0.0061$). Both drugs were relative-

Table VI. Efficacy results from STAR (Solifenacin and Tolterodine as an Active comparator in a Randomized study)[41]

Mean actual change in efficacy parameter (baseline to endpoint)	Solifenacin 5 and 10mg od	Tolterodine ER 4mg od
Urgency episodes/24h	−2.85*	−2.42
Urge incontinence episodes/24h	−1.42**	−0.83
Incontinence episodes/24h	−1.60**	−1.11
Pad usage/24h	−1.72***	−1.19
Perception of bladder condition	−1.51*†	−1.33

ER = extended release; **od** = once daily; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.0023$, *† $p < 0.0061$ vs tolterodine ER.

Table VII. Adverse effects recorded during STAR (Solifenacin and Tolterodine as an Active comparator in a Randomized study) [reproduced from Chapple et al.,[41] © 2005, with permission from the European Association of Urology]

Effect	Mild adverse effect (%)		Moderate adverse effect (%)		Severe adverse effect (%)	
	solifenacin	tolterodine	solifenacin	tolterodine	solifenacin	tolterodine
Dry mouth	17.5	14.8	10.8	7.7	1.7	1.5
Constipation	3.2	1.3	2.7	1.0	0.5	0.2
Blurred vision	0.7	0.7	0.0	1.0	0.0	0.0

ly well tolerated with very few severe adverse events (table VII) and a discontinuation rate of 3.0% for tolterodine and 3.5% for solifenacin.

Perhaps the single most important finding from the study was that approximately 50% of subjects in each arm requested a higher dose at the 4-week titration visit. This certainly implies that standard drug therapy is not adequate for many patients and correlates with the relatively low prescription refill data.[42] Although the clinical translation of these head-to-head results is not yet clear, this trial demonstrates the improved efficacy of a flexible dose regimen of solifenacin compared with fixed-dose tolterodine.

4. Discussion and Conclusions

Phase III trials including >2800 patients demonstrated that solifenacin at dosages of 5 and 10mg once daily statistically significantly reduced the key symptoms of OAB, including urgency, incontinence and frequency. Continence was restored in more than half of incontinent patients after 12 weeks of treatment with both solifenacin 5 and 10 mg/day. Improvements in symptoms were evident by the first treatment visit (4 weeks) and continued throughout the 12-week study period. Importantly, solifenacin statistically significantly reduced episodes of urgency, which is the key distressing symptom for many patients with OAB.[43,44] Solifenacin therapy also improved functional bladder capacity, with statistically significant increases in volume voided with both the 5 and 10 mg/day dosages. Treatment with solifenacin was well tolerated and was associated with a relatively low incidence of anticholinergic adverse effects.

The data also show that >90% of all patients who initiated solifenacin treatment during the 12-week phase III clinical trials completed these trials. Over 90% of these patients elected to continue solifenacin treatment by enrolling in a 40-week, open-label extension study and 81% remained on treatment at 1 year. The additional/incremental improvement in OAB symptoms documented during the extension study demonstrated the durability of the antimuscarinic effect of solifenacin. These findings suggest a favourable balance of efficacy and tolerability, which is supported by improvements in quality of life in nine of ten domains of the KHQ. By effectively reducing symptoms of OAB, with an acceptable tolerability profile, solifenacin may permit individuals to return to normal daily functioning. The ultimate proof of a drug's utility, however, comes when persistence and satisfaction are demonstrated in real life experience, outside of clinical trials.

Solifenacin provides a new therapeutic option for patients with OAB. Solifenacin therapy provides broad and sustained efficacy against the key symptoms of OAB, high patient persistence and a good tolerability profile.

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