"Solifenacin in the treatment of urgency and other symptoms of overactive bladder: results from a randomized, double-blind, placebo-controlled, rising-dose trial"

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Abstract

OBJECTIVES: To examine the effects of the antimuscarinic agent solifenacin on urinary urgency, using a range of novel and established outcome measures, as urgency is the principal symptom of the overactive bladder syndrome (OAB).

PATIENTS AND METHODS: The study (SUNRISE, solifenacin in the treatment of urgency symptoms of OAB in a rising dose, randomized, placebo-controlled, double-blind, efficacy trial) was a randomized, double-blind, 16-week, placebo-controlled, multicentre study of solifenacin 5/10 mg in 863 patients with symptoms of OAB for > or = 3 months. The primary efficacy variable was the change from baseline to endpoint in the number of episodes of severe urgency with or without urgency incontinence per 24 h, as measured using the Patient Perception of Intensity of Urgency Scale, grade 3 + 4. Secondary efficacy variables included patient-reported outcomes for bladder condition, urgency bother and treatment satisfaction. A 3-day voiding diary was used to record micturition ...

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Solifenacin in the treatment of urgency and other symptoms of overactive bladder: results from a randomized, double-blind, placebo-controlled, rising-dose trial

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Level of Evidence 1b

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RESULTS
Solifenacin 5/10 mg was significantly more effective than placebo in reducing the mean number of episodes of severe urgency with or without incontinence per 24 h from baseline to endpoint (−2.6 vs −1.8, P < 0.001). There were also statistically significant differences in favour of solifenacin 5/10 mg over placebo for all secondary variables measured at endpoint, including patient-reported outcomes. There was a significant improvement in urgency as early as day 3 of treatment. Treatment-emergent adverse events with solifenacin 5/10 mg were mainly mild or moderate in severity, and only led to discontinuation in 3.6% of patients.

CONCLUSION
Solifenacin significantly reduced the number of urgency episodes and the extent of urgency bother, and was well tolerated; it was effective as early as day 3 of treatment.

KEYWORDS
solifenacin, urgency, incontinence, overactive bladder, PPIUS

INTRODUCTION
Overactive bladder (OAB) syndrome is a common problem [1–3]. It is defined by the ICS as urgency with or without urgency incontinence, usually accompanied by daytime frequency and nocturia, in the absence of infection or other obvious pathology [4,5]. The cornerstone symptom is urgency, which can be described as the complaint of a sudden compelling desire to pass urine which is difficult to defer [4]. The ICS definition of OAB implies that urgency must be present for a diagnosis of OAB to be made, irrespective of whether patients are ‘wet’ or ‘dry’. Although other symptoms contribute to the bother caused by OAB, it is generally understood that urgency drives the other OAB symptoms either directly or indirectly [6]. This central role of urgency makes it an important target for treating OAB [7].

Urgency has rarely been used as a primary endpoint in clinical trials of antimuscarinic agents in patients with OAB, partly because it is a subjective sensation and its measurement is not well defined. Instead, most trials have tended to use voiding diaries.
to capture changes in micturition frequency or number of incontinence episodes as the primary endpoints. In this report we present data from the solifenacin SUNRISE study [deriving its acronym from Solifenacin in the treatment of Urgency symptoms of overactive bladder in a RISing-dose, randomized, placebo-controlled, double-blind, Efficacy trial], which is the first documented study to measure urgency severity as the primary endpoint, along with several other outcome measures.

Solifenacin succinate is an oral antimuscarinic agent which was first marketed in Europe in 2004 and which is now licensed for use in over 40 countries worldwide, including the USA, Japan and Oceania. Phase III studies with solifenacin 5 and 10 mg consistently showed it to be more effective than placebo for all OAB variables measured [8]. In a direct comparison between solifenacin 5/10 mg and tolterodine extended-release (ER) 4 mg in a randomized, 12-week, double-blind trial, solifenacin was at least as effective as tolterodine ER in reducing micturition frequency, and was significantly more effective than tolterodine ER in improving most other OAB variables (P < 0.05) [9]. In a meta-analysis of seven placebo-controlled OAB studies, the mean and median percentage reductions in the number of urgency episodes with solifenacin were greater than seen with several other antimuscarinics, including oxybutynin, tolterodine, trospium, propiverine and darifenacin [10].

The SUNRISE study attempted to reflect the treatment of OAB in ‘real-life’ clinical practice by using solifenacin 5/10 mg according to the licensed flexible dosage regimen. This differs from Phase III placebo-controlled registration studies where patients were randomized to fixed doses of 5 or 10 mg solifenacin and remained on these doses to the end of the study.

The objective of this 16-week study was to evaluate the effects of solifenacin on urgency using a range of novel and established subjective outcome measures to assess urgency. The primary efficacy measure was the Patient Perception of Intensity of Urgency Scale (PPIUS), in which grades 3 and 4 represent severe urgency and urgency incontinence, respectively. The PPIUS has been recommended by the Committee for Proprietary Medical Products when assessing the degree of urgency felt by patients at each micturition [11]. Secondary variables included the Patient Perception of Bladder Condition score, visual analogue scales (VAS) for measuring urgency bother and treatment satisfaction, and patient-completed voiding diaries to capture other OAB symptoms.

Some of these outcome measures were being combined in the same study for the first time, and it was postulated that the results might provide an insight into their potential usefulness in routine clinical practice. The study was also designed to assess the speed of onset of action of solifenacin using a 7-day diary during the first week of treatment. The ability to achieve a rapid improvement in urgency would be highly desirable in routine clinical practice, as it could promote patients’ appreciation of the treatment effect.

**PATIENTS AND METHODS**

SUNRISE was a prospective, double-blind, two-arm, parallel-group, 16-week, Phase IIIb, placebo-controlled study of solifenacin 5/10 mg in patients with symptoms of OAB for ≥3 months. The study involved 105 centres in 14 European countries and was conducted in accordance with the principles of the Declaration of Helsinki (1996 version) and the International Conference on Harmonization Guidelines for Good Clinical Practice. The study protocol, patient information and informed consent forms were reviewed and approved by independent ethical committees at each study site, and all patients were informed of the nature and purpose of the study. Patients were eligible for study entry if all of the following applied: male or female aged ≥18 years, from whom written informed consent had been obtained, and who were willing and able to complete a voiding diary correctly; symptoms of OAB (including urinary frequency, urgency or urgency incontinence) for ≥3 months and three or more episodes of urgency with or without incontinence in the last 3 days. Table 1 shows the main exclusion criteria at study entry.

Figure 1 summarizes the study plan. Patients first entered into a single-blind, placebo-controlled, run-in period of 2 weeks. To be eligible for randomization after this initial placebo run-in, patients had to have three or more episodes of severe urgency with or without incontinence during the 3-day voiding diary period, and on average eight or more micturitions/24 h. Severe urgency with or without incontinence was defined as PPIUS grade 3 + 4 (‘I could not postpone voiding but had to rush to the toilet in order not to wet myself’, or ‘I leaked before arriving at the toilet’). The PPIUS is described in Table 2.

![Figure 1](image-url)

Those patients satisfying all selection criteria at the end of the run-in period were randomized to receive 8 weeks of double-blind treatment with solifenacin 5 mg or placebo once-daily in a 3:1 ratio. After 8 weeks of double-blind treatment, patients were given the option of either continuing on the original dose or requesting a dose.
increase. This was based on a consideration of efficacy and tolerability, discussed jointly between the patient and doctor. Patients were aware from the Informed Consent form that they would have the opportunity to request a dose increase at 8 weeks.

Patients who requested a dose increase were subject to a second randomization in the solifenacin arm in a 1:1 ratio, which meant that half of the patients requesting a dose increase remained on the original 5 mg starting dose. Throughout the study, all patients received two unmarked tablets of solifenacin/placebo (i.e. a dose increase request did not result in any additional tablets being given). Patients visited the study centre at screening, at the end of the single-blind placebo run-in period (week 0 baseline), and at weeks 1, 8 and 16 of the double-blind period. Patients were instructed to decide a convenient time to take the medication and to use this time for all subsequent doses. Medication was taken with fluid and could be taken with or without food. Each patient completed a voiding diary in the 3 days preceding each scheduled visit, and received a 7-day diary for completion during the first week of double-blind treatment.

Times of micturition, urgency and incontinence episodes were recorded, together with the PPIUS score at each void or leakage. Before each diary collection, the study centres were instructed to call the patient to remind him/her to complete the diary, emphasizing the importance of accuracy in documenting information. The investigator, co-investigator or research nurse were also instructed to review the diaries to ensure accuracy of completion.

Efficacy was assessed at 0, 1, 8 and 12 weeks, and at the study endpoint. The primary variable was the mean change from baseline to endpoint in the number of episodes of severe urgency with or without urgency incontinence per 24 h, defined as grade 3 + 4 on the 5-point PPIUS (Table 2). Secondary efficacy variables included changes from baseline in the mean number of total urgency episodes/24 h (PPIUS 1–4), maximum urgency intensity rated by the PPIUS, number of incontinence episodes/24 h, number of urgency incontinence episodes/24 h, and micturition frequency/24 h. A 7-day diary was used in the first week of double-blind treatment for recording variables relating to speed of onset of efficacy, including time of micturition, urgency and incontinence episodes, together with PPIUS score at each void.

Other efficacy measures included patient-reported outcomes for changes from baseline in the Patient Perception of Bladder Condition (PBC) score (Table 3), and the use of VAS to measure urgency bother and treatment satisfaction. For urgency bother, patients answered the question ‘How much bother has urgency been for you in the past week?’ by...
FIG. 2. The disposition of the patients.

Changes from baseline to endpoint were subjected to a mixed model analysis with baseline values included as a covariate. Study centre was included as a random factor; treatment group and previous treatment for OAB were fixed factors. The speed-of-onset analysis is presented as the median percentage change from baseline for all patients who received solifenacin 5 mg and placebo, irrespective of any subsequent request for a dose increase at 8 weeks. The chi-square or Fisher’s exact test were used to compare the incidence of expected antimuscarinic adverse events (dry mouth, blurred vision and constipation) across treatment groups.

The full analysis set included all patients randomized at baseline who took one or more dose of double-blind medication, and who had data at baseline (Visit 2) and during double-blind treatment. The safety population included all patients who were randomized at baseline and who took at least one dose of double-blind study medication.

The sample size calculation was based on the change from baseline to endpoint in the mean number of episodes of severe urgency with or without urgency incontinence defined as PPIUS grade 3 + 4 (the primary variable). In all, 616 evaluable patients were required (462 in the solifenacin arm and 154 in the placebo arm) to detect a statistically significant difference between solifenacin and placebo with a power of 80% for a two-sided test and significance level of 0.05.

RESULTS

The study period was April 2004 to October 2005. The disposition of patients to each treatment arm is summarized in Fig. 2. Patient demographics were similar between the treatment groups (Table 4). Over half the patients in each treatment group had urgency incontinence at baseline (50.9% solifenacin, 57.9% placebo). The median time since the onset of OAB was 4.17 years for solifenacin patients and 3.17 years for placebo patients. About 45% of patients had received previous drug therapy for OAB within a year of the start of the study. Baseline variables for key efficacy variables are summarized in Table 5. Values for all these variables were similar between the solifenacin and placebo groups.
After 8 weeks, 46.5% of patients randomized to receive solifenacin 5 mg at the start of treatment requested a dose increase, compared with 65.8% of those who had been randomized to receive placebo. The mean compliance with medication throughout the study period was >98% in the solifenacin and placebo groups.

The primary efficacy variable was the change in PPIUS grade 3 + 4; solifenacin 5/10 mg was significantly more effective than placebo in reducing the mean number of episodes of PPIUS grade 3 + 4 per 24 h from baseline to endpoint (−2.6 vs −1.8, p < 0.001; Fig. 3). This represented a −70% median reduction from baseline with solifenacin and a −50% reduction with placebo.

There were statistically significant differences in favour of solifenacin 5/10 mg over placebo for all secondary variables measured at endpoint, including significant reductions in the mean number of all urgency episodes (PPIUS grades 1–4) and in maximum urgency intensity/24 h (Fig. 4). Patient-reported outcomes for urgency bother, patient PBC score and treatment satisfaction were significantly reduced vs placebo at endpoint (all p < 0.001; Fig. 5).

Figure 6 summarizes the time-course results at baseline, 1, 8 and 16 weeks for PPIUS grade 3 + 4, micturition frequency, incontinence episodes and urgency incontinence episodes. There were improvements in these variables progressively throughout the study. These time-course results were obtained using data from the 3-day diaries, which showed a statistically significant benefit for solifenacin over placebo at the week 1 clinic visit.

The use of a 7-day diary during the first week of double-blind treatment provided additional data on the speed of onset of the effect. Figure 7 shows the median percentage changes in PPIUS grade 3 + 4 during the first week of treatment with solifenacin 5 mg and placebo, based on the 7-day diary results. Solifenacin was significantly more effective than placebo as

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**TABLE 4 Demographics for the safety population at baseline.** Data for solifenacin are for patients treated with 5 mg increased at 8 weeks to 10 mg if requested.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Solifenacin 5/10 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>505</td>
<td>223</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>57.7</td>
<td>57.9</td>
</tr>
<tr>
<td>% in group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>69.5</td>
<td>65.5</td>
</tr>
<tr>
<td>&gt;65</td>
<td>30.5</td>
<td>34.5</td>
</tr>
<tr>
<td>&gt;75</td>
<td>5.0</td>
<td>8.1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10.9</td>
<td>14.3</td>
</tr>
<tr>
<td>Female</td>
<td>89.1</td>
<td>85.7</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>98.4</td>
<td>99.1</td>
</tr>
<tr>
<td>Black</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Asian</td>
<td>0.8</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*All data are for the mean number of episodes per 24 h except for PBC and VAS.

**TABLE 5 Mean baseline (week 0) values for efficacy variables.** Data for solifenacin are for patients treated with 5 mg increased at 8 weeks to 10 mg if requested.

<table>
<thead>
<tr>
<th>Efficacy variable*</th>
<th>Solifenacin 5/10 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>503</td>
<td>216</td>
</tr>
<tr>
<td>Number of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgency episodes PPIUS grade 3 + 4</td>
<td>5.11</td>
<td>5.54</td>
</tr>
<tr>
<td>Urgency episodes PPIUS grade 1–4</td>
<td>10.72</td>
<td>10.81</td>
</tr>
<tr>
<td>Maximum urgency intensity at void (PPIUS grade 0–4)</td>
<td>3.53</td>
<td>3.59</td>
</tr>
<tr>
<td>Number of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micturition episodes</td>
<td>11.10</td>
<td>11.14</td>
</tr>
<tr>
<td>Incontinence episodes</td>
<td>1.63</td>
<td>2.01</td>
</tr>
<tr>
<td>Urgency incontinence episodes</td>
<td>1.58</td>
<td>1.96</td>
</tr>
<tr>
<td>PBC score</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Urgency bother (VAS, mm)</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>Treatment satisfaction (VAS, mm)</td>
<td>29</td>
<td>29</td>
</tr>
</tbody>
</table>

+p-values are for solifenacin vs placebo at endpoint; SD = Standard Deviation

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**FIG. 3.** The change in the mean number of episodes of PPIUS grade 3 + 4 (severe urgency with or without urgency incontinence) per 24 h from baseline to endpoint after 16 weeks of treatment with solifenacin 5/10 mg (5 mg increased at 8 weeks to 10 mg if requested) or placebo.

**FIG. 4.** The mean change in secondary efficacy variables per 24 h from baseline to endpoint after 16 weeks of treatment with solifenacin 5/10 mg (5 mg increased at 8 weeks to 10 mg if requested) or placebo.
The median percentage improvement from baseline to endpoint in urgency bother VAS, patient PBC score and treatment satisfaction after 16 weeks of treatment with solifenacin 5/10 mg (5 mg increased at 8 weeks to 10 mg if requested) or placebo.

FIG. 5. The time-course results; the median percentage change from baseline in PPIUS grade 3 + 4, micturition frequency, incontinence episodes and urgency incontinence episodes at 1, 8 and 16 weeks after treatment with solifenacin 5/10 mg (5 mg increased at 8 weeks to 10 mg if requested) or placebo. Results are from the 3-day diaries.

FIG. 6. The time-course results; the median percentage change from baseline in PPIUS grade 3 + 4, micturition frequency, incontinence episodes and urgency incontinence episodes at 1, 8 and 16 weeks after treatment with solifenacin 5/10 mg (5 mg increased at 8 weeks to 10 mg if requested) or placebo. Results are from the 3-day diaries.

early as day 3. There was also an early onset of significant treatment effect for micturition frequency, incontinence episodes/24 h and urgency incontinence episodes/24 h (data not shown).

The incidence of treatment-emergent antimuscarinic adverse events (the most common adverse events) is summarized in Table 6. Most adverse events were of mild or moderate severity, and only 3.8% of patients reported one or more severe adverse events with solifenacin 5/10 mg (vs 2.2% with placebo). The rate of discontinuation due to treatment-emergent adverse events was 3.6% with solifenacin and 2.7% with placebo.

DISCUSSION

Urgency is the principal symptom of OAB [4]; urgency leads directly to increased frequency and reduced intervoid interval, which in turn can lead to urinary incontinence, reduced volume voided and nocturia (Fig. 8) [6]. This makes urgency a primary focus for therapeutic intervention in OAB, and implies that a treatment effective in reducing urgency should also be effective in improving all other OAB symptoms.

The present study is the first to assess urgency as the primary endpoint using the PPIUS, in which grades 3 and 4 equate to severe urgency and urgency incontinence, respectively. Solifenacin 5/10 mg was significantly more effective than placebo in reducing the mean number of episodes of PPIUS grade 3 + 4 per 24 h, from baseline to endpoint, and produced significant reductions in all grades of urgency (PPIUS grades 1–4). Solifenacin was associated with significant improvements in other patient-reported outcomes, including the PBC score and VAS scores for treatment satisfaction and reduction in urgency bother. There were significant reductions in voiding diary scores for micturition frequency, incontinence episodes and urgency incontinence episodes.

At the week 8 clinic visit when the patients were allowed to request a dose increase, fewer than half the patients (46.5%) chose to increase their solifenacin dose from 5 to 10 mg (compared with 65.8% requesting a dose increase on placebo). This is consistent with results from the STAR study, in which about half of patients who received a starting dose of solifenacin 5 mg or tolterodine ER 4 mg requested a dose increase at 4 weeks [9]. Both the SUNRISE and STAR studies were carried out in a secondary-care specialist environment with referred patients who had been told that a dose increase was possible. In routine clinical practice, clinicians might not always inform a patient that a dose increase is available, and this could influence the proportion of patients who receive the 10 mg dosage. A postmarketing surveillance study of solifenacin in 4450 patients conducted in Germany has indicated that only about 21%
of patients receive the 10 mg dose in routine practice [12].

Patients’ expectations for treatment might be high in OAB, and they can become disillusioned with treatment if these expectations are not met [13]. The various subjective and objective outcome measures used in the SUNRISE study showed that solifenacin treatment was highly effective in reducing urgency severity and all other OAB symptoms, and was regarded favourably by most patients. The high level of treatment satisfaction indicates that benefits associated with symptom relief were not substantially influenced by any potentially negative influences such as adverse events.

The ability to achieve a rapid improvement in urgency might be highly desirable in routine clinical practice, as it should enable patients to recognize that treatment is starting to work, thus providing confidence that OAB is being treated successfully. In this study, solifenacin 5 mg had an early onset of effect, with significant differences over placebo as early as day 3 for PPIUS grade 3+4 and several other OAB symptoms.

There was a large placebo effect in the study, as shown by the fact that about a third of patients who started on placebo did not request a dose increase at 8 weeks. The placebo effect in clinical trials in patients with LUTS has a strong behavioural component, partly because voiding diaries tend to make patients more aware of their micturition habits and thus might be regarded as part of the overall treatment package [14]. This could have been a factor contributing to the placebo response in the present study, perhaps reinforced by patients receiving more personal medical attention than would generally be possible in clinical practice. The placebo effect in OAB trials requires further investigation, but it has been suggested that even a relatively small difference between active treatment and placebo outcomes might have a large influence on quality of life and treatment success [14].

There are many different tools available for assessing treatment success in OAB. Measuring subjective symptoms such as urgency is important, and in the present study a novel approach of using the PPIUS as the primary measure of urgency was adopted, together with VAS and PBC scores, some of which have not previously been combined in clinical trials. The results confirm the consistent effect of solifenacin on urgency and other OAB symptoms measured. Simple scoring scales such as PPIUS, together with a VAS to assess urgency bother and treatment satisfaction, could be useful in routine practice, as they are easily applied and appear to be reliable measures of treatment outcome. The PPIUS merits further investigation in other OAB clinical trials.

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**CONFLICT OF INTEREST**

The study was supported by Astellas Pharma Europe Ltd. The authors declare the following for research, consultancy and/or advisory
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Abbreviations: OAB, overactive bladder; PPIUS, Patient Perception of Intensity of Urgency Scale; ER, extended release; SUNRISE, Solifenacin in the treatment of Urgency symptoms of overactive bladder in a rising dose, randomised, placebo-controlled, double-blind, efficacy trial; PBC, Perception of Bladder Condition; VAS, visual analogue scale.

APPENDIX

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