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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name Guodong Fang
Review Completion Date Nov. 18, 2004

Established Name Solifenacin Succinate
(Proposed) Trade Name Vesicare
Therapeutic Class M₃ muscarinic-receptor antagonist
Applicant Yamanouchi Pharma America,

Formulation Tablet
Dosing Regimen 5 mg and 10 mg
Indication Treatment of overactive bladder with
symptoms of urge urinary incontinence,
urgency, and urinary frequency
Intended Population Men & women with overactive bladder

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

In the opinion of this reviewer, from a clinical perspective, solifenacin succinate 5 mg tablet and 10 mg tablets taken once daily **should be approved** for the indication of **"treatment of overactive bladder (OAB) with symptoms of urge incontinence, urgency, and urinary frequency."** in men and women 18 years of age and older.

The evidence presented in the original submission of this NDA is adequate to support the effectiveness of solifenacin succinate for the overactive bladder. The three deficiencies of this NDA determined by the Division in the approvable letter on October 17, 2003, including one for chemistry and two for clinical safety, were resolved in the amendment submission of complete response. The adverse events profile of solifenacin succinate appears to be similar to other approved anticholinergic drugs in its class. The safety evaluation meets the ICH guidance for the number of subjects exposed to solifenacin and for the duration of exposure. The prevention and management of constipation and its serious sequelae are adequately addressed in the revised labeling. QT safety assessment from study CL-043 showed no significant effect of solifenacin on the QT interval at the maximum clinical dose of 10 mg. The 30 mg dose showed an effect of less than 10 msec which was lower than that seen with the active control moxifloxacin.

1.2 Recommendation on Postmarketing Actions

The reviewer has no specific recommendations.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Solifenacin succinate is a muscarinic M₃ receptor antagonist. There are three other antimuscarinic drugs currently on the market (oxybutynin, tolterodine, and trospium) indicated for the treatment of overactive bladder (OAB). The sponsor requests approval for 2 doses (5 and 10 mg). The recommended starting dose of solifenacin is 5 mg which may be increased to 10 mg based on efficacy and tolerability.

The original NDA was submitted December 22, 2002, contained 4 pivotal Phase 3 efficacy studies (two US studies [Study 905-CL-013 and 014] evaluating 10 mg dose and two European studies [Study 905-CL-015 and 018] evaluating the 5 mg and 10 mg doses of solifenacin) and other supporting Phase 2 and Phase 1 studies. 4-month safety update was submitted April 25, 2003, and FCG results of an open-label, long-term safety study (905-CL-022) were submitted July 15, 2003.

The NDA contained several deficiencies which were outlined in the "approvable" letter dated October 17, 2003:

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- **Deficiency #1:** This application lacks sufficient information to conclude that solifenacin is not associated with clinically relevant QT interval prolongation.
The sponsor was advised to submit the results from a randomized, placebo-controlled study of solifenacin with the primary objective of determining the effect of solifenacin on the QT interval at the plasma concentrations achieved at steady state when solifenacin is co-administered with a potent CYP3A4 inhibitor. The Agency further advised the sponsor to submit a protocol for review prior to initiating this study.
- **Deficiency #2:** The current dissolution acceptance criterion (t_{50} at 30 minutes) is unacceptable. The sponsor was advised to submit additional dissolution data obtained at 20 minutes and 30 minutes from the additional t_{50} batches produced since the submission of the original NDA as part of the complete response.
- **Deficiency #3:** Labeling remains unresolved. Overall comments on labeling are deferred until data are available from the QT study.
The sponsor was advised to submit revised draft labeling, updated to include the results of this QT study. In addition, solifenacin appeared to be associated with the occurrence of constipation, and rarely, serious sequelae of this adverse event. The sponsor was requested to address the prevention and management of such serious sequelae in the revised labeling. Additional risk management strategies, including emphasis on using the lowest effective dose for an individual patient, might be needed.

The sponsor was further requested to submit a safety update when they respond to the above deficiencies.

A complete response to the "approvable" action was submitted on May 18, 2004, to address these deficiencies. The amendment includes four major sections: 1) Evaluation of the effect of solifenacin on QT interval (a statistical report for Study 905-CL-043, a final report will be submitted on June 18, 2004) 2) Analysis of constipation and related adverse events 3) Safety update and 4) Revised labeling. The amendment contains data from four completed and three ongoing clinical studies.

A complete study report for an open-label, long-term safety and efficacy follow-up study of solifenacin 5 mg and 10 mg in patients with OAB in Europe (905-CL-019) was also submitted on May 18, 2004.

In addition, most recent safety update (covering the period of April 15, 2004 to September 15, 2004) was submitted on September 30, 2004.

**APPEARS THIS WAY
ON ORIGINAL**

Table 1 Summary of solifenacin clinical studies in the amendment

Phase Study #	Population	Objectives	Design	Location	05/2004 status # completed	Safety information
Phase 1						
CL-024	Healthy elderly/ non-elderly	PK / safety	Non-blinded, multiple-dose	JP	complete / 64	SAEs, Narratives DC-AEs, CRFs narratives
CL-043	Healthy subjects	Effects of 2 dosag of solifenacin & single dose of moxifloxacin on QTc interval	Randomized, 5-period sequential	US	complete / 76	SAEs: narratives, DC-AEs: CRFs. narratives
Phase 2						
CL-023	Pts with OAB	Efficacy/safety	Randomized, DB, Placebo, parallel, dose-response	JP	complete / 317	SAEs, Narratives DC-AEs: CRFs narratives
Phase 3						
CL-037	Pts with OAB	Efficacy/safety	Randomized, DB	JP	ongoing / 1455	SAEs, narratives Deaths, narratives DC-AEs: narratives
CL-038	Pts with OAB	PK, Long-term efficacy/safety	Open-label, non-comparative	JP	ongoing / 252	SAEs, Narratives DC-AEs: CRFs narratives
Phase 3b						
UC-001	Pts with OAB	Long-term efficacy/safety	Prospective, open-label	US	complete / 159	SAEs, Narratives DC-AEs: CRFs narratives
EC-001	Pts with OAB	Efficacy/safety vs. tolterodine	Randomized, DB	EU	ongoing / 674 (planned)	SAEs: narratives
UC-005	Pts with OAB, not exposed to anticholinergic drugs before	Efficacy/safety	Randomized, DB, placebo-controlled	US	ongoing	SAEs: narratives
UC-006	Pts with OAB, treated with tolterodine	Efficacy/safety	Open-label	US	ongoing	None
UC-007	Pts. with OAB	Efficacy/Safety	Open-label	US	ongoing	SAEs: narratives

DB = double blind; DC-AEs = discontinuations due to adverse events. JP = Japan

1.3.2 Efficacy

In the original NDA review, there were four randomized, double-blind, placebo-controlled, parallel-arm, multicenter clinical studies of primary interest for assessing the efficacy of solifenacin 5 and 10 mg tablets. All four studies included the 10 mg solifenacin dose, and two studies included the 5 mg dose. For the primary endpoint, the mean change in number of micturitions per 24 hours, the statistical reviewer concluded that the results were consistent and were statistically significant in favor of both solifenacin doses versus placebo for the primary efficacy endpoint (the mean change in number of micturitions per 24 hours) and for one of the two secondary endpoints of interest (the mean change in volume voided per micturition). For the other secondary endpoint of interest (the mean change in number of incontinence episodes), three of the four studies showed statistical significance for both solifenacin doses over placebo. The statistical reviewer further concluded that the results of these four pivotal studies supported the efficacy claim for both solifenacin 5 and 10 mg doses for the treatment of symptoms of overactive bladder.

1.3.3 Safety

Safety data from additional completed and ongoing studies included in this amendment indicate that the safety profile of solifenacin is similar to that observed in the pivotal phase 3 studies presented in the original NDA and its subsequent safety update. Observations regarding the type, incidence, and severity of adverse events (AEs), serious adverse events (SAEs), and discontinuations due to AEs, reported in the submitted studies were consistent with that observed previously.

1.3.3.1 Total drug exposure

At the time of NDA Amendment submission, 3942 patients with OAB had been treated in phase 2 and phase 3 trials, which included 2621 from the original review and 1321 from this amendment. In completed phase 2 or phase 3 trials submitted in the amendment, a total of 2282 patients (961 had been exposed in previous double-blind studies) have been exposed to solifenacin 2.5 mg, or 5 mg, or 10 mg. Among them, 436 (19.1%) completed up to 12 weeks of exposure, 146 (6.4%) completed between 12 and 24 weeks of exposure, 64 (2.8%) completed between 24 and 27 weeks of exposure, and 1636 (71.7%) completed more than 27 weeks of exposure (639 or 28% completed 40 to 52 weeks, and 645 or 28.3% completed more than 52 weeks).

1.3.3.2 Deaths and other serious adverse events (SAEs)

Deaths: A total of 15 deaths have been reported during drug development. Eleven of the deaths were reported in the original NDA submission. The remaining 4 cases were reported since the original NDA submission and are included within the amendment. Two of these 4 deaths occurred in a Japanese study (905-CL-037) which was placebo-controlled, and one each occurred in European (905 CL-019) and US (905 UC-007) open label studies. One patient (Patient #152-2, Japanese study 037) was found dead in the bathroom (medical examiner stated that the death occurred 4 days prior to the discovery), the investigator considered the event unassessable due to lack of information. The second patient (Patient #253-2, Japanese study 037) developed acute bronchitis and pneumonia complicated by respiratory distress followed by cardiac "distress," resulting in death. The investigator considered this death unrelated to study drug. The third death (Patient #10551, European study 019) occurred after discontinuation of the study. This 76-year-old female with well-controlled diabetes who was randomized to solifenacin 10 mg in the double-blind study received 5 mg at the start of the extension study, and 35 days later the dose was increased to 10 mg. Study drug was discontinued another 10 days later after 133 days of solifenacin treatment. Two days later she collapsed at home due to postural hypotension and was hospitalized. The patient forgot to take the study medication 2 days before the event. The investigator considered the collapse probably to be treatment-related. The patient recovered after one-week hospitalization with sequelae. Two months after withdrawal from the trial the patient died of pulmonary embolism as a result of right leg vein thrombosis. The cause of death was considered unrelated by the sponsor. The fourth patient (Patient #01503, Study UC-007), who was an 84-year-old female with a medical history of hypertension and transient ischemic attack, died suddenly 18 days after she was randomized to solifenacin 5 mg. The investigator considered the death secondary to the patient's arteriosclerotic cardiovascular disease and unrelated to solifenacin.

Serious treatment-emergent adverse events: In the current amendment submission, fewer than 5% of patients in any solifenacin treatment group experienced an SAE. SAEs were reported in 3.4% of patients treated with solifenacin 5 mg or 10 mg in Europe and the US combined (Studies 019, UC-001, EC-001, 84 SAEs in 2440 patients), and in 2.1% of patients treated with solifenacin 2.5 mg, 5 mg, or 10 mg in Japan (40 SAEs in 1949 patients). In a total of 139 reported SAEs (updated September 15, 2004), 24 SAEs were considered to be probably or possibly related with study drug. The overall incidence of serious adverse events and the nature of individual serious adverse events in the updated pools do not suggest a specific risk pattern and no new safety concerns were identified.

1.3.3.3 Frequent adverse events:

For the combined three US (UC-001), European (CL-019), and Japanese (CL-038) open label, extension studies, the overall frequency of treatment-emergent adverse events (TEAEs) was 65.9% in patients with solifenacin. In the CL-019 European study, more patients treated with solifenacin 10 mg developed TEAEs (55.0%) than patients treated with solifenacin 5 mg (46.4%). In the US, EU, and JPN trials, the majority of the TEAEs in all treatment groups were considered mild or moderate in severity.

1.3.3.4 Prevention and management of constipation and its serious sequelae in the labeling

Treatment-emergent constipation, one of known adverse events associated with anticholinergic agents, was observed in 2.9%, 5.4% and 13.5% of patients on placebo, 5 mg and 10 mg of solifenacin, respectively. The overall incidence of constipation and discontinuations due to constipation were both dose-dependent, occurring more frequently in the solifenacin 10 mg group. Most events of constipation were mild or moderate, and were manageable by the patients and their physicians with diet modifications, and use of laxatives. The dose of solifenacin appears to be the only contributory factor associated with the occurrence of constipation. The reviewer agrees that it is important to recommend that the starting dose for solifenacin treatment is 5 mg.

In an analysis of serious sequelae of constipation in patients taking solifenacin [including Phase 3 double-blind studies (905-CL-013, 905-CL-014, 905-CL-015, and 905-CL-018) and open-label studies 905-CL-016 and 905-CL-019], six patients (4 of these 6 taking solifenacin 10 mg) with serious sequelae of constipation were found in the SAE database including fecal impaction (2), colonic obstruction (1), intestinal obstruction (1), intestinal ischemia / perforation (1) and severe constipation (1). The sponsor plans to manage the risk associated with the occurrence of constipation through product labeling including the physician package insert. The sponsor will emphasize to physicians that the recommended dose of solifenacin is 5 mg once daily and, if 5 mg is well tolerated, the dose may be increased to 10 mg once daily.

Reviewer's comment: Based on the analysis of constipation and the proposed risk management strategy mainly focusing on the minimum recommended dose of 5 mg once daily, this reviewer agrees that the management of the risk of constipation is adequately addressed

1.3.3.5 Effect of solifenacin on the QT interval

In addition to ECG related safety portion of safety update submission Study CL-043, "A study to evaluate the effect of repeat oral doses of solifenacin 10 mg and 30 mg on Cardiac conduction as assessed by 12-lead ECG as compared to placebo and single oral doses of moxifloxacin" in 86 healthy female volunteers was reviewed. The 30 mg dose was chosen for use in the study because this dose

resulted in a solifenacin exposure covering those observed upon co-administration of 10 mg of solifenacin with potent CYP 3A4 inhibitors (e.g. ketoconazole 400 mg). Calculation of maximum QTcF changes from baseline performed by a variety of methods (both intra- and interpatient analyses) resulted that the following changes occurred: solifenacin 10 mg, 3-5 msec; solifenacin 30 mg, 8-10 msec; and moxifloxacin 400 mg, 10-12 msec.

This reviewer believes that the highest proposed clinical dose of solifenacin to be marketed (10 mg) is associated with a small prolongation of the QT interval in the range of less than 5 msec. At supratherapeutic plasma concentrations seen following administration of solifenacin 30 mg qd, a QT interval prolongation of 8-10 msec was observed. The QT interval prolongation for moxifloxacin 400 mg as positive control is in the range of 10-12 msec. It is concluded that the QT interval prolongation associated with recommended solifenacin doses does not pose a clinical risk. The effect of supratherapeutic doses of solifenacin on QT interval prolongation should be included in labeling as precaution.

Reviewer's comment: At the 10 mg dose level, the effect of solifenacin on QTcF appears to be less than 5 msec. Information concerning the QT dose response from 10 to 30 mg solifenacin should be included in labeling.

1.3.4 Dosing Regimen and Administration

The recommended dose of solifenacin is 5 mg once daily. If the 5 mg dose is well tolerated, the dose may be increased to 10 mg once daily.

1.3.5 Special Populations

1.3.5.1 Effect of age, gender and race

TEAEs in the included additional Phase 3 and open label studies were reviewed by age (<65 years, ≥ 65 years, ≥ 75 years), and by gender. No clinically important differences in the adverse event profile of solifenacin were found by age, by gender, or by race for the categories examined.

The vast majority of patients in both the solifenacin and placebo treatment groups were Caucasian. The number of patients in racial sub-groups other than Caucasians was too small to detect any meaningful differences in the rates of adverse events in solifenacin treated patients across racial subgroups.

Two clinical pharmacology studies evaluating the effect of gender by solifenacin gave disparate results. One study showed no effect while the other showed a 30-60% increase in C_{max} in females.

Thus, based on both pharmacokinetic studies in healthy subjects and clinical trial experience in patients with OAB, it may be concluded that no specific labeling statements or dosing adjustments based on age, gender, or race are necessary for safe use of solifenacin.

1.3.5.2 Pediatric issues

Solifenacin is indicated only for men and women with OAB. The safety and effectiveness of solifenacin in pediatric patients have not been established. In a letter of June 23, 2004 to the sponsor, the Division

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denied the sponsor's request for a waiver from the requirement to conduct pediatric studies and deferred the sponsor's submission of its pediatric studies until May 18, 2009. However, the sponsor was requested to submit pediatric development plans within 120 days from the date of that letter. The sponsor submitted a pediatric development proposal on October 22, 2004, including an outline of a protocol designed to investigate the pharmacokinetics of solifenacin in pediatric patients.

**APPEARS THIS WAY
ON ORIGINAL**

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Solifenacin succinate is a muscarinic M₃ receptor antagonist. There are three other antimuscarinic drugs currently on the market (oxybutynin, tolterodine, and trospium) indicated for the treatment of overactive bladder (OAB). The sponsor requests approval for 2 doses (5 and 10 mg). The recommended starting dose of solifenacin is 5 mg which may be increased to 10 mg based on efficacy and tolerability.

2.2 Previous Submission Related Regulatory Activity

The original NDA was submitted December 22, 2002, and contained 4 pivotal Phase 3 efficacy studies (two US studies [Study 905-CL-013 and 014 which evaluated the 10 mg dose] and two European studies [Study 905-CL-015 and 018 which evaluated the 5 mg and 10 mg doses]) and other supporting Phase 2 and Phase 1 studies. The 4-month safety update was submitted April 25, 2003, and ECG results of an open-label, long-term safety study (905-CL-022, a dedicated QT study) was submitted July 15, 2003.

The NDA contained several deficiencies that were outlined in the "approvable" letter dated October 17, 2003:

- **Deficiency #1:** This application lacks sufficient information to conclude that solifenacin is not associated with clinically relevant QT interval prolongation.
The sponsor was advised to submit the results from a randomized, placebo and positive-controlled study of solifenacin with the primary objective of determining the effect of solifenacin on the QT interval at the plasma concentrations achieved at steady state when solifenacin is co-administered with a potent CYP3A4 inhibitor. The Agency further advised the sponsor to submit a protocol for review prior to initiating this study.
- **Deficiency #2:** The current dissolution acceptance criterion (— at 30 minutes) is unacceptable.
The sponsor was advised to "submit additional dissolution data obtained at 20 minutes and 30 minutes from the additional — batches produced since the submission of your original NDA as part of your complete response."
- **Deficiency #3:** Labeling remains unresolved. Overall comments on labeling are deferred until data are available from the QT study.
The sponsor was advised to submit revised draft labeling, updated to include the results of this study. In addition, solifenacin appeared to be associated with the occurrence of constipation, and rarely, serious sequelae of this adverse event. The sponsor was requested to address the prevention and management of such serious sequelae in the revised labeling. Additional risk management strategies, including emphasis on using the lowest effective dose for an individual patient, might be needed.

The sponsor was further requested to submit a safety update when they respond to the above deficiencies. The safety update will need to include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

The deficiency #2 sent to the sponsor in the Division's approvable letter dated on October 17, 2003, was an CMC issue, which stated that the dissolution acceptance criterion (Q = 75% at 30 minutes) was unacceptable. The sponsor was advised to submit additional dissolution data (obtained at 20 minutes and 30 minutes from the additional batches produced since the submission of original NDA as part of your complete response).

The sponsor has submitted dissolution data on 10 additional batches of solifenacin succinate tablets. 5 batches are for the 10 mg tablets, while 5 are for the 5 mg tablets. Dissolution conditions are 37°C, paddle method at 100 rpm, 100 mL. Current specifications are Q = 75% at 30 minutes. The Division requested a specification of Q = 75% at 20 minutes. Analysis of the submitted data was performed. For the 10 mg tablets (5 batches), all of the batches passed dissolution at 30 minutes with Stage 1 testing, with an average of 99.2% released. At 20 minutes, two of the batches required Stage 2 testing to pass, with an average release of 93.2%. No batches required Stage 3 testing.

Tablets strength	Number of batches	Testing stage		Outcome
		20 minutes	30 minutes	
10 mg	5	Stage 2	Stage 1	Passed
10 mg	5	Stage 1	Stage 1	Passed

For the 5 mg tablets (5 batches) 3 batches passed with Stage 1 testing at both 20 and 30 minutes. 2 batches required Stage 2 testing for 30 minutes and Stage 3 testing at 20 minutes in order to pass. The 10 mg batch passed at 30 minutes with Stage 1 testing (one tablet was at the limit of 75%, but failed at 20 minutes with Stage 3 testing because more than two tablets were below 75%) (See Stage Specification table).

Tablets strength	Number of batches	Testing stage		Outcome
		20 minutes	30 minutes	
5 mg	9	Stage 1	Stage 1	Passed
5 mg	3	Stage 3	Stage 2	Passed
5 mg	1	Stage 3	Stage 1: One tablet at limit	Failed at Stage 3: 3 tablets

The sponsor states that the 30 minute time point is more suitable and describes the reasons, then requests to keep the Dissolution Acceptance Criteria at Q = 75% at 30 minutes.

The chemistry reviewer makes the following comments: Analysis of the 5 mg tablet data shows that if Stage 3 testing is required at 20 minutes, Stage 2 testing is required at 30 minutes. Therefore, with the current specifications, the same lots would be captured for quality control. The 10 mg tablets did not

show the same correlation. In light of the fact that there is no IVIVC, the tablets are not fully disintegrated at 20 minutes under the mild dissolution conditions, and testing at additional stages was required at both 30 and 20 minutes for the same 5 mg batches. The current dissolution specifications are adequate to monitor the quality of the tablets.

The chemistry reviewer further concludes: The sponsor submitted the additional dissolution data requested at the end of the first review cycle and outlined in the APPROVABLE letter. Analysis of the data led to the conclusion that the original dissolution criteria ($Q=75\%$ at 30 minutes) are adequate to monitor the quality of the tablets.

The chemistry reviewer recommends that this application can be APPROVED from a CMC standpoint pending acceptable labeling.

3.2 Animal Pharmacology/Toxicology

Brief Pharm/Tox updated review: Nonclinical safety issues relevant to clinical use:

- 1) Solifenacin succinate has been shown to potentially reduce heart rate and induce prolongation of the P-wave and PR interval and the QRS duration and QT interval. *In vitro*, solifenacin succinate was shown to inhibit the HERG potassium current at a concentration of 0.27 μ M.
- 2) A relationship between cleft palate in mice and *in utero* exposures to solifenacin succinate could not be ruled out.
- 3) *In utero* and lactational exposures resulted in reduced fetal and pre-weaning pup weights, peripartum and postpartum mortalities, and delayed development.
- 4) Severe and seemingly irreversible ocular mucosal damage, especially opacity and edema to the cornea and falling of the nictitating membrane was observed in rabbits with 10 and 100 mg/eye (unrinsed). Rinsing appeared to ameliorate the effect. Effects were reversible over time at 1 mg (unrinsed) and following rinsing 10-30 seconds after instillation at higher concentrations.

The Pharmacology/Toxicology reviewer recommends that this application can be approved from a pharmacology/toxicology standpoint pending acceptable labeling.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The following materials were reviewed:

- 1) Phase 2 / 3 studies 905 CL-023, 037, 038, UC-001, EC-001
- 2) QTc study CL-043
- 3) Phase 1 study CL-024
- 4) Safety updates submitted on May 18 and September 30, 2004
- 5) Serious adverse events from ongoing studies UC-005, 006, and 007.

4.2 Tables of Clinical Studies

Table 1 Summary of solifenacin clinical studies in the amendment

Phase Study #	Population	Objectives	Design	Location	05/2004 status # completed	Safety information
Phase 1						
CL-024	Healthy elderly/ non-elderly	PK / safety	Non-blinded, multiple-dose	JP	complete / 64	SAEs. Narratives DC-AEs, CRFs narratives
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Phase 2						
CL-023	Pts with OAB	Efficacy/safety	Randomized, DB, Placebo, parallel, dose-response	JP	complete / 317	SAEs. Narratives DC-AEs: CRFs narratives
Phase 3						
CL-037	Pts with OAB	Efficacy/safety	Randomized, DB	JP	ongoing / 1459	SAEs. narratives Deaths, narratives DC-AEs: narratives
CL-038	Pts with OAB	PK, Long-term efficacy/safety	Open-label, non-comparative	JP	ongoing / 252	SAEs. Narratives DC-AEs: CRFs narratives
Phase 3b						
UC-001	Pts with OAB	Long-term efficacy/safety	Prospective, open-label	US	complete / 159	SAEs. Narratives DC-AEs: CRFs narratives
EC-001	Pts with OAB	Efficacy/safety vs. tolterodine	Randomized, DB	EU	ongoing / 674 (planned)	SAEs: narratives
UC-005	Pts with OAB, not exposed to anticholinergic drugs before	Efficacy/safety	Randomized, DB, placebo-controlled	US	ongoing	SAEs: narratives
UC-006	Pts with OAB, treated with tolterodine	Efficacy/safety	Open-label	US	Ongoing	None
UC-007	Pts. with OAB	Efficacy/Safety	Open-label	US	Ongoing	SAEs: narratives

DB = double blind; DC-AEs = discontinuations due to adverse events. JP = Japan

In addition, a complete study report for an open-label, long-term safety and efficacy follow-up study of solifenacin 5 mg and 10 mg in patients with OAB in Europe (905-CL-019) was also submitted on May 18, 2004.

5 CLINICAL PHARMACOLOGY

Pharmacokinetics and pharmacodynamics were part of QT study CL-043

6 INTEGRATED REVIEW OF EFFICACY

In the original NDA review, there were four randomized, double-blind, placebo-controlled, parallel-arm, multicenter clinical studies for assessing the efficacy of solifenacin 5 and 10 mg tablets. All four studies included the 10 mg solifenacin dose, and two studies included the 5 mg dose. For the primary endpoint, the mean change in number of micturitions per 24 hours, the statistical reviewer concluded that the results were consistent and were statistically significant in favor of both solifenacin doses versus placebo for the primary efficacy endpoint (the mean change in number of micturitions per 24 hours). The statistician drew the same conclusion for one of the two secondary endpoints of interest (the mean change in volume voided per micturition). For the other secondary endpoint of interest (the mean change in number of incontinence episodes), three of the four studies showed statistical significance for both solifenacin doses over placebo. The statistical reviewer further concluded that the results of these four pivotal studies supported the OAB efficacy claim for both solifenacin 5 and 10 mg doses.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The NDA application submitted on May 18 and June 18, 2004, as well as most recent safety update submitted on September 30, 2004 were reviewed. The following studies were reviewed in detail:

- 905-CL-019 (Open label, extension study in EU)
- 905-CL-043 (specially designed QT study)
- 905-CL-038 (Open label, extension study in Japan)
- 905-UC-001 (Open label, extension study in US)

Other trials were reviewed in less depth:

- 905-CL-023 (Phase 2 in Japan)
- 905-CL-024 (Phase 1 in Japan)
- 905-CL-037 (Phase 2 in Japan)
- 905-EC-001 (randomized, double-blind, active comparator, parallel study in EU, ongoing)

Additional cases of death and serious adverse events were reviewed: death reported in 905-UC-007, and SAEs reported in 905-UC-005 and 905-UC-007.

Following the review of the above studies, solifenacin succinate (doses of 5 mg and 10 mg once daily) was found to be reasonably safe for use in the treatment of patients with OAB under the conditions put forth in the proposed labeling

7.1.1 Deaths

Deaths: A total of 15 deaths have been reported during drug development. Eleven of the deaths were reported in the original NDA submission. The remaining 4 cases were reported since the NDA submission and are included within the amendment and safety update. Two of these 4 deaths occurred in a Japanese study (905-CL-037) which was placebo-controlled. The third one occurred in European open label study (905-CL-019). The last one occurred in ongoing US study 905-UC-007. One patient (Patient #152-2, Japanese study 037) was found dead in the bathroom (medical examiner stated that the death

occurred 4 days prior to the discovery and the investigator considered the event inaccessible due to lack of information). The second patient (Patient #253-2, Japanese study 037) developed acute bronchitis and pneumonia complicated by respiratory "distress" followed by cardiac distress, resulting in death. The investigator considered this death unrelated to study drug. The third death (Patient #10551, European study 019) occurred 2 months after withdrawal from the clinical trial. This 76-year-old female with well-controlled diabetes who was randomized to solifenacin 10 mg in the double-blind study received 5 mg at the start of the extension study, and 35 days later the dose was increased to 10 mg. Study drug was discontinued another 10 days later after 133 days of solifenacin treatment. Two days later she collapsed at home due to postural hypotension and was hospitalized. The patient forgot to take the study medication 2 days before the event. The investigator considered the "collapse" to be probably treatment-related. The patient recovered after one-week hospitalization. Two months after withdrawal from the trial the patient died of pulmonary embolism as a result of right leg vein thrombosis. The cause of death was considered unrelated to the study drug by the sponsor. The fourth patient (Patient #01503, Study UC-007), who was an 84-year-old female with a medical history of hypertension and transient ischemic attack, died suddenly 18 days after she was randomized to solifenacin 5 mg. The investigator considered the death secondary to the patient's arteriosclerotic cardiovascular disease and unrelated to solifenacin.

7.1.2 Other Serious Adverse Events

In the current submission, fewer than 5% of patients in any solifenacin treatment group experienced an SAE. SAEs were reported in 3.4% of patients treated with solifenacin 5 mg or 10 mg in Europe and the US combined (Studies 019, UC-001, EC-001, 84 SAEs in 2440 patients), and in 2.1% of patients treated with solifenacin 2.5 mg, 5 mg, or 10 mg in Japan (40 SAEs in 1949 patients). In the total of 139 reported SAEs, 24 SAEs were considered to be probably or possibly related with study drug.

In the European open-label, phase 3 extension Study CL-019, 73 patients had SAEs, for 24 patients the SAE or 1 of the SAEs began during the preceding double-blind studies. In 13 patients (0.8%), the SAE was considered to be possibly (n=11) or probably (n=2) treatment-related. 11 of them had been reviewed in original review, and 2 have been reviewed in current review.

Three of the 26 SAEs in Phase 2 Japanese study CL-037, two of the 11 SAEs in Japanese study CL-038, and 4 of the 9 SAEs in European study EC-001 were considered to be treatment-related.

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Table 2 Serious Adverse Events (SAE's) considered possibly or probably related to Study drug: Double blind studies [CL-037 (JPN), EC-001(EU)] and Open-label, extension studies [CL-019 (EU), CL-038 (JPN)]

Patient #	Age (yrs)	Sex	MedDRA preferred term	Onset Day (days ^a)	Relationship to study medication	Intensity	Action taken/outcome
Solifenacin 5 mg qd							
<i>Study CL-019</i>							
11086	74	M	Left ventricular hypertrophy	1	Possible	Moderate	None/recovered
20815	45	F	Menometrorrhagia	59	Possible	Mild	Discontinued/RCV
<i>Study CL-037</i>							
39-2	56	F	Left back pain (angina pectoris suspect); nausea	70	Possible	Mild	Discontinued/RCV
<i>Study CL-038</i>							
1107	77	M	Arthralgia, Hepatic function abnormal NOS	275 280	Possible	Moderate Mild	Interrupt /Discontinued
Solifenacin 10 mg qd							
<i>Study CL-038</i>							
1201	69	F	Asthma NOS Bronchitis NOS	296 176	Possible Possible	Moderate Mild	Discontinued/RCV Discontinued/RCV
Solifenacin 5 mg or 10 mg qd, or placebo							
<i>Study CL-037</i>							
342-4	87	F	Constipation	16	Possible	Moderate	None/recovered
348-4	68	F	Acute hepatitis	68	Possible	Moderate	Interrupt/resume/RCV
407-4	71	F	Dizziness, nausea	4	Possible	Moderate	
<i>Study EC-001</i>							
10319	69	F	Dry mouth	5	Probable	Mild	Discontinued/Unkown
			Laryngeal edema	74	Probable	Moderate	Continued/RCV
			Apthous stomatitis	76	Probable	Moderate	Continued/RCV
			Vocal cord paralysis	76	Probable	Moderate	Continue/Not RCV yet
10434	75	F	Cerebrovascular accident	86	Possible	Mild	Discontinued/RCV
10657	67	M	Cardiac failure NOS Atrial fibrillation Pulmonary embolism Angina pectoris Fatigue/sweating	24	Possible	Unknown	Temporarily discontinued/Not yet recovered
10990	58	F	Angioneurotic edema	13	Probably	Moderate	Discontinued/RCV
12243	56	F	Probable myocardial infarction	25	Possible	Moderate	Unknown

nos = not otherwise specified; RCV = recovered

^a Relative to day of first dose of study drug, (post-treatment day relative to first day after the last dose is indicated with a + sign)

Study CL-019

Patient #11086 (randomized to placebo in the double-blind study) was a 74-year-old male with a medical history of heart valve replacement and coronary artery surgery. He was treated with solifenacin 5 mg for 152 days in the open label trial. During the double-blind study, he developed moderate left ventricular hypertrophy. The patient was asymptomatic but a routine ECG at the end of this study showed incidental changes on the ECG differing from Visit 1 (left ventricular hypertrophy). No corrective treatment was

initiated. As an ECG performed in the open label extension study was normal, the patient was considered to be recovered. This event was considered to be possibly treatment-related by the investigator. After 146 days of solifenacin therapy, he developed a moderate worsening of hypercoagulation which was considered possibly treatment related by the investigator. The treatment was discontinued six days later.

Reviewer's comment: The reviewer agrees that the events were possibly related with study medication.

Patient #20815 was a 45-year-old female, who was randomized to solifenacin 5 mg in the double-blind study, and was continuously treated with solifenacin 5 mg in open labeling extension trial for a total of 135 days, and then the dose was increased to 10 mg. 130 days after starting therapy, the patient was hospitalized for mild menometrorrhagia and moderate uterine fibroids. The menometrorrhagia (considered to be possibly treatment-related by the investigator) was experienced 59 days after starting solifenacin 5 mg but the decision to perform a hysterectomy was made on the 98th day of solifenacin therapy when the uterine fibroids (not related to solifenacin according to the investigator) were detected by ultrasonography. On the 116th day of therapy, the patient again developed moderate menometrorrhagia. The operation was carried out on the 131st day. The patient developed moderate deep venous thrombosis 1 day after increasing the solifenacin dose to 10 mg. Both the second menometrorrhagia and the deep venous thrombosis were considered not treatment related by the investigator. The patient completed the study with a total of 378 days of solifenacin treatment.

Reviewer's comment: The event of menometrorrhagia was possibly related to study drug.

Study CL-037

Patient #342-4: This 87-year-old woman with no significant medical history was randomized to double-blind study drug. Sixteen days later she was hospitalized for constipation of moderate intensity. After treatment the constipation resolved within the same day. Study drug was also discontinued. Because of her advanced age, she remained hospitalized for a week. The event was considered resolved another ten days later. The investigator considered the event unrelated to study drug.

Reviewer's comment: The reviewer considers that the event of constipation was probably related to study drug.

Patient #348-4: This 68-year-old woman, with a relevant medical history of hyper-cholesterolemia, was randomized to double-blind study drug. Sixty-eight days later the patient discontinued study drug for personal reasons. End-of-study laboratory tests performed on discontinuation revealed that the liver function tests were elevated (AST 253, ALT 260, gamma GT 1102, and ALP 843) from the results of earlier laboratory tests (the 24th day of the study: AST, ALT and gamma GT were within normal limits, the ALP [265] was elevated). One week later, per the investigator's instructions, the patient presented to the hospital and an examination revealed a further increase in liver function tests (ALT 719, AST 1056, gamma GT 1436, and ALP 1276). The patient was hospitalized for treatment of acute hepatitis (she was asymptomatic). Her abdominal CT revealed no specific abnormalities, and HBsAg, HCV and ANA were negative. After initiating therapy with Stronger Neo-Minophagen C and Soldem 3A (maintenance medium), a significant decrease in hepatic enzymes was seen the next day, with a further decrease another two days later (ALT 215, AST 596, gamma GT 699, ALP 839). The patient was discharged after hospitalization for three weeks (by discharge her ALT 45, AST 91, gamma GT 205, ALP 520). The investigator considered the event possibly related to study drug.

Reviewer's comment: The reviewer considers the abnormal levels of liver enzymes were possibly related to study drug.

(Follow-up: As of April 19, 2004, liver enzymes ALT, AST, gamma GT and ALP have normalized; patient recovered without sequelae. Viral hepatitis tests were negative. Atorvastatin treatment was resumed. The investigator noted that the relationship of acute hepatitis to atorvastatin could not be ruled out, nor could study drug or griseofulvin treatments. As a result of study code-breaking, the patient's study drug was solifenacin 10 mg.)

Patient #407-4: This 71-year-old woman, with no relevant medical history, was randomized to double-blind study drug. The following day the patient developed nausea and dizziness. The nausea worsened during the evening of the next day. On the 4th day, she stopped taking study drug, and presented to the hospital with intense dizziness, dry mouth, and nausea, and was hospitalized. She received treatment for two days and the nausea and dizziness resolved. The patient recovered and was discharged from the hospital. The investigator considered the events possibly related to study drug.

Reviewer's comment: The reviewer judges the events probably related to study drug.

Patient #39-2: This 56-year-old female with a medical history of urinary calculus and hypertension, developed nausea and back pain 70 days after starting solifenacin 5 mg. ECG showed ST change secondary to myocardial ischemia. Her symptoms spontaneously disappeared approximately 2 hours later without treatment. Study drug was discontinued one week later. Cardiology evaluation confirmed the initial diagnosis. Six days later the patient underwent coronary arteriography which did not reveal significant coronary artery stenosis. The ST-T change in the ECG was considered non-specific. The physician believed the possibility of atypical (spastic) angina pectoris could not be ruled out. The investigator considered the event to be possibly related to study drug.

Reviewer's comment: The reviewer agrees that the event is possibly related to the study drug.

Study CL-038

Patient #1107 was a 77-year-old male with medical history of hyperuricemia, intestinal polyps, diarrhea, anorexia, and constipation. Nine months after starting solifenacin 5 mg daily, he developed arthralgia of the hands and feet, and was diagnosed as suffering from a gout attack and treated with non-steroid anti-inflammatory medicine. Because of his elevated hepatic enzymes steroid therapy was initiated and the study medication was interrupted for 18 days. His hepatic dysfunction improved, and the study medication was resumed. Over the next 33 days the patient continued to have difficulty in walking and the study drug was discontinued. One week later his hepatic dysfunction had further improved but he still had difficulty in walking. The investigator could not rule out a possible relationship with the study drug.

Reviewer's comment: The SAEs developed slowly, but the arthralgia re-emerged after the study drug was resumed. This whole process supports the possible relationship between the event and solifenacin.

(Follow-up: Ten months after initiation of the treatment of solifenacin, gout was ruled out as a diagnosis. Liver biopsy was normal one month later. His arthralgia, which persisted for more than 5 months after discontinuing study drug, was considered an autoimmune disease. Hepatic enzymes fluctuated up to another 3 months, at which time the physician considered this event a hepatic disorder due to steroid therapy the patient was taking to treat his arthralgia. Relationship of hepatic

dysfunction to study drug could not be ruled out completely even though it persisted after discontinuing solifenacin.)

Patient #1201 was a 69-year-old female with medical history of allergy, asthma and/or bronchitis. She started solifenacin 5 mg and 55 days later increased to solifenacin 10 mg daily. After 176 days of solifenacin therapy, the patient was diagnosed with bronchitis. Twenty days later, she was further diagnosed with acute bronchitis, and steroid was added to her treatment. Following antibiotic and steroid therapy for more than three months, her condition did not improve and she developed asthma. She was hospitalized for bronchial asthma and bronchitis and study drug was discontinued four days later. Two and half months after stopping solifenacin, the asthma and bronchitis were completely resolved. The investigator considered the events possibly related to study drug.

Reviewer's comment: The persistence of the events during the treatment with solifenacin and its resolution after the study drug was stopped suggests the events were possibly related to the study drug.

Study EC-001

Patient #10319 was a 69-year-old female with a relevant medical history of hiatal hernia, chronic obstructive lung disease, and hypercholesterolemia. She started double-blind study drug in the low dose period. Five days later she developed dry mouth. After therapy for 67 days study drug was temporarily discontinued. The next day she developed painful blisters on her tongue and throat. The patient was hospitalized with a diagnosis of laryngeal edema, laryngeal aphthae, and left vocal cord paralysis. She was treated with steroids and discharged after hospitalization for 13 days but the vocal paralysis was ongoing and being treated with corticosteroids. The investigator considered all the events probably related to study drug.

Reviewer's comment: The reviewer considers that the events were possibly related to study drug.

Patient #10434 was a 75-year-old female who started low dose, double-blind study drug. The double-blind study finished 84 days later. Then compassionate use of solifenacin commenced. Two days later the patient developed a cerebrovascular accident and was hospitalized for observation. One week later the event was considered resolved and the patient was discharged. The investigator considered the event possibly related to study drug.

Reviewer's comment: The reviewer agrees with the investigator that the events were possibly related to study drug.

Patient #10657 was a 67-year-old male and 24 days after starting double-blind study drug, the patient developed cardiac failure, atrial fibrillation, possible pulmonary embolism, fatigue, sweating, and angina pectoris. The next day he was hospitalized and stayed in intensive care for an unknown period of time. The investigator considered the events possibly related to study drug.

Reviewer's comment: The reviewer agrees with the investigator that the events were possibly related to study drug.

(Follow-up: Investigator changed the reported event term to "Heart attack" and the patient recovered.)

Patient #10990 was a 58-year-old female, with a relevant medical history of anterior wall colpoptosis and right eye keratopathy. She started the low-dose, double-blind period. On the 3rd day of therapy

(approximately 6 hours after intake of study drug), the patient developed edema of the face, lips, oral cavity, and tongue. Study medication was stopped and she was treated with steroid at home, and the edema diminished. Study drug was discontinued, and the patient recovered. The investigator considered the event probably related to study drug.

Reviewer's comment: The reviewer agrees with the investigator that the events were probably related to study drug.

Patient #12243, a 56-year-old female, was randomized to study (either solifenacin 5 mg, tolterodine 4 mg, or placebo). 25 days after starting treatment, she experienced sudden chest pain and was hospitalized. A diagnosis of probable myocardial infarction was made and further evaluation was planned. The investigator considered the event possibly related to study drug.

Reviewer's comment: The possible relationship between the event and study drug can not be ruled out.

Review's comment: The overall incidence of serious adverse events and the nature of individual serious adverse events in the updated pools do not suggest a specific risk pattern and the case of angioneurotic edema (patient #10990) should be described in labeling.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Overall discontinuation rate was 15% (594/3955) for the pool of patients in studies 019, 023, 037, 038 and UC-001

Table 3 Discontinuation in Phase 2 and Phase 3 studies

Studies	CL-019	CL-023	CL-037	CL-038	UC-001	Overall
Discontinuation rate (n/n)	18.6% (304/1633)	2.2% (7/317)	8.4% (134/1593)	8.3% (21/252)	80% (128/160)	15% (594/3955)

Study CL-019 (extension study): Overall discontinuation rate was 18.6% (304/1633), and in 76 patients (4.7%) an adverse event was the primary reason for discontinuation.

Study CL-023 (6 weeks): Overall discontinuation rate due to an adverse event was 2.2% (7/317), distributing in 1.3% for placebo (1/79), 1.2% for solifenacin 2.5 mg (1/83), 1.3% for 5 mg (1/75) and 5.0% for 10 mg (4/80).

Study CL-037 (12 weeks): 134 patients discontinued prematurely (134/1593 8.4%). No further data were available.

Study CL-038 (up to 28 weeks): 8.3% patients (21/252) discontinued, including 14 (5.6%) by patient's decision, 10 (4%) by an adverse event, and 3 (1.2%) for other reasons.

Study UC-001 (12 weeks): 80% (128/160) patients discontinued, including 13 (8.1%) by an adverse event, 3 (1.9%) by withdrawal of consent, 3 (1.9%) by lost to follow-up, 3 (1.9%) by insufficient

response, and 106 (66.3%) by other reason (study was terminated on November 8, 2003, to redirect clinical research efforts to address issues raised by the Agency in the approvable letter for solifenacin dated October 17, 2003).

7.1.3.2 Adverse events associated with dropouts

Overall discontinuation rate due to an adverse event was 4.7% (110/2362 patients).

Table 4 Discontinuation due to AEs in Phase 2 and Phase 3 studies

Studies	CL-019	CL-023	CL-038	UC-001	Overall
Discontinuation rate (n/n)	4.7% (76/1633)	2.2% (7/317)	5.6% (14/252)	8.1% (13/160)	4.7% (110/2362)

Table 5 Discontinuation due to AEs related to solifenacin treatment in Open label studies

	CL-019	CL-038	UC-001	Overall
Dry mouth	3	3	1	7
Constipation	6	2	3	11
Blurred vision	6	3	2	11
Dyspepsia	5	1	1	7
Abdominal pain NOS	5	1	0	6
Dizziness	1	1	1	3
Urinary tract infection	2	0	0	2
Rash/pruritus/itching	3	0	2	2
Urinary retention	1	0	0	1
Dysuria	0	2		2
QT correct interval	2	0	0	2
Other cardiac related	1	0	1	2
Visual acuity reduced	2	0	0	2
Headache	0	1	0	1
Arthralgia/hepatic abnormal	0	1	0	1
Asthma/bronchitis	0	1	0	1

7.1.3.3 Other significant adverse events

The occurrence of laryngeal edema (patient #10319 in study EC-001) and angioneurotic edema (patient #10990 in EC-001) have been reviewed in the section of other serious adverse events..

7.1.4 Other Search Strategies

No other search strategies were used.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the current amendment submission, detailed data of adverse events were reported from one European open label study (CL-019), one Japanese open label study (CL-038), and one US open label study (UC-001). The incidence of treatment emergent adverse events (TEAEs) was consistent with that reported in the original NDA. As was observed in the pivotal Phase 3 studies, most AEs were mild or moderate in severity. 4.8% of patients discontinued the study due to adverse events.

Table 6 Overall summary of TEAEs: combined US, EU and Japan Phase 2/3 studies

	CL-019	CL-038	UC-001	All
Number of patients	1633	252	159	2044
Number of patients with TEAEs	1040 (63.7%)	217 (86.1%)	91 (57.1%)	1348 (65.9%)
Number of SAEs	97	13	3	113
Number of patients with SAEs	72 (4.4%)	11 (4.4%)	2 (1.3%)	85 (4.2%)
Number of patients with AEs by severity				
Mild	482 (29.5%)	193 (76.6)	51 (32.1%)	726 (35.5%)
Moderate	440 (26.9%)	21 (8.3%)	35 (22.0%)	496 (24.3%)
Severe	118 (7.2%)	3 (1.2%)	5 (3.1%)	126 (6.2%)
N of patients discontinued due to TEAE	76 (4.7%)	10 (4.0%)	13 (8.1%)	99 (4.8%)
N of patients with treatment-related AEs	711 (43.5%)	142 (56.3%)	67 (42.1%)	920 (45.0%)
Number of deaths	5	0	0	5

7.1.5.2 Incidence of common adverse events

For the combined three US (UC-001), European (CL-019), and Japanese (CL-038) open label, extension studies, overall frequency of treatment-emergent adverse events (TEAEs) was 65.9% in patients with solifenacin. In the CL-019 European study, more patients treated with solifenacin 10 mg developed TEAEs (55.0%) than patients treated with solifenacin 5 mg (46.4%). In the US, EU, and JPN trials, the majority of the TEAEs in all treatment groups were considered mild or moderate in severity.

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Table 7 Number and % of subjects with TEAEs by system organ class (SOC):
 Three open label extension studies

System Organ Class MedDRA preferred term	Frequencies of TEAEs: n (%)			
	CL-019	CL-038	UC-001	All
Number of patients	1633	252	159	2044
Number of patients with any AE	1040 (63.7)	217 (86.1)	91 (57.2)	1348 (65.9)
Gastrointestinal disorders	544 (33.3)	143 (56.8)	58 (36.5)	745 (36.5)
Dry mouth	339 (20.8)	102 (40.5)	36 (22.6)	477 (23.3)
Constipation	157 (9.6)	52 (20.6)	21 (13.2)	230 (11.3)
Dyspepsia	55 (3.4)	3 (1.2)	1 (0.6)	59 (2.9)
Abdominal pain upper	24 (1.5)	7 (2.8)	1 (0.6)	32 (1.6)
Infections and infestations	382 (23.4)	100 (39.7)	20 (12.6)	502 (24.6)
UTI NOS	104 (6.4)	17 (6.8)	6 (3.1)	127 (6.2)
Nervous system disorders	129 (7.9)	31 (12.3)	9 (5.7)	169 (8.3)
Headache NOS	48 (2.9)	5 (2.0)	6 (3.8)	59 (2.9)
Musculoskeletal & connective tissue	141 (8.6)	27 (10.7)	7 (4.4)	175 (8.6)
Eye disorders	162 (9.9)	23 (9.1)	6 (3.8)	191 (9.3)
Vision blurred	113 (6.9)	14 (5.6)	5 (3.1)	132 (6.5)
Dry eye NOS	12 (0.7)	3 (1.2)	1 (0.6)	16 (0.8)
General disorders	96 (5.9)	11 (4.4)	6 (3.8)	113 (5.5)
Renal and urinary disorders	112 (6.9)	16 (6.4)	6 (3.8)	134 (6.6)
Urinary retention	2 (0.1)	0	1 (0.6)	3 (0.1)
Dysuria	17 (1.0)	12 (4.8)	0 (0.0)	29 (1.4)
Psychiatric disorders	62 (3.8)	2 (0.8)	3 (1.9)	67 (3.3)
Respiratory disorders	45 (2.8)	33 (13.1)	6 (3.8)	84 (4.1)
Cough	17 (1.0)	5 (2.0)	2 (1.3)	24 (1.2)
Vascular disorders	90 (5.5)	6 (2.4)	1 (0.6)	97 (4.7)
Hypertension NOS	46 (2.8)	5 (2.0)	0 (0.0)	51 (2.5)

7.1.5.3 Identifying common and drug-related adverse events

As dry mouth, constipation and blurred vision are all expected AEs of solifenacin and other anticholinergics, it is not surprising that almost all reports related to these AEs were considered possibly or probably treatment-related by the investigators.

Table 8 Number and percentage of patients with expected antimuscarinic events by severity

System Organ Class MedDRA preferred term	Frequencies of TEAEs: n (%)			
	CL-019 (n=1633)	CL-038 (N=252)	UC-001 (N=159)	All (N=2044)
Dry mouth	339	102	36	477 (23.3)
Mild	235	99	31	365 (17.9)
Moderate	82	3	5	90 (4.4)
Severe	22	0	0	22 (1.1)
Constipation	157	52	21	230 (11.3)
Mild	96	51	15	162 (7.9)
Moderate	44	1	5	50 (2.5)
Severe	17	0	1	18 (0.9)
Vision Blurred	113	14	5	132 (6.5)
Mild	85	14	3	102 (5.0)
Moderate	25	0	2	27 (1.3)
Severe	3	0	0	3 (0.2)

7.1.5.3 Special concern of common AE of constipation

In the Division's approvable letter to the sponsor on October 17, 2003, the third deficiency was the occurrence of constipation, one of the most common adverse events associated with solifenacin, and a cause of severe SAE's. The sponsor was requested to address the prevention and management of such serious sequelae in the revised labeling. "Additional risk management strategies, including emphasis on using the lowest effective dose for an individual patient, might be needed."

In response to the request, on December 5, 2003, the sponsor proposed that the recommended dose of solifenacin be 5 mg, and that this dose can be increased to 10 mg if the drug is well tolerated at the 5 mg dose. In the response of 8 March 2004, the Agency agreed with this dosing recommendation and the sponsor's proposal for investigating the incidence of constipation associated with solifenacin use. An analysis along with a proposal for the prevention and management of this risk were submitted on May 18, 2004. The analysis evaluated the occurrence of constipation across all 4 pivotal Phase 3 studies and the rare occurrence of serious sequelae associated with this adverse event in those pivotal studies as well as in studies submitted in the current safety update (submitted May 18, 2004). The analysis population across studies 905-CL-013, -014, -015, and -018 comprised 1216 placebo-treated patients, 578 solifenacin 5 mg-treated patients, and 1233 solifenacin 10 mg-treated patients.

Analysis of constipation as an adverse event

The incidence of constipation was dose-dependent: placebo, 2.9%; solifenacin 5 mg, 5.4%; solifenacin 10 mg, 13.5%.

Table 9 Treatment-emergent constipation events reported in the pooled Phase 3 studies

	Placebo (N=1216)	Solifenacin	
		5 mg (N=578)	10 mg (N=1233)
Number patients with constipation n (%)	35 (2.9)	31 (5.4)	166 (13.5)
Number of constipation events	36	31	186
Number patients with 1 constipation	34	31	153
Number patients with 2 constipation	1	0	9
Number patients with > 2 constipation	0	0	4*

- Of these 4 patients, 3 patients had 3 events each, and 1 had 6 events.

Most patients experiencing constipation continued taking study drug. Discontinuations due to constipation were higher in the solifenacin 10 mg group (1.7%,) and were similar in the solifenacin 5 mg and placebo groups (0.2% in each). Discontinuations due to constipation events were further analyzed by maximum severity for patients experiencing constipation. Of patients experiencing constipation, only 1 patient treated with solifenacin 5 mg experienced mild constipation resulting in discontinuation. In the solifenacin 10 mg group, 5 (6.5%), 9 (12.3%), and 7 (43.8%) patients discontinued with mild, moderate, and severe constipation, respectively. Those who discontinued due to severe constipation represent 0.4% (7/1811) of all solifenacin -treated patients.

Reviewer's comment: Discontinuation rate due to severe constipation was high in the group of patients treated with solifenacin 10 mg, and was relative high in all treated population.

Severity: The severity of constipation was dose-dependent. More patients in the solifenacin 10 mg group had severe constipation (1.3%), as compared to patients in the solifenacin 5 mg group (0.2%)

Frequency: Of the 232 patients (all treatment groups) experiencing constipation, the majority (218, 94%) had only 1 event of constipation.

Age and gender: The increase in constipation with increasing age was observed for all treatment groups. No gender effect was shown in the incidence. The effect on the severity of constipation was similar for age and gender in all treatment groups.

Conclusions regarding analysis of occurrence of constipation: Treatment-emergent constipation, a known effect of anticholinergic agents, was observed in 2.9%, 5.4% and 13.5% of patients on placebo, 5 mg and 10 mg of solifenacin, respectively. The majority of patients with constipation continued taking the study drug, and opted to enroll in the open-label extension with solifenacin. The overall incidence of constipation and discontinuations due to constipation were both dose-dependent, occurring more frequently in the solifenacin 10 mg group. Most events of constipation were mild or moderate, and were manageable by the patients and their physicians with diet modifications, and use of laxatives. The dose of solifenacin appears to be the only contributory factor associated with the occurrence of constipation.

Reviewer's comment: It is important to recommend that the starting dose for solifenacin treatment be 5 mg.

Analysis of serious sequelae of constipation in patients taking solifenacin

In the Phase 3 double-blind studies (905-CL-013, 905-CL-014, 905-CL-015 and 905-CL-018) and open-label studies 905-CL-016 and 905-CL-019, the total cumulative exposure to solifenacin in 2,960 patients was 26,610 treatment months. The SAE database from all solifenacin studies conducted to date was reviewed for all events under the system organ class (SOC) of "Gastrointestinal disorders." From this list, events considered to be commonly related to constipation, gastrointestinal (GI) obstruction, intestinal ischemia disorders, and GI motility disorders were further evaluated. This database search identified 6 patients with events of this type.

Table 10 Patients with serious sequelae of constipation

Study	Patient #	Country	Dose solifenacin	Event
905-CL-019	#20256	Australia	5 mg	Fecal impaction
905-CL-037	#342-4	Japan	Blinded	Constipation
905-CL-014	#5024	US	10 mg	Fecal impaction
905-CL-013	#29005	US	10 mg	Colonic obstruction
905-CL-018	#20723	France	10 mg	Intestinal obstruction
905-CL-016	#1311005	US	10 mg	Intestinal ischemia / perforation

The patient narratives for these serious sequelae events are summarized as follows:

905-CL-019: Patient #20256 was a 67-year-old male who completed a 12-week double blind study in which he was randomized to placebo. He opted to go into this open-label extension, and received solifenacin 5 mg daily. 23 days later he was admitted to the hospital with symptoms of severe abdominal pain and constipation. Study medication was withdrawn, and he was treated with conservative management and discharged the next day. No obvious additional contributory factor was identified.

905-CL-037: Patient #342-4, a 87-year-old female with no history of constipation, was enrolled in this double-blind study evaluating solifenacin 5 mg, 10 mg, propiverine or placebo. On Day 16 of treatment, she presented to the hospital with severe constipation and was given glycerin enemas. Study drug was discontinued, and the patient recovered under observation. The blind was not broken to identify treatment assignment. No obvious additional contributory factor was identified.

905-CL-014: Patient #5024, a 71-year-old male, was randomized to solifenacin 10 mg daily for 12 weeks in this double-blind, placebo-controlled study. Relevant medical history included hypercholesterolemia, constipation, colonic polyps with lower GI bleeding, and obesity. During the first few weeks of taking the drug he complained of mild constipation. On Day 44 of treatment, he complained of severe constipation, with cramping and leakage of stools, and was not relieved after taking medication. He was taken to the hospital with increasing abdominal distention. He was treated with another laxative and the event resolved rapidly. The patient restarted solifenacin and completed the study. He opted to go into the open-label extension study receiving solifenacin 10 mg/day for an additional 52 weeks. No obvious additional contributory factor was identified.

905-CL-013: Patient #29005, a 62-year-old female, was randomized to solifenacin 10 mg/day for 12 weeks. Relevant medical history included peptic ulcer disease, bilateral tubal ligation, and osteoarthritis, but no previous history of constipation. On Day 11 of the study, she developed diffuse crampy lower abdominal pain, nausea, vomiting and decreased caliber of stools with fever. The patient interrupted the study medication for 2 days but her symptoms worsened, and she was admitted to the hospital. Computed tomography (CT) scan showed a bulky mass in the sigmoid colon and the abdominal x-ray revealed dilated loops of bowel with air/fluid levels consistent with bowel obstruction. A colonoscopy with biopsy revealed fragments of colonic mucosa with focal hemorrhage, and a nearly obstructive lesion in the distal colon, with no evidence of malignancy. On Day 24, she underwent exploratory laparotomy when an inflammatory mass suggestive of diverticulitis was found in the distal sigmoid colon and rectum with involvement of the left ovary and fallopian tube. She underwent celiotomy with salpingo-oophorectomy and colorectal anastomosis. She recovered and was discharged from the hospital on Day 26. Pre-existing diverticulosis may have been a contributory factor for this event.

905-CL-018: Patient #20723, a 66-year-old female, was randomized to solifenacin 10 mg daily for 12-weeks. She had history of ileal resection and a history of intestinal motility disorder for which she was receiving medication. On study Day 61, she was admitted to the hospital for intestinal obstruction of unknown etiology, which was treated with dilatation, without resection. She recovered and started taking solifenacin following discharge from the hospital. She opted to go into an open-label extension study in which she completed an additional 40 weeks of treatment with solifenacin. Previous history of GI motility disorders, and intestinal surgery, and concomitant medication used for GI motility disorders were considered to be pre-disposing factors for this event.

905-CL-016: Patient #1311005, a 76-year-old female, was randomized to placebo in a double-blind Phase 3 study and opted to go into this open-label extension study, receiving solifenacin 10 mg/day. She had 2 episodes of constipation. 9 months after starting treatment with solifenacin, she was admitted to the hospital with increasing abdominal pain. Abdominal CT showed gaseous distention and abnormal bowel pattern suggestive of infectious pathology, possibly with pneumatosis intestinalis. She had an exploratory laparotomy, which showed ischemic bowel. She underwent subtotal colectomy and end ileostomy. Her postoperative course was complicated by peritonitis secondary to perforation of the colon, at the site of sutures, near the appendix. She had a second exploration for closure of the perforation and recovered without further complications.

Reviewer's comment: The reviewer believes that the study drug was unlikely to be the direct causative factor.

Conclusions regarding serious sequelae of constipation

- The majority of the events (4 of 6) discussed above were reported with the 10 mg dose of solifenacin.
- Four (4) of these events occurred in double-blind studies (905-CL-013, 905-CL-014, 905-CL-018 and 905-CL-037) and 2 occurred in open-label extension studies (905-CL-016 and 905-CL-019).
- One of these 6 patients (#5024) had a previous history of constipation. The 3 patients with constipation or fecal impaction (patients #5024, #20256, and #342-4) recovered with conservative management.
- Patients requiring surgical intervention did not consistently have constipation preceding the event.
 - One patient (#20723) had a previous history of motility disorder.
 - Two patients (#1311005 and #29005) had infectious pathology (pneumatosis intestinalis, diverticulitis, respectively), contributing to their obstructive complications.
- Based on the review of these SAEs, the serious sequelae occurred mainly in patients taking 10 mg solifenacin and who had either an infective pathology or GI motility disorder. An analysis of the serious sequelae of constipation for any predisposing factors or concomitant medications that may be contributory or predictive of the event did not reveal any such associations.

The sponsor plans to manage the risk associated with the occurrence of constipation through

- 1) Product labeling including physician package insert (dosage and administration, contraindications, precautions, serious adverse events) and information for patients. Most importantly the sponsor's recommended dose is 5 mg once daily; if the 5 mg dose is well tolerated, the dose may be increased to 10 mg once daily.
- 2) Product packaging: to minimize the incidence of constipation, the same safety message and patient information appearing in the Physician Package Insert are also reflected in the Patient Information Leaflet.

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The sponsor believes the management of the risk of constipation is adequately addressed.

Reviewer's comment: Based on the analysis of constipation and the proposed risk management strategy mainly focusing on the minimum recommended dose of 5 mg once daily, the reviewer agrees that the management of the risk of constipation is adequately addressed.

7.1.6 Laboratory Findings

7.1.6.1 Overview of laboratory testing in the development program

In the complete response to "approvable" action, laboratory evaluation was only available from Study CL-019. There were no clinically relevant shifts from normal to abnormal for any of the biochemistry, hematology or urinalysis parameters with solifenacin treatment in all patient groups. The shifts were

comparable to those found in the original placebo treatment group at Visit 5, when these patients were still receiving placebo. Treatment – emergent laboratory abnormalities related to hepatic and renal function are summarized in Table 11:

Table 11 Hepatic and renal function parameters: Number (%) of patients with solifenacin treatment-emergent abnormalities compared to baseline (Visit 5) for all patients and original treatment groups

Parameters	Visit	Placebo N=450	Solifenacin		Tolterodine 2 mg bid N=222	All N=1633
			5 mg qd N=476	10 mg qd N=485		
Alkaline phosphatase	Visit 5	12 (2.9)	15 (3.5)	17 (3.9)	3 (1.5)	32 (3.7)
	Visit 9	12 (3.7)	19 (5.2)	19 (5.1)	8 (4.8)	58 (4.7)
Gamma-GT	Visit 5	23 (6.1)	20 (5.2)	16 (4.0)	8 (4.5)	36 (4.6)
	Visit 9	24 (7.9)	26 (8.1)	17 (5.0)	13 (8.7)	80 (7.2)
ALT	Visit 5	23 (6.0)	22 (5.3)	20 (4.7)	12 (6.3)	42 (5.0)
	Visit 9	21 (6.9)	23 (6.6)	33 (9.2)	15 (9.4)	92 (7.8)
AST	Visit 5	16 (3.9)	10 (2.3)	12 (2.7)	3 (1.5)	22 (2.5)
	Visit 9	8 (2.5)	8 (2.2)	18 (4.7)	3 (1.8)	37 (3.0)
Total bilirubin	Visit 5	8 (1.9)	9 (2.0)	8 (1.7)	1 (0.5)	17 (1.9)
	Visit 9	3 (0.9)	2 (0.5)	5 (1.3)	1 (0.6)	11 (0.9)
Creatinine	Visit 5	2 (0.5)	3 (0.7)	1 (0.2)	2 (0.9)	4 (0.4)
	Visit 9	2 (0.6)	0 (0.0)	2 (0.5)	3 (1.7)	7 (0.5)
Urea	Visit 5	27 (6.8)	31 (7.2)	26 (5.9)	12 (6.1)	57 (6.6)
	Visit 9	19 (6.1)	31 (8.6)	27 (7.2)	13 (7.9)	90 (7.4)

Number of patients at each assessment may vary, depending on visit and variable. Visit 5 values for the all patient group refer only to patients receiving solifenacin (5 or 10 mg) in the double-blind studies (N=961). Visit 9 values refer to all patients receiving solifenacin in the extension study.

7.1.6.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Clinically significant laboratory abnormalities were found in 55 patients (3.4%) that were probably or possibly treatment-related in the opinion of the investigator. One AE was considered to be probably treatment-related; all other AEs were possibly treatment-related in the opinion of the investigator. Most of the AEs were of mild intensity and none were severe. The most frequently reported treatment-related AE involving laboratory abnormalities was an increase in gamma-GT in 22 patients (1.3%). For 21 patients they were reported as possibly treatment-related and for 1 patient it was reported as probably related. In 18 of these 22 patients the patient had a hepatic disorder and/or an increased gamma-GT concentration at the screening Visit 1.

7.1.7 Vital Signs

For vital signs including systolic and diastolic blood pressure and pulse rate, there were no clinically relevant changes and there were no relevant differences between the 4 original treatment groups (placebo, solifenacin 5 mg and 10 mg, qd; and tolterodine 2 mg bid).

7.1.8. Electrocardiograms (ECGs)

Two analyses of ECG related safety are included in the submission: 1) Safety update and 2) special protocol CL-043 "A Study to Evaluate the Effect of Repeat Oral Doses of Solifenacin on Cardiac

Conduction as assessed by 12-lead Electrocardiogram as Compared to Placebo and Single Oral Doses of Moxifloxacin."

7.1.8.1 Overview of ECG testing in the development program

In the safety update submission, only the data from Study CL-019 were available for ECG analysis.

7.1.8.2 Standard analyses and explorations of ECG data

In the all patients group of Study CL-019, there were 7 patients (0.7%) at Visit 5, 21 patients (1.4%) at Visit 7 and 17 patients (1.2%) at the end of the study (ES) with a clinically significant shift to an abnormal ECG from a normal ECG at screening (Visit 1). At visit 5 (the end of double blind study), this was comparable to the shift in the original placebo treatment group between Visit 1 and Visit 5 (0.7%), when these patients were still receiving placebo.

7.1.8.2.1 Analyses focused on measures of central tendency

Two sets of data were defined from Study CL-019: Set A reported the results based on all available data and Set B reported the results with exclusion of ECGs that were inappropriate for QTc measurements.

The data from the central reading are summarized in Table 12. In set A, at the end of double-blind treatment (Visit 5), there was a small increase in the QTcB (3.1 ms) compared to baseline on solifenacin treatment. At Visit 7, the mean QTcB was increased by 2.2 ms and at the end of study by 3.5 ms. There were no major differences in the changes from baseline at Visit 5, Visit 7 or End of Study between set A and set B.

Table 12 Mean±SD QTcB values (msec) and Mean±SD changes from baseline (Visit 1) to Visits 5, 7 and end of study (ES) in QTcB for all patients and original treatment groups

QTcB (Bazett's) (msec)	Placebo N=450	Solifenacin		Folterodine 2 mg bid N=222	All N=1633
		5 mg qd N=476	10 mg qd N=485		
Set A					
Baseline	401.9±24.5	402.8±25.0	401.6±25.7	405.7±23.4	402.6±24.9
V5 change	-0.1±21.6	+1.2±21.4	+5.0±21.4	-1.3±18.3	+3.1±21.5
V7 change	+3.0±21.1	+1.4±21.0	+3.4±21.9	-0.0±18.8	+2.2±21.0
ES change	+2.3±22.5	+4.1±21.7	+5.0±24.0	+0.9±20.1	+3.5±22.4
Set B					
Baseline	400.9±22.9	400.4±24.2	400.6±23.7	405.6±22.7	401.3±23.5
V5 change	+0.4±21.2	+1.6±21.2	+4.7±20.8	+2.0±16.9	+3.1±21.1
V7 change	+3.5±20.8	+3.0±20.6	+3.7±21.6	-0.5±17.5	+2.8±20.6
ES change	+2.5±21.5	+4.4±22.0	+4.5±22.4	+0.0±19.5	+3.3±21.7

7.1.8.2.2 Analyses focused on outliers or shifts from normal to abnormal

Table 13 Number (%) of patients with QTcB abnormalities at screening (Visit 1), Visits 5, 7 and end of study (ES) for all patients and original treatment groups in Study CL-019

	Placebo N=450	Solifenacin		Tolterodine 2 mg bid N=222	All N=1633
		5 mg qd N=476	10 mg qd N=485		
Set A	N (%)	N (%)	N (%)	N (%)	N (%)
QTcB ≥ 500 ms					
Visit 1	0 (0)	0 (0)	0 (0)	1 (0.5)	1 (0.1)
Visit 5	0 (0)	0 (0)	2 (0.4)	1 (0.5)	2 (0.2)
Visit 7	0 (0)	0 (0)	1 (0.2)	0 (0)	1 (0.1)
ES visit	0 (0)	0 (0)	1 (0.2)	0 (0)	1 (0.1)
QTcB change > 60 ms					
Visit 5	3 (0.7)	2 (0.4)	7 (1.5)	0 (0)	9 (1.0)
Visit 7	0 (0)	2 (0.5)	4 (0.9)	0 (0)	8 (0.4)
ES visit	3 (0.8)	2 (0.5)	5 (1.2)	1 (0.5)	11 (0.8)
QTcB change 30-60 ms					
Visit 5	31 (7.2)	41 (9.0)	41 (8.9)	10 (4.7)	82 (8.9)
Visit 7	44 (11.2)	38 (8.9)	40 (9.1)	10 (5.0)	127 (8.7)
ES visit	41 (11.2)	45 (11.3)	56 (13.8)	11 (5.9)	148 (10.9)
Set B	N (%)	N (%)	N (%)	N (%)	N (%)
QTcB ≥ 500 ms					
Visit 1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Visit 5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Visit 7	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ES visit	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
QTcB change > 60 ms					
Visit 5	2 (0.5)	2 (0.5)	5 (1.3)	0 (0)	7 (0.9)
Visit 7	0 (0)	2 (0.5)	4 (1.1)	0 (0)	6 (0.5)
ES visit	3 (1.0)	2 (0.6)	3 (0.9)	1 (0.6)	9 (0.8)
QTcB change 30-60 ms					
Visit 5	27 (7.4)	33 (8.2)	32 (8.1)	8 (4.2)	65 (8.2)
Visit 7	35 (10.4)	36 (9.7)	34 (9.2)	6 (3.5)	111 (8.9)
ES visit	27 (8.6)	41 (11.8)	45 (13.0)	8 (4.9)	121 (10.3)

Compared to baseline, there was in set A no significant increase during treatment with solifenacin (all patients) in the percentage of patients with a QTcB interval \geq 500 ms. Two patients receiving solifenacin treatment had a QTcB interval $>$ 500 ms at Visit 5, one at Visit 7 and one at the end of the study. In only 1 patient the change was $>$ 60 ms (patient #11681) (see the Table below). In set B, none of the patients had a QTcB interval \geq 500 ms.

Compared to Visit 5, there was no increase in the percentage of patients with a prolonged or (borderline) QTcB interval. (prolonged: QTcB $>$ 450 ms for men or $>$ 470 ms for women; borderline: QTcB 431-450 ms for men or 451-470 ms for women)

In set A, the percentage of all patients with a change in QTcB interval of 30-60 ms was 8.9% at Visit 5, 8.7% at Visit 7 and 10.9% at the end of study. A change $>$ 60 ms was found in 1.0% of all patients at Visit 5, in 0.4% of all patients at Visit 7 and in 0.8% of all patients at the end of the study. A change in QTcB interval $>$ 60 ms at Visit 5 was found in 0.7% of patients who originally received placebo treatment and they were still receiving placebo. There were no major differences between set A and set B.

Table 14 Patients with QTcB > 500 ms at Visit 5, Visit 7, and/or end of study (ES) during solifenacin treatment in Study CL-019

Patient ID	Sex	Ventricular rate [bpm]			QTcB [ms]		QTc change [ms]	Remarks / cardiac adverse events		
		Bsl	V5	V7	Bsl	V5				
Present at Visit 5 only, Double blind treatment: solifenacin 10 mg qd										
11503 Set A	M	66	70		459	468	480	506*	26	Left bundle branch block
20672 Set A	F	67	72		461	482	487	527*	40	Left bundle branch block
			72			454		496	9	
			65			459		480	-7	
Present at Visit 7 only, Double blind treatment: solifenacin 10 mg qd										
20419 Set A	F	88	92		383	384	462	473	11	Left bundle branch block
			93			405		506*	44	
			93			420		498	36	
Present at ES only, Double blind treatment: solifenacin 10 mg qd										
11681 Set A	M	62	65		359	394	364	408	44	Atrial fibrillation
			79			358		409	45	Artificial pacemaker
			72			463		507*	143*	

* QTc > 500 ms; Bsl: Baseline; V5: Visit 5; V7: Visit 7; ES: End of Study
 A: Not included in set B

7.1.8.3.3 Marked outliers and dropouts for ECG abnormalities

For 12 patients, a prolonged QT interval was reported as an AE patients #21405, #11016, #11623, #10961, #11460, #11624, #11541, #10926, #11020, #11021, #11479 and #21402. In 3 of these patients (patients #11016, #10926 and #11020), this AE was the primary reason for discontinuing from the study.

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Table 15 Patients with Prolonged QTc which was the primary reason for discontinuing from the study

Visit	Treatmt. at date of ECG	Reading	Vent. rate [bpm]	QT [ms]	QTc [ms]	Δ QTc [ms]	Remarks / cardiac adverse events
Patient #11016 (female)							
Screening	None	Local	60	390	390	-	
		Central	59	393	383	-	
Visit 5	Placebo	Local	70	450	487	97	
		Central	69	388	416	33	
Visit 7	Solif. 10 mg	Local	67	410	436	46	Prolonged QTc, probably related
		Central	64	388	402	19	
Visit 9	Solif. 10 mg	Local	62	420	425	35	
		Central	60	404	404	21	
Patient #10926 (male)							
Screening	None	Local	43	508	429	-	
		Central	43	481	409	-	
Visit 5	Solif. 5 mg	Local	46	540	481	52	QTc prolonged, probably related
		Central	49	438	393	-16	
End of study	Solif. 5 mg	Local	50	472	430	1	
		Central	50	452	414	5	
Patient #11020 (female)							
Screening	None	Local	80	350	390	-	
		Central	77	367	416	-	
Visit 5	Solif. 10 mg	Local	72	450	495	105	
		Central	70	369	398	-18	
Unscheduled	Solif. 10 mg	Local	80	420	486	96	Prolonged QTc, probably related
		Central	76	369	415	-1	
Visit 7	Solif. 10 mg	Local	80	390	451	61	
		Central	75	379	424	8	

Prolonged: QTcB > 450 ms for men or > 470 ms for women.

Patient #11016 was a 79-year-old female who was randomized to placebo in double blind (DB) study and continued with solifenacin 5 mg in the open label extension period. 28 days later the dose was increased to 10 mg. At Visit 9, 74 days after treatment with solifenacin 10 mg (total solifenacin treatment 102 days), the investigator reported a mild prolongation of the QTc interval (Δ QTc=35 ms by local; Δ QTc=21 ms by central reading). The investigator considered all ECGs as normal. According to the central reading all ECGs were also normal. The QTc prolongation was probably treatment-related according to the investigator. The patient was permanently discontinued from the study. The solifenacin 10 mg treatment period was 87 days and the total solifenacin treatment duration was 115 days.

Reviewer's comment: The marked discrepancy between the local and central readings of the QTc makes drawing meaningful conclusion difficult.

Patient #10926 was a 69-year-old male randomized to solifenacin 5 mg with, according to the investigator, a moderately prolonged QTc interval (Δ QTc=52 ms by local; but Δ QTc=-16 ms by central) on Visit 5, 85 days after treatment with solifenacin 5 mg. The adverse event lasted 36 days after which the patient was recovered with no QTc prolongation and permanently discontinued from the study. According to the investigator this ECG abnormality was clinically significant; the Visit 1 ECG was considered normal and the Visit 9 ECG as abnormal not clinically significant. The QTc prolongation was probably treatment-related according to the investigator. According to the central reading, all ECGs were normal.

The patient was taking a relatively high dose of atenolol (200 mg) until the 102nd day of solifenacin treatment when the dose was first reduced for 1 day to 100 mg and then to 50 mg. On the 95th day of solifenacin treatment, the ACE inhibitor captopril was replaced by the ACE inhibitor enalapril 20 mg.

Reviewer's comment: The marked discrepancy between the local and central readings of the QTc makes drawing meaningful conclusion difficult.

Patient #11020 was a 58-year-old female who was randomized to solifenacin 10 mg in the preceding double-blind study for a period of 99 days. She continued with the 5 mg dose in the open-label study. 201 days after starting solifenacin treatment, she had, according to the investigator, a mild prolongation of the QTc interval (Δ QTc=96 ms by local; Δ QTc= -1 ms by central). This ECG was taken at an unscheduled visit. The investigator considered all ECGs as normal. This was confirmed by the central reading. The QTc prolongation was probably treatment-related according to the investigator. The patient was permanently discontinued from the study. The total duration of solifenacin treatment was 212 days (99 days with 10 mg and 113 days with 5 mg).

Reviewer's comment: The marked discrepancy between the local and central readings of the QTc makes drawing meaningful conclusion difficult.

7.1.8.4 Additional analyses and explorations

7.1.8.4.1 Overview of specially designed QT interval study

One of several deficiencies contained that were outlined in the original NDA, was lack of sufficient information to conclude that solifenacin is not associated with clinically relevant QT interval prolongation. The sponsor was advised to submit the results from a randomized, placebo-controlled study of solifenacin with the primary objective of determining the effect of solifenacin on the QT interval at the plasma concentrations achieved at steady state when solifenacin is co-administered with a potent CYP3A4 inhibitor. The Agency further advised the sponsor to submit a protocol for review prior to initiating this study. The sponsor submitted a QT study protocol 905-CL-043 on December 9, 2003. The Division approved the protocol and sent the following comments to the sponsor:

1. *The patient population, solifenacin doses, and study design with respect to Group A are acceptable. The Division agrees with the sponsor that data from Group B are considered exploratory. Comparisons between Group A and Group B are considered hypothesis generating only.*
2. *The analysis of the primary endpoint QTcF should demonstrate that the upper bounds of the 90% confidence interval for the QTcF interval for solifenacin (minus placebo) is less than 10 msec.*
3. *Multiple baseline determinations of QT interval are obtained. How will these different baselines be used in calculating QT changes in the different sessions (particularly in Group A)? Please specify in the protocol how these different baselines will be used to calculate the QT interval change in the five sessions.*
4. *Please verify that: 1) ECG assessment will be digitized and 2) there is no "rounding" of QT data*
5. *Annotated ECG recordings should be submitted with the study report.*
6. *An "outlier" analysis should be submitted.*

Protocol: "A Study to Evaluate the Effect of Repeat Oral Doses of Solifenacin on Cardiac Conduction as Assessed by 12-lead Electrocardiogram as Compared to Placebo and Single Oral Doses of Moxifloxacin" (protocol 905-CL-043)

Study design: This was a five-period, sequential study. Subjects were randomized to one of two treatment groups (A or B) according to the following scheme.

	Treatment Group A	Treatment Group B
Session 1	1-day baseline (no drug) moxifloxacin (400 mg) on Day 1	
Session 2	1-day baseline (no drug) placebo on Day 1	
Session 3	1-day baseline (no drug) solifenacin 10 mg x 14 days	1-day baseline (no drug) placebo x 13 days ; moxifloxacin (400 mg) on Day 14
Session 4	Solifenacin 20 mg x 5 days	Placebo x 5 days
Session 5	Solifenacin 30 mg x 14 days	placebo x 13 days ; moxifloxacin (400 mg) on Day 14

Methods: Dosing was single-blind in Sessions 1 and 2. All subjects received a single oral dose of 400 mg moxifloxacin in Session 1 and a single oral dose of placebo in Session 2. There was at least a 3 day washout between Sessions 1 and 2. There was no washout between Session 2 and the start of dosing in Session 3. Dosing was double-blind in Sessions 3 to 5. Subjects in Group A received increasing doses of solifenacin in Session 3 (10 mg/day x 14 days), Session 4 (20 mg/day x 5 days) and Session 5 (30 mg/day x 14 days). Subjects in group B received placebo on each corresponding study day excepting for Session 3, Day 14 and Session 5, Day 14 when they received a 400 mg dose of moxifloxacin. There was no washout between Session 2 through Session 5. In Sessions 1, 2, and 3 there was a one-day baseline (no drug) prior to the start of dosing. Subjects had a screening assessment within 30 days of the start of the study and a final follow-up visit at least 10-14 days after their last dose of study medication. The total duration of each subject's participation in the study, from screening through follow-up, was approximately 12 weeks.

Placebo tablets for solifenacin were available. On those days when moxifloxacin was administered, subjects were blind-folded prior to taking the medication and the medication was administered by an individual not involved with the evaluation of study subjects.

ECG assessment:

Conduction intervals from the 12-lead ECGs were manually read and confirmed by an external cardiologist/vendor. All ECGs were read blinded. The final conduction intervals entered into the database were those generated by the reading cardiologist/vendor.

During Sessions 1, 2, and 3, eleven baseline 12-lead ECGs were obtained over 24 hrs prior to the start of dosing at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours. Three 12-lead ECGs taken approximately 1 minute apart were obtained prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post dose on the following days: Session 1, Day 1; Session 2, Day 1; Session 3, Days 13 and 14; and Session 5, Days 13 and 14. For each session, baseline was the average of all individual ECGs obtained on Day 1.

Other safety assessments including blood pressure and pulse rate measurements, adverse events, and clinical laboratory safety tests were obtained throughout the study.

Pharmacokinetic study: Blood samples for PK analysis of both moxifloxacin and solifenacin were obtained for all subjects (Group A and Group B). Blood samples for solifenacin and moxifloxacin PK analysis were obtained at predose and over 24 hrs postdose on Session 1 Day 1 (moxifloxacin only), Session 2 Day 1 ('dummy' moxifloxacin samples), Session 3 Day 14 (10 mg solifenacin and 400 mg

moxifloxacin), and Session 5 Day 14 (30 mg solifenacin and 400 mg moxifloxacin). Blood samples for trough solifenacin PK levels were also obtained on Session 3 Day 5, 10, and 12, and on Session 5, Day 2, 9, and 13.

Reviewer's comment: The timing and number of ECGs obtained for analysis are acceptable.

Statistical methods: The primary endpoints, Δ_i (time-matched QTc effect at t_{max} , adjusting for baseline) for QTcF, QTci, and QTciL, were separately analyzed by analysis of covariance (ANCOVA) fitting terms appropriate to the study design, including subject and regimen (400 mg moxifloxacin, 10mg solifenacin, and 30mg solifenacin). Point estimates (for Δ_i) and 90% confidence intervals were constructed for each active regimen using the appropriate error term. Secondary endpoints, Δ_i for QTcB, QT, and HR were similarly analyzed. These analyses were performed for both session-averaged and time-matched baselines. For the secondary endpoints, QTcB, manually read QT interval and heart rate (HR), the comparison of interest was also Δ_i where Δ_i is defined similar to the above.

The endpoints, Δ_i (time-matched QTc effect at t_{max} , adjusting for baseline) for QTcF, QTci, and QTciL, from Group B were separately analyzed by analysis of covariance (ANCOVA) fitting terms appropriate to the study design, including subject and regimen (M, M3, M5, P3 and P5) in order to characterize any session effects. Point estimates (for Δ_i) and 90% confidence intervals were constructed for each regimen in sessions 1, 3, and 5 using the appropriate error term. For placebo in sessions 3 and 5, those Δ_i were obtained using the t_{max} of the corresponding moxifloxacin regimens in sessions 3 and 5, respectively. These analyses were performed for both session averaged and time-matched baselines.

Abbreviations: S10 = solifenacin 10 mg (Session 3), S30 = solifenacin 30 mg (Session 5), M = moxifloxacin (Session 1), M3 = moxifloxacin (Session 3), M5 = moxifloxacin (Session 5), P = placebo (Session 2), P3 = placebo (Session 3), P5 = placebo (Session 5)

The above analysis of Group B indicated significant session effects. Therefore the following analyses were performed, and considered to be more appropriate to the data than the initial analysis of central tendency.

Changes from baseline for QTc (QTcF, QTci, QTcB and QTciL), QT and HR on Day 14 at t_{max} of solifenacin 10 mg (Session 3) and solifenacin 30mg (Session 5) (Group A) were compared to Group B, sessions 3 and 5 Placebo respectively on Day 13. t_{max} -matched placebo values were determined at the corresponding solifenacin t_{max} for each subject separately. Point estimates and 90% confidence intervals were computed using Hodges-Lehmann-Moses large sample approximation for a nonparametric confidence interval based on Wilcoxon's rank sum.

In order to adjust for the observed session-related effects for moxifloxacin relative to placebo (for both sessions 3 and 5), Group B was analyzed using a paired t-test approach.

QTc statistical definitions: For the subjects in Group A, and for the primary endpoints QTcF, QTci, and QTciL, the primary comparison of interest was Δ_i , defined as the change from baseline at time of the maximum concentration (t_{max}) for each active regimen relative to placebo at the same time point. For an individual subject and active regimen, this comparison was calculated as:

$$\Delta_i = (\text{QTc of active regimen } i \text{ @ } t_{max} \text{ of active regimen } i - \text{baseline } i) - (\text{QTc of placebo @ } t_{max} \text{ of active regimen } i - \text{baseline placebo}).$$

The above Δ_i was calculated based on both the session-averaged and time-matched baselines for each endpoint and regimen.

Baseline for QTc (all correction methods), QT, and HR for each individual and for each regimen (or session) was obtained by two methods:

- (i) Session-averaged baseline (n=33): Baseline for each session (1, 2 and 3) was defined as the average of pre-dose values collected on Day -1 (11 pre-dose time points, with 3 replicate ECG measurements = $11 \times 3 = 33$ ECG measurements)
- (ii) Time-matched baseline (n=3): Baseline for each session (1, 2 and 3) was defined as the average of pre-dose (Day -1) values at a time point (3 replicate ECG measurements) corresponding to the same post-dose time point.

For both methods, baseline values for sessions 3 and 5 were determined from Session 3 (Day -1).

QT Correction

Four methods were used to correct measured QT intervals [Preliminary Concept paper, 2002; Malik, 2002]:

Population Approaches:

1. Fridericia's correction $QTcF = QT/RR^{1/3}$
2. Bazett's Correction $QTcB = QT/RR^{1/2}$

Individual Approaches:

1. Individual (linear) correction QTci
2. Individual (non-linear) correction QTciL

The steps involved in the estimation of the individual correction factor for each subject were as follows:

- 1) The QT interval was supplied by eRT, and was a manual measurement from the onset of the QRS complex to the end of the T wave. RR was calculated as $RR = 60/HR$. HR was supplied by eRT as the result of up to 3 consecutive RR intervals. These were the cycles which best represented the rate over the 10 seconds of the ECG and could be considered an instantaneous rate.
- 2) All baseline time point values of QT and RR for each subject before the start of each session (1, 2 and 3) were utilized for estimating the correction factor (3 baseline session days, 11 time points, and 3 replicates, for a total of 99 pre-dose ECG's). A linear [$QT = \alpha + \beta(RR)$] regression model and a non-linear regression model [$QT = \alpha \times RR^\beta$] (equivalent to the linear regression model, $\ln QT = \ln \alpha + \beta \times \ln RR$) were fit, and the slopes (β) for the above linear regression models were estimated.
- 3) Individual QT values were corrected to obtain QTci and QTciL values as follows:

$$QTci = QT + \beta (1 - RR) \text{ and } QTciL = QT / RR^\beta$$

where β is the estimate of the correction factor obtained in step 1 from the respective models. These QTci and QTciL values were averaged at each time point.

QTci and QTciL values (baseline data) were plotted against RR along with Pearson correlation coefficient, r, between QTci and RR and to show whether the pattern attested to a fairly independent relationship between the two parameters.

Abbreviations: S10 = solifenacin 10 mg (Session 3), S30 = solifenacin 30 mg (Session 5), M = moxifloxacin (Session 1), M3 = moxifloxacin (Session 3), M5 = moxifloxacin (Session 5), P = placebo (Session 2), P3 = placebo (Session 3), P5 = placebo (Session 5)

7.1.8.4.2 Analyses focused on measures of central tendency

Results

Study population: A total of 91 subjects were enrolled into the study, and 86 received at least one dose of study medication. Of these 86 subjects, 58 were randomized to Group A and 28 to Group B. A total of 76 subjects completed the study, 51 in Group A and 25 in Group B. Subjects in this study were adult women with a mean age of 51 years (Table 16). In accordance with the protocol, 35 women (41%) were under 55 with a mean BMI of 24.68 and 51 women (59%) were 55 years of age or older with a mean BMI of 26.96. This age distribution was maintained at each site as well as for the study overall. Half the women were white and one-third were Hispanic.

Table 16 Demographic characteristics of population

Parameters	Mean ± SD	Range
Age (yr)	51 ± 13.3	19–79
Height (m)	1.60 ± 0.07	1.47–1.77
Weight (kg)	67.0 ± 9.9	40.4–97.7
BMI(%)		
< 55 yo (n=35, 41%)	24.68	
≥ 55 yo (n=51, 59%)	26.96	

100% female: 48% White, 34% Hispanic, 6% Black, 6% Oriental, 7% other

Pharmacokinetic results:

Moxifloxacin:

Table 17 Summary of mean Moxifloxacin PK parameters after a single 400 mg dose to healthy volunteers

	Group	Session 1	Session 3	Session 5
AUC₍₀₋₂₄₎ (ng·hr/mL): Mean (CV%) (range)	A	28548 (17.8%)	na	na
	B	28404 (17.2%)	29678 (15.2%)	30128 (17.3%)
C_{max} (ng/mL): Mean (CV%) (range)	A	2698 (20.2%)	na	na
	B	2707 (19.5%)	2974 (17.4%)	2778 (14.1%)
T_{max} (hr): Median (range)	A	1.60	na	na
	B	2.06	1.59	1.98
t_{1/2} (hr): Mean (CV%) (range)	A	9.05 (14.4%)	na	na
	B	9.03 (11.5%)	8.95 (17.3%)	9.33 (16.7%)

CV% = Coefficient of variation; na = not applicable

Reviewer's comment: Peak and total exposure of moxifloxacin were consistent for Group A and Group B, and for Session 1, Session 3, and Session 5.

Solifenacin: The steady-state pharmacokinetics of solifenacin are linear in the range studied, with both the AUC₍₀₋₂₄₎ and C_{max} of solifenacin in Session 5 about 3-fold higher than that observed in Session 3. Half-life estimates are reported only for Session 5, since this was the last dose of solifenacin given in the study.

Table 18 Summary of mean solifenacin PK parameters after 10 mg and 30 mg q.d. x 14 days in healthy volunteers

Parameter	Solifenacin 10 mg q.d. Day 14	Solifenacin 30 mg q.d. Day 14
AUC₍₀₋₂₄₎ (ng·hr/mL): Mean (CV%) (range)	918.2 (44.9%) —	3192 (49.8%) —
C_{max} (ng/mL): Mean (CV%) (range)	48.15 (41.5%) —	161.3(46.1%) —
T_{max} (hr): Median (range)	5.11 —	5.98 —
t_{1/2} (hr): Mean (CV%) (range)	na	56.5 (36.9%) —

CV% = Coefficient of variation; na = not applicable

Reviewer's comment: The total exposure of solifenacin achieved and mean C_{max} (161.3 ng/mL) observed in this study seemed to be comparable with those recorded in the ketoconazole-solifenacin drug interaction study (C_{max} = 181 ng/mL, Study RAYAU00110) (ketoconazole 400 mg q.d., followed by a single 10 mg dose of solifenacin). Overall, the peak and total exposures achieved in Session 5 were equivalent to what would be observed in patients taking 10 mg solifenacin and a potent CYP3A4 inhibitor.

Pharmacokinetic conclusions:

1. Peak and total exposure of moxifloxacin were consistent throughout the study and comparable to published values.
2. The steady state solifenacin peak and total exposures achieved in this study in Session 5 (30 mg q.d. x 14 days) were equivalent to what would be achieved if a patient took the clinical dose of solifenacin (10 mg q.d.) along with a potent CYP3A4 inhibitor. Therefore, the QTc effects seen in this study are likely the maximum that one would expect to observe in drug interactions with a potent metabolic inhibitor.

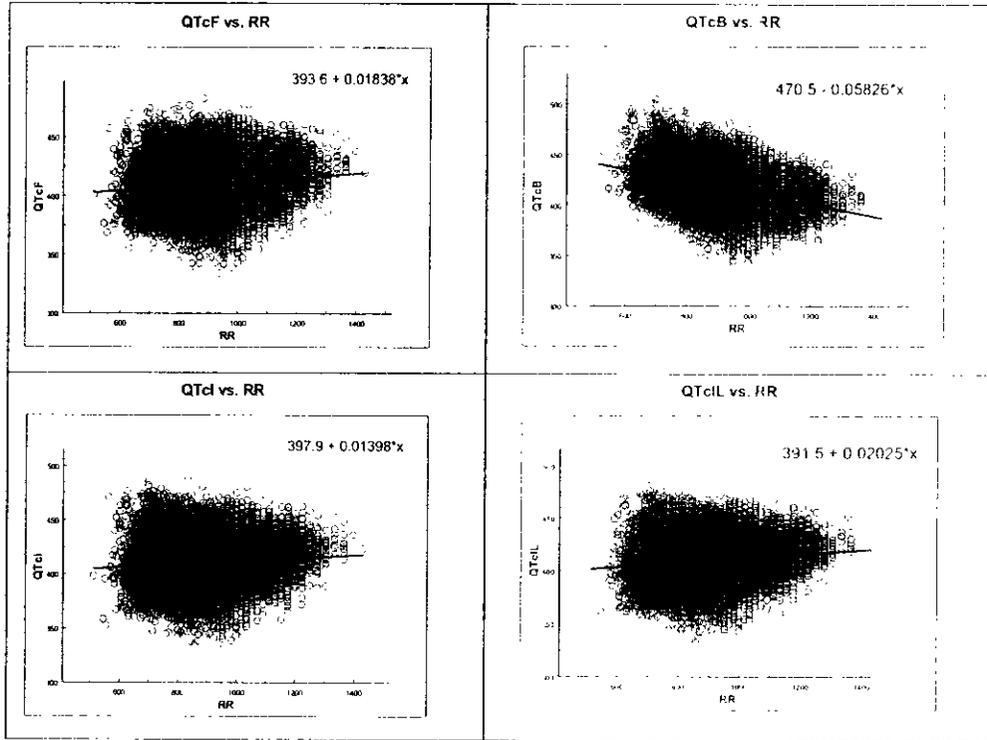
Pharmacodynamic

Note that the sponsor uses the following abbreviations throughout the pharmacodynamic statistical analysis and results sections:

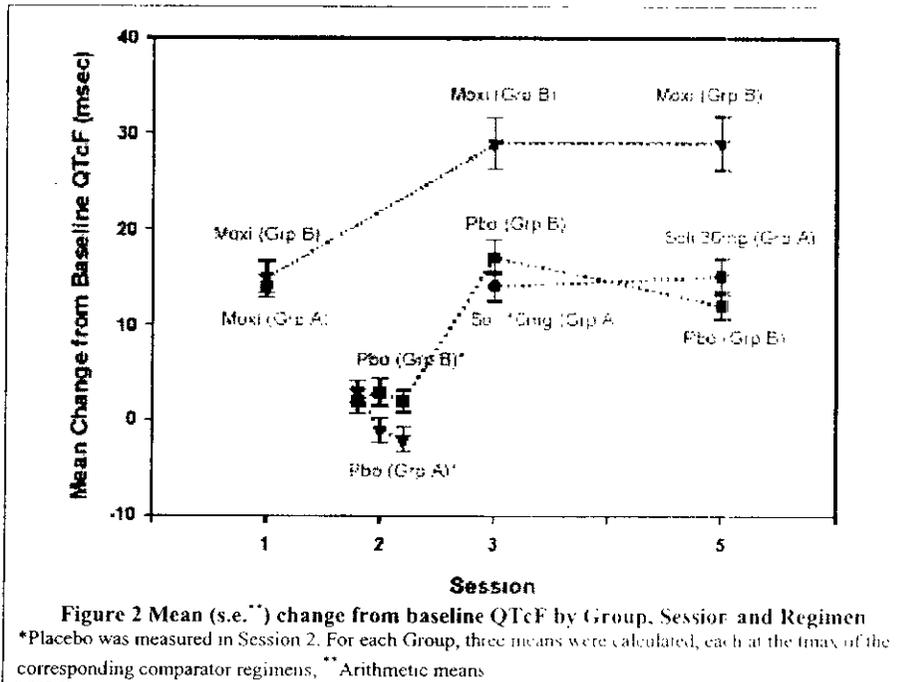
S10	Solifenacin 10 mg (Session 3)
S30	Solifenacin 30 mg (Session 5)
M	Moxifloxacin (Session 1)
M3	Moxifloxacin (Session 3)
M5	Moxifloxacin (Session 5)
P	Placebo (Session 2)
P3	Placebo (Session 3)
P5	Placebo (Session 5)

The following are plots of QTc vs. RR with a linear regression fit for each. The closer to zero the slopes of these regression lines, the more appropriate a correction method for this data. According to these graphs, the best correction for this data is the individual (linear) correction, QTci

Figure 1. Corrected QT vs. RR



Results of QTc change



For both Group A and Group B, the analyses unadjusted for session effects were deemed by the sponsor to be inappropriate to the data. In order to adjust for the observed session-related effects for solifenacin relative to placebo, Group A and B were compared in a parallel group fashion using the nonparametric Hodges-Lehmann-Moses method. Estimated median differences in change from baseline at t_{max} of solifenacin for Group A (solifenacin, session 3 and 5) compared to Group B (placebo, session 3 and 5) were calculated. For Session 3, N = 54 subjects in Group A and N = 24 subjects in Group B contributed to the comparison of interest. For Session 5, N = 51 subjects in Group A and N = 23 subjects in Group B contributed to the comparison of interest. In order to adjust for the observed session-related effects for moxifloxacin relative to placebo (for both session 3 and 5), Group B was analyzed using a paired t-test approach.

Outlier Measurements

The following table lists the number percent of QTc > 450 msec. No QTc was greater than 500 msec.

Table 19 Outlier QTcF > 450 msec

Regimen	Treatment Group A		Treatment Group B	
	N	N Outliers (%)	N	N Outliers (%)
M	3537	19 (0.54)	1751	31 (1.77)
M3	-	-	782	24 (3.07)
M5	-	-	750	21 (2.80)
P	3423	5 (0.15)	1667	1 (0.06)
P3	-	-	1563	10 (0.64)
P5	-	-	751	3 (0.40)
S10	4957	68 (1.37)	-	-
S30	3060	181 (5.92)	-	-

Table 20 QTcF Change from Baseline Outliers: 30 < QTcF ≤ 60 msec and QTcF > 60 msec

Regimen	Treatment Group A			Treatment Group B		
	N	30 < QTcF ≤ 60 msec	QTcF > 60 msec	N	30 < QTcF ≤ 60 msec	QTcF > 60 msec
M	638	23 (3.6)	0 (0.0)	289	18 (5.9)	0 (0.0)
M3	-	-	-	232	53 (18.5)	1 (0.3)
M5	-	-	-	232	43 (15.6)	0 (0.0)
P	625	2 (0.3)	0 (0.0)	304	0 (0.0)	0 (0.0)
P3	-	-	-	262	24 (8.4)	0 (0.0)
P5	-	-	-	267	43 (15.6)	0 (0.0)
S10	1060	128 (10.8)	0 (0.0)	-	-	-
S30	880	239 (21.3)	3 (0.3)	-	-	-

Mean Baseline-corrected QT_c and Baseline- and Placebo-corrected QT_c

Clinical pharmacology reviewer believes that Initial analysis should focus on data from Treatment Group A alone as Treatment Group B was proposed for "exploratory purposes only" when the protocol was reviewed.

Table 21 Mean Change in Baseline-corrected QT_cF, and Mean Change in both Baseline- and Placebo- (Treatment A, Session 1) corrected QT_cF

Treatment Group	Mean Change in Baseline-corrected QT _c (msec) ^a	Mean Change in Baseline- and Placebo-corrected QT _c (msec) ^a
Placebo (Treatment A)	-0.025 (-0.91 - 0.86)	-
Moxifloxacin 400mg (Treatment A, Session 1)	9.27 (8.37 - 10.17)	9.30 (8.40 - 10.22)
Solifenacin 10 mg	13.30 (11.65 - 14.95)	13.33 (11.69 - 15.00)
Solifenacin 30 mg	17.51 (16.85 - 18.16)	17.53 (16.90 - 18.22)

Table 22 Mean Change in Baseline-corrected QT_CI, and Mean Change in both Baseline- and Placebo- (Treatment A, Session 1) corrected QT_CI

Treatment Group	Mean Change in Baseline-corrected QT _C (msec) ^a	Mean Change in Baseline- and Placebo-corrected QT _C (msec) ^a
Placebo (Treatment A)	0.38 (-0.48 – 1.25)	-
Moxifloxacin 400mg (Treatment A, Session 1)	8.92 (8.06 – 9.79)	8.89 (8.05 – 9.78)
Solifenacin 10 mg	12.90 (11.30 – 14.50)	12.86 (11.27 – 14.46)
Solifenacin 30 mg	16.55 (15.92 – 17.19)	16.51 (15.89 – 17.16)

Both Solifenacin 10 and 30 mg responses are greater than the moxifloxacin response. However, as has been seen from other datasets, placebo response appears to change with time and is not captured when placebo correcting with Group A placebo response. Placebo response in Group B is measured in a similar time frame to the solifenacin measurements in Group A. Those placebo responses, along with session-corrected moxifloxacin and solifenacin responses, are presented in the following two tables.

Table 23 Mean Change in Baseline-corrected QT_CF, and Mean Change in both Baseline- and Placebo- (Treatment B) corrected QT_CF

Treatment Group	Mean Change in Baseline-corrected QT _C (msec) ^a	Mean Change in Baseline- and Placebo-corrected QT _C (msec) ^a
Placebo (Treatment B, Session 3)	13.47 (12.02 – 14.92)	-
Placebo (Treatment B, Session 5)	9.74 (8.38 – 11.10)	-
Moxifloxacin 400mg (Treatment B, Session 3)	18.41 (16.71 – 20.12)	4.94 (3.44 – 6.45)
Moxifloxacin 400mg (Treatment B, Session 5)	16.83 (15.25 – 18.41)	7.09 (5.75 – 8.43)
Solifenacin 10 mg	13.79 (13.08 – 14.51)	0.32
Solifenacin 30 mg	19.57 (18.78 – 20.38)	9.83

Table 24 Mean Change in Baseline-corrected QT_CI, and Mean Change in both Baseline- and Placebo- (Treatment B) corrected QT_CI

Treatment Group	Mean Change in Baseline-corrected QT _C (msec) ^a	Mean Change in Baseline- and Placebo-corrected QT _C (msec) ^a
Placebo (Treatment B, Session 3)	13.42 (12.02 – 14.81)	-
Placebo (Treatment B, Session 5)	9.82 (8.50 – 11.15)	-
Moxifloxacin 400mg (Treatment B, Session 3)	17.97 (16.27 – 19.66)	4.54 (3.04 – 6.06)
Moxifloxacin 400mg (Treatment B, Session 5)	16.70 (15.16 – 18.25)	6.88 (5.52 – 8.23)
Solifenacin 10 mg	12.65 (11.95 – 13.35)	-0.77
Solifenacin 30 mg	18.17 (17.40 – 18.94)	8.35

The assumption implicit in these corrections is that the mean baseline QT_C intervals are equal between treatment groups. However, as seen in the following two tables, the mean baseline QT_C intervals are not equal between the groups.

Table 25 Mean Baseline QT_CF by Treatment Group – [msec (95% CI)]

Baseline	Mean QT _C F		
	All subjects	Treatment A	Treatment B
Session 1	405.00 (404.04 – 405.97)	405.36 (404.28 – 406.45)	404.30 (402.38 – 406.22)
Session 2	404.68 (403.68 – 405.68)	405.84 (404.70 – 406.99)	402.32 (400.40 – 404.23)
Session 3	399.87 (398.71 – 401.03)	401.11 (400.10 – 402.13)	397.93 (396.12 – 399.74)

Table 26 . Mean Baseline QTcI by Treatment Group -- [msec (95% CI)]

Baseline	Mean QTcI		
	All subjects	Treatment A	Treatment B
Session 1	405.33 (404.26 – 406.40)	406.4 (405.26 – 407.72)	403.0 (401.01 – 405.10)
Session 2	404.8 (403.71 – 405.99)	406.5 (405.20 – 407.89)	401.8 (399.34 – 403.46)
Session 3	401.8 (400.56 – 403.20)	402.4 (401.29 – 403.66)	397.7 (395.72 – 399.70)

As seen above, the mean baseline reading between groups is significantly different, particularly in Session 3. The Session 3 difference between Group A and Group B in QTcF and QTcI is 3.18 and 4.76 msec, respectively.

The following table lists the mean QTc's for moxifloxacin, placebo and solifenacin by treatment group. As seen in the shaded areas, the Group B subjects showed considerably different placebo responses across sessions.

Table 27 Mean QTc's for moxifloxacin, placebo and solifenacin by treatment group

	Treatment A		Treatment B	
	Mean QTcF	Mean QTcI	Mean QTcF	Mean QTcI
Moxifloxacin 400 mg Session 1	414.30 (413.13-415.47)	415.00 (413.65-416.35)	413.26 (411.32-415.21)	412.44 (410.28-414.61)
Moxifloxacin 400 mg Session 3	-	-	416.34 (414.42-418.26)	415.67 (413.51-417.83)
Moxifloxacin 400 mg Session 5	-	-	414.30 (412.37-416.22)	413.82 (411.70-415.94)
Placebo, Session 2	405.82 (404.75-406.89)	406.93 (405.73-408.13)	402.30 (400.44-404.16)	402.29 (400.28-404.30)
Placebo, Session 3	-	-	411.40 (409.47-413.32)	411.13 (409.01-413.24)
Placebo, Session 5	-	-	407.21 (405.51-408.91)	406.94 (405.02-408.86)
Solifenacin 10 mg	415.08 (414.21-415.96)	415.75 (414.79-416.71)		
Solifenacin 30 mg	421.34 (420.41-422.26)	421.74 (420.72-422.75)		

Clinical Pharmacology reviewer's comment: Due to the nature of solifenacin (long half-life, need for dose-escalation), the protocol design of the study was particularly difficult. Initially, treatment group B was included by the sponsor for "exploratory" purposes and may not be statistically powered for making the session corrections proposed by the sponsor. The statistician will need to assess the sponsor's use of the Group B in QTc corrections.

Sponsor's Analyses

The sponsor believes that for both Group A and Group B, the analyses unadjusted for session effects were inappropriate to the data. In order to adjust for the observed session-related effects for solifenacin relative to placebo, Groups A and B were compared in a parallel group fashion using the **nonparametric Hodges-Lehmann-Moses** method. Estimated median differences in change from baseline at t_{max} of solifenacin for Group A (solifenacin, sessions 3 and 5) compared to Group B (placebo, session 3 and 5) were calculated. For Session 3, a total of 54 subjects in Group A and 24 subjects in Group B contributed to the comparison of interest. For Session 5, a total of 51 subjects in Group A and 23 subjects in Group B

contributed to the comparison of interest. In order to adjust for the observed session-related effects for moxifloxacin relative to placebo (for both session 3 and 5), Group B was analyzed using a paired t-test approach.

For Group A, following repeat dosing of 10 mg of solifenacin compared to placebo, the upper bounds of the 90% CI for the **median** differences were all contained within 10 msec, regardless of QTc correction method or choice of baseline. Following repeat dosing of 30 mg of solifenacin compared to placebo, the upper bounds of the 90% CI for the **median** differences were greater than 10 msec, with a maximum upper bound of 13msec.

For Group B, following a single dose of moxifloxacin 400 mg compared to placebo, the point estimates were all ≥ 12 msec, regardless of QTc correction method or choice of baseline, and the 90% CI for the **mean** differences were all ≥ 16 msec, with a maximum upper bound of 24 msec.

Figure 3 Point estimate and 90% CI for comparison of interest after adjustment for session effects

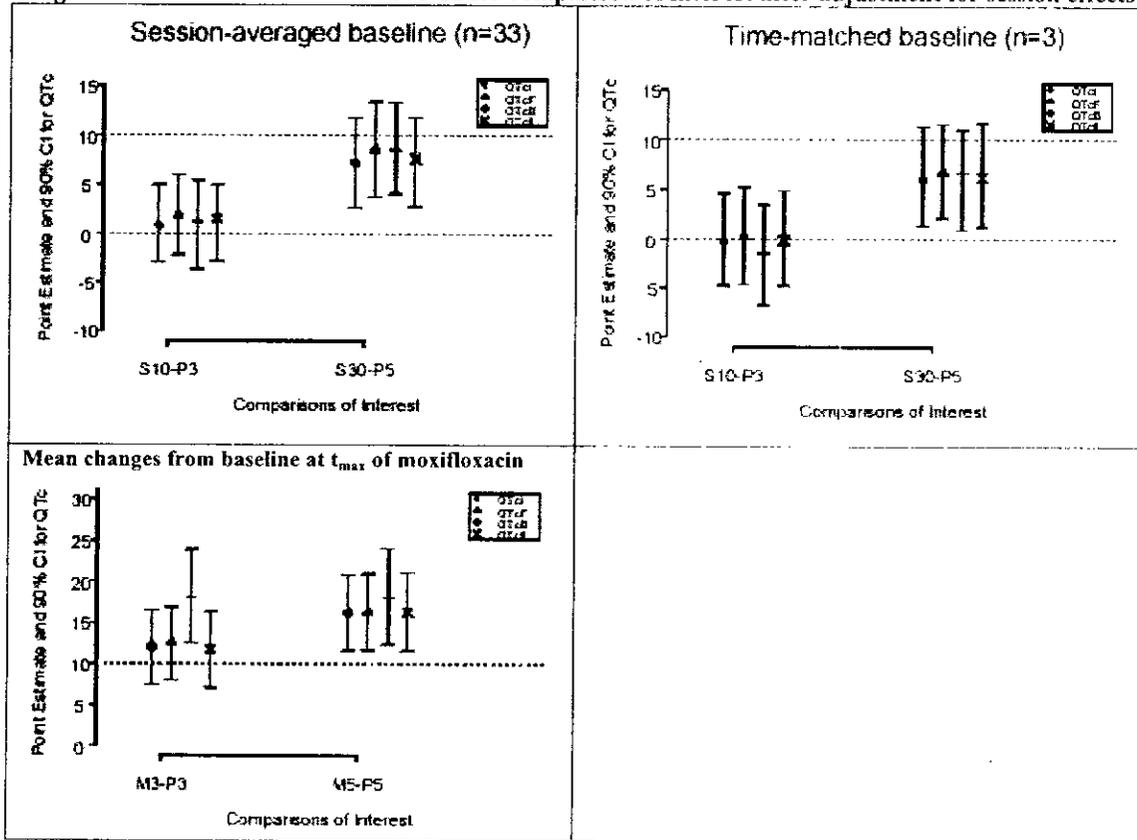


Table 28 Results for comparison of interest using the Hodges -- Lehmann - Moses estimator

Parameter	Session	Comparison (Group A – Group B)	Time-matched baseline (n = 3)		Session-averaged baseline (n = 33)	
			Point estimate ¹	90% CI	Point estimate ¹	90% CI
QTcF	Session 3	Solifenacin 10 mg – Placebo (P3)	0	(-5, 5)	2	(-2, 6)
	Session 5	Solifenacin 30 mg – Placebo (P5)	7	(2, 12)	9	(4, 13)
QTcI	Session 3	Solifenacin 10 mg – Placebo (P3)	0	(-5, 5)	1	(-3, 5)
	Session 5	Solifenacin 30 mg – Placebo (P5)	6	(1, 11)	7	(3, 12)
HR	Session 3	Solifenacin 10 mg – Placebo (P3)	-2	(-4, 1)	0	(-3, 2)
	Session 5	Solifenacin 30 mg – Placebo (P5)	0	(-3, 2)	1	(-1, 3)

¹ represents difference of adjusted medians. Above results are rounded to the nearest integer (accounts for asymmetry of CI).

Table 29 Results for comparison of interest using paired t-test (Group B)

Parameter	Session	Comparison	Point estimate ¹	90% CI
QTcF	Session 3	Moxi 400 mg – Placebo (P3)	12	(6, 17)
	Session 5	Moxi 400 mg – Placebo (P5)	16	(12, 21)
QTcI	Session 3	Moxi 400 mg – Placebo (P3)	12	(7, 17)
	Session 5	Moxi 400 mg – Placebo (P5)	16	(12, 21)
HR	Session 3	Moxi 400 mg – Placebo (P3)	5	(3, 8)
	Session 5	Moxi 400 mg – Placebo (P5)	1	(-1, 4)

¹ represents difference of adjusted means. Above results are rounded to the nearest integer (accounts for asymmetry of CI)

Reviewer's comment: A statistical consult has been requested

The sponsor's presentation at the meeting with the Division on 10/25/2004 showed the effect of repeat doses of solifenacin on cardiac conduction as compared to placebo, and single doses of moxifloxacin:

Table 30 Comparison of both Baseline- and Placebo- corrected Δ QTc in subjects given repeated doses of solifenacin vs. single dose of moxifloxacin

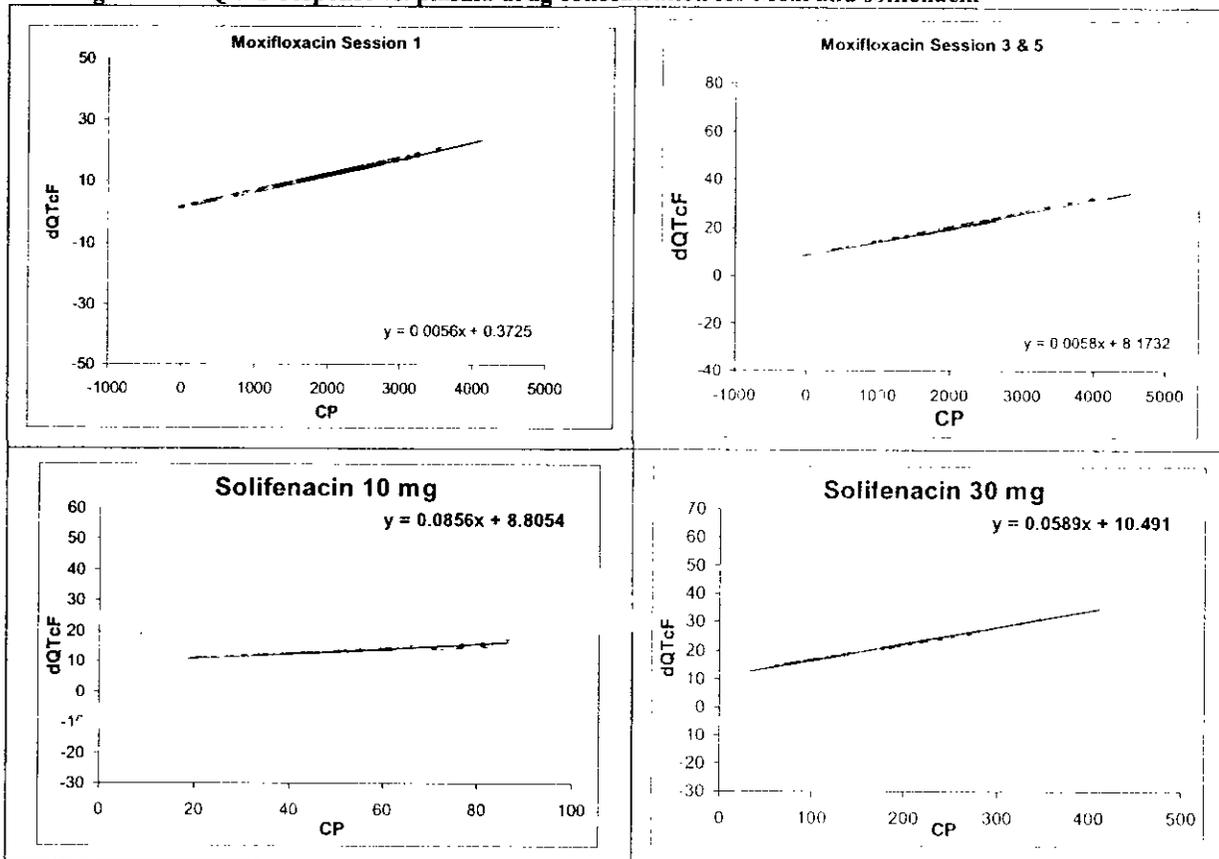
Group	Session	Comparison	Point estimate	90% CI
A-B*	#3	Solifenacin 10 mg – Placebo (P3)	0	(-5, 5)
A-B*	#5	Solifenacin 30 mg – Placebo (P5)	7	(2, 12)
A^	#1	Moxi 400 mg – Placebo (P)	11	(7, 14)
B^	#1	Moxi 400 mg – Placebo (P)	12	(8, 17)
B^	#3	Moxi 400 mg – Placebo (P3)	12	(8, 17)
B^	#5	Moxi 400 mg – Placebo (P5)	16	(12, 21)

* represents difference of adjusted medians calculated using Hodges-Lehmann-Moses Estimator.

^ represents difference of adjusted means calculated using paired t-test

The sponsor subsequently submitted the data set for drug plasma concentration and Δ QTcF. This reviewer and CPB reviewer analyzed the data and the results were included in following figures.

Figure 4 QTcF response vs. plasma drug concentration for Moxi and solifenacin



This is baseline-corrected data without placebo-correction.

Statistician's analyses resulted in the following table:

Table 31 Mean Δ QTcF at T_{max} (msec) based on a simple t test

Mean Δ QTcF at T_{max} (msec)	Session	Point Estimate	Lowest Limit of 90% CI	Upper Limit of 90% CI	Lowest Limit of 95% CI	Upper Limit of 95% CI
Group A vs. Group B*	S10 – P3	1.841	-2.775	6.458	-3.659	7.342
	S30 – P5	8.379	3.663	13.095	2.760	13.998
Group A alone**	S10 – P	15.350	11.742	18.958	11.051	19.649
	S30 – P	16.522	12.522	20.520	11.760	21.285
Time-matched Moxi Effect***	M – P	10.668	6.856	14.480	6.126	15.210
	M3 – P3	11.836	7.596	16.077	6.784	16.889
	M5 – P5	15.676	11.558	19.793	10.769	20.582

S10 – solifenacin 10 mg; S30 – solifenacin 30 mg.; M, P – Moxi and placebo at Session 2; M3, P3 – Moxi and placebo at Session 3; M5, P5 – Moxi and placebo at Session 5.

* Means of QTcF values at actual T_{max} for Group A subjects compared with mean QTcF for Group B (Sessions 3 & 5) at 6 hr (the average T_{max} from Group A is 5.3 hr)

** This is the original plan written in the protocol: Mean differences for Group A at time-matched QTcF at T_{max} of drug vs placebo (Sessions 3 & 5 drug vs. Session 2 placebo)

*** For the Moxi effect, M-P is the Session 1 vs. Session 1 at T_{max} ; M3-P3 is based on Session 3 at T_{max} , and M5-P5 is based on Session 5 at T_{max} . The sponsor reported M-P in the labeling

The method for Group A vs. Group B analysis:

- (1) Calculating the QTcF for each individual from Group A at her T_{max} , and adjusted by her baseline at T_{max} . There were 54 of those. Calculating the mean of those 54 numbers. Suppose it is Mean1.
- (2) For Group B, calculating QTcF at 6 hr for each individual and adjusted by her baseline at 6 hr, then taking the average, suppose it is Mean2. (The reason for 6 hr is because the mean T_{max} is 5.33 hr)
- (3) The point estimator is (Mean1 - Mean2). Then 90% CI is approximated by (Mean1-Mean2) \pm 1.645*(s.d.) and 95% CI is approx. (Mean1-Mean2) \pm 1.96*(s.d.).

Table 32 Comparison of Δ QTc at T_{max} based on different analyses: Sponsor's vs. Agency's

Group	Session	Comparison	Sponsor's analyses (Δ QTcF)		Agency's analyses (Δ QTcF)	
			Point estimate	90% CI	Point estimate**	90% CI
A-B*	#3	S10 - P3	0*	(-5, 5)	2	(-3, 6)
A-B*	#5	S30 - P5	7*	(2, 12)	8	(4, 13)
A*	#1	M - P	11*	(7, 14)	11	(7, 14)
B^	#1	M - P	12^	(8, 17)		
B^	#3	M3 - P3	12^	(8, 17)	12	(8, 16)
B^	#5	M5 - P5	16^	(12, 21)	16	(12, 20)

* represents difference of adjusted medians calculated using Hodges-Lehmann-Moses Estimator.

^ represents difference of adjusted means calculated using paired t-test

** Means based on simple t test

Reviewer's comment: The analyses from both the Agency and the sponsor showed that no significant effect of solifenacin on the QT interval at the maximum clinical dose of 10 mg. the 30 mg dose showed an effect of less than 10 msec which was lower than that seen with the active control moxifloxacin.

7.1.8.4.3 Analyses focused on outliers or shifts from normal to abnormal

Outlier analysis: The outlier analyses were not adjusted for session effects. Due to the sequential nature of the study design, session and treatment effects were confounded. The sponsor believes that the outlier analyses should be interpreted in the context of observed session effects. QTc outlier narratives were to be generated for all subjects with 1) a mean QTcF > 500 msec or 2) an increase in mean QTcF that was > 60 msec from the time-matched baseline or 3) an increase in mean QTcF that was > 60 msec from the session-matched baseline.

- QTcF > 500 msec: There were no subjects with a mean QTcF > 500 msec.
- QTcF increase > 60 msec from the session matched baseline: There were no subjects with a mean QTcF increase that was > 60 msec from the session-matched baseline.
- QTcF increase > 60 msec from the time matched baseline: A total of four subjects experienced increases in mean QTcF that were > 60 msec from the time-matched baseline. Three subjects (Subject #118, #204, and #414) were receiving 30 mg solifenacin in Session 5 at the time that the increase in QTcF was observed, and the fourth (Subject #104) was receiving 400 mg moxifloxacin in Session 3.

Table 33 QTcF: outliers or shift from normal to abnormal

Session/Regimen	QTcF (msec) change from baseline (n = 3)			Total
	Increase ≤ 30	30 < increase ≤ 60	Increase > 60	
Treatment Group A				
1/ Moxi 400 mg	42 (72.4%)	16 (27.6%)	0	58
2/ Placebo	55 (96.5%)	2 (3.5%)	0	57
3/ Soli 10 mg	25 (46.3%)	29 (53.7%)	0	54
5/ Soli 30 mg	17 (33.3%)	31 (60.8%)	3 (5.9%)	51
Treatment Group B				
1/ Moxi 400 mg	17 (60.7%)	11 (39.9%)	0	28
2/ Placebo	28 (100%)	0	0	28
3/ Placebo	15 (57.7%)	11 (42.3%)	0	26
Moxi 400 mg	7 (26.9%)	18 (69.2%)	1 (3.8%)	26
5/ Placebo	20 (80.0%)	5 (20.0%)	0	25
Moxi 400 mg	7 (28.0%)	18 (72.0%)	0	25

7.1.8.4.4 Marked outliers and dropouts for ECG abnormalities

Case narratives for mean QTcF outliers

Subject # 118, a healthy, 60-year-old Hispanic female, was randomized to Treatment Group A. In accordance with the study protocol, the subject did not take any other medications concomitantly with study drug. The subject experienced an increase in mean QTcF of 63.8 msec above baseline at 12 hours after administration of 30 mg solifenacin on Session 5, Day 13. The subject's mean QTcF at this timepoint was 431.2 msec as compared to the time-matched baseline QTcF of 367.0 msec on Session 3, Day -1, Hour 12. No other increases in mean QTcF of greater than 60 msec were observed for this subject during the study. At the conclusion of this dosing session, i.e., on Session 5, Day 14, Hour 24, the subject's mean QTcF was 408.2 msec. No action was taken as a result of the QTcF finding and the subject completed the study.

Subject # 204, a healthy, 45-year-old female of unspecified race, was randomized to Treatment Group A. In accordance with the study protocol, the subject did not take any other medications concomitantly with study drug. The subject experienced an increase in mean QTcF of 70.2 msec above baseline at 24 hours after administration of 30mg solifenacin on Session 5, Day 13. The subject's mean QTcF at this timepoint was 441.0 msec as compared to the time-matched baseline QTcF of 371.0 msec on Session 3, Day -1, Hr 24. No other increases in mean QTcF of greater than 60 msec were observed for this subject during the study. At the conclusion of this dosing session, i.e., on Session 5, Day 14, Hr 24, the subject's mean QTcF was 418.0 msec. This QTcF prolongation was not associated with any symptoms. No action was taken as a result of the QTcF finding and the subject completed the study.

Subject #414, a healthy, 62-year-old Hispanic female, was randomized to Treatment Group A. In accordance with the study protocol, the subject did not take any other medications concomitantly with study drug. The subject experienced an increase in mean QTcF of 60.4 msec above baseline at 2 hrs after administration of 30mg solifenacin on Session 5, Day 13. The subject's mean QTcF at this timepoint was 467.5 msec as compared to the time-matched baseline QTcF of 407.0 msec on Session 3, Day -1, Hr 2. No other increases in mean QTcF of greater than 60 msec were observed for this subject during the study. At the conclusion of this dosing session, i.e., on Session 5, Day 14, Hour 24, the subject's mean QTcF was 442.0 msec. This QTcF prolongation was not clinically significant and was not associated with any symptoms. No action was taken as a result of the QTcF finding and the subject completed the study.

Subject #104, a healthy, 54-year-old Hispanic female, was randomized to Treatment Group B. The subject received Benadryl orally on Session 5, Day 4 for urticaria; this was considered a protocol violation. The subject experienced an increase in mean QTcF of 64.0 msec above baseline at 0.5 hour following administration of a single dose of 400mg moxifloxacin on Session 3, Day 14. The subject's mean QTcF at this timepoint was 427.4 msec as compared to the time-matched baseline QTcF of 363.0 msec on Session 3, Day -1, Hr 0.5. No other increases in mean QTcF of greater than 60 msec were observed for this subject during the study. At the conclusion of this dosing session, i.e., on Session 3, Day 14, Hr 24, the subject's mean QTcF was 393.0 msec. This QTcF prolongation was not clinically significant and was not associated with any symptoms. No action was taken as a result of the QTcF finding and the subject completed the study.

Conclusion of QTc change:

From the analyses both from the Agency (Clin Pharm reviewer and statistician) and from the sponsor, this reviewer believes the following can be concluded:

- Single oral dose of moxifloxacin 400 mg can cause QTcF change of + 12-16 msec
- Solifenacin 10 mg at steady state can cause QTcF change of + 2-3 msec
- Solifenacin 30 mg at steady state can cause QTcF change of + 6-9 msec

Reviewer's conclusion: At the 5 mg and 10 mg dose levels, the effect of solifenacin on QTcF appears to be less than 10 msec. A dose response from 10 mg to 30 mg of solifenacin appears to exist and this should be included in labeling.

7.1.8.4.5 Safety results of the study

Extent of Exposure: A total of 86 subjects were treated with at least one dose of study medication. Ten subjects discontinued from the study prematurely. Four subjects (#203, #412, #602, #610) discontinued without receiving solifenacin. Subject #203 was randomized to Treatment Group A, but discontinued in Session 1 (moxifloxacin) due to schedule conflicts. Subjects #412, #602, and #610 were randomized to Treatment Group B. Subject #412 withdrew in Session 3 and Subjects #602 and #610 in Session 2. Six (6) subjects (#202, #304, #313, #507, #515, #601) discontinued after receiving solifenacin. Four (4) subjects withdrew in Session 3, Subject #304 after receiving 14 doses, Subject #507 after 3 doses, Subject #515 after 2 doses, and Subject #601 after 9 doses of solifenacin 10 mg. Subject #313 withdrew after completing Session 4. Subject #202 withdrew in Session 5 after receiving 12 doses of solifenacin 30 mg. A total of 76 subjects completed the study as planned.

Adverse events

Serious adverse events (SAEs): One SAE of severe cholecystitis (subject #15) was reported. This 56-year-old female, with no significant medical history, was randomized to Treatment Group A (moxifloxacin/placebo/increasing doses of YM905). On the tenth day of the study, the patient was on solifenacin 10 mg in Session 3 and had received 2 doses of solifenacin at 10 mg daily, when she developed abdominal pain, and was admitted to the hospital with severe cholecystitis. Gallbladder ultrasound revealed gallbladder wall edema with stones and sludge. The patient was diagnosed with cholecystitis with cholelithiasis. The next day she underwent a cholecystectomy and was discharged from the hospital one day after surgery. The investigator considered the event unlikely related to study drug.

Reviewer's comment: The reviewer agrees that the SAE is not related to the study medication.

The majority of events were considered to be mild or moderate in severity. Three subjects had severe headaches, and severe dizziness, severe migraine, and severe upper abdominal pain were reported by 1 subject each. Except for severe migraine in 1 subject randomized to Treatment Group B, all severe AEs occurred in subjects randomized to Treatment Group A.

The overall occurrence of AEs was similar between Treatment Group A and Treatment Group B. Headache was the most frequently reported AE in Treatment Group B, followed by dry mouth, constipation, and nausea.

One subject (#216, Treatment Group A) had blood in her stool reported during Session 1 and Session 3-5. She had concurrent constipation, requiring daily metamucil and, on occasion, glycerin suppositories. The subject had a history of GERD but no history of hemorrhoids or evidence of upper GI bleeding. Local swelling reported for Subject #519 (Treatment Group A) in Session 5 was scar tissue that was the result of scleral therapy for spider veins on the right calf.

Table 34 Post-dose adverse events in Session 3, 4, and 5

Adverse events	Treatment Group A			Treatment Group B		
	S10	S20	S30	PM3	P4	PM5
Dry mouth	22	12	17	4	3	3
Constipation	6	3	16	0	3	6
Headache	5	3	9	4	4	7
Vision blurred	3	3	12	3	1	2
Dizziness	2	0	10	3	0	2
Total # of AEs	77	33	166	33	15	65
# of subjects exposed	57	53	52	26	25	25
# of subjects with AE	41	21	46	15	9	18

Adverse Events Leading to Premature Discontinuation from Study: A total of 7 subjects withdrew from the study due to adverse events, including the above SAE (#515). The remaining 6 subjects who withdrew due to adverse events are summarized in Table 34. Four subjects were randomized to Treatment Group A and 3 subjects were randomized to Treatment Group B. Three subjects withdrew due to AEs that were suspected or considered probably related to study medication, only 1 of these subjects was receiving solifenacin (Subject #304, AEs of dermatitis and pruritis). All events resolved by the end of the study.

Table 35 Subjects withdrawn prematurely due to adverse events

Subject number	Adverse event	Last treatment	Relation to study medication	outcome
304	Dermatitis, Pruritus	Session 3: 14 doses solifenacin 10 mg	Probable	Resolved
412	Hypertension	Session 3: 13 doses placebo, 1 dose moxifloxacin	Suspected	Resolved
507	Headache	Session 3: 3 doses solifenacin 10 mg	Unlikely	Resolved
601	Sinusitis	Session 3: 9 doses solifenacin	Not related	Resolved
602	Eye pruritus, nasal congestion, throat irritation	Session 2: 1 dose placebo	All probable	All resolved
610	ECG QT prolonged	Session 2: 1 dose placebo	Not related	Resolved

Clinical laboratory evaluations

Table 36 Post-dose laboratory tests of potential clinical concern that were normal at baseline

Subject	Study Session	Parameter	Reference Range	Baseline Value	Value of Concern	Time of Change
204	S 5, Tmt A	Glucose	70-110 mg/dL	116	132	1:0:0
	S 5, Tmt A	ALT	0-31 IU/L	40	78	14:96:0
	Final	ALT	0-31 IU/L	40	65	Final
213	S5, Tmt B	GGT	7-33 IU/L	32	87	1:0:0
	S5, Tmt B	GGT	7-33 IU/L	32	126	14:96:0
	Final	GGT	7-33 IU/L	32	99	Final
304	Final	Hematocrit	35.0-45.0%	34.8	30.1	Repeat
	Final	Hemoglobin	11.7-15.5	11.4	10.0	Repeat
312	S 5, Tmt A	Glucose	65-109 mg/dL	98	130	1:0:0
	S 5, Tmt A	Glucose	65-109 mg/dL	98	130	14:96:0
501	Final	WBC	3.8-10.8 K/ μ L	9.1	15.0	Final
515	Final	GGT	2-69 IU/L	24	121	Final
519	S 3, Tmt A	Potassium	3.5-5.3 meq/L	4.7	5.9	1:0:0
520	S5, Tmt B	GGT	2-60 IU/L	66	123	14:96:0
613	S 5, Tmt A	Glucose	65-99 mg/dL	97	131	14:96:0

Nine subjects had laboratory values that were within normal limits at baseline but reached values of potential clinical concern during the study (Table 36).

Elevated liver function enzymes were recorded for 4 subjects: Subjects #204 (Treatment Group A), a woman of Asian heritage, entered with screening GGT values that were 2xULN (GGT remained elevated throughout the study), and screening ALT and AST values that were above the ULN but were not 2XULN. ALT levels reached levels of potential clinical concern in Session 5. Subject #213 (Treatment Group B), also of Asian heritage, entered with screening values for GGT that were above the ULN and a repeat screen that was just within normal limits, GGT increased during Session 5 to above potential concern levels. Both subjects were improving at follow-up. Subject #515 (Treatment Group A) had a high GGT value at her follow-up visit (after cholecystectomy); all her previous GGT values were within normal limits as were all other liver function tests. None of these laboratory values were considered clinically significant by the investigator. Subject #520 (Treatment Group B) had GGT values that were high at baseline and rose steadily during the study. The investigator recorded elevated GGT as an adverse event probably related to study medication in Session 5. At follow-up, GGT was 86 IU/L.

Glucose levels for Subject #312 and #613 (both in Treatment Group A) were high at screening and throughout the study, and reached levels of potential clinical concern for both subjects in Session 5. At follow-up, glucose levels had decreased (117 mg/dL for Subject #312 and 94 mg/dL for Subject #613). Elevated potassium for Subject #519 (Treatment Group A) was due to a hemolyzed sample, all other potassium values for this subject were within normal limits. Hematology values for Subjects #304 (Treatment Group A) and #501 (Treatment Group B) were recorded at the final follow-up visit. None of these laboratory values were considered clinically significant by the investigator.

Vital signs: Changes of potential clinical concern in vital signs were recorded for 6 subjects. The majority of these were isolated changes that returned to within normal limits by the end of the study and were not of clinical significance. However, elevated systolic blood pressure for Subject #412 (Treatment Group B), who was mildly hypertensive at baseline, led to her premature withdrawal from the study.

Table 37 Subjects with post-dose vital signs of potential clinical concern

Subject	Regimen	Parameter	Baseline Value	Value of Concern	Time of Assessment
113	S1	DBP	82 mm Hg	60 mm Hg	1:24
121	S5, Tmt A	SBP	108 mm Hg	170 mm Hg	14:0
		SBP	108 mm Hg	160 mm Hg	14:24
		DBP	72 mm Hg	100 mm Hg	14:0
		SBP	72 mm Hg	100 mm Hg	14:0
210	P5, Tmt B	SBP	147 mm Hg	110 mm Hg	14:0
211	S2	SBP	136 mm Hg	105 mm Hg	1:24
	S3, Tmt A	SBP	117 mm Hg	157 mm Hg	14:24
215	S1	SBP	152 mm Hg	119 mm Hg	1:24
		DBP	94 mm Hg	72 mm Hg	1:24
412	S3, Tmt B	SBP	158 mm Hg	192 mm Hg	14:0

Safety Conclusions: Solifenacin 10 mg q.d., 20 mg q.d., and 30 mg q.d. were tolerated with adverse experiences consistent with the known pharmacology of the drug. Seven (7) subjects were withdrawn prematurely for adverse events, 4 subjects in Treatment Group A and 3 subjects in Treatment Group B; dermatitis and pruritus for 1 subject in Treatment Group A was considered probably drug-related. One of the withdrawn subjects had the serious adverse event of cholecystitis (Treatment Group A), considered not related to study medication. All AEs resolved without sequelae. Changes in clinical laboratory and vital signs were not clinically significant.

7.1.8.4.6 Conclusion of special designed QT study

Reviewer's conclusion on QT study: This reviewer believes that

Pharmacodynamics:

- 1) The point estimate of solifenacin 10 mg – placebo Δ QTcF is 3-5 msec.
- 2) The point estimate of solifenacin 30 mg – placebo Δ QTcF is 8-10 msec.
- 3) The point estimate of moxifloxacin 400 mg - placebo Δ QTcF is 10-12 msec
- 4) The QTcI results are similar to QTcF.

Safety:

- The most frequently reported adverse events following repeat administration of solifenacin 10 to 30 mg were dry mouth, constipation, headache, vision blurred, and dizziness, all of which were suspected or considered probably related to study medication. The majority of these cases were mild to moderate.
- No deaths were reported in this study, the single serious adverse event of cholecystitis was considered not related to study medication.
- A total of 7 subjects withdrew prematurely from the study (including the subject with SAE); 3 subjects withdrew due to adverse events suspected or considered probably related to study medication (dermatitis, pruritis, hypertension, eye pruritis, nasal congestion, throat irritation).
- Clinical laboratory and vital signs were not clinically significant with the exception of 1 subject who experienced elevated GGT values in Session 5.

The steady state solifenacin peak and total exposures achieved in this study in Session 5 (30 mg qd X 14 days) were equivalent to what would be achieved if a patient took the clinical dose of solifenacin (10 mg qd) along with a potent CYP3A4 inhibitor. Therefore, the QTc effects seen in this study are likely the maximum that one would expect to observe in drug interactions with a potent metabolic inhibitor. The

change in QTc (8-10 msec) seen at plasma concentrations resulting from administration of solifenacin at a dose 3 times the maximum dose to be marketed should be included in labeling.

7.1.8.5 Final conclusions regarding the effect of solifenacin on QT interval

The effect of solifenacin on QT interval has been evaluated in 2 clinical pharmacology studies (905-CL-022 and 905-CL-043) specifically designed to evaluate this effect, and by analysis of ECG measurements from Phase 3 studies in more than 1800 patients.

This reviewer believes that the highest dose of solifenacin to be marketed (10 mg), is associated with a small prolongation of the QT interval in the range of 3-5 msec. At supratherapeutic plasma concentrations seen following administration of solifenacin 30 mg qd, a QT interval prolongation of 5-10 msec was observed.

It is concluded that the QT interval prolongation associated with recommended solifenacin doses does not pose a significant clinical risk. The dose response effect of solifenacin on the QT interval should be included in labeling.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Extent of exposure (dose/duration)

Total drug exposure: At the time of NDA Amendment submission, 3942 patients with OAB had been treated in Phase 2 and Phase 3 trials, which included 2621 from the original review and 1321 from this review. In completed Phase 2 or Phase 3 trials submitted in the amendment, a total of 2282 patients (961 had been exposed in previous double-blind studies) have been exposed to solifenacin 2.5 mg, or 5 mg, or 10 mg. Among them, 436 (19.1%) completed up to 12 weeks of exposure, 146 (6.4%) completed between 12 and 24 weeks of exposure, 64 (2.8%) completed between 24 and 27 weeks of exposure, and 1636 (71.7%) completed more than 27 weeks of exposure (639 or 28% completed 40 to 52 weeks, and 645 or 28.3% completed more than 52 weeks).

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Guodong Fang
11/18/04 10:42:04 AM
MEDICAL OFFICER

George Benson
11/18/04 03:09:12 PM
MEDICAL OFFICER



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-518
Sponsor: Yamanouchi Pharma America
Request: Consult request from the Division of Reproductive and Urologic Drug Products for consultative review of QT data in study 905-CL-043.

Review date: 25 September 2004

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This is a brief review of QT findings for NDA 21-518 (solifenacin), study 905-CL-043, a complex, multi-dose, placebo- and positive-controlled "thorough" QT study.

Briefly, there were 2 arms and 5 study periods. In the first period, all subjects had 12-lead ECGs recorded over 24 hours prior to and 24 hours after a single oral dose of moxifloxacin 400 mg. In period 2, all subjects had ECGs 24 hours prior to and 24 hours after placebo. All subjects had baseline ECGs over 24 hours prior to period 3. In periods 3-5, subjects in arm B received placebo for 13 days (periods 3 and 5) and a single dose of moxifloxacin on day 14 or 14 days of placebo (period 4). Subjects in arm A received solifenacin 10 mg (period 3), 20 mg (period 4), and 30 mg (period 5) for 14 days. Thus, the baseline day for solifenacin 30 mg was some six weeks earlier, a challenging design.

The first step in evaluating a thorough QT study ought to be an assessment of the ability of the study to detect the effect of moxifloxacin. This study offers several opportunities to do this. Because the signal at any given time point (like T_{max}) is still (usually) pretty small, it makes sense to see if one can discern a time course.

Taking each subject's post-moxifloxacin QTcF in period 1 and subtracting the baseline QTcF from corresponding time points of the previous day should subtract any time-of-day effect and show the effect of moxifloxacin.

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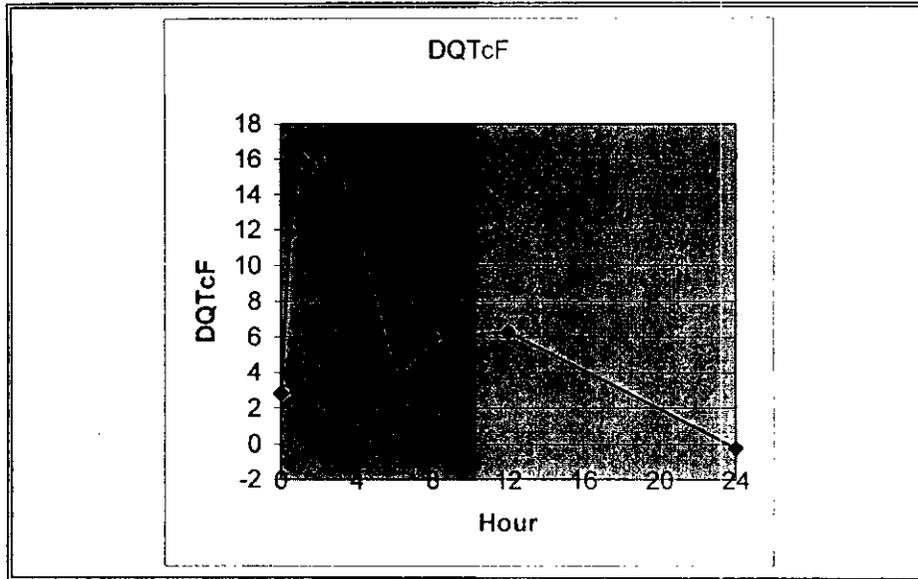


Figure 1. Apparent effect of moxifloxacin in Period 1
Mean effect obtained by subtracting Day -1 from Day 1 values in Period 1.

This "looks right", in the sense of having a peak in the first few hours, but the apparent magnitude of treatment effect is much larger than one expects—around 16 ms instead of 6-8 ms. This large peak is not a single outlier or a few outliers; large early peaks are seen in many subjects.

Performing this same operation in Period 2 should give a flat line.

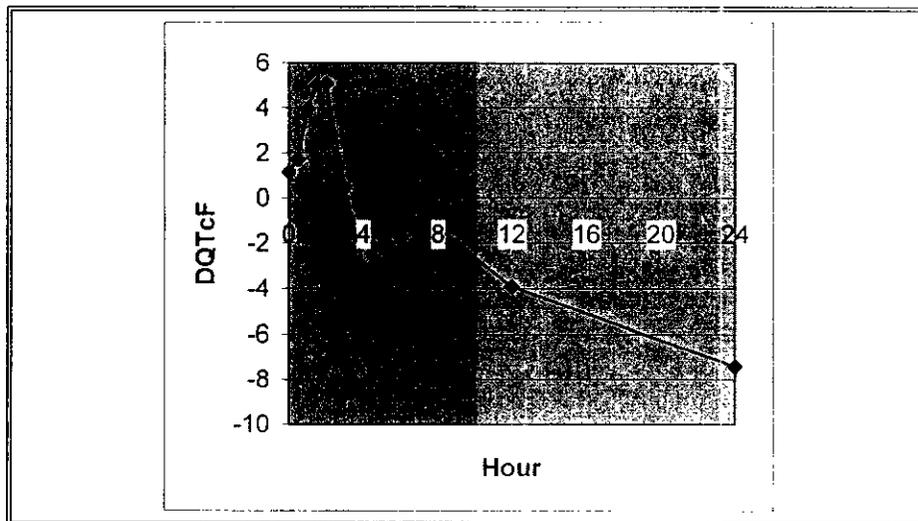


Figure 2. Apparent effect of placebo in Period 2
Mean effect obtained by subtracting Day -1 from Day 1 values in Period 2.

These data look quite similar to the data in Period 1. There is a peak in the first few hours, a second hump in the midday, and an overall amplitude of about 13 ms.

The next opportunity to examine the effect of moxifloxacin is Period 3. This time, the post-treatment data are separated from the baseline by 14 days, and there are only 26 subjects with data.

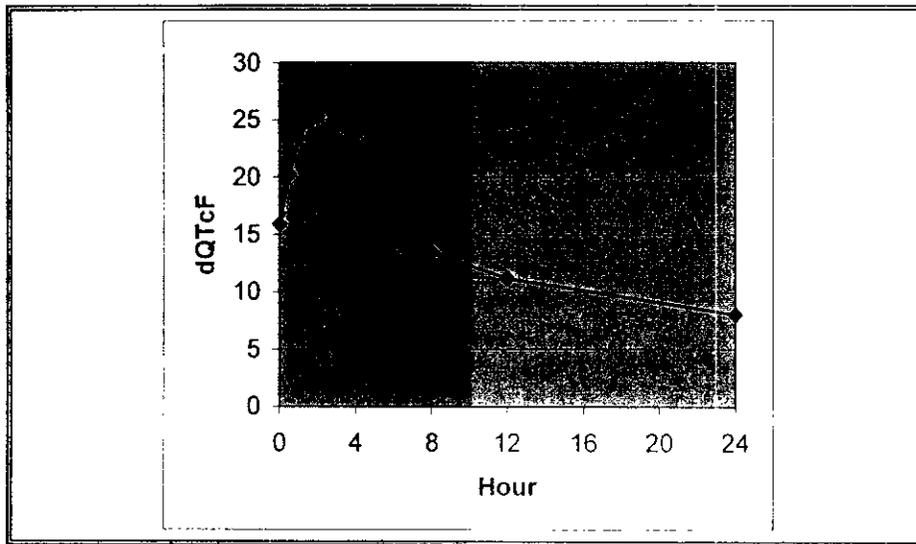


Figure 3. Apparent effect of moxifloxacin in Period 3
Mean effect obtained by subtracting Day -1 from Day 14 values in Period 3.

The overall shape is similar to previous displays, and the amplitude (max minus min) is >15 ms.

The final opportunity to examine the effect of moxifloxacin is in Period 5. This time the results must again be based on the baseline data of Day -1 in Period 3. For comparison, the data from solifenacin 30 mg from Period 5 are shown, too.

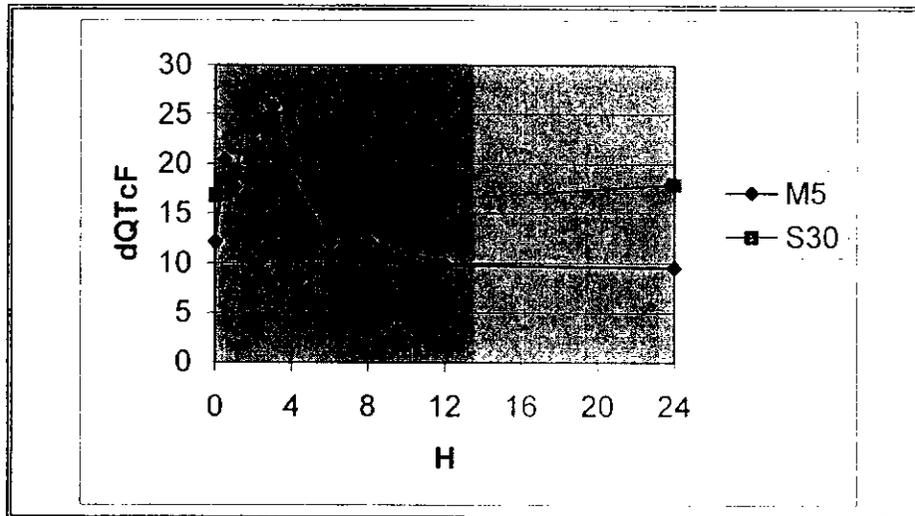


Figure 4. Apparent effect of moxifloxacin and solifenacin in Period 5.
Mean effects obtained by subtracting Day -1 of Period 3 from Day 14 values in Period 5.

Again, these data suggest that the effect of moxifloxacin is 15 ms.

The raw plasma levels of moxifloxacin (and solifenacin) are apparently not submitted, so a proper plot of change in QTcF versus plasma level of moxifloxacin cannot be performed. Only the peak moxifloxacin levels are provided, so these values (from Period 1) were used to construct Figure 5 below.

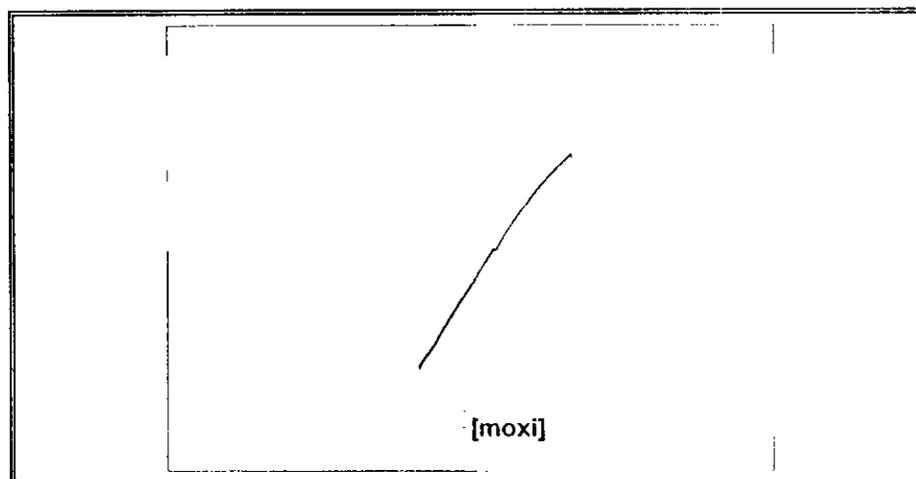


Figure 5. Change in QTcF vs [moxifloxacin] in Period 1.

The concentration data for moxifloxacin were obtained from the Cmax data in the PK dataset. This dataset identified the nearest time point corresponding to an ECG assessment.

There is a weak positive correlation between change in QTcF and plasma concentration of moxifloxacin.

What, then, can one say about the effects of solifenacin? The implausible effect of moxifloxacin suggests that the correct answer is to make no inference regarding solifenacin. However, if one were to say that the effect of moxifloxacin was, in three assessments, on the order of 15 ms, for whatever reason, then the effects of solifenacin are not reassuring. If one interprets the 10-ms offset in the moxifloxacin data of Figure 4 as an artifact, to get the apparent 15 ms effect, one cannot do so with the solifenacin 30 mg data. Here, the "baseline" is 5 ms higher at time 0 or 9 ms higher at 24 hours, and, because of the long half-life, that difference may be real. On top of that one has an apparent treatment effect with the 14th dose of about 8 ms.

I do not know how to make a coherent story based on these data. The effects of placebo in Period 2, moxifloxacin in Periods 1, 3, and 5, and solifenacin 30 mg in Period 5 all look disturbingly similar. I question, therefore, whether this study successfully distinguished the moxifloxacin effect and I cannot hazard a guess about the magnitude of effect of solifenacin excluded.

I would be very happy to work with anyone—medical officer, statistician, biopharmaceutics reviewer, or representative of the sponsor—with further insights on this matter.

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IMTS Meeting Cancellation (Supplemental Form)

Project Manager: Albert Perrine

Application Type	NDA
Application Number	21-518
Date Meeting Cancelled	June 22, 2004
Reason for Cancellation	The meeting scheduled for August was to be a Pre-submission of a Complete Response meeting. Since granting this meeting, the sponsor submitted their Complete Response to our Approvable letter, thus changing the character of the meeting. The Division believes that it would better serve the sponsor by reviewing the data submitted. A meeting at this stage is premature.

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this page is the manifestation of the electronic signature.**

/s/

Albert Perrine
7/9/04 03:08:10 PM
CSO

Margaret Kober
7/12/04 04:23:50 PM
CSO



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-518
Sponsor: Yamanouchi Pharma America
Request: Consult request from the Division of Reproductive and Urologic Drug Products for consultative review of annotated ECGs in study 905-CL-043.

Review date: 31 August 2004

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This is a brief review of annotated ECG findings for NDA 21-518 (solifenacin), study 905-CL-043, a complex, multi-dose, placebo- and positive-controlled "thorough" QT study.

The review was conducted using the XMLFDA viewer application version 2.0.6.

A dozen randomly selected aECG files were examined for high frequency noise, low-frequency noise (baseline wander), and placement of interval markers. A typical example is shown in Figure 1 below.

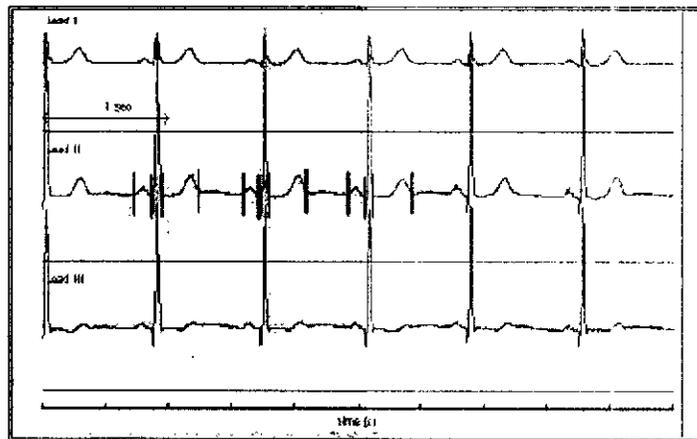


Figure 1. Sample annotated ECG from Study 905-CL-043.

The quality of the records is generally quite satisfactory.

As shown in the example, Lead II was typically annotated, but some records had annotations in a precordial lead or Lead I.

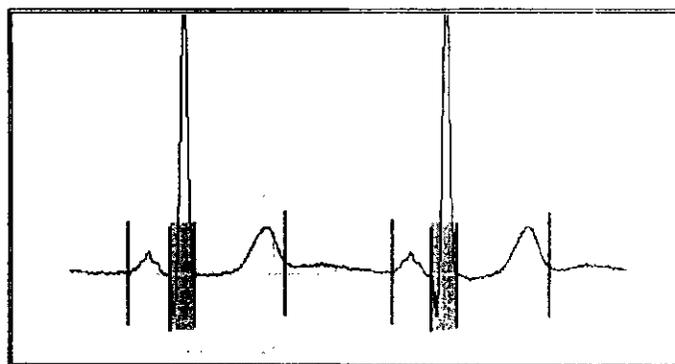


Figure 2. Sample of annotation from Lead II (Study 905-CL-043).

In general, measurements of the end of the T wave on the rhythm series fell short of where some observers would have placed them. Perhaps, the algorithm was based on a tangent to the falling part of the T wave.

In addition to the annotations on the rhythm series, there was (usually) a derived (representative or median) beat, which was also annotated.

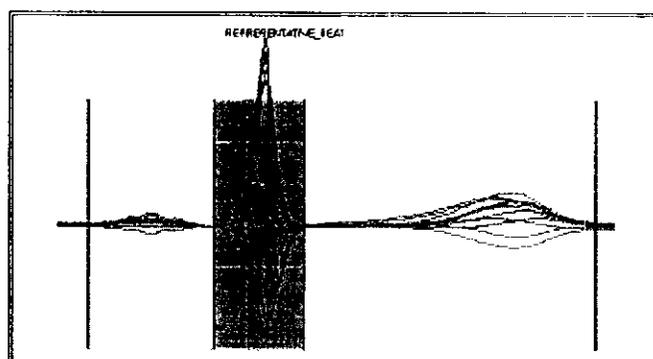


Figure 3. Sample of annotations for a derived beat (Study 905-CL-043)

The end of the T wave as marked in derived beat was closer to where the waveform settles into the baseline.

Across the set of selected records, however, the rhythm-based annotations and the derived waveform-based annotations seemed to be internally consistent. It was not clear which set of annotations were used for the reported values of the interval measurements.

The sponsor's study report and Dr. Fang's draft clinical review cite 4 subjects with outlying QTcF values on study drug (n=3) or moxifloxacin (n=1). Each of these outlying values was at a single time point, making it unlikely that any should be cause for concern. Nevertheless, annotated ECG records were reviewed for each of these subjects, with particular attention to time points for which the outlying values were reported.

In the case of subject 118, with a 64-ms increase in QTcF at hour 12 of day 13 on solifenacin 30 mg, many of this subject's ECGs, including the suspect time, were obtained with equipment that recorded at a lower rate and for shorter times compared to most of the recordings in the database. These files have no median beat. Because of the short record in lead I, the measurements were obtained for one or two beats. In two of the three repeated samples (repeat ECGs obtained at 1 minute intervals averaged to a single time point), the beat was preceded by the shortest RR interval among the larger

set seen in Lead II. Thus, the correction is probably not indicative of the subject's true heart rate.

To look for drug-related changes in T-wave morphology, beats from lead I of various time points were aligned, as shown in Figure 4 below. T-wave morphology does not appear to change much over the dosing interval.

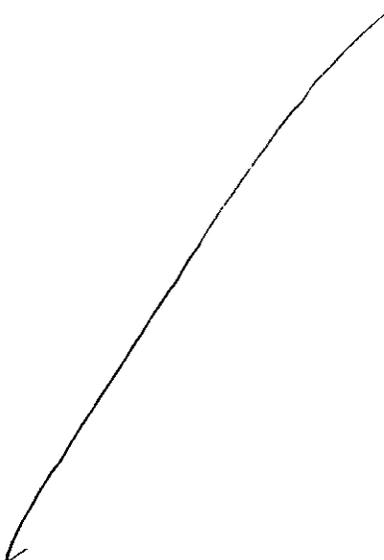


Figure 4. Beat morphology by time after dosing in subject 118 (Study 905-CL-043).

The data are from subject 118 and all of the data are from day 13 of period 5. The lowest curve is pre-dose. The upper curve is 24 hours post-dose. Because the beats being aligned did not all have annotations, the individual records were plotted and manually aligned with a graphics program.

In the case of subject 414, with a 60-ms increase in QTcF at hour 2 after solifenacin 30 mg, the actual increase may be a little larger than reported. Figure 5 below shows the set of 3 repeated ECGs as overlaid traces for the derived beat. Marking the end of the T-wave in the third sample is clearly inconsistent with the measurement for the earlier samples.

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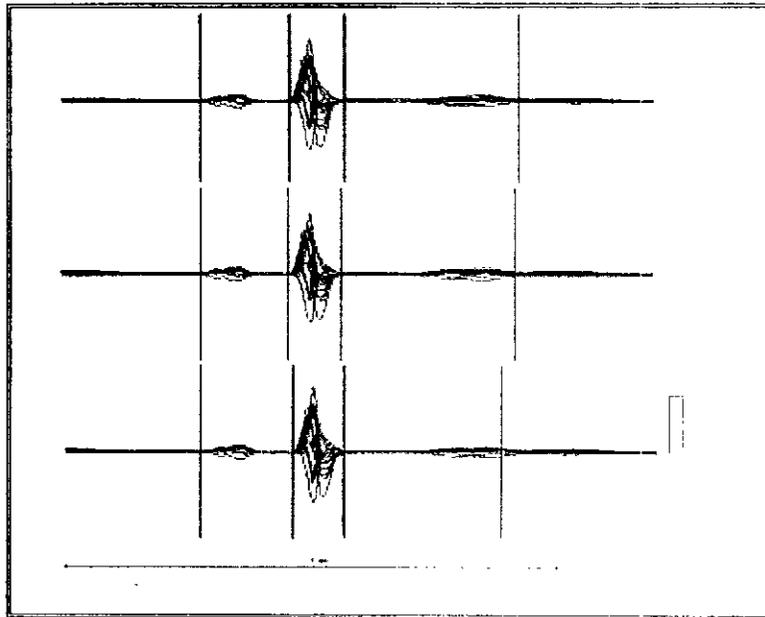


Figure 5. Median beats at 2 hours post-dosing in subject 414 (Study 905-CL-043).

No such problems appear with measurements of the end of the T wave in this subject's ECGs for the 1.5-hour or 3-hour post-dosing times.

In the case of subject 204, with a 70-ms increase in QTcF 24 hours after solifenacin 30 mg, there is a similar problem, again with the third sample, as shown in the figure below.

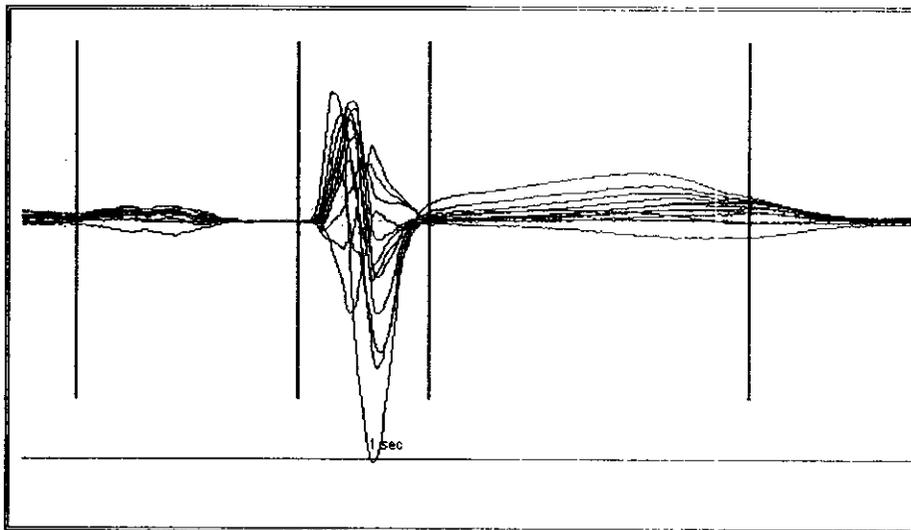


Figure 6. Single median beat 24 hours after dosing in subject 204 (Study 905-CL-043).

In the case of subject 104, there was a 64-ms increase in QTcF 0.5 h after a single oral administration of moxifloxacin 400 mg. There were no obvious problems with these records.

Overall, the quality of these data is adequate for the purpose for which they were intended. Although there were some differences in the intervals assessed by rhythm data and derived data, the measurements within each domain seemed to be consistent.

The study had few outlying values of QTcF. In one case the value was probably a spurious result of atypical preceding beats' RR intervals. In two other cases, there are no obvious recording issues, and the QT interval has probably been somewhat underestimated. Nevertheless, these outliers in single time points are unlikely to herald drug-related risk.

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Consultative Clinical Review

NDA: 21,518 (solifenacin)
Sponsor: Yamanouchi
Submission: Proposed study of QTc.

Review date: 5 January 2004

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Concur: Douglas Throckmorton, M.D., Division Director, HFD-110

Distribution: NDA 21-518

HFD-580/King/Benson/Shames

Background

Solifenacin was issued an Approvable letter on 17 October, for the treatment of overactive bladder. A key issue in the letter was the effect of solifenacin on QT. The sponsor previously outlined a study to address this issue, and the Division of Cardio-Renal Drug Products previously commented on this protocol (4 November 2003). The current submission is a complete protocol and the Division is again invited to comment.

Response

The Division of Cardio-Renal Drug Products has nothing to add to the comments made by Dr. Benson. In particular, the previously expressed concern about the moxifloxacin comparison appears to be adequately addressed in the proposed study.

The Division of Cardio-Renal Drug Products appreciates the opportunity to consult on this drug. DRUDP is welcome to contact DCRDP for further clarification or follow-up.

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Doug Throckmorton
1/5/04 02:51:55 PM
MEDICAL OFFICER



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21,518 (solifenacin)
Sponsor: Yamanouchi
Submission: Proposed study of QTc.

Review date: 4 November 2003

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Concur: Douglas Throckmorton, M.D., Division Director, HFD-110

Distribution: NDA 21-518

HFD-580/King/Benson/Shames

Background

Solifenacin was issued an Approvable letter on 17 October, for the treatment of overactive bladder. A key issue in the letter was the effect of solifenacin on QT, and the sponsor has outlined a study to address this issue. The Division of Cardio-Renal Drug Products is asked to comment on this protocol.

Response

The design of a study addressing QT effects is complicated by the long half-life of the parent compound and some uncertainties about what metabolites may be of concern. The sponsor has picked a dose to study that is probably near maximum tolerance for multiple dosing, even with titration, and this dose produces about the same plasma levels as would the highest to-be-marketed dose in the presence of metabolic inhibition.

The proposed study will utilize normal volunteers in the same age range as the target population. The study has several phases. Subjects will all receive single oral doses of moxifloxacin 400 mg, then open-label placebo for 3 days. The subjects will be randomized to placebo (N=10) or to a forced titration arm (N=40) receiving solifenacin 10 mg for 14 days, 20 mg for 5 days, and 30 mg for 14 days. Time-matched baseline measurements will be used. Multiple ECGs will be taken at each time point. Pharmacokinetic data will be obtained around the time of ECGs. Although no formal hypothesis is proposed, the sponsor will provide analyses of QTcF, QTci, and outlier analyses. The sponsor's power calculations predict 90% power to detect a 5 ms effect.

One problem with the proposed study is that the experimental setting of the moxifloxacin assay validation does not mimic the setting of the principal comparison. Assay validation will be all 50 subjects compared with their (previous day's?) baseline, while the later comparison is a 40-subject vs. 10-subject placebo- and relatively remote baseline-subtracted comparison. There is every reason to suspect that the latter has less power than the former. One way to address this problem would be to do the solifenacin vs. placebo comparison first and then re-randomize subjects (40/10) to placebo or moxifloxacin.

The sponsor should be encouraged to supply PK and QT datasets and annotated digital ECGs.

The Division of Cardio-Renal Drug Products appreciates the opportunity to consult on this drug. DRUDP is welcome to contact DCRDP for further clarification or follow-up.

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Norman Stockbridge
11/24/03 02:14:49 PM
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Doug Throckmorton
11/24/03 03:35:21 PM
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Date NDA Submitted: December 19, 2002
Date NDA Received: December 22, 2002
Review Completed: October 05, 2003
Review Finalized: October 16, 2003

Medical Officer's Original Review

Sponsor: Yamanouchi Pharma America, Inc.,
Mack Centre IV, S 61 Paramus Rd.
Paramus, NJ
[Mr. Rudolph W. Lucek at (201) 909-3041]

Drug Name:
Generic: Solifenacin Succinate
Proposed Trade: Vesicare®
Internal development: YM905
Chemical: (+)-(1*S*, 3'*R*)-quinuclidin-3-yl 1-phenyl-1,2,3,4-Tetrahydro-
isoquinoline-2-carboxylate monosuccinate
Empirical formula: C₂₃H₂₆N₂O₂·C₄H₆O₄

Pharmacologic category: M₃ muscarinic-receptor antagonist

Route of Administration: Oral

Dosage Form: tablet

Strength: 5 mg and 10 mg

Proposed Indications: /

Related IND Submission: IND 58,135 for the same indication

Related Documents: Major amendments received: 4-month safety updates on 04/28/2003

Guodong Fang, MD Medical Officer	_____
George Benson, MD Urology Team Leader	_____
Donna Griebel, MD Deputy Director, DRUDP	_____

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Executive Summary

1. RECOMMENDATIONS

1.1 Recommendations on Approvability

The reviewer recommends, from a clinical perspective, that Vesicare® 5 mg and 10 mg tablets receive an "approvable" action for the indication treatment of symptoms of "overactive bladder (OAB)." No significant safety concerns in addition to the recognized anticholinergic side effects were identified except for the QT issue. Insufficient data have been submitted to determine whether solifenacin has a clinically significant effect on prolongation of the QT interval. This reviewer believes that the solifenacin effect size on the QT interval needs to be clarified with an adequate, "thorough" QT study before the drug can be approved from a safety standpoint.

1.2 Recommendations on Postmarketing Studies and/or Risk Management Steps as Appropriate

The reviewer has no specific recommendations.

2. SUMMARY OF CLINICAL FINDINGS

2.1 Brief Overview of Clinical Program

Vesicare® contains 5 mg or 10 mg solifenacin succinate per tablet. The exact cause of bladder overactivity is unknown, but increased afferent activity, decreased inhibitory control, and increased sensitivity of the detrusor to efferent stimulation are some of the postulated etiologies. Activation of the muscarinic M₃ receptors that mediate contraction of the urinary bladder occurs through binding of acetylcholine to the receptor. Anticholinergic agents which have been approved to treat "overactive bladder" inhibit the binding of acetylcholine to the cholinergic receptor and thus suppress involuntary bladder contractions. Solifenacin (Vesicare®) succinate is a muscarinic antagonist with selectivity for M₃ receptors.

Overall data

The primary efficacy evaluation is based on four Phase 3 pivotal studies: two US studies (Study 905-CL-013 and 014) and two European studies (Study 905-CL-015 and 018) (described below).

The safety evaluation is based on the following completed and ongoing studies:

Completed studies:

- 13 US and European BA (bioavailability)/BE (bioequivalence) and clinical pharmacology (Phase 1) studies (#001, 002, 003, 004, 008, 009, 010, 011, 021, 022, 025, 028, 029)
- 4 US and European Phase 3 pivotal studies (#013, 014, 015, 018)
- 2 US and European Phase 2 studies (#005, 006)
- 2 Japanese studies (#007, 012)

Ongoing studies:

- 1 US Phase open-label extension study (#016)
- 1 European Phase 3 open-label study (#019)
- 2 Japanese studies (#023, 024)
- 2 Phase 1 studies (#026, 030)

Major efficacy study design: Each of the 4 major Phase 3 studies used a multicenter, randomized, double-blind, placebo-controlled, parallel group, fixed-dose design. In addition to a placebo control, one of the European Phase 3 studies (Study #015) also included an active control arm and both European studies (#015

and #018) had a 2-week placebo run-in period, while the 2 US studies had a 2-week washout period. Randomized treatment groups were placebo and solifenacin succinate 10 mg once daily (OD) in studies #013 and #014; placebo, solifenacin succinate 5 mg OD, solifenacin succinate 10 mg OD and tolterodine 2 mg twice daily (BID) in study #015; and placebo, solifenacin succinate 5 mg OD and solifenacin succinate 10 mg OD in study #018. Treatment duration in each of the major Phase 3 studies was 12 weeks. The primary efficacy endpoint was the mean change from baseline in the mean number of micturitions per 24 hrs at endpoint. Secondary endpoints included the mean number of incontinence, urgency, and nocturia episodes per 24 hrs and volume of urine voided per micturition.

Table 1 Dosage regimen in Phase 3 major studies

Study Drug	013/014		015				018		
	Placebo	YM905 10 mg	Placebo	YM905 5 mg	YM905 10 mg	Tolter 2 mg bid	Placebo	YM905 5 mg	YM905 10 mg
Placebo tablet	1		2 A.M.	1 A.M.	1 A.M.	2 A.M.	1		
YM 905 10 mg tablet		1			1 A.M.				1
YM905 5 mg tablet				1 A.M.				1	
Placebo capsule			1 A.M. 1 P.M.	1 AM 1 P.M.	1 A.M. 1 P.M.				
Tolterodine capsule						1 A.M. 1 P.M.			

In studies #013 and #014 patients received solifenacin 10 mg (1 tablet) OD and 1 placebo tablet OD. In study #015, patients randomized to solifenacin received solifenacin 5 mg (1 tablet), or 10 mg (1 tablet), 1 matched placebo tablet and 1 placebo capsule in the morning and 1 placebo capsule in the evening. Patients randomized to tolterodine received 1 tolterodine 2 mg capsule and 2 placebo tablets in the morning and 1 tolterodine 2 mg capsule in the evening. To maintain the blind, placebo patients received 2 placebo tablets and 1 placebo capsule in the morning and 1 placebo capsule in the evening.

Patients who completed each of these double-blind studies had an option to participate in an open-label extension study and receive solifenacin for 1 year to further evaluate its safety. The ongoing results of the US Phase 3 open-label extension study (#016) and the European Phase 3 open-label extension study (#019) were reported to the Division on April 25, 2003, and in the NDA safety update dated April 28, 2003.

2.2 Efficacy

The efficacy of Vesicare® was evaluated in 4 placebo-controlled, parallel-arm, randomized, multicenter 12-week, Phase 3 trials with an active-comparator arm in one of these 4 trials. The efficacy parameters were the changes in overactive bladder related symptoms.

- Primary endpoint: the mean change from baseline in the mean number of micturitions per 24 hrs at endpoint.
- Secondary endpoints: the mean change from baseline in the number of incontinence, urgency, and nocturia episodes per 24 hrs and volume of urine voided per micturition.

Overall Vesicare®, at doses of 5 mg and 10 mg daily reduced the mean number of micturitions per 24 hrs in the majority of patients studied with overactive bladder in all 4 pivotal studies (Table 2).

Reviewer's comment: The primary endpoint was satisfied in all major Phase 3 studies, and most of the secondary endpoints were satisfied in all or in the majority of Phase 3 studies.

Table 2 Comparison with placebo in MEAN CHANGE from baseline to endpoint for primary and secondary efficacy parameters in US and European Phase 3 studies

Efficacy Parameter	Study 015			Study 018		Study 013	Study 014	Studies 015, 018, 013, 014	
	YM905		Tolter	YM905		YM905	YM905	YM905	
	5 mg	10 mg	4 mg	5 mg	10 mg	10 mg	10 mg	5 mg	10 mg
Primary endpoint									
Micturition/24 h	-1.02	-1.39	-0.73	-0.87	-1.25	-1.37	-1.20	-0.94	-1.31
p value	0.0003	0.0001	0.0145	0.0018	0.0001	<0.001	<0.001	<0.001	<0.001
Secondary endpoints									
Incontinence/24 h	-0.68	-0.75	-0.59	-0.66	-0.48	-0.80	-0.74	-0.73	-0.72
p value	0.0080	0.0038	NS	NS	NS	<0.001	<0.001	<0.001	<0.001
Urgency/24 h	-1.29	-1.51	-0.64	-0.72	-0.94	-1.73	-1.74	-1.12	-1.48
p value	0.0001	0.0001	NS	0.003	0.002	<0.001	<0.001	<0.001	<0.001
Volume voided per micturition (mL)	+25.31	+32.11	+17.11	+20.27	+25.33	+43.70	+33.20	25.34	+33.85
p value	0.0001	0.0001	0.0001	0.0001	0.0001	<0.001	<0.001	<0.001	<0.001
Nocturia/24 h	-0.17	-0.11	-0.12	-0.10	-0.24	-0.19	-0.08	-0.13	-0.15
p value	NS	NS	NS	NS	0.036	NS	NS	0.025	<0.001

Vesicare®, at doses of 5 mg and 10 mg daily, reduced the mean number of incontinence episodes per 24 hrs in 3 of the 4 pivotal studies (Table 2).

2.3 Safety

2.3.1 Total drug exposure

The population of OAB patients studied was predominantly female, predominantly Caucasian, and most patients were under 65 years of age. Overall, 2,621 patients (555 men and 2,066 women) with OAB were exposed to solifenacin, administered once daily (qd), in the completed US and European (EU) Phase 3 pivotal studies, the US and European Phase 2 studies, and the ongoing US Phase 3 open-label extension study. Of these 2,621 patients, 667 (146 males and 521 females) were exposed to 5 mg, 1,768 (353 males and 1,415 females) were exposed to 10 mg, and the remainder were exposed to either 2.5 mg or 20 mg. A total of 937 subjects and patients were ≥65 years and 290 were ≥75 years. Including the 12-week treatment period in the Phase 3 pivotal studies and the ongoing open-label extension studies as of the data cutoff of June 1, 2002, a total of 718 patients were exposed to solifenacin for at least 6 months. Of these 718 patients, 308 had completed at least 1 year of treatment with solifenacin as of the data cutoff of June 1, 2002. The database also includes 1,307 OAB patients treated with placebo and 300 treated with tolterodine 2 mg twice daily (bid). In addition, 423 subjects received solifenacin, 85 received placebo, and 6 received oxybutynin 5 mg in completed US and European bioavailability/bioequivalence and clinical pharmacology studies and in completed Japanese studies. Patients with the following conditions were excluded from the 4 Phase 3 pivotal studies and the long-term open-label extensions: neurological detrusor overactivity, Grade III/IV prolapse with cystocele, urinary tract infection, chronic inflammation (eg, interstitial cystitis), bladder stones, pelvic radiation, malignancy of pelvic organs, diabetic neuropathy, clinically significant unstable endocrine, hepatic, renal, immunologic or lung disease, or malignancy other than nonmelanomatous skin cancer, an abnormal 12-lead ECG of clinical concern, insulin-dependent diabetes mellitus with concurrent hypotonic bladder, history of addiction to drug/alcohol in past 5 years, drugs/alcohol abuse in last 1 year, or abnormal laboratory values of clinical significance.

Reviewer's comment: This reviewer considers that the drug exposure for safety evaluation during the clinical studies of solifenacin is adequate to characterize and quantify the safety profile of the drug.

2.3.2 Death and other serious adverse events (SAEs)

Death: There were a total of five deaths in the Phase 3 pivotal studies: two in placebo-treated patients (one died of hemopericardium and one of thromboembolism), 2 were in patients treated with solifenacin 10 mg (acute heart failure in 1 patient and hypertensive crisis in the other), and 1 death was in a tolterodine-treated patient (cerebral atherosclerosis). Six additional deaths were reported in the ongoing open-label extension studies, two in Study 905-CL-016 (open-label extension to the US Phase 3 studies) and four in Study 905-CL-019 (the open-label extension to the EU Phase 3 studies). In Study 016, one patient died of chronic obstructive pulmonary disease and the other died of subdural hematoma. Of the four patients who died in Study 019, one patient died of a ruptured aortic aneurysm; another died of retroperitoneal hemorrhage and hypovolemic shock, resulting in multiorgan failure during hip-replacement surgery; the third died of a malignant brain neoplasm, and the final patient died of bladder cancer and cardiac insufficiency. None of the deaths was considered by the investigator to be related to study medication.

Serious treatment-emergent adverse events: In both the US and European trials, fewer than 3% of patients in any solifenacin treatment group experienced an SAE. SAEs were reported in 2.4% of patients treated with solifenacin 10 mg in Europe and the US combined, and in 2.2% of patients treated with solifenacin 5 mg, which was only investigated in Europe. A number of the SAEs were complications or exacerbations of expected antimuscarinic side effects and included fecal impaction and intestinal obstruction. Among the other SAEs were reports of dizziness, syncope, and tachyarrhythmia, which, when reviewed in conjunction with other clinical and nonclinical data, were concluded not to be attributable to drug-induced prolongation of cardiac repolarization. After eliminating the serious but expected antimuscarinic adverse events and setting aside any SAEs that could have potentially been associated with prolongation of QTc interval, the remaining SAEs across all clinical studies were examined and it was concluded that there was no evidence of solifenacin-induced drug toxicity.

For adverse events that would be unusual in the absence of drug therapy (ie, liver failure, agranulocytosis, significant hemolytic anemia, thrombocytopenia, rhabdomyolysis, idiopathic thrombocytopenic purpura, intussusception, acute renal failure), there was one patient with thrombocytopenia in a solifenacin 5 mg patient (#15-10687) in Study 905-CL-015. The patient had a normal platelet count at screening of $184 \times 10^9/L$ which dropped to $28 \times 10^9/L$ at end of study (92 days on solifenacin). The patient went on to the extension study (905-CL-019) at the 5 mg dose. In the course of Study 019, platelet counts returned to normal ($188 \times 10^9/L$, $183 \times 10^9/L$, and $190 \times 10^9/L$ at 3 different visits during Study 019). No treatment was required. The thrombocytopenia was judged to be moderate in severity and possibly related to the study medication.

2.3.3 Common adverse events

In both the US and EU Phase 3 pivotal studies, the incidence of treatment emergent adverse events (TEAEs) were reported (in $\geq 1.5\%$ patients treated with solifenacin 5 mg or 10 mg qd and at a higher rate with solifenacin than with placebo) as shown in the following table. The majority of TEAEs reported in all treatment groups were considered mild or moderate in severity. The types of TEAEs were similar in the US and EU trials and were typical of antimuscarinic agents. The system organ class (SOC) for which the largest percentage of patients reported TEAEs was gastrointestinal disorders, and within this SOC, the most commonly reported TEAEs were dry mouth and constipation, the incidence of each tending to increase with the dose. The incidence of blurred vision was low ($< 5\%$ overall), but was consistently higher in the solifenacin groups than in the placebo group, and also appeared to increase with the dose.

Kaplan-Meier plots of the time to first occurrence of the most common antimuscarinic effects (eg, dry mouth, constipation, blurred vision) in the Phase 3 clinical studies indicated that these events tended to occur within the first few days or weeks of starting treatment and were dose-related. The rates of discontinuation due to these antimuscarinic events were low, generally <1.0% and the highest 2.0%.

Table 3 Summary (% of patients) of common TEAEs occurring in patients in combined 4 Phase 3 pivotal studies (≥1.5% of patients)

System organ class MedSRA Preferred Term	Treatment		
	Placebo (N=1216)	Solifenacin succinate	
		5 mg (N=578)	10 mg (N=1233)
Gastrointestinal disorders			
Dry mouth	4.2	10.9	27.6
Constipation	2.9	5.4	13.4
Nausea	2.0	1.7	3.3
Dyspepsia	1.0	1.4	3.9
Abdominal pain upper	1.0	1.9	1.2
Infections & infestations			
Urinary tract infection NOS	2.8	2.8	4.8
Influenza	1.3	2.2	0.9
Eye disorders			
Vision blurred	1.8	3.8	4.8
Dry eyes NOS	0.6	0.3	1.6
General disorders & Administration site conditions			
Fatigue	1.1	1.0	2.1

NOS = Not otherwise specified

2.3.4 Discontinuation

Discontinuation: Across all clinical studies in patients with OAB, 45 patients discontinued treatment because of constipation. Of these, 8 patients (2 for placebo, 1 for solifenacin 5 mg, 4 for solifenacin succinate 10 mg, and 1 for tolterodine) required other therapy for constipation. In 3 patients, constipation resulted in hospitalization because of fecal impaction. Urinary retention was seen in 0.6% of patients on placebo, 0% on solifenacin 5 mg, but 1.5 % on solifenacin 10 mg. Nine patients on solifenacin 10 mg withdrew from the study because of urinary retention. Five patients reported urinary retention that required other therapy: 4 with solifenacin 10 mg and 1 with solifenacin 20 mg. In addition, in the dose-rising QTc study, at the 30 mg dose level, one patient required hospitalization and catheterization for urinary retention.

Table 4 % of patients discontinuing from treatment because of adverse events in combined 4 Phase 3 pivotal studies

MedDRA Preferred term	Treatment			
	Placebo	Solifenacin		Tolterodine 2 mg bid
		5 mg	10 mg	
Dry mouth	0.2	0.5	2.0	0.8
Constipation	0.2	0.2	1.6	0.4
Nausea	0.5	0.2	0.9	0.4
Blurred vision	0.2	0.2	0.6	0

2.3.5 Potential effects on ECG and QTc interval

The electrocardiographic observations from all clinical studies, with special attention to effects on QTc and a specially designed dose-escalation pharmacokinetic study with focus on change of QTc (CL-022) but without an active control, were reviewed, as were all relevant *in vitro* and *in vivo* nonclinical studies. In the dose-escalation study (CL-022), doses up to 50 mg once daily were administered to men, pre- and postmenopausal women.

Table 5 Mean Change in baseline-corrected QTc (Fridericia) and Baseline- and placebo- corrected QTc (Fridericia) by Treatment Group

Treatment Group	Mean Change in Heart Rate (bpm)	Mean Change in baseline-corrected QTc (msec) ^a	Mean Change in baseline- and placebo-corrected QTc (msec) ^a
Placebo (N=540)	-0.34	0.89 (-0.95, 2.73)	-
10 mg (N=660)	-1.09	0.26 (-1.36, 1.87)	-1.44 (-3.12, 0.25)
20 mg (N=641)	0.33	3.46 (1.76, 5.15)	2.09 (0.35, 3.82)
30 mg (N=616)	1.70	0.77 (-1.03, 2.57)	0.31 (-1.52, 2.14)
40 mg (N=462)	2.42	-3.82 (-5.90, -1.74)	-5.39 (-7.65, -3.12)
50 mg (N=125)	1.52	-8.46 (-12.71, -4.21)	-12.41 (-16.88, -7.94)

^a Results reported as mean (95% confidence interval)

The results showed:

- The maximum mean change in baseline-corrected QTc (msec) (Fridericia) of 3.46 msec was detected at the dose of 20 mg
- There was no significant relationship between either plasma concentration or dose of solifenacin and baseline-corrected QTc change.
- There were only 16 patients in 50 mg group and all withdrew from the study prematurely (The 50 mg dose was discontinued because of adverse events).

Reviewer's comment: Study (CL-022) did not include an active control or a placebo control.

The only ECG observations of note in all of the clinical trials with solifenacin were those related to QTc change from baseline in the 4 Phase 3 pivotal studies in which increases in QTc of 1.2 to 1.9 msec at 5 mg solifenacin and 2.8 to 4.9 msec at 10 mg were observed. These changes were statistically significant in 3 of the 4 studies.

2.3.6 Hepatic effects:

Clinical laboratory values for alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (ALKP), and gamma-glutamyl transferase (γ -GGT) were examined to investigate the potential effects of solifenacin on hepatic function. The results showed that the proportions of patients with abnormalities for these 5 analytes exceeding 3 times the upper limit of normal (ULN) or exceeding 10x ULN were similar for placebo and solifenacin groups. In addition, no patient in the clinical database had AST 3xULN, and abnormal bilirubin or had ALT 3xULN and abnormal bilirubin. There were also no reports of jaundice in the clinical study database.

Reviewer's note: There is a case report from Japanese study CL-038. She was a 69-year-old woman who received 5 mg solifenacin once daily. Six months after the start of solifenacin treatment she had to interrupt her study drug because of abnormal values of her liver function test ($>3xULN$ for ALT and ALKP, $>5xULN$ for AST and γ -GGT). She had also started taking a herbal medicine later in the study. She became unconsciousness and was admitted to the hospital with a diagnosis of acute interstitial pneumonia and hypoxemia. Her medical status went into remission 4 days after hospitalization (she received steroid therapy).

but her liver function tests showed further deterioration. Her discharge diagnosis was motor speech disorder due to cerebral infarction, and the relationship between interstitial pneumonia and cerebral infarction could not be completely rule out. The investigator judged the event was not related to the study medication solifenacin based on the results of a drug lymphocyte stimulation test (DLST):

Results of DLST	
Herb medicine Saibokutou	solifenacin
Negative	N/A
Positive	Negative

Reviewer's comment: The specificity of the DLST and its clinical impact are unknown to this reviewer.

2.4 Dosing, Regimen and Administration

Dose determination: The placebo-controlled Phase 2 studies in patients with OAB evaluated solifenacin at doses of 2.5 mg, 5 mg, 10 mg, and 20 mg, each administered once daily for 4 weeks. Based on comparison with placebo, the 2.5 mg dose showed little pharmacologic effect. Both the 5 mg and 10 mg doses appeared better tolerated than the 20 mg dose, which had the highest rate and severity of adverse events overall, and the highest rate of antimuscarinic side effects, particularly dry mouth.

Reviewer's comment: This reviewer considers the dosage selection of 5 mg and 10 mg reasonable. The incidence of AEs with solifenacin 10 mg, although higher than with 5 mg, is acceptable.

The recommended starting dose is 5 mg with up or down titration to 10 mg.

Reviewer's comment: The reviewer believes that, based on efficacy and safety, the proposed doses are acceptable.

2.5 Drug-drug interactions

Solifenacin is metabolized primarily by the CYP 3A4 enzyme system in the liver with minor contributions from CYP 2C19. The sponsor conducted drug interaction studies to determine PK drug interactions with ketoconazole (both 200 mg and 400 mg dose QD), digoxin, combination oral contraceptive and a PK/PD interaction study with warfarin. The only result of consequence was that there is a 3 and 1.5 fold increase in solifenacin AUC and C_{max} respectively, when solifenacin is given in combination with 400 mg QD ketoconazole. Hence, a 10 mg solifenacin dose would appear to be a 30 mg dose. Based on the tolerability profile, it is recommended not to exceed a 5 mg dose of solifenacin when used in combination with ketoconazole.

2.6 Special Populations

Solifenacin is indicated for the treatment of men and women with overactive bladder.

Age, Gender, and Race/ethnicity:

TEAEs in the Phase 3 pivotal studies were reviewed by age (<65 years, > 65years, ≥75 years), by gender (male, female), and by race (Caucasian, Black, Hispanic). No clinically important differences in the adverse event profile of solifenacin succinate were found by age, by gender, or by race for the categories examined.

The vast majority of patients in both the solifenacin and placebo treatment groups were Caucasian. The number of patients in racial sub-groups other than Caucasians was too small to detect any meaningful differences in the rates of adverse events in solifenacin treated patients across racial subgroups.

The pharmacokinetics of solifenacin is not significantly affected by age, gender, or by race for the categories examined.

Thus, based on both pharmacokinetic studies in healthy subjects and clinical trial experience in patients with OAB, it may be concluded that no specific labeling statements or dosing adjustments based on age, gender, or race are necessary for safe use of solifenacin succinate.

Pediatric population: solifenacin is indicated only for men and women with OAB. No study has been conducted in children. The sponsor has requested _____, a pediatric waiver.

Renal impairment: The extensive metabolism of solifenacin and the subsequent excretion of these metabolites and solifenacin itself by the kidneys prompted an investigation of the drug in patients with renal impairment. The data indicate that dosage reduction is not required in patients with mild to moderate renal impairment. Doses of solifenacin over 5 mg are not recommended in patients with severe renal insufficiency.

Reviewer's comment: This reviewer notifies that solifenacin has not been studied in patients on dialysis.

Hepatic impairment: Since solifenacin is extensively metabolized by CYP3A4, it is expected that its clearance will be reduced and exposure increased in patients with hepatic impairment. Accordingly, a clinical pharmacology study (Study 905-CL-026) was conducted in patients with moderate hepatic impairment administered 10 mg solifenacin to assess the pharmacokinetics of solifenacin and its metabolites. The results of Study 905-CL-026 demonstrated that solifenacin can be safely administered to patients with moderate hepatic impairment, but the dosage should not exceed 5 mg once daily in these patients.

As with other antimuscarinic drugs, solifenacin should be contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma.

APPEARS THIS WAY
ON ORIGINAL

Clinical Review

1. Introduction and Background

1.1 Proposed Drug

Solifenacin succinate is a muscarinic M₃ receptor antagonist. There are two other antimuscarinic drugs currently on the market (oxybutynin and tolterodine,) indicated for the treatment of overactive bladder (OAB). The sponsor requests approval for 2 doses (5 and 10 mg). The recommended starting dose of solifenacin is 5 mg which may be increased to 10 mg based on efficacy and tolerability. The sponsor has requested a pediatric waiver.

1.2 Milestones in Product Development

The milestones in the clinical program of drug development included:

December 15, 1998: Pre-IND meeting

April 2, 1999: IND filed with assigned # 58,135

September 19, 2000: End of Phase 2 meeting

November 8, 2000: Teleconference for the design of Phase 3 studies

July 5, 2001: Protocol for QTc study submitted (Study 905-CL-022)

- Provide evidence to rule out QT prolongation due to solifenacin
- Characterize the solifenacin plasma concentration relationship for QT interval prolongation
- Evaluate the degree of QT prolongation at plasma concentrations following maximal potential interaction between solifenacin and CYP3A4 inhibitors

July 1, 2002: Pre-NDA Meeting with decision that the efficacy claims would be based on the 2 European and 2 US pivotal Phase 3 studies and the primary safety profile would be based on these 4 pivotal Phase 3 studies, combined with the Phase 2 European and US studies; the support for the efficacy and safety of the 5 mg dose would come from the 2 European pivotal studies.

December 22, 2002: NDA was submitted with assigned # 21,518

April 25, 2003: 4-month safety update was submitted including study report for the hepatic impairment study

July 15, 2003: ECG results of open-label, long-term safety study 905-CL-022 was submitted

CMC issues -- submissions on May 8, July 18, July 24, 2003

Pharmacology/toxicology issues -- submission on August 25, 2003

1.3 Foreign Market History

Since the submission of the NDA, solifenacin (5 and 10 mg) has not been approved by any foreign countries.

1.4 Important Issues with Pharmacologically Related Agents

Two other pharmacologically related agents have been approved for the treatment of OAB:

- Oxybutynin
- Tolterodine

The common antimuscarinic side effects associated with these drugs are dry mouth, blurred vision, nausea, and constipation.

2. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, and Statistics

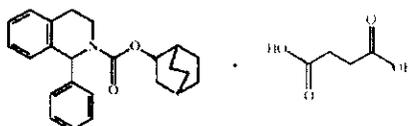
There is no unresolved chemistry, microbiology, pre-clinical pharmacology/toxicology, or statistical issues (see each discipline's complete review).

CAS number: None

Molecular Weight: 480.56

Molecular Formula: C₂₃H₂₆N₂O₂ · C₄H₆O₄

Structural Formula:



3. Human Pharmacokinetics and Pharmacodynamics

The pharmacokinetics of solifenacin were demonstrated to be linear over the therapeutic dose range and above. The **population pharmacokinetic analysis** demonstrated that the PK behavior of solifenacin in patients with OAB is similar to the PK in healthy subjects. Solifenacin is slowly and extensively absorbed after oral administration with a mean absolute bioavailability of 88%. Average T_{max} values ranged between 3 and 8 h with a mean of about 5hrs. The slow absorption results in an almost constant plasma concentration over a period of several hours. Plasma protein binding of solifenacin is approximately 98% with most of this binding being attributable to α₁-acid-glycoprotein. The mean volume of distribution (V_{ss}) is approximately 599 L, clearance is 9.4 L/h and elimination half-life is 52.4 h. Solifenacin undergoes extensive biotransformation. In plasma, unchanged parent compound accounts for about 70% of dose-related material. Solifenacin and its metabolites are excreted in urine and feces, which account for approximately 70% and 23% of dose-related material respectively. Only 11% of the dose is excreted unchanged in urine. Of the 4 metabolites of solifenacin (M2, M3, M4, and M5), only M3 (4R-hydroxy solifenacin) possesses pharmacological activity. Solifenacin and its metabolites are 92.7 to 96.1% bound to plasma proteins. The C_{max} after a single dose of 10 mg varied between 11.8±1.6 and 15.8±5.9 ng/mL, and after multiple dosing C_{max} varied between 40.6±8.5 and 63.7±24.7 ng/mL. Due to the long T_{1/2}, drug accumulation was observed: the AUC_{0-inf} after a single dose of 10 mg ranged between 765±272 and 1210±474 ng·h/mL. The AUC₀₋₂₄ after multiple dosing produced a similar range but with the majority of values closer to the upper end of the range. On repeated dosing with solifenacin, steady state is achieved after approximately 10 days in the young and 12 days in the elderly.

Solifenacin is metabolized primarily by oxidation of cytochrome P450 oxidase enzyme CYP3A4. Other P450 isozymes, in particular 2C19, as well as 3A5, 2C8, 2D6, and 1A1 have the ability to participate in the metabolism but to a much lesser extent.

Drug-drug interactions: Inhibition of CYP3A4 by concomitant ingestion of ketoconazole doubled exposure to solifenacin. Steady state concentrations of solifenacin did not affect the PK of single doses of R- or S-warfarin, or their anticoagulant activity. No effect of solifenacin on the PK of ethinyl estradiol or levonorgestrel was observed. Solifenacin was shown not to affect plasma concentrations of digoxin in healthy volunteers at steady state of both drugs.

Effect of impaired renal function: An increased exposure in patients with severe renal impairment was observed after single 10 mg doses of solifenacin, implying that dosage should be reduced in such patients.

Effect of hepatic impairment: An increase in exposure was observed in patients with moderate hepatic impairment. Solifenacin has not been evaluated in patients with severe hepatic impairment. Patients with severe hepatic impairment can be expected to show reduced clearance and increased exposure to solifenacin. Until further data are available, solifenacin should — in such patients.

Effect of age: PK data from the multiple dose escalation study in young subjects were compared with those from the study in the elderly. Another comparison was from study 905-CL-029 in which PKs at steady state were compared in 24 young with 23 elderly male and female healthy subjects at doses of 5 mg and 10 mg daily. Mean C_{max} and AUC_{0-24h} were proportional to dose and were slightly higher in the elderly (1.16 and 1.2 fold, respectively) than the young, the difference for AUC being statistically significant. In the elderly, mean T_{max} was about an hour later. Mean $t_{1/2}$ was also somewhat greater in the elderly with mean values ranging from 51 to 59 h in the young and 65 to 75 h in the elderly. The magnitude of the differences between young and elderly are not of clinical importance and there is no reason to adjust dosage of solifenacin dependent on age.

Other issues: Several other significant PK/PD interactions are discussed in the safety section of this review (section 7) and in the Review from Clinical Pharmacology reviewer.

Cardiac depolarization: Study 905 CL-022

Ketoconazole (200 mg, 400 mg) interaction: Studies CL-010 and CL-036

4. Description of Clinical Data and Sources

The following materials were reviewed:

- 1) Phase 3 studies 905 CL-013, 014, 015, and 018
- 2) Integrated safety summary
- 3) Integrated efficacy summary
- 4) 4-Month safety update
- 5) QTc prolongation study CL-022

4.1 Tables listing Clinical Trials

In support of NDA 21518, the sponsor submitted, in the original NDA, the results of 4 pivotal Phase 3 efficacy studies (Studies CL-013 and 014 in the US, Studies CL-015 and 018 in Europe). The intent-to-treat population in these 4 trials combined was 2400. These trials are outlined in Table 3.

In addition, the sponsor submitted results of 2 Phase 2 studies (CL-005 and 006). Efficacy study CL-023 was conducted in Japan. The NDA also included reports from two completed biopharmaceutical studies (CL-003, 009), six human pharmacokinetic (PK) studies (CL-001, 002, 007, 008, 012, 022), four intrinsic factor PK studies (CL-004, 021, 026, 029), four extrinsic factor PK studies (CL-010, 011, 025, 028), and interim reports from three ongoing studies [PK (CL-024), biopharmaceutical (CL-030), and efficacy (CL-023)].

Updated safety data include open-label, long-term safety studies in the US (CL-016) and Europe (CL-019, partial results). Through an amendment the sponsor further submitted results from study CL-019 with ECG data and results from a study of drug interaction (CL-036).

Overall, solifenacin was administered to 2,172 patients with OAB (Phase 3 and Phase 2b trials). The mean duration of treatment for the Phase 3 studies was between 80 and 82 days with a median of 84 days.

Table 6 Major Efficacy Trials

Study #	Study Design	Test Product & Dose	Number in SAF on YM 905	Mean age (range)	Sex (SAF/FAS)	Patients Diagnosis	Treat. Duration
905-CL-013 (US) pivotal	Phase 3, rando. DB., Placebo contr. parallel	YM905: 10 mg Placebo	Total 672/YM 340: <65=232, ≥65=108; ≥75=38	58 (18-88)	123 M 549 F	Patients with OAB	12 wks
905-CL-014 (US) pivotal	Phase 3, rando. DB., Placebo contr. parallel	YM905: 10 mg Placebo	Total 634/YM 318: <65=184; ≥65=134; ≥75=49	60 (22-88)	114 M 520 F	Patients with OAB	12 wks
905-CL-015 (EU) pivotal	Phase 3, rando. Placebo & active contr., DB., parallel	YM 5, 10 mg, Tolter: 2 mg bid Placebo	Total 1077/ YM 5 mg 279 YM 10 mg 268	58 (19-85)	268 M 809 F	Patients with OAB	12 wks
905-CL-018 (EU) pivotal	Phase 3, rando. DB., Placebo contr. parallel	YM 5, 10 mg, Placebo	Total 907 / YM: 606	56 (18-85)	163 M 744 F	Patients with OAB	12 wks
905-CL-005 (EU) dose-response	Phase 2, rando. Placebo & active contr., DB., parallel	YM 2.5, 5, 10, 20 mg, placebo Tolter 2 mg bid	Total 225 / YM 150	57 (21-83)	89 M 136 F	Pts. With detrusor instability	4 wks
905-CL-006 (US) dose-response	Phase 2, rando. DB., Placebo contr. parallel	YM 2.5, 5, 10, 20 mg, placebo	Total 264 / YM 211	60 (30-86)	58 M 203 F	Patients with OAB	4 wks

4.2 Post-marketing Experience

None.

4.3 Literature review

The references about the effects of antimuscarinic agents on OAB were reviewed.

5. Clinical Review Methods

5.1 Conduct of Review

The NDA application was entirely electronically submitted. The following studies were reviewed in detail:

- 905-CL-013 (Phase 3 in US) (see Appendix A)
- 905-CL-014 (Phase 3 in US) (see Appendix B)
- 905-CL-015 (Phase 3 in EU) (see Appendix C)
- 905-CL-018 (Phase 3 in EU) (see Appendix D)

Other trials were reviewed in less depth and not included in the appendices:

- 905-CL-005 (Phase 2 in EU)
- 905-CL-006 (Phase 2 in US)

5.2 Overview of Methods Used to Evaluate Data Quality and Integrity

DSI inspections were performed at 6 clinical sites (3 in the US and 3 in Europe) and the data submitted appear acceptable.

5.3 Financial Disclosure

Financial disclosure information was submitted and is acceptable.

6. Integrated Review of Efficacy

6.1 Efficacy Conclusions

In the opinion of this reviewer, the 5 and 10 mg doses of solifenacin are effective for the "treatment of over active bladder." The sponsor proposes to begin patients on the 5 mg dose and this reviewer agrees with this proposal.

6.2 Approach to Review of Efficacy

In this NDA review, four major pivotal Phase 3 efficacy trials (C1-013, 014, 015, and 018) were reviewed in detail (see Appendices A, B, C, and D of the review). Trials CL-005 and 006 were also reviewed.

6.3 Review of Trials

- Trial 905-CL-013 and 014: to assess the efficacy and safety of solifenacin (YM905) in the treatment of patients with OAB in the US
- Trial 905-CL-015 and 018: to assess the efficacy and safety of solifenacin (YM905) in the treatment of patients with OAB in Europe, Africa, Australia, and New Zealand.
- Trial 905-CL-005: to assess dose-response of solifenacin (YM905) in the treatment of patients with detrusor instability in Europe, Africa, Australia, and New Zealand.
- Trial 905-CL-006: to assess dose-response of solifenacin (YM905) in the treatment of patients with OAB in the US

6.3.1 Evaluations/Endpoints

The primary efficacy endpoint for all 4 pivotal efficacy trials was identical. Studies 905-CL-013 and 014 are identical 12-wk placebo-controlled studies conducted in the US. Studies 905-CL-015 and 018 are 12-wk placebo controlled studies, one with an active control arm (tolterodine); both were conducted by Yamanouchi Europe. The inclusion/exclusion criteria for entry into the 4 studies were similar.

The primary efficacy endpoint was the mean change from baseline to endpoint in number of micturations/24h. Micturition was defined as any voiding episode recorded by the patient in the 3-day diary as either "urinated" with or without "incontinence".

The secondary efficacy endpoints were:

- 1) Mean change from baseline to endpoint in number of incontinence episodes/24 h
- 2) Mean change from baseline to endpoint in number of urgency episodes/24h
- 3) Mean volume voided/micturition
- 4) Mean change from baseline to endpoint in number of nocturnal voids/24h
- 5) Mean change from baseline to endpoint in number of nocturia episodes/24h

*Nocturia : A micturition that wakes the patient from sleep between the time the patient went to bed and the time the patient got up the next morning, i.e., any voiding episode recorded by the patient onto a 3-day diary between the time the patient went to bed and the time the patient got up the next morning as "urinated" with or without "incontinence" and where sleep was interrupted. Pure incontinence episodes without voluntary voiding will not be included

*Nocturnal void: Micturition occurring between the time the patient goes to bed and the time patient get up the next morning.

Reviewer's comment: These primary endpoint and secondary endpoints are currently accepted as the endpoints for all studies involving treatment of OAB.

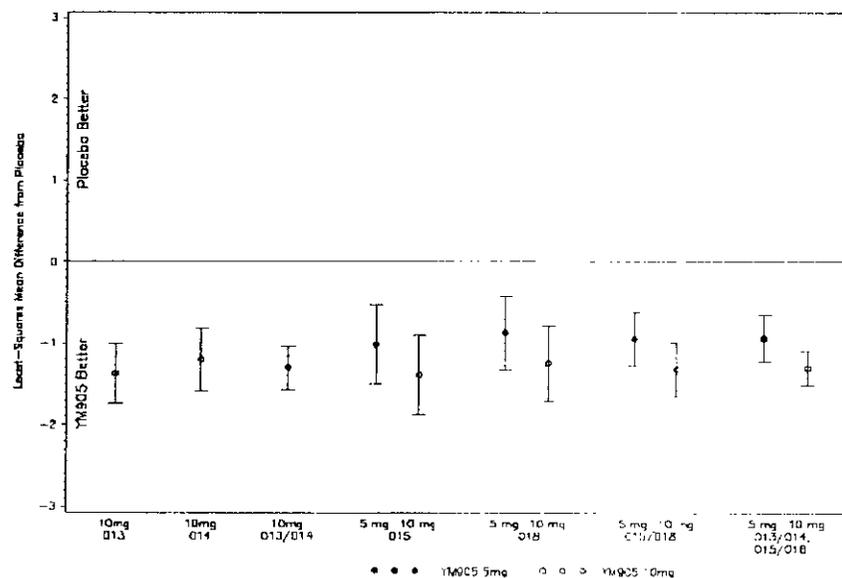
6.3.2 Results

The results of the **primary efficacy** analyses of the 4 major Phase 3 trials are shown in the following table.

Table 7 Mean change from baseline to endpoint in mean number of micturitions/24 h: pivotal Phase 3 studies

Study	Treatment Group	Number of Micturitions/24 h (Mean±SE)					p-value	Bonferroni-Holm adjusted p value
		n	Baseline	Change from baseline to endpoint	Model-based Estimate of Mean Difference from Placebo (95% CI)			
013	Placebo	309	11.5±0.18	-1.5±0.15	-1.37 (-1.74, -1.01)	<0.001	N/A	
	YM905 10 mg	306	11.7±0.18	-3.0±0.15				
014	Placebo	295	11.8±0.18	-1.3±0.16	1.20 (-1.59, -0.81)	<0.001	N/A	
	YM905 10 mg	298	11.5±0.18	-2.4±0.15				
013/014	Placebo	604	11.7±0.13	-1.4±0.11	-1.30 (-1.56, -1.03)	<0.001	N/A	
	YM905 10 mg	604	11.6±0.12	-2.7±0.11				
015	Placebo	253	12.2±0.26	-1.2±0.21	-1.02 (-1.50, -0.53)	<0.001	<0.001	
	YM905 5 mg	266	12.1±0.24	-2.2±0.18				
	YM905 10 mg	264	12.3±0.24	-2.6±0.20				
	Tolter 4 mg	250	12.1±0.22	-1.9±0.19				
018	Placebo	281	12.3±0.23	-1.7±0.19	-0.87 (-1.33, -0.42)	<0.001	<0.001	
	YM905 5 mg	286	12.1±0.23	-2.4±0.17				
	YM905 10 mg	290	12.1±0.21	-2.9±0.18				
015/018	Placebo	534	12.3±0.17	-1.4±0.14	0.94 (-1.28, -0.61)	<0.001	<0.001	
	YM905 5 mg	552	12.1±0.16	-2.3±0.12				
	YM905 10 mg	554	12.2±0.16	-2.8±0.13				
US & EU combined (13/14,15/18)	Placebo	1138	11.9±0.11	-1.4±0.09	-0.94 (-1.23, -0.65)	<0.001	<0.001	
	YM905 5 mg	552	12.1±0.16	-2.3±0.12				
	YM905 10 mg	1158	11.9±0.10	-2.7±0.09				

95% Confidence intervals for micturition / 24 h change from baseline means for individual studies, combined US, combined EU and combined US/EU studies are shown in the following figure



Secondary endpoints**Table 8 Mean change from baseline to endpoint in mean number of incontinence/24 h: pivotal Phase 3 studies**

Study	Treatment Group	Number of Micturitions/24 h (Mean±SE)					
		n	Baseline	Change from baseline to endpoint	Model-based Estimate of Mean Difference from Placebo (95% CI)	p-value	Bonferroni-Holm adjusted p value
013	Placebo	237	3.0±0.20	-1.1±0.16	-0.80 (-1.19, 0.42)	<0.001	N/A
	YM905 10 mg	225	3.1±0.22	-2.0±0.19			
014	Placebo	238	2.9±0.18	-1.2±0.15	-0.74 (-1.07, -0.41)	<0.001	N/A
	YM905 10 mg	230	2.9±0.17	-2.0±0.15			
013/014	Placebo	475	2.9±0.13	-1.2±0.11	-0.77 (-1.03, -0.52)	<0.001	N/A
	YM905 10 mg	455	3.0±0.14	-2.0±0.12			
015	Placebo	153	2.7±0.23	-0.8±0.18	-0.68 (-1.13, -0.23)	0.003	0.003
	YM905 5 mg	141	2.6±0.22	-1.4±0.15			
	YM905 10 mg	158	2.6±0.23	-1.5±0.18			
	Tolter 4 mg	157	2.3±0.15	-1.1±0.17			
018	Placebo	153	3.2±0.24	-1.3±0.19	-0.66 (-1.07, 0.24)	0.002	0.004
	YM905 5 mg	173	2.6±0.18	-1.6±0.16			
	YM905 10 mg	165	2.8±0.20	-1.6±0.18			
015/018	Placebo	306	3.0±0.17	-1.0±0.13	-0.66 (-0.96, -0.35)	<0.001	<0.001
	YM905 5 mg	314	2.6±0.14	-1.5±0.11			
	YM905 10 mg	323	2.7±0.15	-1.5±0.13			
US & EU combined (13/14,15/18)	Placebo	781	2.9±0.10	-1.1±0.09	-0.73 (-1.01, -0.45)	<0.001	<0.001
	YM905 5 mg	314	2.6±0.14	-1.5±0.11			
	YM905 10 mg	778	2.9±0.10	-1.8±0.09			

Table 9 Mean change from baseline to endpoint in mean number of urgency episodes/24 h: Pivotal Phase 3 studies

Study	Treatment Group	Number of Micturitions/24 h (Mean±SE)					
		n	Baseline	Change from baseline to endpoint	Model-based Estimate of Mean Difference from Placebo (95% CI)	p-value	Bonferroni-Holm adjusted p value
013	Placebo	306	7.2±0.24	-2.5±0.20	-1.73 (-2.22, -1.24)	<0.001	N/A
	YM905 10 mg	305	6.9±0.23	-4.1±0.20			
014	Placebo	292	6.8±0.22	-1.8±0.22	-1.74 (-2.29, -1.19)	<0.001	N/A
	YM905 10 mg	296	6.3±0.22	-3.3±0.23			
013/014	Placebo	598	7.0±0.16	-2.2±0.15	-1.73 (-2.10, -1.37)	<0.001	N/A
	YM905 10 mg	601	6.6±0.16	-3.7±0.15			
015	Placebo	248	5.3±0.25	-1.4±0.23	-1.29 (-1.86, -0.71)	<0.001	<0.001
	YM905 5 mg	264	5.8±0.30	-2.8±0.23			
	YM905 10 mg	261	5.8±0.28	-3.1±0.24			
	Tolter 4 mg	250	5.4±0.24	-2.1±0.23			
018	Placebo	278	5.6±0.24	-2.1±0.22	-0.72 (-1.22, -0.21)	0.005	0.005
	YM905 5 mg	284	6.0±0.28	-3.0±0.22			
	YM905 10 mg	289	5.5±0.24	-3.0±0.22			
015/018	Placebo	526	5.5±0.17	-1.7±0.16	-0.99 (-1.37, -0.60)	<0.001	<0.001
	YM905 5 mg	548	5.9±0.20	-2.9±0.16			
	YM905 10 mg	550	5.7±0.18	-2.0±0.16			
US & EU combined (13/14,15/18)	Placebo	1124	6.3±0.12	-2.0±0.11	-1.12 (-1.48, -0.75)	<0.001	<0.001
	YM905 5 mg	548	5.9±0.20	-2.9±0.16			
	YM905 10 mg	1151	6.2±0.12	-3.4±0.11			

Table 10 Mean change from baseline to endpoint in mean volume voided per micturition: Pivotal Phase 3 studies

Study	Treatment Group	Number of Micturitions/24 h (Mean±SE)					p-value	Bonferroni-Holm adjusted p value
		n	Baseline	Change from baseline to endpoint	Model-based Estimate of Mean Difference from Placebo (95% CI)			
013	Placebo	308	190.3±5.48	2.7±3.15	43.70 (34.18, 53.22)	<0.001	N/A	
	YM905 10 mg	305	183.5±4.97	47.2±3.79				
014	Placebo	293	175.7±4.44	13.0±3.45	33.20 (23.31, 43.10)	<0.001	N/A	
	YM905 10 mg	297	174.1±4.15	46.4±3.73				
013/014	Placebo	601	183.2±3.55	7.7±2.34	38.62 (31.76, 45.48)	<0.001	N/A	
	YM905 10 mg	602	178.9±3.25	46.8±2.66				
015	Placebo	253	143.8±3.37	7.4±2.28	25.31 (17.38, 33.24)	<0.001	<0.001	
	YM905 5 mg	266	149.6±3.35	32.9±2.92				
	YM905 10 mg	254	147.2±3.15	39.2±3.11				
	Tolter 4 mg	250	147.0±3.18	24.4±3.11				
018	Placebo	281	147.2±3.18	11.3±2.52	20.27(12.65, 27.85)	<0.001	<0.001	
	YM905 5 mg	286	148.5±3.16	31.8±2.94				
	YM905 10 mg	290	145.9±3.42	36.6±3.04				
015/018	Placebo	534	145.6±2.31	9.5±1.71	22.70 (17.21, 28.19)	<0.001	<0.001	
	YM905 5 mg	552	149.0±2.30	32.3±2.07				
	YM905 10 mg	554	146.5±2.33	37.8±2.17				
US & EU combined (13/14,15/18)	Placebo	1132	165.5±2.24	8.5±1.48	25.34 (19.56, 31.12)	<0.001	<0.001	
	YM905 5 mg	552	149.0±2.30	32.3±2.07				
	YM905 10 mg	1156	163.4±2.08	42.5±1.74				

Table 11 Mean change from baseline to endpoint in mean number of nocturia episodes/24 h: Pivotal Phase 3 studies

Study	Treatment Group	Number of Micturitions/24 h (Mean±SE)					p-value	Bonferroni-Holm adjusted p value
		n	Baseline	Change from baseline to endpoint	Model-based Estimate of Mean Difference from Placebo (95% CI)			
013	Placebo	279	1.7±0.08	-0.4±0.06	-0.19 (-0.34, -0.04)	0.012	N/A	
	YM905 10 mg	267	1.6±0.07	-0.6±0.06				
014	Placebo	267	1.6±0.06	-0.3±0.06	-0.08 (-0.23, 0.07)	0.276	N/A	
	YM905 10 mg	274	1.7±0.06	-0.5±0.06				
013/014	Placebo	546	1.7±0.05	-0.4±0.04	-0.13 (-0.24, -0.03)	0.012	N/A	
	YM905 10 mg	541	1.7±0.05	-0.5±0.04				
015	Placebo	219	2.0±0.10	-0.4±0.08	-0.17 (-0.35, 0.01)	0.062	0.124	
	YM905 5 mg	240	1.9±0.08	-0.6±0.07				
	YM905 10 mg	235	2.0±0.09	-0.5±0.06				
	Tolter 4 mg	232	1.9±0.08	-0.5±0.07				
018	Placebo	240	2.0±0.09	-0.5±0.07	-0.10 (-0.27, 0.07)	0.246	0.246	
	YM905 5 mg	254	2.0±0.07	-0.6±0.10				
	YM905 10 mg	259	1.9±0.08	-0.7±0.06				
015/018	Placebo	459	2.0±0.07	-0.5±0.05	-0.13 (-0.26, 0.01)	0.033	0.032	
	YM905 5 mg	494	2.0±0.05	-0.6±0.05				
	YM905 10 mg	494	2.0±0.06	-0.6±0.04				
US & EU combined (13/14,15/18)	Placebo	1005	1.8±0.04	-0.4±0.03	0.13 (-0.24, 0.02)	0.025	0.025	
	YM905 5 mg	494	2.0±0.05	-0.6±0.05				
	YM905 10 mg	1035	1.8±0.04	-0.6±0.03				

Summary of all efficacy parameters:

Solifenacin 5 mg and placebo were compared in both of the European pivotal Phase 3 studies, and both demonstrated that compared to placebo, solifenacin succinate 5 mg statistically significantly decreased the

number of micturitions/24 h, the number of incontinence episodes/24 h, and the number of urgency episodes/24 h. The 5 mg dose increased the volume voided per micturition.

All 4 pivotal Phase 3 studies compared solifenacin succinate 10 mg with placebo, and each demonstrated that solifenacin succinate 10 mg statistically significantly decreased the number of micturitions/24 h, the number of incontinence episodes/24 h, and the number of urgency episodes/24 h. The 10 mg dose also increased volume voided per micturition.

The results from the combined analysis of the 4 US and European pivotal Phase 3 studies are in agreement with the individual study results, and further demonstrate that both solifenacin succinate 5 mg and solifenacin succinate 10 mg statistically significantly decreased the number of micturitions/24 h, the number of incontinence episodes/24 h, and the number of urgency episodes/24 h, in addition to increasing volume voided per micturition.

Summary of improvement from combined analyses

Summary of improvement in micturitions per 24 hrs

Table 12 % of patients with improvement of $\geq 25\%$ and $\geq 50\%$ from baseline to endpoint in mean number of micturitions/24 h, combined US & European pivotal Phase 3 studies

Variable	013, 014, 015, and 018 combined			
	Placebo	YM905 5 mg	YM905 10 mg	Tolter 2 mg bid
Improvement of $\geq 25\%$ from baseline to endpoint	57	72***	75***	66*
Improvement of $\geq 50\%$ from baseline to endpoint	44	61***	64***	50
Per 24h Mean micturition number < 8 at endpoint	22	33***	37***	26

*p<0.05; **p<0.01; ***p<0.001

Table 13 Summary of sustained improvement in mean number of micturitions/24 h

Variable	n (%) in 013, 014, 015, and 018 combined			
	Placebo	YM905 5 mg	YM905 10 mg	Tolter 4 mg
Number of patients	1138	552	1158	250
Sustained improvement of $\geq 25\%$ from baseline to WK 4, WK 8, and WK 12	346 (30.4)	274 (49.6)***	623 (53.8)***	102 (40.8)**
Sustained improvement of $\geq 35\%$ from baseline to WK 4, WK 8, and WK 12	299 (26.3)	240 (43.5)***	573 (49.5)***	86 (34.4)*
Sustained improvement of $\geq 50\%$ from baseline to WK 4, WK 8, and WK 12	238 (20.9)	188 (34.1)	453 (39.1)**	62 (24.8)
Sustained mean of < 8 per 24 hrs at WK 4, WK 8, and WK 12	46 (4.0)	75 (13.6)***	122 (10.5)***	27 (10.8)***

*p<0.05; **p<0.01; ***p<0.001

*Summary of improvement in incontinence, urgency, and nocturia***Table 14** % of patients becoming symptom-free at endpoint:
combined US & European pivotal Phase 3 studies

Variable	n (%) in 013, 014, 015, and 018 combined			
	Placebo	YM905 5 mg	YM905 10 mg	Tolter 2 mg bid
Incontinence at baseline but continent at endpoint	266 (34.1)	159 (50.6)***	403 (51.8)***	76 (48.4)***
Urgency at baseline but no urgency at endpoint	174 (15.5)	157 (28.6)***	293 (25.5)***	62 (24.8)***
Nocturia at baseline but no nocturia at endpoint	146 (14.5)	80 (16.2)	197 (19.0)**	35 (15.1)

*p<0.05; **p<0.01; ***p<0.001

*Improvement across efficacy parameters***Table 15** % of patients becoming continent, free of urgency, free of nocturia, or having mean micturitions <8 per 24 h

Variable	013, 014, 015, and 018 Combined			
	Placebo	YM905 5 mg	YM905 10 mg	Tolter 2 mg bid
Proportion of patients who become continent, become free of urgency, or become free of nocturia	41	52***	55***	50**
Proportion of patients who have mean micturitions < 8 per 24 h at endpoint, or become continent, become free of urgency, or become free of nocturia	51	61***	66***	60**

*p<0.05; **p<0.01; ***p<0.001

Comparison of primary efficacy endpoint in subpopulations in Combined US & European pivotal Phase 3 studies**Table 16** Gender

Treatment Group	Gender	Number of micturitions per 24 hrs (mean±SE)		
		n	Baseline	Change from baseline to endpoint
Placebo	M	219	12.2±0.27	-1.2±0.22
	F	919	11.9±0.11	-1.5±0.09
YM905 5 mg	M	121	11.9±0.34	-1.9±0.22
	F	431	12.1±0.19	-2.4±0.14
YM905 10 mg	M	242	12.1±0.22	-2.5±0.20
	F	916	11.9±0.11	-2.8±0.09
Tolter 4 mg	M	50	12.2±0.49	-1.3±0.42
	F	200	12.1±0.24	-2.0 ±0.21

Table 17 Age

Treatment Group	Age	Number of micturitions per 24 hrs (mean±SE)		
		n	Baseline	Change from baseline to endpoint
Placebo	<65	742	12.1±0.13	-1.6±0.11
	≥65	396	11.6±0.17	-1.1±0.13
	≥75	121	11.5±0.30	-0.9±0.23
YM905 5 mg	<65	370	12.3±0.21	-2.5±0.16
	≥65	182	11.7±0.25	-2.2±0.27
	≥75	51	11.6±0.46	-2.8±0.11
YM905 10 mg	<65	756	12.1±0.13	-2.5±0.13
	≥65	402	11.6±0.15	-2.3±0.21
	≥75	123	11.4±0.29	-1.2±0.22
Tolter 4 mg	<65	172	12.1±0.26	-1.6±0.24
	≥65	78	12.1±0.39	-2.6 ±0.30
	≥75	17	11.6±0.84	-2.0±0.72

Table 18 Race

Treatment Group	Race	Number of micturitions per 24 hrs (mean±SE)		
		n	Baseline	Change from baseline to endpoint
Placebo	C	1044	11.9±0.11	-1.4±0.09
	B	62	11.8±0.52	-1.7±0.47
	H	17	12.5±1.35	-0.8±0.60
	A	7	11.1±0.69	-1.3±0.89
	O	8	12.5±1.56	-1.6±1.25
YM905 5 mg	C	541	12.1±0.17	-2.3±0.12
	B	4	10.4±0.44	-1.8±2.28
	H	0		
	A	6	10.7±1.10	-2.8±1.18
	O	1	11.3	-5.3
YM905 10 mg	C	1067	12.0±0.11	-2.7±0.09
	B	45	10.8±0.35	-2.8±0.40
	H	24	11.8±0.61	-3.3±0.48
	A	10	12.5±1.25	-2.8±1.32
	O	12	11.4±0.97	-1.7±0.83
Tolter 4 mg	C	247	12.1±0.22	-1.9±0.19
	B	1	8.0	-3.0
	H	0		
	A	2	17.3±3.33	-2.0±0.33
	O	0		

Patients with no symptomatic episodes during the baseline period were excluded
 C=Caucasian; B=Black; H=Hispanic; A=Asian; O=Other.

History of the disease

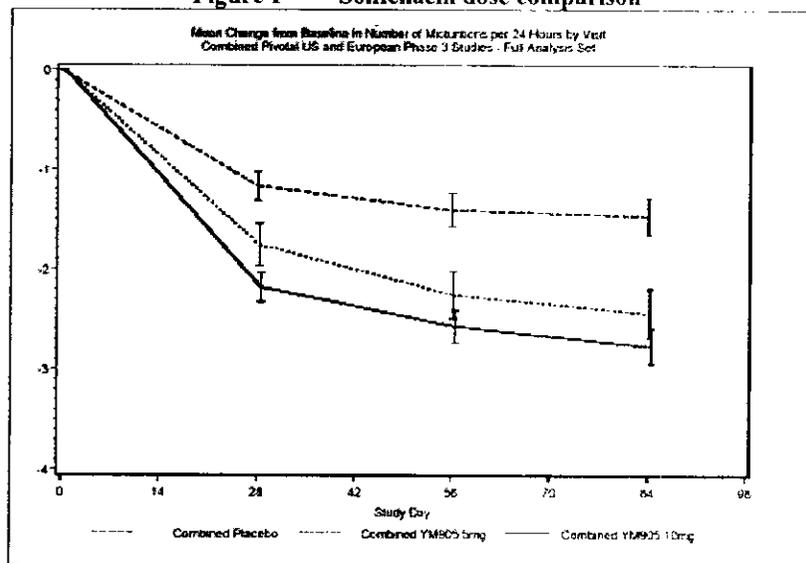
Table 19 Summary of micturitions by history of OAB in combined US & European pivotal Phase 3 studies

Treatment Group	History of OAB (yrs)	Number of micturitions per 24 hrs (mean±SE)		
		n	Baseline	Change from baseline to endpoint
Placebo	<3	351	11.7±0.20	-1.6±0.15
	3-10	453	12.0±0.16	-1.5±0.14
	>10	331	12.1±0.19	-1.2±0.16
YM905 5 mg	<3	172	11.9±0.28	-2.7±0.23
	3-10	229	12.2±0.25	-2.3±0.18
	>10	151	12.0±0.34	-2.0±0.23
YM905 10 mg	<3	349	11.6±0.17	-2.8±0.15
	3-10	450	11.8±0.16	-2.5±0.14
	>10	354	12.3±0.19	-2.9±0.16
Tolter 4 mg	<3	73	12.4±0.46	-2.7±0.38
	3-10	109	11.9±0.31	-1.6±0.14
	>10	68	12.0±0.38	-1.5±0.29

The effectiveness of solifenacin 5 mg and 10 mg is not affected by duration of OAB history.

Dosing recommendation

Figure 1 Solifenacin dose comparison



The recommended doses of solifenacin for the treatment of patients with OAB are 5 mg and 10 mg taken once daily. This recommendation is based primarily on the results of the 4 pivotal Phase 3 studies, 015, 018, 013, and 014, and further supported by the dose-response data from the Phase 2 studies, 005 and 006.

When data from all 4 studies are combined and mean change from baseline in number of micturitions/24 h is displayed by visit, solifenacin 5 mg and 10 mg each afford statistically significant improvement compared with placebo from Day 28 (WK 4). It also appears that the benefit provided by solifenacin 10 mg is greater than that provided by solifenacin 5 mg at each timepoint, but the difference between solifenacin dose groups

was not statistically significant except at Day 28. None of the studies was designed or powered to detect a difference between the 5 and 10 mg doses of solifenacin.

The Phase 2 studies CL-005 and 006 explored the dose response over the range of 0 to 20 mg solifenacin. Each of these Phase 2 studies was a 4-week, multicenter, randomized, double-blind, placebo-controlled, parallel group, fixed-dose trial in which patients received placebo, 2.5, 5, 10, or 20 mg solifenacin once daily. In Study CL-005, a parallel group of patients received 2 mg tolterodine 2 times daily. In each study, treatment with both solifenacin 10 and 20 mg was statistically significantly superior to placebo in reducing the mean number of micturitions/24 h from baseline to endpoint. There were, however, no clinically important differences in effectiveness between the 10 mg and 20 mg doses for this parameter in either study. Accordingly, all 4 pivotal Phase 3 studies included a solifenacin 10 mg dose arm. In the European Phase 2 study, Study CL-005, solifenacin 5 mg was also significantly better than placebo. Thus, the European pivotal Phase 3 studies each included a solifenacin 5 mg dose arm as well. In US Study CL-006, the 5 mg dose group did not exhibit a statistically significant difference from placebo in reducing the mean number of micturitions/24 h from baseline to endpoint. Accordingly in the US, each of the pivotal Phase 3 studies did not include a 5 mg solifenacin dose group. However, the 5 mg dose group (as well as the 10 mg and 20 mg dose groups) in Study CL-006 exhibited a significant increase from baseline to endpoint in volume voided per micturition.

Table 20 Solifenacin Phase 2 studies

Study	Mean change from baseline in placebo	Mean difference (Active-Placebo)				Tolterodine 2 mg bid
		Dose YM905 (mg)				
		2.5	5	10	20	
European Phase 2 study						
005	-1.0	-0.5	1.2*	-1.5**	1.7**	-0.8
US Phase 2 study						
006	-1.0	1.0	0.8	-2.0***	-1.8**	

*p<0.05; **p<0.01; ***p<0.001 in pairwise comparisons between treatment groups and placebo.

6.3.3 Statistical Plan

There are no technical statistical issues which need to be addressed in this review since the statistician concluded that these are "no realistic issues concerning Type 1 error or bias."

6.4 Efficacy Conclusions

In the opinion of this reviewer, the 5 and 10 mg doses of solifenacin are effective for the "treatment of OAB." The sponsor proposes to begin patients on the 5 mg dose and this reviewer agrees with this proposal.

7. Integrated Review of Safety

7.1 Safety conclusion

Solifenacin succinate (dosage of 5 mg and 10 mg once daily) is reasonably safe for use in the treatment of patients with OAB under the conditions put forth in the proposed labeling.

7.2 Drug exposure

7.2.1 Introduction and patient exposure

The numbers of OAB patients included in the clinical studies are summarized by study and dose in the following table. A total of 3779 patients were included in this group of studies. Of 2621 OAB patients treated with solifenacin, 667 received 5 mg daily and 1768 received 10 mg daily.

Table 21 Enumeration of OAB patients in the clinical studies

Study	Treatment Groups						
	Solifenacin					Placebo	Tolterodine 2 mg bid
	2.5 mg	5 mg	10 mg	20 mg	Any dose		
Phase 3 studies							
905-CL-013 (US)			340		340	332	
905-CL-014 (US)			318		318	316	
Subtotal US			658		658	648	
905-CL-015 (EU)		279	268		547	267	263
905-CL-018 (EU)		299	307		606	301	
Subtotal EU		578	575		1153	568	263
SUBTOTAL (Phase 3)		578	1233		1811	1216	263
Phase 2 studies							
905-CL-005 (EU)	41	37	35	37	150	38	37
905-CL-006 (US)	54	52	51	54	211	53	
Sutotal	95	89	86	91	361	91	37
SUBTOTAL (Phase 3+Phase 2)	95	667	1319	91	2172	1307	300
Open-label, extension study							
905-CL-016 (US)			892 (443 ¹)		892 (443 ¹)		
TOTAL OAB Patients (All patient safety data)	95	667	1768	91	2621	1307	300

¹ Patients who previously received 10 mg YM905 in Studies 013 and 014.

Duration of exposure

Table 22 Study medication exposure: combined US & EU Phase 3 studies

Study medication exposure	Combined studies (013/014, 015/018): n (%)			
	Placebo	YM905 5 mg	YM905 10 mg	Tolter 4 mg
Number of patients	1216	578	1233	263
Length of exposure (Days)				
N	1195	569	1222	257
Mean	80.0	82.3	79.5	82.1
SD	18.39	13.71	19.33	14.72
Median	84.0	84.0	84.0	84.0
Minimum, Maximum	2, 119	3, 112	1, 122	8, 106
At least 77 days	1032 (84.9)	511 (88.4)	1044 (84.7)	231 (87.8)
Person-Months of exposure	3151.6	1544.5	3201.8	695.7

> 80% of patients in each group had at least 77 days of exposure to study medication. The median duration of exposure in every group was 84 days. The difference between groups in person-months of exposure is a function of the differences in the number of patients in each group, not in the time patients spent on therapy.

7.2.2 Pooling

Data from four Phase 3 and two Phase 2 studies, as well as one Phase 3 extension study were pooled.

Table 23 Study medication exposure: All patient safety data

Study medication exposure	Combined studies* (006/013/014/016, 005/015/018): n (%)					
	Placebo	Solifenacin				Tolter 2 mg bid
		2.5 mg	5 mg	10 mg	20 mg	
Number of patients	1307	95	667	1768	91	300
Length of exposure (Days)						
n	1285	94	658	1751	91	294
Mean	76.4	28.8	75.1	168.0	26.6	75.6
SD	22.10	5.11	22.40	124.78	8.04	22.16
Median	84.0	28.0	84.0	91.0	28.0	84.0
Minimum, Maximum	2, 119	7, 40	3, 112	1, 464	3, 43	8, 106
At least 77 days	1032 (79.0)		511 (76.6)	1454 (82.2)		231 (77.0)
At least 28 days		68 (71.6)			57 (62.6)	
Person-Months of exposure	3236.3	89.4	1629.1	9700.6	79.8	732.5

*Study 019 was not included at the time the report was submitted.

In all, the pooled safety database for all patient safety data comprises a total of 1629.1 person-months of exposure to solifenacin 5 mg and 9700.6 person-months of exposure to solifenacin 10 mg.

Gender and age: Overall, 2621 patients (555 men and 2066 women) with OAB were exposed to solifenacin in these trials. Of these 2621 patients, 667 (146 men and 521 women) were exposed to 5 mg, 1768 (353 men and 1415 women) were exposed to 10 mg, and the remainder were exposed to either 2.5 mg or 20 mg. A total of 937 were 65 years of age or older and 290 were 75 years of age or older.

For calculating long-term exposure, visit windows were considered. For each 12-week or 3-month visit, the protocol allowed a 7-day window. Thus, a patient could complete the 12-month study and have 365 days±28 days (337 days to 393 days) of exposure, or a patient could complete the 6-month visit and have 183±14 days (169 days to 197 days) of exposure. Patients with at least 337 days of exposure are counted as having 1 year of exposure, and patients with at least 169 days of exposure are counted as having 6 months of exposure. Using these windows, 718 patients had at least 6 months of exposure for solifenacin 10 mg and 308 patients had at least 1 year of exposure. If visit windows are not considered, 648 patients had 181 days of exposure and 122 patients had at least 365 days of exposure.

Reviewer's comment: The total and average exposures to the study medication are adequate for safety analysis.

This review also includes safety information from a 4-month safety update **June 1, 2002 through March 1, 2003** that was provided in the NDA 21518 submission on April 25, 2003. The 4-Month safety update summary includes data from Study 905-CL-016 (an open-label, long-term tolerability study of daily administration of 10 mg YM905 in patients with OAB) and Study 905-CL-019 (open-label, long-term safety and efficacy follow-up study of YM905 5 mg and 10 mg in patients with OAB). In the open-label, extension studies in the US (CL-016) and Europe (CL-019), the total exposure is shown in Tables 24 and 25.

Table 24 Total exposure to solifenacin 10 mg : Studies 013/014+016

Length of exposure	Studies 013/014+016: Total exposure to solifenacin 10 mg (N=1135): n (%)
Mean±SD (days)	262±156
Median (days)	334
Minimum, maximum (days)	1, 519
Person-months exposure	9513
≥ 92 days	826 (73%)
≥ 184 days	680 (60%)
≥ 275 days	607 (54%)
≥ 366 days	337 (30%)
≥ 457 days	45 (4%)

Table 25 Total exposure to solifenacin 5 mg : Study 019

Length of exposure	Study CL-019: Total exposure to solifenacin 5 mg (N=519): n (%)
Mean±SD (days)	285±94
Median (days)	290
Minimum, maximum (days)	1, 417
196 to 279 days	63 (12%)
280 to 363 days	243 (47%)
≥ 364 days	139 (27 %)

In combination, under long-term treatment of solifenacin with either 10 mg or 5 mg daily doses, a total of 986 patients were treated for ≥ 6 months, and 476 patients for ≥ one year.

Reviewer's comment: The treatment groups were balanced in terms of exposure time, so that comparisons between or among treatments in safety parameters for the Phase 3 studies are not likely to be confounded by time on therapy. The long-term exposure should be adequate.

7.2.3 Listing of studies

The sources of safety data in this submission include 4 completed Phase III trials, 2 ongoing Phase III trials, 2 completed Phase 2 studies, 15 completed clinical pharmacology trials, 3 ongoing clinical pharmacology trials, and 1 ongoing dose response and dose ranging study.

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Table 26 Grouping of clinical studies for purposes of summarizing the safety of solifenacin

Study	Indication	Design	Control
Completed US & European Phase 3 Studies			
013	OAB	Randomized, DB, parallel group, controlled	Placebo
014	OAB	Randomized, DB, parallel group, controlled	Placebo
015	OAB	Randomized, DB, parallel group, controlled	Placebo/tolterodine
018	OAB	Randomized, DB, parallel group, controlled	Placebo
Completed US & European Phase 2 Studies			
005	OAB	Randomized, DB, parallel group, dose-response	Placebo/tolterodine
006	OAB	Randomized, DB, parallel group, dose-response	
Ongoing US Phase 3 open-label extension Study (interim report)			
016	OAB	Open-label, extension of 013 and 014	
Completed US & European BA/BE and clinical pharmacology (Phase 1) Studies			
001	PD/PK	DB, randomized, controlled, single dose	Placebo, oxybutynin
002	PK	DB, randomized, controlled, multi dose, dose rising	Placebo
003	PK	Open label, crossover, food effect, single dose	
004	PK	DB, randomized, controlled, dose-rising, elderly	Placebo
008	PK	Open label, mass balance, metabolite	
009	Absolute BA	Single dose, open-label, randomized, crossover	
010	PK/ketoconazole	Open label, monosequence crossover, drug-drug interaction	
011	PK/oral contraceptives	DB, controlled, crossover, drug-drug interaction	Placebo
021	PK	Open-label, single dose, renal impairment	
022	PK	Open-label, sequential rising dose, QTc	
025	PK/dogoxin	DB, crossover, drug-drug interaction	
028	PK/warfarin	DB, controlled, crossover, drug-drug interaction	Placebo
029	PK	Open-label, crossover, elderly	
Completed Japanese Studies			
007	PK	SB, single dose, controlled	Placebo
012	PK	SB, controlled, multi dose	Placebo
Other ongoing Studies			
European Phase 3 open-label extension Study			
019	OAB	Open-label, extension of 015 and 018	
Phase 1 studies			
026	PK	Open-label, hepatic impairment	
030	PK	Food effect	
Ongoing Japanese Studies			
023	OAB	Randomized, DB, parallel-group, dose response & ranging	Placebo
024	PK	DB, randomized, controlled, elderly	Placebo

Reviewer's comment: The PK studies in renal and hepatic impairment subjects are included.

7.2.4 Demographics:

Table 27 Demographics of major Phase 3 and Phase 2 studies

Characteristics	Combined studies (006/013/014/016, 005/015/018): n (%)			
	Placebo	YM905 5 mg	YM905 10 mg	Tolter 4 mg
Number of patients	1307	667	1768	300
Age				
Mean	57.9	57.0	58.4	57.6
Minimum, Maximum	18, 88	18, 85	18, 88	19, 82
< 65	857 (65.6)	436 (65.4)	1136 (64.3)	203 (67.7)
≥ 65	450 (34.4)	231 (34.6)	632 (35.7)	97 (32.3)
≥ 75	141 (10.8)	67 (10.0)	197 (11.1)	21 (7.0)
Gender				
Male	263 (20.1)	146 (21.9)	353 (20.0)	68 (22.2)
Female	1044 (79.9)	521 (78.1)	1415 (80.0)	232 (77.3)
Race				
Caucasian	1194 (91.4)	645 (96.7)	1605 (90.8)	295 (98.3)
Black	71 (5.4)	8 (1.2)	42 (5.1)	3 (1.0)
Hispanic	24 (1.8)	5 (0.7)	42 (2.4)	0
Asian	8 (0.6)	7 (1.0)	18 (1.0)	2 (0.7)
Other	10 (0.8)	2 (0.3)	13 (0.7)	0

The summary of demography by treatment group for extension Study 016 combined with the placebo-controlled studies revealed 449 patients who received placebo during the double-blind study and received 10 mg during the open-label study. These patients are counted in both the placebo group and also the 10 mg group.

Approximately 80% of the patients were women, a total of 1410 patients were age of ≥ 65 in the placebo group, 231 in the solifenacin 5 mg, 632 in the solifenacin 10 mg, and 97 in the tolterodine groups. A total of 426 patients were age ≥ 75 with 141 in the placebo, 67 in the solifenacin 5 mg, 197 in the solifenacin 10 mg, and 21 in the tolterodine groups. The majority of patients (91-98%) were Caucasian, while there were more Black and Hispanic patients in the US studies compared with the European studies.

Reviewer's comment: The treatment groups were balanced with respect to age and gender.

7.3. Adverse events

7.3.1 Deaths

Table 28 List of patient deaths –All patient safety data

Study	Subject #	First dose / Last dose	MedDRA Preferred term	Relationship to study medication [#]
Placebo				
013	31008	Mar 05 2001/	Hemopericardium	Unrelated
018	21316	Nov 01 2001/	Hypertensive crisis/stroke	Unrelated
Solifenacin 5 mg and 10 mg				
015	11533	Aug 21 2001/	Active heart failure	Unrelated
018	20638	Sept 15 2001/	Pulmonary thromboembolism	Unrelated
016	014-16038	July 26 2002/	Subdural hematoma	Unrelated
016	014-33011	June 15 2001	chronic obstructive pulmonary disease	Unrelated
019	019-10125	Jan 03 2002/	Bladder cancer/cardiac insufficiency	Unrelated
019	019-10151	Sept 05 2001/	Malignant brain neoplasm	Unrelated
019	019-11081	Oct 29 2001/	Multi organ failure during surgery	Unrelated
019	019-20280	Oct 30 2001/	Ruptured aortic aneurysm	Unrelated
Tolterodine 4 mg				
015	11882	Oct 12 2001/	Cerebral atherosclerosis	Unrelated

[#] According to the investigator's opinion.

There have been a total of eleven deaths reported among patients in the combined Phase 2/3 and extension studies. One patient died in Study 013, two patients died in each of Studies 015 and 018, two patients died in Study 016 and four patients died in Study 019. Two of the deaths were in placebo-treated patients, eight were in solifenacin 10 mg or 5 mg-treated patients, and one death was in a tolterodine-treated patient.

Narratives of patients who died

Placebo group

Patient #013-31008 (placebo) took study drug for 57 days. During the follow-up period, 20 days after the last dose of study drug, the patient experienced hemopericardium and died. Autopsy revealed rupture of the left ventricle at the site of recent myocardial infarction. The investigator considered the death was not related to study drug.

Reviewer's comment: This reviewer considers the death not related to the study drug.

Patient #018-21316 (placebo) was a 72-year old Caucasian man with a history of arterial hypertension at study entry. He died of hypertensive crisis and stroke — after start of the double blind (DB) treatment period. No autopsy was performed. The investigator considered the death unrelated to study drug.

Reviewer's comment: This reviewer agrees the death was not related to the study drug.

Solifenacin group

Patient #015-11533 (10 mg solifenacin) was a 75-year old Caucasian woman. The investigator was informed by phone that she died — after starting study drug. Presumptive cause of death was indicated as acute heart failure. Autopsy was not performed. The last contact with the patient was on Visit 3. No further information could be obtained. The investigator considered the death was not related to study drug.

Reviewer's comment: This reviewer believes that the relationship of the death to study drug can not be excluded.

Patient #018-20638 (10 mg solifenacin) was a 68-year old Caucasian woman with a history of myocardial infarction, arterial hypertension, ischemic heart disease and diabetes mellitus type II, which were active at the start of the study. The patient did not attend the Wk - visit and the investigator was later informed by the patient's daughter that her mother suffered right sided hemiparesis — after start of the double blind treatment period. Study drug was stopped. The patient died of pulmonary thromboembolism 2 wks later. The investigator judged the death unrelated to treatment.

Reviewer's comment: This reviewer believes the death was probably not related to study drug.

Patient #014-16038 (10 mg solifenacin) was an 80-year-old Caucasian man with a medical history of evacuation of a subdural hematoma, depression, arthritis, and tinea cruris. The patient took placebo during the preceding 12-week double-blind study. Approximately — after entering the open-label study, the patient experienced a 3-day history of progressive right-sided arm and leg weakness that led to stumbling and frequent falls without evidence of any neurological impairment. He was transported to ER, where a CT scan found a non-depressed skull fracture and a large left-sided subdural hematoma. The patient underwent an operation to evacuate the subdural hematoma. However, he developed postoperative complications including cerebral edema and aspiration pneumonia, and he lost consciousness. On the 20th day of hospitalization, the patient's family decided to withdraw life support and the patient died the next day. The investigator considered the event unrelated to study drug.

Reviewer's comment: This reviewer agrees that the relationship between this death and study drug is unlikely.

Patient #014-33011 (solifenacin 10 mg) was an 86-year-old man with a medical history of chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD). He had been treated with placebo in the preceding double blind study and then had been enrolled in the open-label study for [redacted] when he was admitted to the hospital with chest pain. Three days later, the patient underwent a coronary artery bypass graft (CABG) for triple-vessel disease. The patient's hospital course post-CABG was uneventful, until the time of death 17 days after the CABG. The patient's death certificate listed the cause of death as COPD and CAD. The investigator considered the death unrelated to study drug.

Reviewer's comment: This reviewer believes the death was probably not related to the study drug.

Patient #019-20280 (solifenacin 5 mg and 10 mg) was a 75-year-old man with a history of hypertension and asthma treated with budesonide and salbutamol. The patient took part in short-term double blind study with solifenacin 5 mg and continued in the open-label extension study with 10 mg solifenacin. He was hospitalized for a thoracic aneurysm [redacted] after the start of treatment. He died from a ruptured aortic aneurysm a week later (after [redacted] of treatment). The investigator considered the event unrelated to study drug.

Reviewer's comment: This reviewer considers the death was unrelated to the study drug.

Patient #019-11081 (solifenacin 5 mg and 10 mg) was a 63-year-old woman on hormone replacement for osteoporosis and had a history of depression. She had been treated with solifenacin 5 mg in the preceding double blind study and then had been enrolled in the open-label study with solifenacin 10 mg. The patient was scheduled for a total hip replacement in [redacted] of the study. Study drug was discontinued prior to surgery. During the surgery, the patient had retro-peritoneal hemorrhage and hypovolemic shock, resulting in multiorgan failure and death. The investigator considered the event unrelated to study drug.

Reviewer's comment: This reviewer considers that the relationship between this death and study drug is unlikely.

Patient #019-10151 (solifenacin 5 mg and 10 mg) was a 76-year-old woman with a history of hypertension. She had been treated with solifenacin 5 mg in the preceding double blind study and then had been enrolled in the open-label study with solifenacin 10 mg for [redacted]. She was diagnosed with a malignant brain neoplasm during [redacted] of the double blind treatment period. She stopped study drug [redacted] after the start of extension study and died five and one-half months later. The investigator considered the event unrelated to study drug.

Reviewer's comment: This reviewer agrees the death was not related to the study drug.

Patient #019-10125 (solifenacin 5 mg) was a 75-year-old Caucasian man with a history of myocardial infarction and idiopathic thrombocytolysis. The patient took part in short-term double blind study CL-015 and continued in the open-label extension study with 5 mg solifenacin. After [redacted] in the extension study he was hospitalized due to bladder hemorrhage and was diagnosed with low-grade bladder cancer. One month later he died of cardiac insufficiency. The investigator judged that death was not related to the study drug.

Reviewer's comment: The reviewer agrees that this death was not related to study drug.

Tolterodine group

Patient #015-11882 (tolterodine 2 mg bid) was a 79-year old Caucasian woman with a medical history of ischemic heart disease, essential arterial hypertension and bronchial asthma. The patient's relative notified the center of the patient's sudden death on the evening of the [redacted] after the start of study medication in her daughter's presence. She apparently became unconscious and after a few moments died. No autopsy was performed but the cause of death was reported as cerebral arteriosclerosis. The investigator judged the death was unrelated to the study drug.

Reviewer's comment: The reviewer considers that this death was not related to study drug.

7.3.2 Other serious adverse events (SAEs)

SAEs were reported in 2.4% of patients in the solifenacin 10 mg groups in the European and the US trials combined, and in 2.2% of patients in the solifenacin 5 mg group, which was only investigated in Europe.

Three SAEs were considered to be complications or exacerbations of expected antimuscarinic side effects and included fecal impaction, intestinal obstruction, and fecal loading. There were a total of ten SAEs judged as probably or possibly related to solifenacin treatment in the four pivotal Phase 3 studies.

Table 29 Patients with serious adverse events: combined Studies CL-013/014, 015/018

Patient #	Age (yrs)	Sex	MedDRA preferred term	Onset day (days ^a)	Relationship to study medication	Intensity	Action taken/outcome
Solifenacin 5 mg							
<i>CL-015</i>							
11024	52	M	Syncope	45	Possible	Severe	None/recovered
11579	74	F	Tachyarrhythmia	16	Possible	Severe	Discontinued/RCV
<i>CL-018</i>							
20815	45	F	Menometrorrhagia	59	Possible	Mild	None/recovered
Solifenacin 10 mg							
<i>CL-013</i>							
29005	62	F	Colonic obstruction/sigmoid colon obstruction	11	Possibly		Discontinued/RCV
<i>CL-014</i>							
1002	46	F	Hyponatremia/hyponatremia secondary to polydipsia	17	Possibly		Discontinued/RCV
5024	71	M	Fecal impaction/fecal impaction	44	Probably		None/recovered
14003	76	M	Hypotension nos/hypotension	54 (+1)	Possibly		Discontinued/RCV
<i>CL-015</i>							
10886	68	M	Myocardial infarction	N/A	Possible	Mild	None/recovered
<i>CL-018</i>							
21449	56	F	Nausea & vomiting NOS	12	Possible	Moderate	None/recovered
			Abdominal pain upper	12	Not related	Mild	
21454	72	F	Syncope	7	Possible	Moderate	None/recovered

nos = not otherwise specified

^a Relative to day of first dose of study drug, (post-treatment day relative to first day after the last dose is indicated with a + sign)

Narratives are located in each individual study review in the appendix.

In the US Open-label, Phase 3 extension Study CL-016, 46 SAEs were reported with only 2 were considered possibly related to solifenacin treatment. In the European open-label, Phase 3 extension Study CL-019, 61 patients had SAEs and ten were considered probably or possibly related to solifenacin treatment.

**Table 30 Serious Adverse Events (SAE's) considered possibly or probably related to Study drug:
Open-label, Extension Studies CL-016 (US) and CL-019 (Europe)**

Patient #	Age (yrs)	Sex	MedDRA preferred term	Onset Day (days ^a)	Relationship to study medication	Intensity	Action taken/outcome
Solifenacin 5 mg qd (Study CL-019)							
10608	55	M	Hypertension NOS	105	Possible	Moderate	None/recovered
20256	67	M	Fecal impaction	24	Probably	Severe	Discontinued/RCV
20523	74	F	Cardiac failure congestive	130	Possible	Mild	Reduced dose/RCV
Solifenacin 10 mg qd Study CL-016							
1325015	63	F	Diverticulitis aggravated Rectal hemorrhage /bleeding	60	Possible Possible	Severe Severe	None/recovered
1405006	71	F	Gastritis NOS/gastritis	245	Possible	Moderate	Interrupt/resume/RCV
Study CL-019							
10551	77	F	Circulatory collapse	10	probably	Severe	Discontinued/RCV
10603	77	F	Renal failure NOS	76	Possible	Severe	Discontinued/RCV
10645	53	F	Gastroesophageal reflux dis.	75	Possible	Severe	None-recovered
10878	78	F	Cerebrovascular accident	135	Possible	Severe	Discontinued/RCV
11576	62	M	Epididymitis NOS	43	Possible	Moderate	None/recovered
12032	77	F	Renal impair. NOS, Liver funct. tests NOS abnormal	135	Possible Possible	Moderate	Discontinued/no change
21572	71	F	UTI NOS, back pain, pyrexia, Nausea, constipation	141	Possible Possible	Severe Mild	Interrupt/resumed/RCV
Solifenacin 30 mg qd Study CL-022							
022-15	72	M	Urinary retention	8	Probably	Severe	Discontinued/RCV

nos = not otherwise specified

^a Relative to day of first dose of study drug, (post-treatment day relative to first day after the last dose is indicated with a + sign)**Study CL-016**

Patient #1325015 was a 68-year-old woman (on placebo in the preceding double blind study) with a medical history of diverticulitis, hypothyroidism, spinal stenosis, and hypertension. She was hospitalized with symptoms of acute diverticulitis with rectal bleeding on Day 60 of treatment. The patient was diagnosed with internal hemorrhoids during the hospitalization and was treated with intravenous fluids and intravenous Cipro. The patient remained in the study and the event was resolved. She was discharged. The investigator considered this event possibly related to study drug.

Reviewer's comment: The reviewer agrees that the relationship of the event to the study drug was possible.

Patient #1405006 was a 71-year-old woman (on placebo in the preceding double-blind study) with a medical history including osteoarthritis, heartburn, diabetes, angina, coronary artery disease, obesity, and hypercholesteremia. She was hospitalized with gastritis on Day 245 of treatment. The gastritis lasted for 15 days

and the event was resolved with medical treatment. Study drug was interrupted temporarily and resumed as the patient remained in the study. The investigator considered the gastritis possibly related to study drug.

Reviewer's comment: The reviewer agrees that the event was possibly related to the study drug.

Study CL-019

Patient #019-10551 was a 77-year-old female (on solifenacin 5 mg in the proceeding double blind study) with a medical history of diabetes. She was enrolled into the extension study with 5 mg solifenacin for 4 weeks, then dependent on response, 5 mg or 10 mg, then started 10 mg. Ten days after starting 10 mg solifenacin, she collapsed at home and was hospitalized. The event was judged as postural hypotension, and the patient recovered with sequelae and withdrew from the trial. The investigator judged the event was probably related to the study drug.

Reviewer's comment: The reviewer agrees that the event was possibly related to the study drug.

Patient #10603 was 77-year-old woman (on solifenacin 5 mg in the proceeding DB study) with a medical history of renal insufficiency. She started 5 mg solifenacin for 4 weeks, and increased to 10 mg. Thirty-eight days after starting solifenacin 10 mg she suffered from renal failure and was hospitalized and underwent surgical treatment. The study drug was reduced to 5 mg for 2 weeks due to another AE (dry mouth), then, resumed 10 mg for 4 weeks. The drug was permanently discontinued when renal function returned to previous status. The investigator considered the event was possibly related to the study drug.

Reviewer's comment: The reviewer considered that the event was possibly related to the study drug.

Patient #10608 was a 55-year-old man (on solifenacin 5 mg in the proceeding double blind study) with a medical history of hypertension. 105 days after start of 5 mg solifenacin in the extension study the patient was hospitalized for hypertension. Two days later he was discharged and the event resolved without sequelae. He remained in the study. The investigator judged the event was possibly related to the study drug.

Reviewer's comment: The reviewer wonders why the event was judged by the investigator to be possibly related to the study drug.

Patient #10645 was a 53-year-old woman (on solifenacin 5 mg in the proceeding double blind study) with a medical history of gastro-esophageal reflux, depression and anxiety. 75 days after start extension study of 5 mg and 10 mg solifenacin, she was hospitalized due to worsening of gastro-esophageal reflux. She improved and recovered. She remained on study drug. The investigator considered that the event was possibly related to the study drug.

Reviewer's comment: The reviewer agrees that the event was possibly related to the study drug.

Patient #10878 was a 78-year-old woman (in the proceeding double blind study CL-015) with a medical history of epilepsy and cerebro-vascular accident (CVA). 135 days after she started the extension study with solifenacin 5 mg (x 4wks) and 10 mg (x107 days) she was hospitalized for another CVA. The diagnosis was confirmed by CT scan. The patient recovered with sequelae and the study drug was discontinued. The investigator considered the event was possibly related to the study drug.

Reviewer's comment: The reviewer considered that the event was possibly related to the study drug.

Patient #11576 was a 62-year-old man (in proceeding double blind short-term study) with a medical history of otis urethrotomy TURP. 43 days after start of the extension study the patient came to the emergency room following a few days of dysuria. He was hospitalized for left epididymitis. Study medication was continued and the patient was discharged and recovered completely.

Reviewer's comment: The reviewer agrees that the event was possibly related to the study drug.

Patient #12032 was a 77-year-old woman (in proceeding double blind study) with a medical history of hypothyroidism, osteoporosis and peptic ulcer. 135 days after the start of the extension study (solifenacin 5 mg x 4 wks, and then 10 mg since) the patient was hospitalized for an elevated creatinine, hyperkalemia and an elevated alkaline phosphatase (140 IU/L, normal 25-130). The study drug was discontinued and the investigator considered the event was possibly related to the study drug.

Reviewer's comment: The reviewer agrees that the event was possibly related to the study drug.

Patient #20256 was a 67-year-old man (in proceeding double blind study) with a medical history of diabetes, asthma, hypercholesterolemia, and was taking multi-drugs. 24 days after start of the extension study with 5 mg solifenacin, the patient developed abdominal pain and was hospitalized. The results of CT and ultrasound confirmed the diagnosis of fecal loading possibly due to study medication. The patient was withdrawn from the study and he recovered. The investigator judged the event was probably related to the study drug.

Reviewer's comment: The reviewer considered that the relationship between the event and the study drug was probable.

Patient #20523 was a 74-year-old woman (in proceeding double blind study) with medical history of abnormal ECG. She had taken tolterodine 1 mg bid previously. 130 days after start of the extension study with solifenacin 5 mg x 90 days and 10 mg x 40 days, the patient suffered 3-4 episodes of severe chest tightness. She was hospitalized and diagnosed as mild congestive cardiac failure. The study drug dose was reduced to 5 mg and she recovered. The investigator considered the event was possibly related to the study drug.

Reviewer's comment: The reviewer agrees that the event was possibly related to the study drug.

Patient #21572 was a 71-year-old woman (in proceeding double blind study) with a medical history of benign lung lesion, melanoma, arthritis, gastric reflux, fibromyalgia and hot flush. 141 days after the start of the extension study (solifenacin 5 mg x 4 weeks, 10 mg x 113 days) the patient suffered acute urinary infection and was hospitalized. The study drug was temporarily interrupted. She recovered with mild nausea and lower back pain. The study drug was resumed. The investigator considered the event was possibly related to the study drug.

Reviewer's comment: The reviewer agrees that the event was possibly related to the study drug.

An additional case of an SAE which was considered to be related to solifenacin was a patient from Study CL-022:

Patient #022-015 was a 72-year-old Black man with a medical history of benign prostate hyperplasia and urinary retention, which had required Foley catheterization 5 to 6 years earlier. The patient had been treated with solifenacin 14 days at 10 mg/day and 14 days at 20 mg/day. On Day 8 of treatment with 30 mg solifenacin dose level, the patient presented with urinary retention and had to be hospitalized for catheterization. The event was resolved a week later and the patient was discontinued from the study. The investigator judged the event was severe and possibly related to study drug.

Reviewer's comment: The reviewer considers that the event was probably related to the study drug.

In addition, there were another five cases of SAEs coming from non-Phase 2/3 studies. All five cases judged by investigator to be not related to study medication. This reviewer agrees with investigator's judgement.

Study 905-CL-004: one serious adverse event was reported by 1 subject (#004-19). On Day 16 of the study, a male patient #004-19 (solifenacin 20 mg) complained about a very mild pain in his left inguinal region. Next day (Day 17) (—), he complained about severe pain in the same region and was withdrawn from the study. He did not receive study medication on Day 17. A tentative diagnosis of inguinal hernia was made. The subject was hospitalized and underwent a laparoscopy and surgery for inguinal hernia. The subject recovered and was discharged and recovered.

Study 905-CL-009: One male patient (#009-9007) suffered from 2 SAEs, personality disorder (reported term: impulse control disorder) and depression (reported term: suicidal tendency). On Day 7 of the IV treatment on solifenacin 10 mg, the patient was made aware of some very bad personal/business related news. He became extremely angry and tried to leave the unit. On Day 8, he attempted to commit suicide by jumping out the window. The psychiatrist succeeded in calming the subject down. At 5 pm the psychiatrist judged the patient was no longer a danger to himself, and made a diagnosis of impulse control disorder. On this same day, it was learned from the subject's general practitioner (GP) that the subject has been suffering from both personal and business problems and that he had a previous history of a suicide attempt with admission to a hospital. None of this information was available at the screening interview. The event was judged to be unlikely related to the study medication, according to the investigator.

Study 905-CL-024: Three cases of SAEs:

Patient #024-59-2 was a 77-year-old Japanese woman who was enrolled into this Phase 2 solifenacin study on solifenacin 5 mg. On Day 6, she complained of lower abdominal pain and a mass (3.8x2.9 cm²) was revealed on abdominal echography located in patient's liver. She was hospitalized and underwent liver biopsy resulting in liver carcinoma (primary or metastatic). Study drug was discontinued and the investigator judged the event was not related to study drug.

Patient # 024-52-1 was a 66-year-old man on solifenacin 2.5 mg daily. On Day 5 a small urethral polyp was indicated by cystoscopy and was judged not to affect the continuation of the treatment. He went on to complete the study. During hospitalization he underwent surgery and was diagnosed as bladder tumor. The investigator judged the event was not related to study drug.

Patient #024-14-1 was a 60-year-old woman on solifenacin 10 mg daily. On Day 13, she underwent cystoscopy examination and was indicated to have an extensive superficial tumor located mainly in urinary bladder trigone, which was diagnosed as bladder tumor secondary to the ureteric tumor. The study medication was discontinued on that day. The patient was hospitalized and underwent endoscopic urinary bladder tumor resection. The investigator judged the event was not related to study drug.

7.3.3 Other adverse events

For the combined four US and European Phase 3 studies, overall frequency of treatment-emergent adverse events (TEAEs) was 52.1% in placebo, 45.8% in solifenacin 5 mg, 62.7% in solifenacin 10 mg, and 48.3% in the tolterodine group. More patients treated with solifenacin 10 mg developed TEAEs (62.7%) than placebo treated patients. In both the US and EU trials, the majority of the TEAEs in all treatment groups were considered mild or moderate in severity. More patients in the solifenacin 10 mg discontinued because of TEAEs compared to the placebo group.

Table 31 Overall summary of TEAEs: combined US & EU Phase 3 pivotal studies

	Combined Studies (013/014, 015/018): n (%)			
	Placebo	YM 905 5 mg	YM 905 10 mg	Tolter 4 mg
Number of patients	1216	578	1233	263
Number of TEAEs reported	1355	486	1961	248
Number of patients with TEAEs	634 (52.1)	265 (45.8)	773 (62.7)	127 (48.3)
Number of SAEs	30	13	36	3
Number of patients with SAEs	27 (2.2)	13 (2.2)	30 (2.4)	3 (1.1)
Number of patients with AEs by severity				
Mild	284 (44.8)	157 (59.2)	337 (43.6)	72 (56.7)
Moderate	287 (45.3)	93 (35.1)	341 (44.1)	47 (37.0)
Severe	63 (9.9)	14 (5.3)	95 (12.3)	7 (5.5)
Severity unknown or not reported	0	1 (0.4)	0	1 (0.8)
Number of patients discontinued study medication due to AE	66 (5.4)	21 (3.6)	85 (6.9)	7 (2.7)
Patients with treatment-related AEs	281 (23.1)	171 (29.6)	588 (47.7)	74 (28.1)
Number of deaths	2	0	2	1

Reviewer's comment: In general, solifenacin in doses up to 10 mg once daily, was well-tolerated.

Table 32 Number and % of subjects with TEAEs by system organ class (SOC): Combined US & EU Phase 3 studies

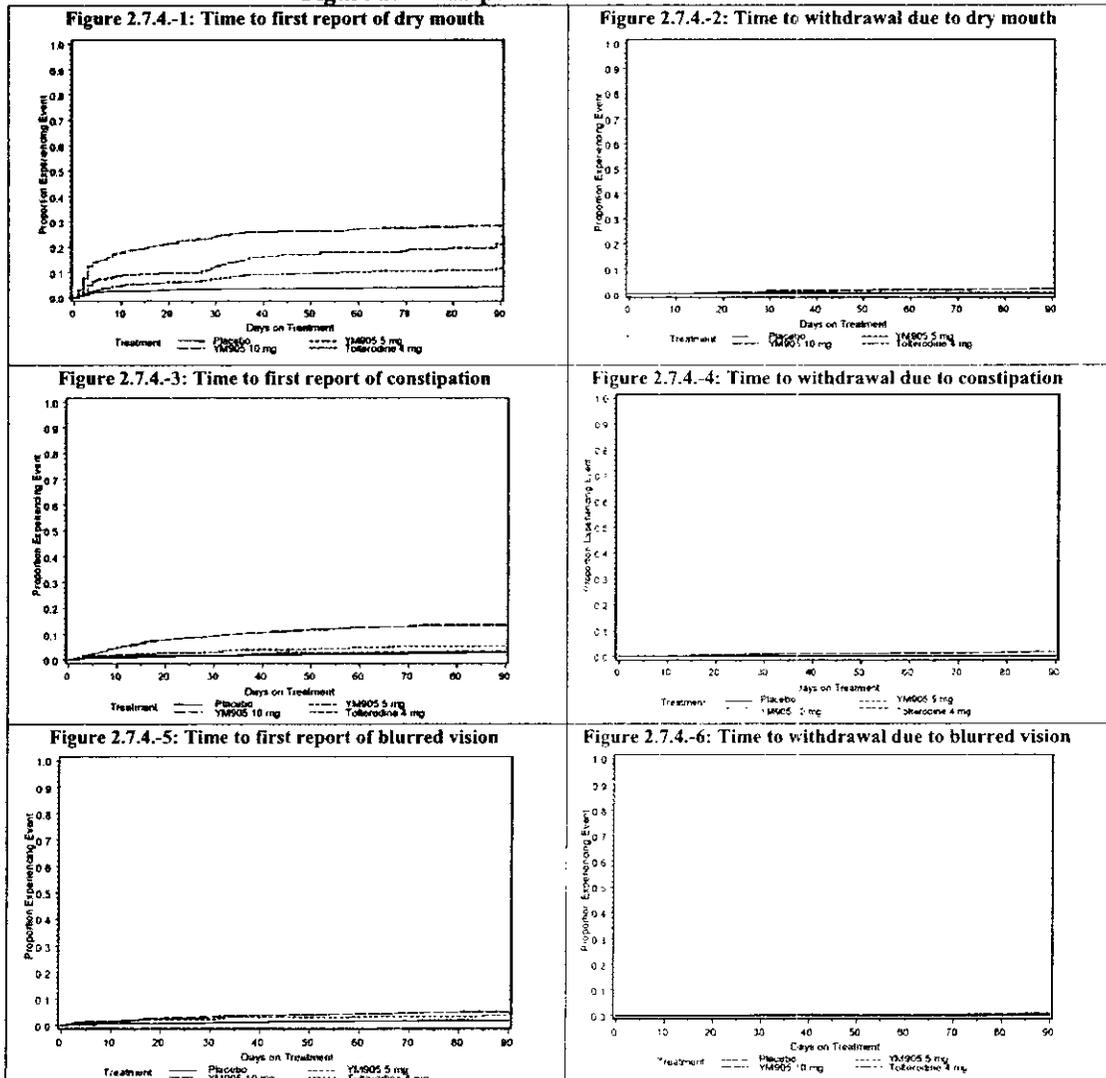
System Organ Class MedDRA preferred term	Combined Studies (013/014, 015/018): n (%)			
	Placebo	YM 905 5 mg	YM 905 10 mg	Tolter 4 mg
Number of patients	1216	578	1233	263
Number of patients with any AE	634 (52.1)	265 (45.8)	773 (62.7)	127 (48.3)
Gastrointestinal disorders	198 (16.3)	117 (20.2)	495 (40.1)	69 (26.2)
Dry mouth	51 (4.2)	63 (10.9)	340(27.6)	51 (19.4)
Constipation	35 (2.9)	31 (5.4)	165 (13.4)	8 (3.0)
Nausea	24 (2.0)	10(1.7)	40(3.3)	3 (1.1)
Dyspepsia	12 (1.0)	8 (1.4)	48 (3.9)	4 (1.5)
Abdominal pain upper	12 (1.0)	11 (1.9)	15 (1.2)	4 (1.5)
Vomiting NOS	11 (0.9)	1 (0.2)	14 (1.1)	0
Infections and infestations	189 (15.5)	67 (11.6)	182 (14.8)	23 (8.7)
UTI NOS	34 (2.8)	16 (2.8)	59 (4.8)	2 (0.8)
Nervous system disorders	113 (9.3)	29 (5.0)	114 (9.2)	16 (6.1)
Headach NOS	55 (4.5)	11 (1.9)	52 (4.2)	12 (4.6)
Musculoskeletal & connective tissue	94 (7.7)	22 (3.8)	92 (7.5)	14 (5.3)
Eye disorders	52 (4.3)	32 (5.5)	99 (8.0)	8 (3.0)
Vision blurred	22 (1.8)	22 (3.8)	59 (4.8)	4 (1.5)
Dry eye NOS	7 (0.6)	2 (0.3)	20(1.6)	0
General disorders	62 (5.1)	16 (2.8)	83 (6.7)	13 (4.9)
Renal and urinary disorders	41 (3.4)	17 (2.9)	60 (4.9)	13 (4.9)
Urinary retention	7 (0.6)	0	17 (1.4)	0
Dysuria	5 (0.4)	2 (0.3)	9 (0.7)	3 (1.1)
Psychiatric disorders	41 (3.4)	10(1.7)	41 (3.3)	6 (2.3)
Respiratory disorders	30 (2.5)	3 (0.5)	55 (4.5)	5 (1.9)
Cough	3 (0.2)	1 (0.2)	13 (1.1)	1 (0.4)
Vascular disorders	27 (2.2)	16 (2.8)	22 (1.8)	5 (1.9)
Hypertension NOS	7 (0.6)	8 (1.4)	6 (0.5)	3 (1.1)

In general, the largest percentage of patients who reported TEAEs had gastrointestinal disorders. Within this system organ class (SOC) the most commonly reported TEAEs were dry mouth, constipation and nausea. The incidence of blurred vision was relative low (<5% overall), but was consistently higher in solifenacin groups than in the placebo group. There were four solifenacin cases of SAEs related to constipation or other colon problems (#013-29005, and #019-21572 with constipation, #014-5024 and #019-20256 with fecal impaction,).

Adverse events by demographic subgroups: The results from analyses of adverse events by sex, by age, and by race in the 4 pivotal Phase 3 studies, plus the 2 Phase 2 studies (CL-005 and 006) and the 1 Phase 3 open-label, extension study (CL-016), showed that no clinically important differences in the AE profile of solifenacin were found by gender, by age, and by race.

Expected adverse events by time of onset: Kaplan-Meier curves displaying the time to event, by severity levels, for expected AEs, dry mouth, constipation, and vision blurred,

Figure 2: Kaplan-Meier curves for adverse events



The rates of reporting the first event of dry mouth, and constipation tended to be highest during the first 30 days, and then leveled off. The rate of blurred vision appeared to increase the first month, and then leveled off. The solifenacin 10 mg group showed the highest rate of all three expected AEs. The discontinuations due to dry mouth and constipation were also highest for solifenacin 10 mg group.

For open-label, extension studies CL-016 and CL-019

Table 33 Overall summary of TEAEs: Long-term vs. 12-wk exposure (US and EU)

	US		EU	
	CL-016 (10 mg)	NDA (12-wk)	CL-019 (5 mg)	NDA (12-wk)
Number of patients	1135	658	519	578
Number of patients with TEAEs	922 (81)	487 (74)	285 (55)	265 (46)
Number of SAEs	69	19	31	13
Number of patients with SAEs	51 (5)	17 (3)	21 (4)	13 (2)
Number of patients with AEs by severity				
Mild	250 (27)	171 (35)	148 (52)	157 (59)
Moderate	497 (54)	242 (50)	108 (38)	93 (35)
Severe	174 (19)	74 (15)	29 (10)	14 (5)
Number of patients discontinued				
Because of adverse events	193 (17)	65 (10)	28 (5)	16 (3)
Patients with drug-related AEs	632 (56)	372 (57)	182 (35)	171 (30)

Table 34 Number and % of subjects with TEAEs by system organ class (SOC): Extension studies

System Organ Class MedDRA preferred term	Long-term, open-label solifenacin	
	CL-016 (10 mg)	CL-019 (5 mg)
Number of patients	1135	519
Number of patients with any TEAEs	922 (81)	285 (55)
Gastrointestinal disorders	556 (49)	131 (25)
Dry mouth	344 (30)	72 (14)
Constipation	200(18)	31 (6)
Nausea	58 (5)	9 (2)
Dyspepsia	58 (5)	13 (3)
Abdominal pain upper	14 (1)	N/A
Vomiting NOS	19 (2)	N/A
Dry throat	12 (1)	N/A
Infections and infestations	338 (30)	103 (20)
UTI NOS	130 (12)	22 (4)
Nervous system disorders	149 (13)	32 (6)
Headach NOS	53 (5)	12 (2)
Musculoskeletal & connective tissue	193 (17)	34 (7)
Eye disorders	103 (9)	42 (8)
Vision blurred	43 (4)	37 (7)
Dry eye NOS	30(3)	N/A
General disorders	115 (10)	N/A
Renal and urinary disorders	138 (12)	31 (6)
Urinary retention	26 (2)	N/A
Dysuria	25 (2)	6 (1)
Skin & subcutaneous tissue disorders	97 (9)	N/A
Dry skin	13 (1)	
Respiratory disorders	104 (9)	15 (3)
Cough	24 (2)	7 (1)
Vascular disorders	34 (3)	33 (6)
Hypertension NOS	18 (2)	16 (3)

7.3.4 Treatment-emergent adverse events leading to discontinuation

For the 4 pivotal Phase 3 studies combined, a total of 179 patients discontinued because of adverse events: 66 (5.4%) placebo patients, 21 (3.6%) solifenacin 5 mg patients, 85 (6.9%) solifenacin 10 mg patients, and 7 (2.7%) tolterodine 2 mg bid patients. The 4 TEAEs most commonly associated with discontinuation were antimuscarinic side effects, for placebo, solifenacin 5 mg, solifenacin 10 mg and tolterodine 2 mg bid, respectively, dry mouth (3 [0.2%], 3 [0.5%], 25 [2.0%], and 2 [0.8%]); constipation (3 [0.2%], 1 [0.2%], 20 [1.6%], and 1 [0.4%]); nausea (6 [0.5%], 1 [0.2%], 11 [0.9%], and 1 [0.4%]); and blurred vision (2 [0.2%], 1 [0.2%], 7 [0.6%], and 0)

Other TEAEs leading to discontinuation and occurring in more than 1 solifenacin patient and more often than in the placebo group were: dyspepsia, gastroesophageal reflux, abdominal pain upper, dizziness, headache, urinary retention, micturition urgency, urinary hesitation, difficulty in micturition, dysuria, incontinence, urinary tract infection, GGT increased, dry throat, dry eye NOS, vision abnormal NOS, liver function abnormal, and dry skin.

In long-term, open-label studies, the rates of discontinuation due to AEs were higher than with 12-wk treatment (for Study CL-016, 17% vs. 10%; for Study CL-019, 5% vs. 3%). Most discontinuations were caused by antimuscarinic events (dry mouth, constipation, dyspepsia, nausea, and blurred vision), which were the same as in 12-week studies.

Discontinuation secondary to urinary retention or constipation:

Table 35 Patients with constipation or urinary retention leading to interruption or discontinuation of treatment requiring intervention: Combined Phase 2/3 Studies

	Combined Phase 2/3 Studies (005, 006, 013, 014, 015, 018, 016): n (%)				
	Placebo	YM905 5 mg	YM905 10 mg	YM 905 20 mg	Tolter 4 mg
Number of patients	1307	667	1768	91	300
Number of patients with any AE	681	310	1117	67	150
Urinary retention:					
Number of patients who interrupted or discontinued treatment	1 (0.08)	0	9 (0.5)	1	0
Number of patients who required other therapy	0	0	4 (0.2)	1	0
Constipation					
Number of patients who interrupted or discontinued treatment	3 (0.2)	2 (0.3)	37 (2.1)	2	1
Number of patients who required other therapy	2 (0.2)	1 (0.15)	4 (0.2)	0	1

In long-term open-label studies, solifenacin treatment was discontinued in five patients (all at 10 mg) of Study CL-016 and three patients (two at 10 mg and one at 5 mg) of Study CL-019 because of urinary retention.

7.3.5 Expected antimuscarinic events:

In combined US and EU Phase 2/3 studies (005, 006, 013/014, 015/018, 016 and 019), constipation was reported in 2.7% of patients on placebo, 6.1% on solifenacin 5 mg, 12.6% on solifenacin 10 mg, and 2.7% on

tolterodine, respectively. A total of 45 patients discontinued treatment because of constipation. The incidence was higher with 10 mg solifenacin than with 5 mg or with placebo. Of the patients who discontinued study drug, 8 required other therapy for constipation: 2 placebo, 1 solifenacin 5 mg (Patient #015-10763), 4 solifenacin 10 mg (Patients #013-6037, #013-30012, #013-35010, and #015-11923), and 1 tolterodine 2 mg bid (Patient #015-11970). Other therapies for constipation included dietary adjustments, medication, and enemas. In 4 patients (#013-29005; #014-5024; #019-20256, and #019-21572), constipation resulted in hospitalization because of fecal loading and fecal impaction.

Urinary retention was seen in 0.6% of patients on placebo, 0% on solifenacin 5 mg, and 1.5% on solifenacin 10 mg. In many patients, this was reported as an adverse event of increased post-residual volume on ultrasound, which was coded in MedDRA as urinary retention. Nine patients on solifenacin 10 mg withdrew from the study because of urinary retention. Five patients reported urinary retention that required other therapy: 4 on solifenacin 10 mg (Patients #013-17010, #014-7019, #016-23005, and #016-29013) and 1 on solifenacin 20 mg (Patient #005-6218). In Study 905-CL-022, at the 30 mg dose level, one patient (Subject # 022-15) required hospitalization and catheterization for urinary retention.

Table 36 Number & % of patients with expected antimuscarinic events:
Long-term vs. 12-wk exposure (US and EU)

	US		EU	
	CL-016 (10 mg)	NDA (12-wk)	CL-019 (5 mg)	NDA (12-wk)
Number of patients	1135	658	519	578
Dry mouth	344 (30)	212 (32)	72 (14)	63 (11)
Constipation	200 (18)	117 (18)	31 (6)	22 (4)
Blurred vision	43 (4)	25 (4)	37 (7)	31 (5)
Urinary retention	N/A	N/A	2 (0.4)	0 (0)

7.3.6 Laboratory values abnormal reported as adverse events

Study CL-013: Study drug was discontinued in 1 placebo patient (Patient #013-24022) and 1 patient on solifenacin 10 mg (Patient #013-34001) because of elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Patient 013-34001 (female) had elevated ALT and AST at baseline, which further increased at Wk 4 (from 49 U/L to 95 U/L for ALT and from 36 U/L to 85 U/L for AST) when study drug was discontinued. Her bilirubin level remained normal (0.3 mg/dL at baseline and 0.5 mg/dL at Wk 4. (About 8 months later, the patient's AST and ALT had returned to normal.)

Study CL-014: Elevated ALT and AST in three (0.9%) solifenacin patients (patients #29003, #33009 and #34021) (vs. none in the placebo group), led to discontinuation.

Table 37 3 YM905 patients with abnormal liver function tests led to discontinuation (AST & ALT: IU/L)

Patient	#29003				#33009				#34021			
	Base	WK 4	WK 8	WK 12	Base	WK 4	WK 8	WK 12	Base	WK 4	WK 8	WK 12
AST	65	51	234	297	54	79	81	52	27	61		
ALT	104	52	254	304	97	140	141	88	60	115		

#29003: Discontinued Day 62. 105 days after, AST and ALT remained high (161, 143, respectively), with Hepatitis A history as well as an evaluation suggestive of auto immune hepatitis. His alkaline phosphatase and bilirubin remained normal.

#33009: Discontinued Day 35. 56 days after, AST and ALT returned to baseline.

#34021: Discontinued Day 43. 40 days after, AST and ALT returned to normal

Normal range for #29003: AST 9-34 U/L, ALT 6-32 U/L; for #33009 and #34021: ALT 11-36 IU/L, ALT 6-43 IU/L.

Study CL-015: There was no clinically relevant effect of treatment on laboratory safety parameters. For 9 patients, the laboratory abnormalities were considered treatment-related by the investigator. Elevated liver function tests which were assessed by the investigator as treatment-related AEs were in 3 (#11427, #10626,

#11088) of the solifenacin 5 mg (all as mild or moderate), 1 (#10969) of the solifenacin 10 mg (mild), and 1 (#11984) of the tolterodine (mild) groups.

Table 38 Abnormal liver function tests in five patients treated with Solifenacin

Liver function	#11427		#10626		#11088		#10969		#11984	
	Screen	End	Screen	End	Screen	End	Screen	End	Screen	End
AST	109	183	14	91						
ALT	101	127	12	179					33	69
γ-GT	256	705	25	149			59	133	89	170
ALKP									227	504
Bilirubin					9.1	24.9				

#11427 and #10626: Normal range: AST 1-30, ALT 1-32 and γ-GT 6-32 IU/L.

#11088: Normal range: bilirubin 1.7-18.8 μmol/L.

#10969: Normal range: γ-GT 6-32 IU/L.

#11984: Normal range: ALT 1-39 IU/L, γ-GT 10-49 IU/L, ALKP 98-277 IU/L.

For patients with elevated liver enzymes, serum bilirubin remained within normal limits. Patient #11088 had mild elevated bilirubin but with liver enzymes within normal limits.

Study CL-018: Elevated liver function tests which were assessed by the investigator as treatment-related AEs were in 2 (#21563, #21095) in the solifenacin 5 mg group and 2 (#20817, #21130) in the solifenacin 10 mg group.

Table 39 Abnormal liver function tests in four patients treated with Solifenacin

Liver function	#21563		#21095		#20817		#21130	
	Screen	End	Screen	End	Screen	End	Screen	End
γ-GT	147	213	41	84	32	222	34	107
ALKP			270	279				

#21563: Normal range: γ-GT 10 - 49 IU/L.

#21095: Normal range: γ-GT 6-32 IU/L, ALKP 98-277 IU/L.

#20817 and #21130: Normal range: γ-GT 6-32 IU/L.

There was no clear dose-related pattern. For those patients with elevated liver enzymes, serum bilirubin remained within normal limits.

7.4. Clinical laboratory evaluations

Analysis of routine clinical laboratory parameters indicated no evidence of influence of solifenacin on hematology analytes, clinical chemistry analytes, or urinalysis parameters.

7.5. Vital signs, physical examinations findings, and other observations related to safety

Analysis of vital signs data showed no evidence of influence of solifenacin on systolic blood pressure, diastolic blood pressure, or pulse rate.

7.6. Discontinuation

Total discontinuation rates were: 18% in US pivotal Phase 3 studies (013/014), 12% in EU pivotal Phase 3 studies (015/018); 42% in US Phase 3 open-label extension study (016), and 19% in EU Phase 3 open-label extension study (019). The discontinuation rates due to adverse events (AEs) were 10%, 3%, 17%, and 5% for Phase 3 pivotal US studies (013/014), 3 pivotal EU studies (015/018), Phase 3 open-label, extension US study (016), and Phase 3 open-label, extension EU study (019), respectively.

Table 40 Discontinuation in Phase 3 clinical studies

	12-week Phase 3 pivotal studies		Long-term, open-label studies	
	US Studies (013/014)	EU Studies (015/018)	US Study (016)	EU Study (019)
Discontinuation (%)	18%	12%	42%	19%
Discontinuation due to Adverse Events	10%	3%	17%	5%

7.7. Hepatic effects

Examination of ALT, AST, bilirubin, alkaline phosphatase (ALKP), and γ -GGT was done to investigate the potential effects of solifenacin on hepatic function.

Table 41 Number and % of patients with one or more TEAVs[#] for Hepatic function analytes 1x, 3x, or 10xULN from combined 4 pivotal Phase 3 US & EU studies

Hepatic function Analyte (Limit multiple)	Placebo n (%)	YM905 5 mg n (%)	YM905 10 mg n (%)	Tolterodin 4 mg n (%)
Number of patients	1216	578	1233	263
ALT				
Abnormal	89 (7.3)	41 (7.1)	68 (5.5)	16 (6.1)
3xULN	6 (0.5)	6 (1.0)	6 (0.5)	2 (0.8)
10xULN	1 (0.1)	0	0	0
AST				
Abnormal	70 (5.8)	19 (3.3)	48 (3.9)	4 (1.5)
3xULN	2 (0.2)	3 (0.5)	3 (0.2)	0
10xULN	1 (0.1)	0	0	0
Bilirubin				
Abnormal	68 (5.6)	11 (1.9)	69 (5.6)	1 (0.4)
3xULN	0	0	0	0
10xULN	0	0	0	0
ALKP				
Abnormal	38 (3.1)	32 (5.5)	46 (3.7)	10 (3.8)
3x ULN	1 (0.1)	0	0	0
10x ULN	0	0	0	0
γ-GGT				
Abnormal	61 (5.0)	51 (8.8)	74 (6.0)	21 (8.0)
3xULN	29 (2.4)	16 (2.8)	22 (1.8)	5 (1.9)
10xULN	2 (0.2)	2 (0.3)	0	0
All 5 analytes				
Abnormal	0	0	0	0
3xULN	0	0	0	0
10xULN	0	0	0	0

[#]TEAV: treatment emergent abnormal value

The results showed that the active treatment groups were not distinguished from the placebo group, indicating no evidence of influence of solifenacin on hepatic function as assessed by ALT, AST, bilirubin, ALKP and γ -GGT.

Reviewer's comments: This reviewer did his own analysis with the raw data in IAS submitted by the sponsor. For the patients with normal analytes at the baseline and 3xULN during the treatment, or with abnormal values up to 3xULN at the baseline and further higher abnormal values, there were 19 in placebo group, and 26 in solifenacin 5 mg and 10 mg group for the combined Phase 3 US and EU studies. There were 2 placebo patients, 2 solifenacin 5 mg patients, and 1 solifenacin 10 mg patient who had values 10xULN for at least one hepatic-related analyte.

Table 42 Solifenacin patients with 10xULN values of liver function tests from Phase 3 and extension studies

Study ID	Patient ID	Solifenacin	Visit	Maximum normalized value				
				ALT	AST	Bilirubin	ALKP	γ-GGT
015	#11427	5 mg	Screening	3.45	3.48	0.20	0.43	9.62
			Week 12	4.34	5.87	0.40	0.68	26.88*
016	#1306020	10 mg	Month 0	0.92	1.04	0.10	0.33	4.13
			Month 3	1.08	1.00	0.10	0.36	4.09
			Month 6	1.77	1.32	0.20	1.08	14.42*
			Month 9	1.12	1.04	0.10	0.90	12.93*
018	#20664	5 mg	Screening	1.38	0.81	0.89	0.51	4.92
			Week 12	3.48	0.74	0.70	0.72	14.69*

For the US open-label, extension study (CL-016), this reviewer finds that there were 7 new patients receiving solifenacin 10 mg with normal analytes at the baseline and 3xULN during the treatment, or with abnormal values up to 3xULN at the baseline and further higher abnormal values. The sponsor reported in this study 016, 14 patients (with placebo or solifenacin in the double blind treatment period) had elevations of 3xULN in GGT, SGPT or SGOT, and one (Patient 1306020) had a GGT 10xULN. Patient #1306020 was a 77-year-old woman (on placebo during the double-blind study), after 5 months of treatment, had elevated γ-GGT (10xULN), which was considered moderate and possibly related to study drug. No therapy was required.

For Study 019, there were no detailed data available at this moment. The sponsor only claimed that no patient had 3xULN in bilirubin, and "occasional liver enzyme elevations" were reported.

Further analysis showed, there was no patient in these studies with treatment-emergent abnormal bilirubin (hyperbilirubinemia) with an associated treatment-emergent elevation in AST or ALT that was at least 3xULN; and there was no patient with increases of 3xULN for ALT, AST, bilirubin, ALKP or γ-GGT, combined with jaundice or other events relating to hepatic function.

Reviewer's comment: This reviewer considers that there is no sign to indicate there is significant hepatic toxicity associated with solifenacin 5 mg or 10 mg treatment.

This reviewer notifies that there was a case report from the Study 905-CL-038 conducted in Japan: Patient #2001 was a 69-year-old woman with a medical history of hyperthyroidism. She was enrolled in Phase 2 Study 905-CL-038 at 5 mg solifenacin once daily. Six months after the start of solifenacin treatment, she started taking a herbal medicine of saibokutou for discomfort of the pharynx. Ten days later her liver function tests showed abnormalities. At the 28th-study-week (193 days under solifenacin) the solifenacin was stopped upon the patient's request. Six days later she was urgently admitted to another hospital without consciousness. She was diagnosed as acute interstitial pneumonia and hypoxemia. Her medical status went into remission 4 days after hospitalization under steroid therapy, but her liver function tests showed further deterioration. Her discharge diagnosis was motor speech disorder due to cerebral infarction, and the relationship between interstitial pneumonia and cerebral infarction could not be completely rule out. The investigator judged the event was not related to the study medication solifenacin based on the results of a special test called drug lymphocyte stimulation test (DLST):

Table 43 Summary of results of liver function test from a female patient in Japan

Test (normal range IU/L)	Baseline	3 weeks	8 weeks	13 weeks	27 weeks	Interrupt	Follow-up	
AST (10-40)	25	20	17	21	155	89	64	18
ALT (5-45)	20	16	15	18	164	152	84	32
γ-GGT (16-73)	30	25	21	21	465	632	1233	93
ALKP (104-338)	489	364	415	334	1150	1733	443	N/A

Results of DLST

	Herb medicine Saibokutou	solifenacin
~	Negative	N/A
~	Positive	Negative

Reviewer's comment: The specificity of the DLST and its clinical impact are known to this reviewer. The true relationship between the event and solifenacin needs to be further investigated.

7.8. Potential effects on Cardiac Repolarization (QT Prolongation)

Preclinical studies showed:

- Solifenacin inhibited the potassium current in Chinese hamster ovary (CHO) cells stably expressing the HERG channel (using the whole-cell patch technique) at an IC₅₀ value of 0.27 micromolar.
- Solifenacin at concentrations of 0.003, 0.03, and 0.3 micromolar had no effect on resting membrane potential, upstroke amplitude, or maximum rate of depolarization or action potential duration in an isolated dog Purkinje fiber preparation
- An inconsistent effect on the QT interval was observed in some dogs treated with 30 mg/kg/day of solifenacin for 4 weeks. QT interval values, however, remained within the normal range.

The ECG observations from all clinical studies, with special attention to effects on QTc, were reviewed. Study CL-022 for QTc investigation was reviewed by Cardio-Renal Division ins consultation and also by the clinical pharmacology reviewers.

In the Phase 3 studies in the US (013/014) and EU (015/018) ECG were obtained at baseline and endpoints.

**Table 44 Summary of QTc (Fridericia) changes from baseline Mean (95% confidence interval) (msec)
For the Phase 3 studies**

Study ID		Placebo	Solifenacin		Tolterodine 2 mg bid
			5 mg	10 mg	
013	Mean change from baseline	2.3 (-0.0-4.6)		6.6 (4.3-9.0)	
	Difference from baseline ¹			4.3 (1.1-7.6)	
	Adjusted mean change from baseline ²	2.0 (-0.2-4.3)		6.7 (4.4-9.1)	
	Adjusted difference from baseline ²			4.7 (1.8-7.6)	
014	Mean change from baseline	1.7 (-0.7-4.1)		6.2 (3.6-8.7)	
	Difference from baseline ¹			4.5 (1.0-8.0)	
	Adjusted mean change from baseline ²	0.6 (-1.8-3.1)		5.9 (3.6-8.3)	
	Adjusted difference from baseline ²			5.3 (2.2-8.4)	
013 +	Mean change from baseline	2.0 (0.3-3.7)		6.4 (4.7-8.1)	
	Difference from baseline ¹			4.4 (2.0-6.8)	
	Adjusted mean change from baseline ³	1.2 (-0.5-2.9)		6.2 (4.5-7.9)	
	Adjusted difference from baseline ³			5.0 (2.9-7.1)	
015	Mean change from baseline	-3.4 (-6.7-0.2)	1.5 (-1.6-4.7)	3.7 (0.4-7.0)	0.1 (-3.0-3.3)
	Difference from baseline ¹		5.0 (0.5-9.5)	7.1 (2.5-11.8)	3.6 (-1.0-8.1)
	Adjusted mean change from baseline ⁴	-2.9 (-6.0-0.2)	1.7 (-1.3-4.7)	2.3 (-0.8-5.4)	1.7 (-1.4-4.7)
	Adjusted difference from baseline ⁴		4.6 (0.8-8.4)	5.2 (1.2-9.2)	4.6 (0.7-8.4)
018	Mean change from baseline	-0.5 (-3.6-2.6)	0.7 (-2.3-3.8)	2.2 (-0.9-5.3)	
	Difference from baseline ¹		1.2 (-3.1-5.6)	2.7 (-1.6-7.1)	
	Adjusted mean change from baseline ⁴	-0.7 (-3.7-2.2)	0.7 (-2.2-3.6)	2.5 (-0.4-5.4)	
	Adjusted difference from baseline ⁴		1.4 (-2.4-5.3)	3.2 (-0.6-7.1)	

¹Simple difference from Placebo (no adjustment)

²ANOVA (adjusted by center, baseline, and treatment)

³ANOVA (adjusted by center, baseline, and treatment)

⁴ANOVA (adjusted by center, baseline, and treatment)

Patients on solifenacin 10 mg had a mean increase from placebo in QTc of 4.7 msec in Study 905-CL-013 and of 5.3 msec in Study 905-CL-014 (Fridericia correction). And there were increases of 4.6 and 1.4 msec for solifenacin 5 mg patients, 5.2 and 3.2 msec for solifenacin 10 mg patients (Fridericia) from the placebo in EU studies 015 and 018, respectively.

Reviewer's comment: The sponsor used Fridericia correction for QTc correction in most recent fax submission. Clinical Pharmacology reviewer performed the QTc (Fridericia) calculations.

In the US studies, two patients (both women) on solifenacin had a QTc increase of >60 msec during the study (Patients #014-270003 and #014-50011), and 3 patients, 1 in Study 905-CL-013 (#14014) and 2 in Study 905-CL-014 (#27003 and #23010), had a QTc >500 msec at some time point during treatment. (Bazett, Appendix A and B)

In the EU Study CL-015, a QTc > 500 msec occurred in 2 patients, one on solifenacin 10 mg (#10158) at end of study and 1 on tolterodine at screening. Increases in QTc of >60 msec were comparable in the 4 groups (3, 3, 3, and 2 on placebo, solifenacin 5 mg, solifenacin 10 mg, and tolterodine, respectively). In EU Study CL-018, the numbers of patients with a change from baseline QTc >60 msec were 1, 3 and 1 in the 5 mg, 10 mg and placebo groups, respectively. One patient in the placebo group had a QTc of ≥500 msec at the end of treatment. Four patients in the 10 mg solifenacin group had a QTc ≥500 msec before treatment but not at the end of treatment. (Bazett, Appendix C and D)

Outlier Baseline-corrected QTc and QTc for US studies 013 and 014

Table 45 Outlier Baseline-corrected QTc and QTc for Study 013^a

Treatment Group	Gender	Age	Baseline-corrected QTc		QTc	
			>30 and <60 msec	> 60 msec	>450 and <500 msec	>500 msec
Placebo	Female	18 - 59	10 (1.51)	0 (0)	13 (1.97)	0 (0)
Placebo	Female	59 - 89	10 (1.55)	0 (0)	31 (4.81)	0 (0)
Placebo	Male	18 - 59	9 (6.16)	0 (0)	0 (0)	0 (0)
Placebo	Male	59 - 89	2 (1.73)	0 (0)	0 (0)	0 (0)
Drug	Female	18 - 59	15 (2.38)	0 (0)	19 (3.01)	0 (0)
Drug	Female	59 - 89	18 (2.86)	0 (0)	36 (5.72)	0 (0)
Drug	Male	18 - 59	2 (1.33)	0 (0)	1 (0.67)	0 (0)
Drug	Male	59 - 89	4 (2.53)	0 (0)	8 (5.06)	0 (0)

^aData presented as number of outliers (percentage of total)

Table 46 . Outlier Baseline-corrected QTc and QTc for Study 014^a

Treatment Group	Gender	Age	Baseline-corrected QTc		QTc	
			>30 <60 msec	> 60 msec	>450 <500 msec	>500 msec
Placebo	Female	22 - 60	10 (1.56)	0 (0)	16 (2.49)	0 (0)
Placebo	Female	60 - 89	12 (2.02)	0 (0)	23 (3.87)	0 (0)
Placebo	Male	22 - 60	2 (2.00)	0 (0)	4 (4.00)	0 (0)
Placebo	Male	60 - 89	5 (2.87)	0 (0)	4 (2.30)	0 (0)
Drug	Female	22 - 60	6 (0.98)	1 (0.16)	17 (2.76)	0 (0)
Drug	Female	60 - 89	20 (3.14)	2 (0.31)	44 (6.92)	2 (0.31)
Drug	Male	22 - 60	9 (6.92)	0 (0)	2 (1.53)	0 (0)
Drug	Male	59 - 89	2 (1.44)	0 (0)	9 (6.47)	0 (0)

^aData presented as number of outliers (percentage of total)

A phase 1 clinical pharmacology study 905-CL-022 study was conducted to evaluate the effect on QTc of escalating multiple-doses of solifenacin administered daily QD in healthy male and pre- and post-menopausal female volunteers.

The objective of Study R905-CL-022 was to determine the pharmacokinetic/pharmacodynamic (PK/PD) effect interaction of escalating multiple doses of solifenacin on QTc parameters in men, pre- and postmenopausal women (n=20/group). This study was an open-label, one-sequence crossover, escalating multiple-dose, pharmacokinetic/pharmacodynamic (PK/PD) study of the effect of solifenacin on QTc and other electrocardiographic (ECG) parameters. Subjects sequentially received placebo once daily for 2 days and then escalating doses (10 mg to 50 mg) of YM905 for 14 days each, administered orally once daily (QD) with 240 mL water as described below:

Days 1-2: Placebo x 2 days (1 placebo tablet/day)
Days 3-16: 10mg solifenacin x 14 days (1 x 10mg tablet/day)
Days 17-30: 20mg solifenacin x 14 days (2 x 10mg tablet/day)
Days 31-44: 30mg solifenacin x 14 days (3 x 10mg tablet/day)
Days 45-58: 40mg solifenacin x 14 days (4 x 10mg tablet/day)
Days 59-72: 50mg solifenacin x 14 days (5 x 10mg tablet/day)

Pharmacokinetics (PK) and Pharmacodynamics (PD)

Blood samples for PK analysis of solifenacin were collected as follows: 0 hour (prior to dose) and 1, 2, 4, 6, 8, 12, 16, and 24 hours after the solifenacin dose administered on Day 16, 30, 44, 58 and 64 or 68. In addition, blood samples for PK trough analysis of YM905 were collected at 0 hour (prior to dose) on Days 2 (baseline) 14, 15, 28, 29, 42, 43, 56 and 57. A 12-lead ECG and vital signs (including oral temperature, respiratory rate, and automated seated blood pressure and pulse) were obtained at 0 hour (predose) and approximately 1, 2, 4, 6, 8, 12, 16, and 24 hours after the solifenacin dose administered on Day 16, 30, 44, 58 and 64 or 68. In addition, a 12-lead ECG and vital signs were obtained at 0 hour (predose: steady-state) on Days 14, 15, 28, 29, 42, 43, 56, and 57.

Table 47 shows the demographics of the QT study.

Demographic	Gender Group			Overall
	Male	Premenopausal female	Postmenopausal female	
Age (years)				
N	20	20	20	60
Mean±SD	42.1±10.8	37.0±6.4	60.6±5.1	46.6±12.8
Median	41.0	38.0	61.0	43.0
(Min, Max)	(22,72)	23, 46)	(52, 68)	(22, 72)
Race				
African American	4 (20.0)	2 (10.0)	2 (10.0)	8 (13.3)
Asian	2 (10.0)	0	0	2 (3.3)
Caucasian	7 (35.0)	5 (25.0)	2 (10.0)	14 (23.3)
Hispanic	7 (35.0)	13 (65.0)	16 (80.0)	36 (60.0)
Enrollment Group				
01 through 14	7 (35.0)	3 (15.0)	4 (20.0)	14 (23.3)
15 through 34	8 (40.0)	5 (25.0)	7 (35.0)	20 (33.3)
35 through 48	3 (15.0)	6 (30.0)	5 (25.0)	14 (23.3)
49 through 60	2 (10.0)	6 (30.0)	4 (20.0)	12 (20.0)

Reviewer's comment: The ethnic distribution was: Caucasian 23%, African American 13.3%, Asian 3.3%, and dominant Hispanic at 60%.

Study drug exposure:

Treatment Dose	Number of Doses	Gender group			Overall
		Male	Premenopausal Female	Postmenopausal Female	
A: Placebo	2	20 (100.0)	20 (100.0)	20 (100.0)	60 (100.0)
B: 10 mg	14	20 (100.0)	20 (100.0)	20 (100.0)	60 (100.0)
C: 20 mg	12	0	1 (5.0)	0	1 (1.0)
	13	1 (5.0)	0	0	1 (1.7)
	14	19 (95.0)	19 (95.0)	20 (100.0)	58 (96.7)
D: 30 mg	3	0	0	1 (5.0)	1 (1.7)
	8	1 (5.0)	0	0	1 (1.7)
	14	18 (90.0)	19 (95.0)	19 (95.0)	56 (93.3)
E: 40 mg	14	11 (55.0)	16 (80.0)	15 (75.0)	42 (70.0)
F: 50 mg	6	1 (5.0)	5 (25.0)	3 (15.0)	9 (15.0)
	10	4 (20.0)	0	3 (15.0)	7 (11.7)

T_{max} occurred between 4 and 8 hrs post-dose in approximately half of the subjects.

Withdraw/discontinuation

	Placebo (N=60)	Solifenacin succinate				
		10 mg (N=60)	20 mg (N=60)	30 mg (N=58)	40 mg (N=42)	50 mg (N=16)
Completed treatment	60	60	58	56	42	16
Withdrawn-total	0	0	2	2	0	16
For adverse event			1	1		2
For withdrawn consent			0	1		0
For other reasons			1	0		14

The clinical pharmacology reviewer made the following comments:

- 1) The sponsor chose to define baseline as the **median** of 9 measurements on Day 2 of the **placebo** run-in. Analysis using these baseline measurements was performed along with the average of the 2 true baseline QT intervals (performed at screening and check-in).
- 2) Only one QT measure was used per point.
- 3) RR interval was not measured. Instead, RR was determined from HR. This doesn't account for intra-individual variability in RR length. QT correction (Bazett's correction) was made with HR, not RR.
- 4) No positive control arm was studied. Rationale for not including a positive control was not provided nor were any alternative methods to establish assay sensitivity.
- 5) All QT readings were rounded to the nearest 10 msec.

Results:

QT-RR Correction

The two most common QT correction methods are Bazett's and Fridericia's correction methods. Both corrections were performed with the submitted data. Using either the sponsor-defined baseline data or the true baseline data, the results suggest that the Fridericia correction is the more appropriate of the two.

Figure 3: QT_C vs. RR for Fridericia- and Bazett-corrected QT Intervals using True Baseline Measures

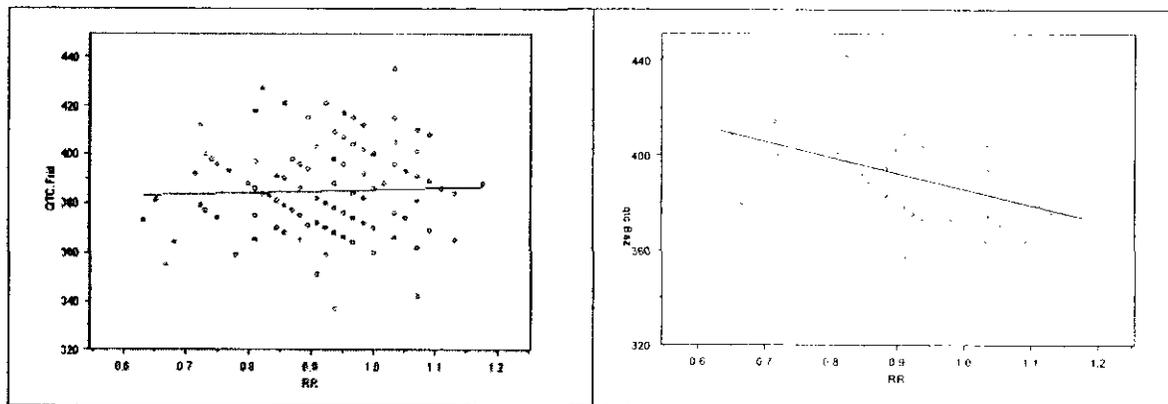


Table 50 Mean Change in baseline-corrected QTc (Fridericia) and Baseline- and placebo-corrected QTc (Fridericia) by Treatment Group

Treatment Group	Mean Change in Heart Rate (bpm)	Mean Change in baseline-corrected QTc (msec) ^a	Mean Change in baseline- and placebo-corrected QTc (msec) ^a
Placebo (N=540)	-0.34	0.89 (-0.95, 2.73)	-
10 mg (N=660)	-1.09	0.26 (-1.36, 1.87)	-1.44 (-3.12, 0.25)
20 mg (N=641)	0.33	3.46 (1.76, 5.15)	2.09 (0.35, 3.82)
30 mg (N=616)	1.70	0.77 (-1.03, 2.57)	0.31 (-1.52, 2.14)
40 mg (N=462)	2.42	-3.82 (-5.90, -1.74)	-5.39 (-7.65, -3.12)
50 mg (N=125)	1.52	-8.46 (-12.71, -4.21)	-12.41 (-16.88, -7.94)

^a Results reported as mean (95% confidence interval)

The results showed:

- The maximum mean change in mean change in baseline-corrected QTc (Fridericia) of 3.46 msec was detected at the dose of 20 mg
- There was no dose response for mean change in baseline-corrected QTc (Fridericia).
- There were only 16 patients in 50 mg group who all withdrew from the study prematurely.

Outlier Analysis

In order to examine those QT_C measures that were greater than 450msec, QT_C measures were plotted by subject for each administered dose. The results for Fridericia-corrected QT measures are presented in table 4.

Table 51 QT_C Measurements > 450msec

	QT _{CB} ^a	QT _{CF} ^b
N (> 450msec)	10 (0.33%)	1 (0.033%)
Max QT_C	468	462
Placebo	1	0
10mg	0	0
20mg	1	1
30mg	7	0
40mg	1	0
50mg	0	0

^aBazett-corrected QT interval^bFridericia-corrected QT interval

In examining Table 4, a number of points lie above the 450msec cutoff. As determined earlier, QT_{CF} is the more appropriate correction method in this investigation. Out of over 3000 (N = 3044) QT measurements, only 1 QT_{CF} interval was over 450msec (0.033%). Regardless of the correction method used, no corrected QT intervals were greater than 500msec.

Table 52 Outlier Values for Baseline-Corrected QT Interval Measurements^a

Category	ΔΔQT _C ^b		N
	30-60 msec	>60msec	
10mg	48 (7.27)	0 (0)	660
20mg	70 (10.92)	0 (0.0)	641
30mg	59 (9.58)	2 (0.32)	616
40mg	32 (6.93)	0 (0)	462
50mg	4 (3.20)	0 (0)	125
Caucasian	37 (5.87)	0 (0)	630
Hispanic	145 (9.86)	1 (0.07)	1470
African American	27 (8.54)	1 (0.32)	316
Asian	4 (4.54)	0 (0)	88
Male	13 (1.64)	0 (0)	794
Post-Meno Female	103 (11.99)	1 (0.12)	859
Pre-Meno Female	97 (11.40)	1 (0.120)	851
0 hour	40 (6.02)	0 (0)	665
1 hour	16 (6.96)	0 (0)	230
2 hour	17 (7.39)	1 (0.43)	230
4 hour	30 (13.04)	0 (0.00)	230
6 hour	27 (11.74)	0 (0.0)	230
8 hour	9 (3.91)	0 (0)	230
12 hour	25 (10.87)	1 (0.43)	230
16 hour	39 (16.96)	0 (0.0)	230
24 hour	10 (4.37)	0 (0)	229

^aresults presented as number of QT intervals (% of total)^bbaseline-corrected dose QTc minus baseline-corrected, time-matched placebo QTc

The above table shows the results of analyzing the baseline-corrected dose response minus the baseline-corrected, time-matched placebo response. These results are further sorted by race, sex, dose administered and time post-dose. Overall, 213 changes greater than 30msec and less than 60msec were measured and 2 greater than 60msec changes were recorded.

When sorted by time post-dose, higher incidences of outliers appeared at the 4 and 6 hour readings, as would be expected from the PK of the parent compound ($T_{max} = 4$ hours). Again, as seen in the Table 51, an increased incidence of outliers also occurred at the 16 hour post-dose reading.

Also the maximum mean or mean maximum change in QTc range of 9.077 msec occurred at 30 mg dose with mean maximum serum concentration of 204.10 ng/mL (Table 53).

Table 53 Mean Maximum Concentrations alongside Mean Change in QTc Range from Placebo

Dose (mg)	Mean Change in QTc Range (msec)	Mean Maximum Concentration	N
10	0.214	63.88	60
20	1.422	124.14	60
30	9.077	204.10	56
40	7.98	253.74	42
50	2.34	266.70	14

Pharmacodynamics reviewer's comments:

- All mean QTc changes were less than 10msec. However, when sorted by race, the upper bound of the 95% CI in Asians exceeded 10msec. It should be noted that this was the smallest subgroup and all readings came from 2 subjects.
- Due to the high variability in these readings, the outlier analysis gives a better sense of those subgroups at higher risk of QT prolongation. Those subgroups at higher risk include women (both pre- and post-menopausal), 20 and 30 mg treatment groups, Hispanics and African-Americans.
- When sorted by time post-dose, the most outliers occur at 4, 6 and 16 hrs post-dose. The 4- and 6-hr readings can be explained by the T_{MAX} of the parent compound. The 16-hr reading may be due to a lag effect of the parent compound or due to a metabolite with proarrhythmic potential (M3 or M4).

The mean changes in QTc corrected for baseline and placebo were less than 3 msec for all the treatment arms (10 mg – 50 mg doses). The highest mean change was in the 20 mg group. There are some limitations associated with the study and data (eg. absence of a positive control arm with a known QTc prolonging drug).

Comments from Cardio-renal consultant dated August 7 and November 20, 2001:

1. Heart rate does appear to be affected by solifenacin.
2. "There are important limitations to these data." Although the Division's review of November 21, 2001, recommended an assay-validating positive control, there is none in this study. The small diurnal variation in QTc, an effect that appears to be a few milliseconds difference between awake and asleep, might be exploited to show the study had the ability to resolve a small QT effect, but all of the data in this study are presumably from awake subjects, so this effect cannot be used to show assay sensitivity either. Consequently, one cannot be certain that a small QT effect would have been detected by this study. A Malik-style individualized QT correction is probably not feasible with these data, because there are not enough measurements off treatment. Acknowledging these limitations, the available data do not indicate an obvious problem.
3. The safety database has no events likely to represent arrhythmias.
4. The distribution in changes in QTcF appears to be fairly symmetric with respect to outliers high and low.
5. The study provided limited data beyond 40 mg, but this dose is a factor of four over the proposed maximum dose, providing some reassurance.
6. Solifenacin is predominantly metabolized by CYP 3A4, but ketoconazole only produced a 40% increase in plasma levels, so metabolic inhibition is not as large a factor as it might be.

7. Thus, for the most part, the setting – dose multiple, tolerance-limiting, pharmacokinetic insensitivity, lack of likely arrhythmia events – and the EKG data - lack of upward trend or high-end outliers – are reassuring. However, given the uncertainties in the discriminatory power, is that reassurance enough? The answer has to depend somewhat on the nature of the benefit achieved with treatment. For a small and unimportant symptomatic benefit, the degree of comfort is probably less than one might expect.
8. The Division Director “reinforced” the consultant’s comments “on the limited adequacy of this trial to exclude an effect on QT interval without the use of an active control or other means of assessing assay sensitivity.”

Most recently, a telecom was held with the sponsor on 10/03/2003 and a face to face meeting was taken place on 10/14/2003. And the sponsor further sent a fax to emphasize its point of view.

Summary

- Solifenacin inhibited the potassium current in Chinese hamster ovary (CHO) cells stably expressing the HERG channel (using the whole-cell patch technique) at an IC₅₀ value of 0.27 micromolar.
- The Phase 3 data appear to show an effect of solifenacin on the QTc interval (perhaps less than 5 msec). Four patients in the phase 3 studies taking solifenacin and one patient taking placebo had QTc values of >500 msec at some point during the trials.
- The results of the designated QT study 022 can be adequately interpreted. There is wide intrasubject variability and the lack of a positive control group and a true (concurrent) placebo group, preclude making conclusions concerning the presence and degree of QT prolongation.
- The opinion of the CardioRenal consultant is that, without further specific information including whether the ECGs were performed while the patients were asleep or awake and the relationship of the ECGs to meals, an opinion concerning the observed diurnal effects can not be confidently given.
- In spite of assuming that the drug prolongs the QT interval (as it appears to do in data from the Phase 3 trials, which the sponsor characterizes as approximately 5 msec), at this moment, there is no sufficient information available to adequately label the product for safe use.

Suggestion for resolving the deficiency of QTc issue

The sponsor should submit the results from a randomized, placebo-controlled study of solifenacin with the primary objective of determining the effect of solifenacin on the QT interval at clinically relevant ranges of plasma concentrations. This study should include a positive control, such as moxifloxacin, in order to assure assay sensitivity and to provide a benchmark for comparison with the QT effect of solifenacin.

7.9. CYP3A4 drug interactions

Based on the results with CYP isoenzymes, only CYP3A4 and CYP2C19 showed potential for metabolism of solifenacin to the major metabolite M2. In another similarly designed *in vitro* experiment with human liver microsomes, based on metabolite formations, it was concluded that CYP3A4 is responsible for the formation of metabolites M2, M3 and M4 under physiologic conditions.

Metabolic Drug-Drug Interactions:

The sponsor conducted several *in vivo* metabolic PK drug-drug interaction studies with solifenacin, as follows:

Effect of Other Drugs on Solifenacin

Sponsor conducted Study 905-CL-010 to determine the effect of 200 mg once daily dose of ketoconazole on the PK of solifenacin.

This was a single-site, open-label, single-sequence crossover PK DDI study. 17 healthy male and female subjects received a single 10-mg oral dose of solifenacin alone on Day 1 (Treatment A) followed 14 days later by 21 consecutive days of 200 mg qd ketoconazole. On the 21st day following starting the ketoconazole treatment, a single dose of 10 mg solifenacin was concomitantly administered with the ketoconazole (Treatment B).

Results:

Figure 4

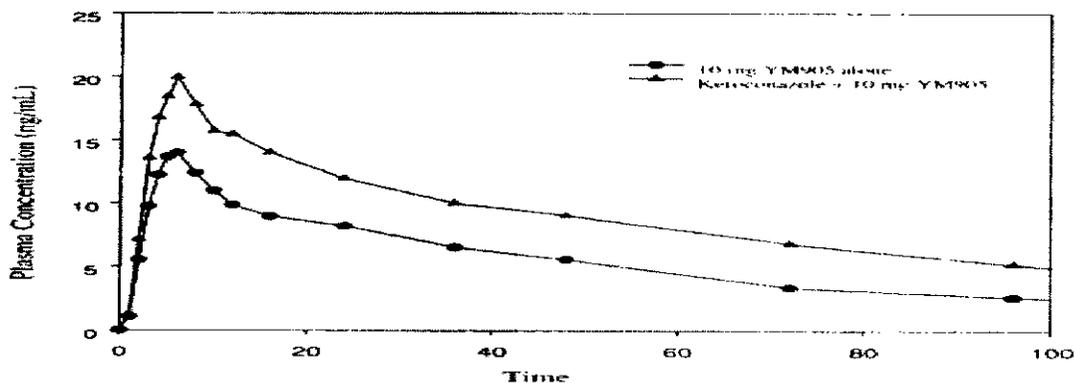


Figure 7.2-1 Mean plasma concentration-time profiles for YM905 from Treatments A and B

Note: For sake of clarity data are shown only up to 100 hours post dose.

Table 54 Comparison of primary and secondary PK parameters of YM905

Parameter	Units	Test Mean Trt B	Reference Mean Trt A	Point estimate Test/reference	90% Confidence Interval
C_{max}	ng/mL	20.4	14.5	141	(130, 152)
$\ln(C_{max})$		20.0	14.1	143	(129, 157)
AUC_{0-inf}	ng/mL	1407	714	197	(180, 214)
$\ln(AUC_{0-inf})$		1360	662	205	(184, 229)
$AUC_{0-\infty}$	ng·hr/mL	1499	765	196	(179, 213)
$\ln(AUC_{0-\infty})$		1447	716	202	(183, 223)
$t_{1/2}$	hr	77.6	49.3	158	(145, 170)
$\ln(t_{1/2})$		75.1	48.0	156	(146, 168)
t_{max}	hr	6.00	6.00	NA	NA

The results showed that there was an increase of 40% in C_{max} and a two fold increase in AUC when solifenacin was administered with ketoconazole, a potent CYP3A4 inhibitor.

More recently (6/16/2003), sponsor submitted the study report of a similar study (Study 905-CL-036) as the one described above using 400 mg qd ketoconazole.

Results:

- There was a mean increase of 2.7 and 2.8 fold in AUC_{last} and AUC_{inf} , respectively.
- There was a mean increase of 1.5 fold in C_{max} .
- There was a mean increase of 2.1 fold in $t_{1/2}$.

- As found in other studies, exposure in females were higher than males. However, the ratios of increases in PK parameters of solifenacin in the presence of 400 mg QD ketoconazole were similar.

Clin Pharm Reviewer's comments:

- Solifenacin is primarily metabolized in the liver by CYP3A4, and to a much lesser extent by CYP2C19. Additionally, solifenacin has an oral bioavailability of > 80%. Therefore, it is not expected that inhibition of CYP3A4 will lead to dramatic increases in exposure, and that was confirmed in these two studies.
- Observation of individual data did not indicate extreme outliers (3-4 fold increases in AUC was observed in some subjects concomitantly on 400 mg qd ketoconazole).
- In the limited scope of these studies, there was a trend in increase in GI related side effects (eg. dry mouth, constipation) in the combination arm as compared to only solifenacin with the 200 mg ketoconazole study. That trend was, however, not as clear in the 400mg ketoconazole study.
- The metabolites of solifenacin were not analyzed (or reported) in this study.
- There were sporadic incidences of QTc prolongation in both the studies based on individual ECGs in all treatment arms. However, a trend towards increases in QTc prolongation in the solifenacin + ketoconazole arm was *not* evident in either study.
- Based on the above information, it is recommended to not exceed a 5 mg dose of solifenacin when in combination with ketoconazole.

Reviewer's comment: Based on the studies, dose adjustment of solifenacin is warranted when administered with CYP3A4 simultaneously.

Studies exploring effect of solifenacin on other drugs conducted by the sponsor included solifenacin-drug interaction with digoxin, warfarin, and combined oral contraceptive. Pharmacokinetic aspects of these studies did not suggest clinical safety concern. No dosage adjustments is necessary when used concomitantly with these medications.

8. Use in Special Populations and Situations

8.1. Effects of Gender, Age, and Race:

There were 20 - 25 % increases in C_{max} , AUC and $t_{1/2}$ in the elderly as compared to the young. TEAEs in the Phase 3 pivotal studies were reviewed by age (<65 years, ≥65 years, ≥75 years); by gender (male, female); and by race (Caucasian, Black, Hispanic, Asian). No clinically important differences in the adverse event profile of solifenacin succinate were found by age, by gender, or by race for the categories examined.

Reviewer's comment: Based on both pharmacokinetic studies in healthy subjects and clinical trial experience in patients with OAB, it may concluded that no specific dosing adjustments based on age, gender, or race are necessary for safe use of solifenacin.

8.2. Pediatric Program:

There are no data in children submitted in this NDA.

8.3 Data available or needed in other populations such as renal or hepatic compromised patients

Effect of renal insufficiency

The effects of renal impairment on the elimination of solifenacin succinate were evaluated in Study 905-CL-021 in which the pharmacokinetics of solifenacin after a single 10 mg dose were compared in groups of 6 patients with mild, moderate and severe renal impairment with those in a reference group of healthy subjects. Oral clearance was reduced by approximately 20-25 % and half-life was increased by approximately 30 % in the mild and moderate groups; C_{max} was unaffected. However, in patients with severe renal impairment (CLCr ≤ 30 ml/min) exposure was significantly greater than in the controls with increase in C_{max} of about 30 %, AUC_{0-inf} of more than 100 % and $t_{1/2}$ of more than 60 %. There were a total of 26 AEs among the 18 renally impaired patients. Of the 26 AEs, 16 AEs were considered to be mild, 9 AEs were considered moderate, and 1 AE of muscle cramps was considered severe. Five of the 26 AEs were considered related to study treatment. The data indicate that dosage reduction should not generally be required in patients with mild to moderate renal impairment but that in patients with severe renal impairment solifenacin succinate should be used cautiously. Doses of solifenacin succinate over 5 mg are not recommended in these patients.

Reviewer's comment: Solifenacin should be administered with caution in patients with any level of renal sufficiency. No more than 5 mg solifenacin should be given to patients with severe renal impairment.

Effect of hepatic impairment:

Eight patients with hepatic impairment were given a single oral dose of 10 mg in Study 905-CL-026. Hepatic impairment affected the pharmacokinetics of solifenacin and its metabolites M2, M3, M4 and M5. A 2-fold increase in mean $t_{1/2}$ was observed in patients and a 1.4-fold increase in AUC_{0-inf} . Plasma concentrations of M2 and M4 were about 2-fold lower in patients, concentrations of M3 were comparable, while M5 concentrations were higher. These differences were also reflected in the amount excreted in urine.

The results of Study 905-CL-026 indicated that there was a 2-fold increase in $t_{1/2}$ and a 1.4-fold increase in AUC_{0-inf} of solifenacin in the moderately hepatic-impaired patients. It is recommended not to exceed a 5 mg daily dose of solifenacin in this group of patients.

Pregnancy

One pregnancy was reported in a subject treated with solifenacin during clinical trials. The pregnancy occurred in Study 905-CL-015. Patient #015-11661 was a 29-year old woman who was confirmed 7 days after the start of double-blind treatment with 5 mg solifenacin succinate to be pregnant for 4 weeks. Two days after the start of double-blind treatment study medication was discontinued, after suspicion of pregnancy. The patient gave birth to a healthy child later.

Reproduction studies have been performed in mice, rats and rabbits. Solifenacin has been shown to cross the placental barrier in mice. No embryotoxicity or teratogenicity was observed in mice treated with 30 mg/kg/day (1.2 times the exposure at the maximum recommended human dose [MRHD]). Solifenacin was not teratogenic in mice at up to 250 mg/kg/day (7.9 times the exposure at the MRHD), although reduced fetal body weights were observed at 100 mg/kg/day (3.6 times the exposure at the MRHD) or greater. Solifenacin succinate was not teratogenic in rats at up to 50 mg/kg/day (did not exceed the exposure at the MRHD) or in rabbits at up to 50 mg/kg/day (1.8 times the exposure at the MRHD). There are no adequate and controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human

response, solifenacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether solifenacin is excreted in human milk. Solifenacin should not be administered during nursing.

9. Conclusions and Recommendations

9.1 Final Safety Conclusions

Based on the ICH E1A guidance, the extent of population exposure was considered adequate to characterize and quantify the safety profile of solifenacin over a reasonable duration of time consistent with its intended long-term use.

The population studied had sufficient representation of men and women, ethnic groups, and a sufficient number of geriatric patients to provide reassurance that results from the population studied could be extrapolated to the target population. In addition, the major clinical studies included adequate representation of patients with comorbidities and concomitant medications typical of the expected user population.

The safety profile of solifenacin 5 mg and 10 mg did not reveal major unusual toxicity, nor were there major safety concerns that require special risk management efforts. Antimuscarinic adverse effects, such as dry mouth, constipation, and blurred vision, were common and occurred in early stages of treatment, and were generally mild or moderate in intensity, and were mostly tolerable.

A study was conducted to detect any potentially adverse effect of solifenacin on cardiac repolarization with the major deficiency of no positive control group.

Solifenacin 5 mg and 10 mg daily, is considered safe for use in the treatment of patients with OAB under the conditions put forth in the proposed labeling.

9.2 Recommendations on Approvability (Regulatory Action):

In the opinion of this reviewer, from a clinical standpoint, solifenacin at doses of 5mg and 10 mg, should be approvable for the indication "treatment of overactive bladder." The risks associated with the use of this drug are acceptable and can be managed adequately with labeling.

**APPEARS THIS WAY
ON ORIGINAL**

Appendix A

Clinical Trials 905-CL-013: A randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, multicenter study to assess efficacy and safety of daily oral administration of 10 mg YM905 (solifenacin succinate) versus placebo in male and female patients with overactive bladder (in the US)

A.1 Design

Studies 905-CL-013 was a randomized, double-blind, parallel-group, fixed-dose, multicenter study of 10 mg solifenacin succinate versus placebo, administered orally once daily for 12 weeks. Patients were evaluated at baseline and at 4, 8 and 12 weeks. The objective of the study was to confirm the efficacy of YM905 versus placebo in reducing the number of micturitions per 24h in patients with overactive bladder (OAB) and evaluate the safety and tolerability of YM905 in patients with OAB.

Inclusion criteria:

Symptoms of OAB (urinary frequency with urgency and/or incontinence), age ≥ 18 years, an average of ≥ 8 micturitions/24h, and either an average of ≥ 1 urinary incontinence episodes/24h or an average of ≥ 1 urinary urgency episode/24h, documented in a 3-day diary in the screening phase.

Exclusion criteria:

Stress incontinence, mixed incontinence with a predominant stress component, or neurological cause for detrusor overactivity.

Methodology:

This is a Phase 3, randomized, double-blind, parallel-group, fixed-dose, multicenter study of 10 mg YM905 versus placebo in the treatment of OAB (frequency, urgency, and/or urge incontinence). The study consisted of a 2-week screening/washout period, a 12-week double-blind treatment period, and a 2-week post-treatment follow-up period. Patients who completed the study had the option to enter an open-label extension study. Patients visited the clinic at screening (Visit 1); baseline (Visit 2); after 4 weeks (Visit 3); 8 weeks (Visit 4); and 12 weeks (Visit 5) of the double-blind treatment; and at the end of the follow-up period (for those who did not enter the extension study) (Visit 6).

Study drug regimen: Solifenacin succinate 10 mg tablet or identical placebo tablet once daily.

Primary efficacy endpoint: the primary endpoint was "mean change from baseline to endpoint in number of micturitions/24h." Micturition was defined as any voiding episode recorded by the patient in the 3-day diary as either "urinated" with or without "incontinence".

Secondary efficacy endpoints: mean change from baseline to endpoint in number of incontinence episodes/24h, number of urgency episodes/24h, mean volume voided/micturition, number of nocturnal voids/24h, and number of nocturia episodes/24h.

Safety was assessed via adverse events, clinical laboratory values (hematology, clinical chemistry, and urinalysis), vital signs, physical examination findings, 12-lead ECG, and post-void residual volume.

The study was initiated in February 2001 and the final study report reflects all available efficacy and safety data from all patients through October 2001. The final observation was on October 17, 2001. Study visits occurred at screening (1) baseline, (2) after 4 weeks, (3) 8 weeks, (4) 12 weeks, (5) at the end of follow-up, (6) or withdrawal from the study.

A.2. Study Population

A total of 672 patients from 33 centers randomized (332 placebo and 340 solifenacin succinate) took study drug and were included in the safety population. Of the 672 patients, 57 (23 for placebo and 34 for YM905) were excluded from the efficacy analysis, so that, the full-analysis set (FAS: all patients who were randomized, received at least one dose of double-blind treatment, had baseline diary data available and on-treatment diary data available) included 615 patients (309 placebo and 306 solifenacin succinate). The per protocol set (PPS: all patients who were randomized, received at least one dose of double-blind treatment, had baseline diary data available, had at least 8-weeks of on-treatment diary data available, had overall treatment compliance of at least 70%, and had no major protocol violations) included 533 patients (269 placebo and 264 YM905). The safety population (SAF: all patients who were randomized and received at least one dose of double-blind treatment) included all 672 randomized patients. There were no notable imbalances between treatment groups in demographic characteristics including age, gender, race, weight, and height. The study population was predominantly Caucasian (83%) and female (82%) with mean age of 58 years. A third of the study population was 65 years or older, and 76 patients (11%) were 75 years or older. The median time since start of symptoms OAB was approximately 5 years in both the placebo and YM905 groups (mean 9 years for both groups).

Table A1 Number of patients in study population

Patient groups	Placebo	YM905 10 mg	Total
Randomized	332	340	672
Treated	332	340	672
FAS	309	306	615
Completed	274	269 ^a	543 ^a
Dropouts	35	37	72
PPS ^b	269	264	533

^a one patient completed the study but had no baseline diary data and was thus not included in the FAS

^b PPS: per protocol set

Reviewer's comment: The treatment groups appeared to be well-balanced at the baseline with respect to important demographic characteristics

The percentage of patients at each visit during the treatment period (Weeks 4, 8, and 12) was similar between the placebo and YM905 groups for each population ranging from 96% to 100% for Week 4, 86% to 100% for Week 8, and 80% to 97% for Week 12 (Table A2). The small percentage of patients at the follow-up visit (10% to 12% for the 3 populations) was due to the fact that the majority of patients entered the open-label extension study (905-CL-016) and only patients who did not go on to the extension had the follow-up visit.

Table A2 Number of patients in each population by treatment group and study visit

Visit	SAF Population: n (%)		FAS population: n (%)		PPS population: n (%)	
	Placebo (N=332)	YM905 10 mg (N=340)	Placebo (N=309)	YM905 10 mg (N=306)	Placebo (N=269)	YM905 10 mg (N=264)
Screening/washout (Visit 1)	332 (100)	340 (100)	309 (100)	306 (100)	269 (100)	264 (100)
Baseline (Visit 2)	332 (100)	340 (100)	309 (100)	306 (100)	269 (100)	264 (100)
Week 4 (Visit 3)	320 (96)	329 (97)	309 (100)	306 (100)	269 (100)	264 (100)
Week 8 (Visit 4)	301 (91)	292 (86)	301 (97)	291 (95)	269 (100)	264 (100)
Week 12 (Visit 5)	281 (85)	273 (80)	281 (91)	272 (89)	257 (96)	255 (97)
Follow-up (Visit 6) ^a	37 (11)	39 (12)	34 (11)	37 (12)	28 (10)	30 (11)

^a Follow-up (Visit 6) visit reflects the number of patients who had a follow-up assessment (2 weeks post-treatment completion) regardless of study completion.

Reviewer's comment: The treatment groups were reasonably balanced in terms of numbers of patients available for analysis at each visit.

The majority of patients in the safety population reported no prior anticholinergic agent use and no history of non-drug treatment. Approximately half of the patients reported having a history of mixed incontinence with urge as predominant factor. Approximately 33% of all patients in the placebo group and 41% of all patients in the YM905 group took previous OAB medications with most common medications being oxybutynin (17% of placebo and 24% of YM905), and tolterodine (19% and 20%), respectively

The two treatment groups were balanced in terms of medical history. Over 86% of patients in the safety population had no history of therapy with biofeedback, exercises, electrical stimulation, behavioral therapy, pessaries, or implants. There were no notable differences between treatment groups in terms of previous treatments of OAB. There were no clinically relevant differences between the two treatment groups in the incidence or severity of baseline signs and symptoms.

Extent of study drug exposure: Mean exposure to study medication was 78 days in the placebo group and 75 days in the YM905 group. The frequency distribution for the number of days of exposure was similar between treatment groups, with the majority of patients in each treatment group exposed to study medication for at least 12 weeks.

Table A3 Study medication exposure (safety population, N=672)

Study Medication Exposure (days) ^a	Placebo (N=332)	YM905 10 mg (N=340)
	n	n
1 to 13 days	9	14
14 to 27 days	8	16
28 to 55 days	15	22
56 to 83 days	62	58
≥ 84 days	232	226
Unknown	6	4
Mean exposure	78 days	75 days

^a Length of treatment exposure is defined as the last day of treatment minus the first day of treatment plus one day. Last visit date is used if the date of last dose of study drug is unknown.

A.3 Withdrawals and compliance

The percentage of patients who prematurely discontinued from the treatment period was similar in the placebo (18%) and YM905 (21%) groups. In both treatment groups, the most common primary reason for discontinuation was adverse event (5% for placebo and 11% for YM905).

Table A4 Summary of study drug discontinuation by primary reason (safety population, N=672)

Disposition	Placebo ^a	YM905 10 mg ^a	Total ^a
Primary reason for discontinuation	n (%)	n (%)	n (%)
Number of patients randomized	332	340	672
Number of patients who received study drug	332 (100)	340 (100)	672 (100)
Number of patients who completed the study ^b	274 (82.5)	270 (79.4)	544 (81)
Number of patients who prematurely discontinued from the treatment period	58 (17.5)	70 (20.6)	128 (19)
Primary reason for discontinuation			
Adverse event ^c	18 (5.4)	37 (10.9)	55 (8.2)
Withdrawal of consent	15 (4.5)	8 (2.4)	23 (3.4)
Patient lost to follow-up	14 (4.2)	12 (3.5)	26 (3.9)
Protocol violation	4 (1.2)	3 (0.9)	7 (1.0)
Insufficient therapeutic response	3 (0.9)	4 (1.2)	7 (1.0)
Patient died	1 (0.3)	0 (0.0)	1 (0.1)
Other	3 (0.9)	6 (1.8)	9 (1.3)

^a Percentage are based on the total number of patients randomized in each treatment group

^b Study completion was defined as having completed the Week 12 (Visit 5) visit

^c Patients for whom adverse event was listed as reason for discontinuation on discontinuation page of the CRF. An additional 3 patients in the placebo group had adverse event list as a secondary reason for discontinuation

In addition to the primary reason for discontinuation summary in above table, 4 patients in the placebo group and 7 patients in the YM905 group had a secondary reason for discontinuation specified by the investigator.

As shown in Table A5, 251 of 332 patients in the placebo group and 246 of 340 patients in the YM905 group were 100% compliant with the dosing schedule. Mean overall compliance was approximately 99% in both the placebo and YM905 groups.

Table A5 Overall compliance (safety population, N=672)

Overall compliance to Dosing schedule (%) ^a	Placebo (N=332)	YM905 10 mg (N=340)
	n	n
<50%	0	0
50 to <60%	0	0
60 to <70%	2	0
70 to <80%	0	3
80 to <90%	3	5
90 to <100%	68	73
>100%	251	246
Unknown	8	13

^a Overall compliance (%) is calculated using visits with study drug information: [(total number of tablets taken between treatment visits) / (total number of days between visits)] x 100

Protocol violation: 57 patients who violated the study protocol were not included in the FAS because they did not have baseline data and/or did not have any on-treatment diary data.

Table A6 Summary of protocol violations for the 57 patients not included in the FAS (Safety population, N=672)

Protocol violation ^a	Placebo (N=332)	YM905 10 mg (N=340)	Total (N=672)
	n (%)	n (%)	n (%)
Number of patients not evaluable for efficacy	23 (6.9)	34 (10.0)	57 (8.5)
Did not have baseline data from 3-day diary	1 (0.3)	1 (0.3)	2 (0.3)
Did not have on-treatment diary data	23 (6.9)	33 (9.7)	56 (8.3)

^a Patients may have more than one protocol violation leading to exclusion from FSA and are counted once under each violation

Excluded visits: For 5 patients in the placebo group and 7 patients in the YM905 group, part or all data from a visit were excluded because the patients were taking prohibited medications.

Reviewer's comment: The overall withdrawal rates for both placebo and YM905 10 mg groups are acceptable and the overall compliance was > 95% in both treatment groups.

A.4 Efficacy analysis

Summary of efficacy

Almost 88% of both placebo and solifenacin succinate 10 mg patients had their final endpoint efficacy evaluation at Week 12.

Table A7 Study 905-CL-013: Number (%) of patients with endpoint representation of Efficacy data by week (FAS population N=615)

Week of assessment used as Endpoint	Placebo n (%)	YM905 10 mg n (%)
Week 4	18 (5.8)	25 (8.2)
Week 8	20 (6.5)	12 (3.9)
Week 12	271 (87.7)	269 (87.9)

Table A8 Efficacy results of Study 905-CL-013 at endpoint^a (FAS N=615)

Efficacy endpoint	Placebo		YM905 10 mg		P value
	Baseline Mean	Mean change from baseline (Mean±SE)	Baseline Mean	Mean change from baseline (Mean±SE)	
Primary efficacy endpoint					
Number of micturitions/24h	N = 309 11.5	N = 309 -1.5±0.15	N = 306 11.7	N = 306 -3.0±0.15	<0.001
Secondary efficacy endpoints					
Number of incontinence episodes/24h	N = 237 3.0	N = 237 -1.1±0.16	N = 225 3.1	N = 225 -2.0±0.19	<0.001
Number of urgency episodes/24h	N = 306 7.2	N = 306 -2.5±0.20	N = 305 6.9	N = 305 -4.1±0.20	<0.001
Volume voided per micturition	N = 308 190.3	N = 308 2.7±3.15	N = 306 183.4	N = 306 47.2±3.79	<0.001
Number of nocturnal void episodes/24h	N = 292 2.1	N = 292 -0.5±0.07	N = 284 2.0	N = 283 -0.7±0.07	0.151
Number of nocturia episodes/24h	N = 279 1.7	N = 279 -0.4±0.06	N = 268 1.6	N = 267 -0.6±0.06	0.097

^a Endpoint is the last available on-treatment visit on or before Week 12 (Visit 5).

As shown in the above table, compared with placebo, YM905 10 mg significantly reduced the number of micturitions per 24hr, the number of incontinence episodes, urgency episodes per 24 hr, and also significantly increased volume voided per micturition. The significant effect of YM905 10 mg over placebo in reduction from baseline in micturitions per 24 hr was first observed at the Week 4 assessment, and was maintained throughout the remainder of the double blind treatment period.

Primary endpoint (Table A9, Figure A2)

Table A9 Summary of change from baseline to endpoint in number of micturitions^a/24 h (FAS, N^a=615)

Statistic	Placebo (N=309)	YM905 10 mg (N=306)	p value ^b
Baseline mean	11.5	11.7	
Mean change±SE	-1.5±0.15	-3.0±0.15	<0.001
Median change (min, max)	-1.3 (-13.7, 9.0)	-2.7 (-12.3, 6.0)	
95% confidence interval	-2.1 to -1.4	-3.2 to -2.5	
p value^c	<0.001	<0.001	

^a n = number of patients with baseline and visit mean

^b p value for testing the treatment difference, based Van Elteren's method for treatment comparisons

^c p value for within-treatment testing of the change from baseline using a paired t-test

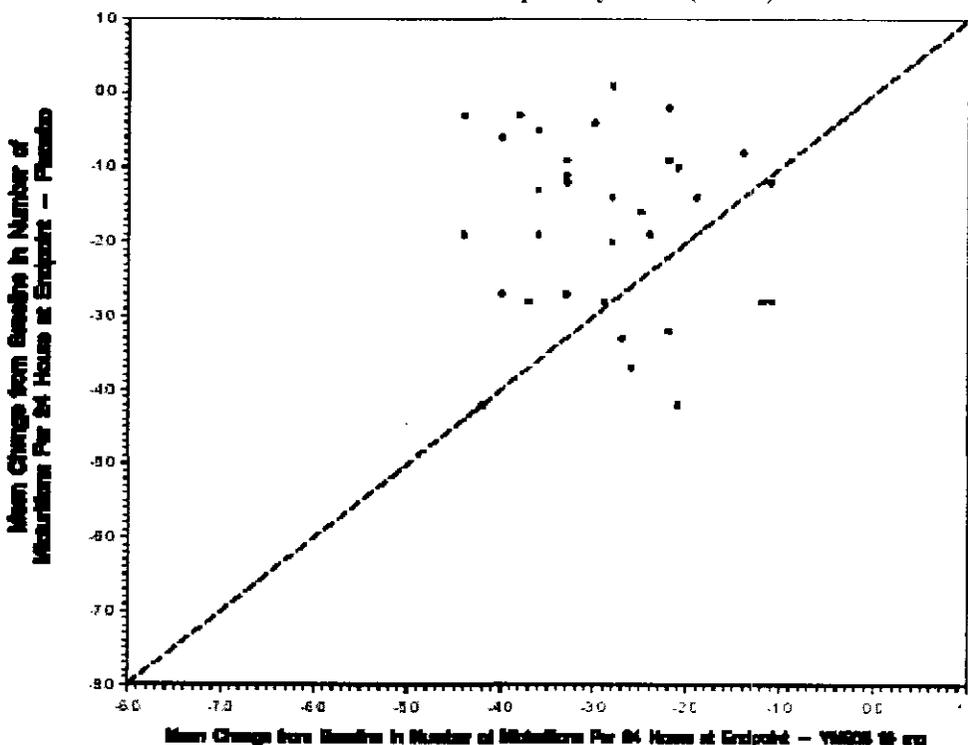
Treatment-by-center interaction

As shown in Figure A1, of the total 33 centers, 25 favored YM905, one center had no difference between YM905 and placebo, and 7 (#003, #008, #020, #021, #024, #032, and #036) favored placebo.

Within-center analyses were carried out using three models: Wilcoxon test, ANCOVA, and 2-sample t-test.

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Figure A1 Mean changes from baseline in number of Micturitions / 24 hr at endpoint by center (N=616)



Influence of dropouts

The dropout rate was balanced between treatment groups. To ensure that the conclusions of the primary analyses on the FAS were not unduly influenced by dropouts or missing data, analyses were done on the 2 partitions of the FAS: completers and dropouts. As shown in Table A10, dropouts tended to have higher baselines than completers and the FAS, but the effect size (the difference between YM905 and placebo in the change from baseline to endpoint in micturitions per 24 hrs) is similar among the groups.

Table A10 Summary of mean change from baseline to endpoint in micturitions / 24 h for FAS, completers, and dropouts

Treatment Group	FAS			Completers			Dropouts		
	Baseline Mean (n)	Mean Change From baseline	Effect size (P-Y)	Baseline Mean (n)	Mean Change From baseline	Effect size (P-Y)	Baseline Mean (n)	Mean Change From baseline	Effect size (P-Y)
Placebo	11.5 (n=309)	-1.5	1.5	11.4 (n=274)	-1.5	1.4	12.3 (n=35)	-1.9	1.4
YM905	11.7 (n=306)	-3.0		11.6 (n=269)	-2.9		12.7 (n=37)	-3.3	

Secondary efficacy analysis

Mean change from baseline to visit in the number of micturitions per 24 hrs: As shown in Figure A2, YM905 statistically significantly decreased the number of micturitions per 24 hrs at Weeks 4, 8, and 12 when compared with the placebo. Among the FAS patients, 83 placebo patients (27%) and 136 YM905 patients (44%) had a mean of fewer than 8 micturitions per 24 hrs at endpoint. The difference was statistically significant (p<0.001)

Mean change from baseline in number of incontinence episodes per 24 hrs: As shown in the Figure A3, at the endpoint and at all study visits (Week 4, 8, and 12), YM905 statistically significantly decreased the number of incontinence episodes per 24 hrs when compared with placebo. Significantly more YM905 than placebo patients became continent during the course of the study. Among the FAS patients who had at least one episode of incontinence during the baseline period, 80 placebo (34%) and 119 YM905 patients (53%) became continent at endpoint ($p < 0.001$).

Table A11 Summary of change from baseline to endpoint in number of incontinence episodes/24 h (FAS, N^a=615)

Statistic	Placebo (N=237)	YM905 10 mg (N=225)	p value ^b
Baseline mean	3.0	3.1	
Mean change±SE	-1.1±0.16	-2.0±0.19	<0.001
Median change (min, max)	-0.7 (-15.0,7.3)	-1.7 (-17.0, 16.7)	
95% confidence interval	-1.70 to 0.73	-2.25 to -1.35	
p value ^c	<0.001	<0.001	

^a n = number of patients with baseline and visit mean

^b p value for testing the treatment difference, based Van Elteren's method for treatment comparisons

^c p value for within-treatment testing of the change from baseline using a paired t-test

Mean change from baseline in number of urgency episodes per 24 hrs: As shown in the Figure A4, at the endpoint and at all study visits (Week 4, 8, and 12), YM905 statistically significantly decreased the number of urgency episodes per 24 hrs when compared with placebo.

Table A12 Summary of change from baseline to endpoint in number of urgency episodes/24 h (FAS, N^a=615)

Statistic	Placebo (N=306)	YM905 10 mg (N=305)	p value ^b
Baseline mean	7.2	6.9	
Mean change±SE	-2.5±0.20	-4.1±0.20	<0.001
Median change (min, max)	-2.0 (-16.3,11.0)	-3.7 (-15.7, 9.0)	
95% confidence interval	-2.90 to -1.90	-4.34 to -3.34	
p value ^c	<0.001	<0.001	

^a n = number of patients with baseline and visit mean

^b p value for testing the treatment difference, based Van Elteren's method for treatment comparisons

^c p value for within-treatment testing of the change from baseline using a paired t-test

Mean change from baseline in volume voided per micturition: As shown in the Figure A5, at the endpoint and at all study visits (Week 4, 8, and 12), YM905 statistically significantly increased volume voided per micturition when compared with placebo. After excluding patients with large volumes, additional analyses did not change the study conclusions.

Table A13 Summary of change from baseline to endpoint in volume voided (mL) /24 h (FAS, N^a=615)

Statistic	Placebo (N=308)	YM905 10 mg (N=305)	p value ^b
Baseline mean	190.3	183.5	
Mean change±SE	2.7±3.15	47.2±3.79	<0.001
Median change (min, max)	0.6 (-194.9,257.8)	47.6 (-224.8, 331.0)	
95% confidence interval	-4.29 to 12.81	43.88 to 61.09	
p value ^c	0.392	<0.001	

^a n = number of patients with baseline and visit mean

^b p value for testing the treatment difference, based Van Elteren's method for treatment comparisons

^c p value for within-treatment testing of the change from baseline using a paired t-test

Mean change from baseline in number of nocturnal void episodes per 24 hrs: A total of 292 patients in the placebo group and 283 patients in the YM905 group with both baseline and endpoint results were evaluated. As shown in the Figure A6, at the endpoint, the mean change from baseline in the number of nocturnal void

episodes per 24 hrs was -0.5 for the placebo and -0.7 for the YM905 group. The difference between treatment groups was statistically significant only at Week 4. Among the FAS patients who had at least one episode of nocturnal void during the baseline period, 30 placebo patients (10%) and 48 YM905 patients (17%) had no episode of nocturnal void at endpoint. This difference was statistically significant ($p = 0.016$).

Mean change from baseline in number of nocturia episodes per 24 hrs: A total of 279 patients in the placebo group and 267 patients in the YM905 group with both baseline and endpoint results were evaluated. As shown in the Figure A7, at endpoint, the mean change from baseline in the number of nocturia episodes per 24 hrs was -0.4 for the placebo group and -0.6 for the YM905 group. The difference between treatment groups was statistically significant only at Week 4. Among the FAS patients who had at least one nocturia episode during the baseline period, 48 placebo patients (17%) and 58 YM905 patients (22%) had no episode of nocturia at endpoint. This difference was not statistically significant ($p = 0.168$).

Efficacy conclusions

- YM905 statistically significantly reduced the number of micturitions per 24 hours at endpoint when compared to the placebo (primary efficacy endpoint). The statistically significant reduction in the number of micturitions per 24 hours with YM905 was observed at the Week 4 assessment and was maintained through Week 12 (end of double-blind treatment period).
- YM905 statistically significantly reduced the number of incontinence episodes per 24 hours when compared to the placebo.
- YM905 statistically significantly reduced the number of urgency episodes per 24 hours compared to the placebo.
- YM905 statistically significantly increased volume voided per micturition compared to the placebo
- The efficacy of YM905 over placebo in reducing the number of incontinence and urgency episodes and in increasing volume voided was observed at the Week 4 assessment and was maintained through Week 12 and at endpoint.
- YM905 did not reduce the number of nocturnal voids and did not significantly lower the number of nocturia episodes compared to the placebo.

In summary, YM905 was effective in treating the symptoms of overactive bladder including frequency, urgency, and urge incontinence. With YM905, 53% of patients became continent at endpoint with increased bladder capacity (demonstrated by the increase in the volume voided per micturition).

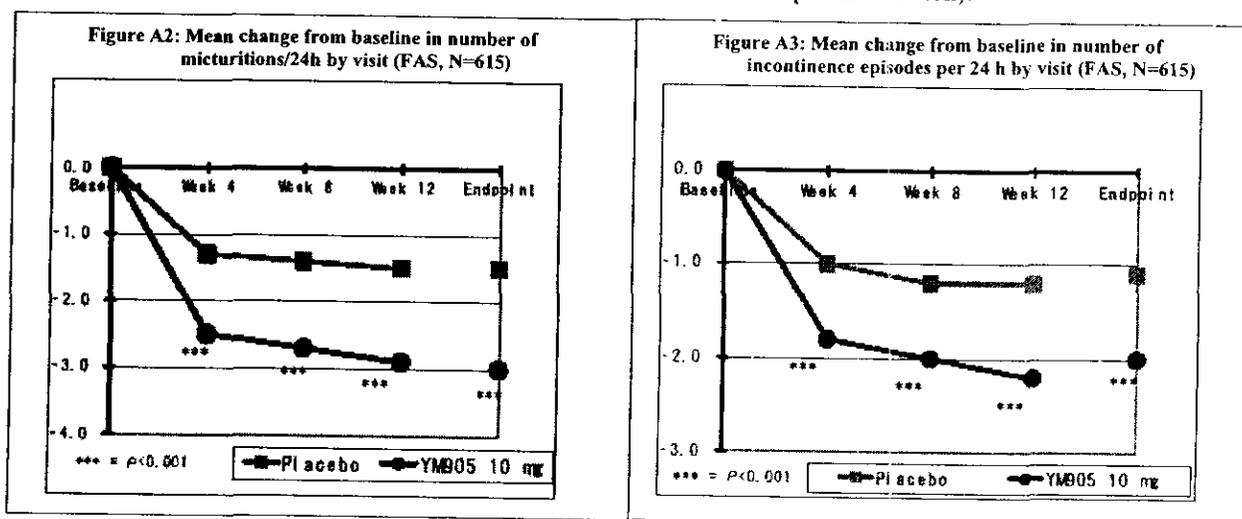


Figure A4: Mean change from baseline in number of urgency episodes /24h by visit (FAS, N=615)

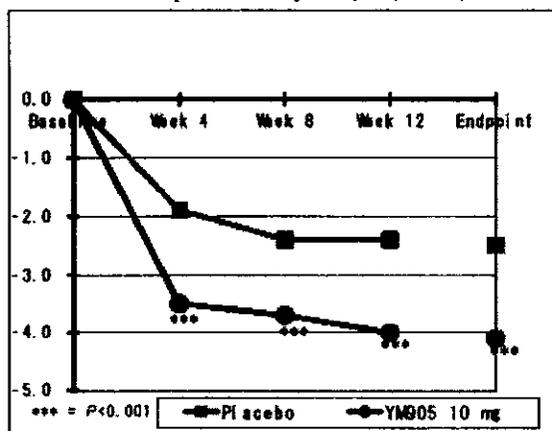


Figure A5: Mean change from baseline in volume voided (mL) /micturition by visit (FAS, N=615)

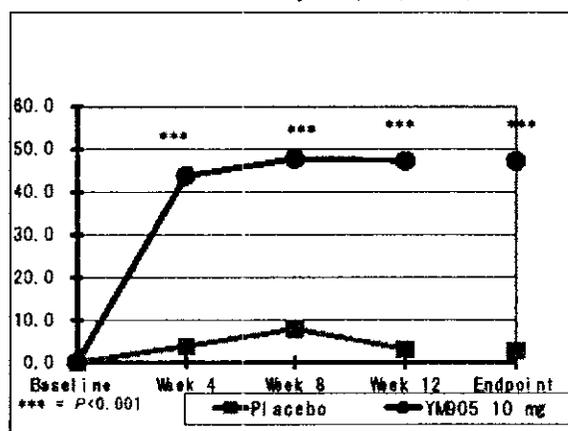


Figure A6: Mean change from baseline in number of nocturnal voids /24h by visit (FAS, N=615)

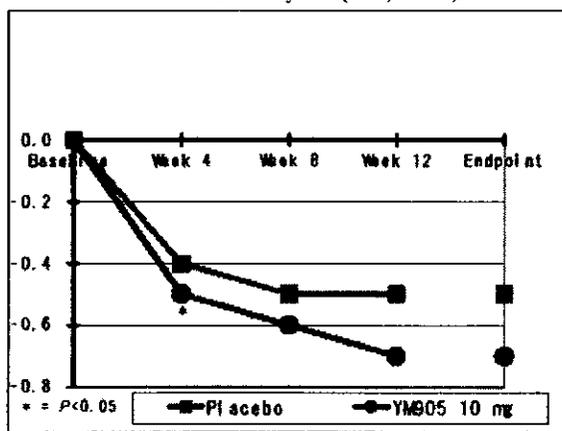
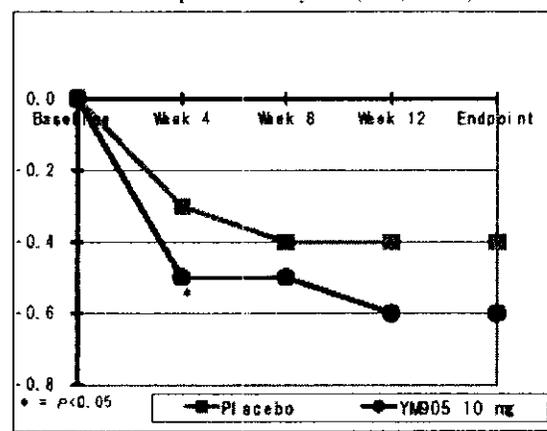


Figure A7: Mean change from baseline in number of nocturia episodes /24h by visit (FAS, N=615)



A.5 Safety analyses

Extent of study drug exposure

Mean exposure to study medication was 78 days in the placebo group and 75 days in the YM905 group. The frequency distribution for the number of days of exposure was similar between treatment groups, with the majority of patients in each treatment group exposed to study medication for at least 12 weeks. Placebo patients were exposed for a total of 842 person-months and YM905 patients were exposed for a total of 831 person-months.

Table A14 Study medication exposure (safety population, N=672)

Study Medication Exposure (days) ^a	Placebo (N=332)	YM905 10 mg (N=340)
	n	n
1 to 13 days	9	14
14 to 27 days	8	16
28 to 55 days	15	22
56 to 83 days	62	58
≥ 84 days	232	226
Unknown	6	4
Mean exposure	78 days	75 days

^a Length of treatment exposure is defined as the last day of treatment minus the first day of treatment plus one day. Last visit date is used if the date of last dose of study drug is unknown.

Reviewer's comment: The extent of exposure in this trial was adequate to make an assessment of safety at 12 weeks.

Deaths

One death (from hemopericardium) was reported in a patient (#31008) in the placebo group. This 82-year-old man took study drug for 57 days. During the follow-up period, 20 days after the last dose of the study drug, the patient had hemopericardium and died. Autopsy revealed rupture of the left ventricle at the site of recent myocardial infarction and was considered by the investigator unrelated to study drug (see a detailed narrative for this patient below).

Serious adverse events (SAEs):

Serious adverse events (SAEs) were reported for three patients in the placebo group and five patients in the YM905 group during the 12-week treatment period.

Table A15 Patients with serious adverse events (SAE's) (safety population, N = 672)

Patient #	MedDRA preferred term/Verbatim term	Start day	Relationship to study medication	Action taken/ Outcome
Placebo				
9003	Chest pain nec/atypical chest pain	33	Unrelated	Discontinued/recovered
16014	Meningitis bacterial nos/bacterial meningitis	67(+1)	Unrelated	Discontinued/recovered
31008	Hemopericardium/hemopericardium	77(+20)	Unrelated	Discontinued/fatal
YM905 10 mg				
2006	Chest pain nec/non-cardiac chest pain	70	Unrelated	None/recovered
11014	Cellulitis/cellulites from cat bite	14	Unrelated	Interrupted/recovered
16002	Dehydration/dehydration	58	Unrelated	None/recovered
29005	Colonic obstruction/sigmoid colon obstruction	11	Possibly	Discontinued/recovered
31003	Chest pain nec/chest pain secondary to esophageal spasm	35	Unrelated	None/recovered

Narratives of SAE's

YM905 group:

Patient #2006: This 58-year-old post-menopausal woman had a medical history of diabetes, osteoarthritis, hypertension, depression, gastroesophageal reflux disease (GERD), and hypercholesteremia. On Day 70 of treatment, the patient was awakened with a sudden onset of intermittent substernal chest pain radiating to both jaws and was admitted to the hospital. She denied having shortness of breath, diaphoresis, nausea, or pain radiating down the arms. Chest x-ray, ECG and cardiac enzymes were normal. She was hospitalized for evaluation and a treadmill test performed the following day was normal. The investigator considered the non-cardiac chest pain to be a symptom of GERD. Study medication was not interrupted, and the patient recovered on Day 71 of treatment. She went on to complete the study and was subsequently enrolled into the open-label extension study. The investigator judged the non-cardiac chest pain to be unrelated to study drug.

Reviewer's comment: The reviewer believes that this event is unlikely to have been related to study drug.

Patient #11014: This 63-year-old woman developed cellulitis of her right leg secondary to a cat bite on Day 14 of treatment. She was admitted to the hospital and blood cultures revealed a gram negative rod, which was sensitive to all antibiotics tested. Study drug was interrupted for 2 days during the hospitalization. She was discharged after 5 days of hospitalization with the erythema improved by 50% from the previous day. She took Augmentin and recovered from the event 37 days after starting study drug. The patient went on to

complete the double-blind treatment period 83 days after starting study drug and subsequently entered the open-label extension study. The investigator considered this event to be unrelated to the study drug.

Reviewer's comment: The reviewer agrees that this event was not related to study drug.

Patient #16002: This 55-year-old woman had a medical history of hypertension, fluid retention, depression, esophageal reflux, irritable bowel, adult onset diabetes, insomnia, arthritic joints, and hypercholesterolemia. On Day 55 of treatment, she reported dizziness. The investigator judged this event to be severe and possibly related to study drug. The event resolved the next day. On Day 58 of treatment, she reported diarrhea, nausea, and vomiting were reported with confusion and worsening unsteady gait. She further developed dehydration and was hospitalized on the same day. During hospitalization, she was treated with IV glucose and trimethobenzamide. A colonoscopy with biopsy revealed findings consistent with irritable bowel syndrome but no pathologic abnormality. The patient was discharged on Day 66. She had continued to take the study medication while hospitalized and went on to complete the double-blind period 84 days after starting study drug. She subsequently entered the open-label study. The investigator assessed the patient's dehydration to be unrelated to study drug.

Reviewer's comment: The reviewer believes that the relationship to study drug is unlikely.

Patient #29005: This 62-year-old woman had a medical history of peptic ulcer disease, osteoporosis, arthritis, and bilateral tubal ligation. On Day 11, the patient complained of diffuse crampy lower abdominal pain, nausea and vomiting, decreased caliber of stools, and fever. The patient interrupted study drug for 2 days (Days 14 and 15) and resumed study drug on Day 16, (final dose). On Day 18, the patient was admitted to the hospital and a CT scan showed a bulky mass in the sigmoid colon. The next day, a kidney ultrasound biopsy (KUB) revealed dilated loops of bowel with air/fluid levels consistent with bowel obstruction. A colonoscopy with biopsy revealed fragments of colonic mucosa with focal acute hemorrhage, lamina propria fibrosis, a nearly obstructive lesion in the distal colon, and no evidence of malignancy. On Day 24, the patient underwent an exploratory laparotomy when an inflammatory mass was found in the distal sigmoid colon and rectum with involvement of the left ovary and fallopian tube. She underwent a celiotomy, left sigmoid and anterior colectomy with left salpingo-oophorectomy and colorectal anastomosis. The patient was discharged from the hospital on Day 28. The investigator assessed the patient's colonic obstruction to be possibly related to study drug.

Reviewer's comment: The reviewer considers the relationship to study drug as possible.

Patient #31003: This 61-year-old post-menopausal woman had a medical history of hypothyroidism and esophageal spasms. On Day 35 of treatment, she was hospitalized for chest pain with radiation to her back and upper jaw to teeth. She described the pain as pressure on her chest, but denied nausea, vomiting, diarrhea, and had no diaphoresis, shortness of breath, or musculoskeletal or pleuritic component. Serial troponin was negative. An ECG and a stress echocardiogram were normal. Laboratory evaluation was within normal limits. Her chest pain was relieved by aspirin, nitroglycerin sublingual and Dilaudid 0.5 mg IV. The patient was discharged from the hospital on Day 36 of the treatment with a diagnosis of chest pain secondary to esophageal spasms. She did not take her study medication on the day of hospitalization. She went on to complete the double-blind period 90 days after starting study drug and subsequently entered the open-label extension study. The investigator assessed the chest pain to be unrelated to the study drug.

Reviewer's comment: The reviewer agrees that this event was not related to study drug.

In addition to the patients with SAE's during the 12-week treatment period, one patient had a SAE at baseline. Patient #31029 (YM905 group) had a baseline AE of chest pain (unstable angina). At the screening visit, the patient had an elevated CPK of 451 U/L and an ECG indicating a possible anteroseptal infarction, which the investigator judged not clinical significant. The patient was randomized to YM905. On Day 2 of treatment, the patient was hospitalized for angioplasty with stent placement and study drug was discontinued.

Overall adverse events

Table A16 Summary of treat-emergent adverse events (TEAEs) (safety population, N = 672)

	Placebo (N = 332)	YM905 10 mg (N = 340)
Number of TEAEs reported	462	652
Number of patients with TEAEs [n (%)]	197 (59)	236 (69)
Number of SAE's	3	5
Number of patients with SAE's [n (%)]	3 (0.9)	5 (1.5)
Patients with AE's by severity [n (%)]		
Mild	73 (22)	73 (22)
Moderate	100 (30)	119 (35)
Severe	24 (7)	44 (13)
Number of patients discontinued because of AE's [n (%)]	23 (7)	37 (11)
Number of patients with drug-related AE's [n (%)]	91 (27)	175 (52)
Number of deaths	1	0

More than half of the patients in both treatment groups reported adverse events (59% for placebo and 69% for YM905). Most of the patients experienced AE's that were mild or moderate, but more patients experienced AE's that were rated severe in the YM905 group (13%) than did patients in the placebo group (7%). Also the number of patients with AE's judged possibly or probably related to study drug was higher for YM905 patients (52%) than for placebo patients (27%). The differences in frequency and severity of AE's between placebo and YM905 were largely due to the anticholinergic effects of YM905, i.e. dry mouth (4% for placebo vs. 27% for YM905), constipation (3% for placebo vs. 17% for YM905), and blurred vision (1.2% for placebo vs. 4% for YM905).

Table A17 Most common (≥2%) TEAEs by system organ class (safety population, N = 672)

System organ class MedDRA preferred term	Placebo (N=332) n (%)	YM905 10 mg (N=340) n (%)
Gastrointestinal disorders	77 (23)	154 (45)
Dry mouth	13 (4)	91 (27)
Constipation	11 (3)	58 (17)
Nausea	13 (4)	19 (6)
Diarrhea	15 (5)	7 (2)
Dyspepsia	3 (0.9)	16 (5)
Infection and infestations	52 (16)	55 (16)
Urinary tract infection nos	11 (3)	21 (6)
Nasopharyngitis	11 (3)	3 (0.9)
Upper respiratory tract infection	7 (2)	6 (1.8)
Nervous system disorders	45 (14)	41 (12)
Headache	24 (7)	16 (5)
Dizziness	8 (2)	10 (3)
Musculoskeletal, connective tissue & bone disorders	37 (11)	33 (10)
Arthralgia	11 (3)	6 (1.8)
Back pain	7 (2)	6 (1.8)
Eye disorders	14 (4)	24 (7)
Vision blurred	4 (1.2)	12 (4)
Renal and urinary disorders	11 (3)	16 (5)
Urinary retention	3 (0.9)	7 (2)

The incidences for both dry mouth and constipation were significantly greater with YM905 than with placebo ($p < 0.001$). Another relevant commonly reported AE was urinary tract infection (UTI), with an incidence of 3% for placebo and 6% for YM905. There is no evidence that the higher incidence of UTI in YM905 patients was due to urinary retention.

The most common drug-related AE's, as expected, were dry mouth and constipation shown in Table A18.

Table A18 Most common ($\geq 2\%$) drug-related TEAEs by system organ class (safety population, N = 672)

System organ class MedDRA preferred term	Placebo (N=332) n (%)	YM905 10 mg (N=340) n (%)
Gastrointestinal disorders	48 (15)	140 (41)
Dry mouth	12 (4)	87 (26)
Constipation	11 (3)	55 (16)
Nausea	6 (1.8)	11 (3)
Dyspepsia	1 (0.3)	13 (4)
Diarrhea nos	8 (2)	4 (1.2)
Nervous system disorders	23 (7)	27 (8)
Headache	13 (4)	9 (3)
Dizziness (excluding vertigo)	3 (0.9)	7 (2)
Eye disorders	6 (1.8)	16 (5)
Vision blurred	4 (1.2)	11 (3)

Other AE's of interest included urinary retention and QT prolongation.

Urinary retention: Reported by 3 patients (0.9%) in the placebo group and 7 patients (2%) in the YM905 group. The majority of this event (2/3 the placebo and 6/7 the YM905 patients) reported as urinary retention were "post-void residual volumes > 150 mL" (≤ 150 mL at baseline) noted on bladder scans at the patient's last available on-treatment visit. Post-void residual volumes for the patients who experienced shifts from baseline to > 150 mL at the last available visit, ranged from 154 mL to 191 mL in the placebo group and from 154 mL to 229 mL in the YM905 group.

Table A19 Number of patients with shift from baseline to Week 12 in post-void residual volume (mL) (safety population, N=672)

Shift of post-void residual volume	Placebo (N=332)		YM905 10 mg (N=340)	
	Male	Female	Male	Female
≤ 150 mL \rightarrow >150 mL	1	1	1	5

QT prolongation:

The mean increase in QT interval (calculated using Bazett's formula) of 3.6 msec relative to placebo reflects a small but statistically significant ($p=0.018$) treatment difference. Similar results are obtained when QTc is calculated using Fridericia's formula.

For the analysis of changes from baseline in QTc intervals, patients were categorized as follows:

- Patients with normal QTc (men, ≤ 430 msec; women, ≤ 450 msec)
- Patients with borderline QTc (men, >430 to ≤ 450 msec; women, >450 to ≤ 470 msec)
- Patients with prolonged QTc (men, >450 to ≤ 500 msec; women, >470 to ≤ 500 msec)
- Patients with prolonged QTc of clinical concern (>500 msec)

The changes from baseline in QTc interval were categorized as follows:

- <30 msec; within normal limits
- Between 30 and 60 msec: borderline
- >60 msec: clinical concern

Table A20 Summary of changes of QT interval values from baseline to endpoint (safety population, N=672)

QT prolongation evaluation	Placebo (N=332)	YM905 10mg (N=340)	P values
QT interval (msec)			
N	227	220	
Baseline mean	394.6	392.8	
Mean change±SE	3.2±1.66	9.4±1.65	<0.002
P value	0.057	<0.001	
QTc interval (msec)			
N	227	220	
Baseline mean	421.2	422.5	
Mean change±SE	1.3±1.24	4.9±1.29	0.018
P value	0.304	<0.001	

Among the female patients, 21 on placebo and 30 on YM905 had a QTc >450 msec at any observation during the study. Of these, 17 on placebo and 26 on YM905 had QTc increases <30 msec from baseline, while 4 in each group had QTc increases 30 - 60 msec from baseline. No patients had a QTc increase from baseline >60 msec.

Among the male patients, 19 on placebo and 28 on YM905 had a QTc >430 msec at any observation during the study. Of these, 10 on placebo and 19 on YM905 had QTc increases <30 msec from baseline, while 9 in each group had QTc increases 30 - 60 msec from baseline. No patient had a QTc increase >60 msec.

One female patient in the YM905 group had a QTc >500 msec at any time during the study (with narrative below). *Patient #14014*: This 78-year-old Caucasian woman had a medical history of transient ischemic attack, angina, aortic stenosis, aortic valve replacement, congestive heart failure (CHF), left ventricular hypertrophy, and hypercholesterolemia. She was randomized to the YM905 group and received her first dose on April 19, 2001. At baseline her QTc interval was 450 msec (HR: 76 bpm) and her ECG showed nonspecific S-T depression. On Day 29 (Week 4), QTc was 440 msec (HR: 76 bpm). QTc then increased over the remainder of the treatment period, reached 490 msec at Week 8 (HR: 80 bpm) and 510 msec at Week 12 (HR: 80 bpm). Non-specific S-T depression was noted at each visit during the treatment period. This patient entered the open-label extension study and her QTc at Week 16 was 460 msec while on YM905.

Table 21 Number of patients with changes of clinical importance from baseline to Week 12 and endpoint in QTc interval (safety population, N=672)

Visit: change from baseline (msec)	Placebo (N=332)	YM905 10 mg (N=340)
Week 12	202	181
Increase > 60	0	0
Increase ≥ 30 to ≤ 60	16	24
Increase or decrease < 30	170	144
Endpoint	227	220
Increase > 60	0	0
Increase ≥ 30 to ≤ 60	20	29
Increase or decrease < 30	190	175

Endpoint is the last available on-treatment visit on or before Week 12 (Visit 5)

No patients in either group had a change in QTc > 60 msec. An increase in QTc between 30 and 60 msec was found in 16 placebo patients vs. 24 YM905 patients at 12 Weeks and in 20 placebo patients vs. 29 YM905 patients at endpoint.

Discontinuations due to adverse events

A total of 23 patients in the placebo group and 37 patients in the YM905 group had adverse events during the 12-week treatment period that led to discontinuation of study drug. The most common AE's leading to discontinuation of study drug were expected anticholinergic adverse events of dry mouth (placebo, 0.3%; YM905, 3.5%), constipation (0%; 3.5%), blurred vision (0%; 1.5%), and nausea (0.9%; 2.1%). No other AE's led to discontinuation for more than 1% of patients in either treatment group.

Table 22 No. (%) of patients discontinued due to AE's (safety population, N=672)

System organ class MedDRA preferred term	Placebo (N=332) n (%)	YM905 10 mg (N=340) n (%)
Gastrointestinal disorders	6 (1.8)	26 (7.6)
Dry mouth	1 (0.3)	12 (3.5)
Constipation	0 (0.0)	12 (3.5)
Nausea	3 (0.3)	7 (2.1)

AE's leading to study discontinuation were judged as severe in 11 patients. Antimuscarinic severe events leading to discontinuation included constipation (4 patients), dry mouth (2 patients), blurred vision (1 patient), colonic obstruction (1 patient), and nausea (1 patient).

Other important AE's leading to discontinuation: Elevated ALT and AST in two patients (one placebo #24022 and one YM905 #34001). In the YM905 patient #34001, the AST and ALT raised from 36 U/L, 49 U/L, respectively, at baseline to 85 U/L, 95 U/L, respectively, at Week 4. Bilirubin was normal. About eight months later, her AST and ALT both had returned to normal (no longer in the study).

Expected AE's:

The overall incidence of both dry mouth and constipation was significantly greater in YM905 group than in the placebo group ($p < 0.001$). All AE's of dry mouth and constipation reported in placebo group had maximum severity of mild or moderate, while in the YM905 group 8 patients (2.4%) had severe dry mouth and 7 patients (2.1%) had severe constipation. Two of the 8 with severe dry mouth and 4 of the 7 with severe constipation discontinued study because of these AE's. For all of these patients, the investigator judged the dry mouth or constipation probably related to the study medication.

Blurred vision and other related visual AE's: blurred vision was also significantly greater in the YM905 group than in the placebo group ($p = 0.048$). Other types of visual disturbances (e.g. photopsia, visual disturbance, visual acuity reduced, dry eye, eye disorder, and vision abnormal) were reported. In the placebo group, 4 patients had mild visual disturbances and 1 had a severe visual disturbance, while in the YM905 group, 19 patients had mild or moderate visual disturbances and 2 had severe visual disturbances.

Other than dry mouth, several patients in each group reported dryness in other organs or locations including dry throat, dry eye nec, vulvovaginal dryness, nasal dryness, and lip dry. All these may be related to the use of an anticholinergic agent.

In summary, most occurrences of expected anticholinergic AE's in both groups were considered by the investigator to be treatment-related. All severe AE's of dry mouth, constipation, and blurred vision in the YM905 group were considered possibly or probably related to study drug.

YM905 10mg had no influence on clinical laboratory parameters or vital signs.

Safety conclusions

- In this study, YM905 10 mg was tolerated
- The most common AE's with YM905 were consistent with the expected pharmacologic effects of the drug, namely dry mouth, constipation, and visual disturbances
- YM905 had no clinically relevant influence on clinical laboratory parameters or vital signs

- YM905 had a statistically significant effect on the QTc interval relative to placebo. The mean difference in effect was small (3.6 msce) and the increase in QTc interval did not exceed 60 msec in any individual patient.

A.6 Reviewer's assessment of safety and efficacy in Clinical Trial CL-905-013

The reviewer believes that YM905 10 mg daily reduces the number of micturitions per 24 hrs in the majority of patients with OAB when compared with placebo. In terms of secondary endpoints, the reviewer agrees that the reduction of urgency episodes, and the increase of volume voided per micturition appeared to support the efficacy of YM905.

The reviewer believes that the positive effects of YM905 on various symptoms of OAB, along with the improvement in incontinence and volume voided, are evidence that treatment with YM905 10 mg provides a clinically meaningful benefit to patients with OAB.

In terms of safety, the reviewer believes that overall, YM905, at daily dose of 10 mg, was safe and well-tolerated. The most common adverse events in the active drug group were anticholinergic events, including dry mouth, constipation, and blurred vision. The reviewer agrees that these AE's are expected and mild to moderate in severity in majority of patients. The reviewer believes that YM905 had no significant influence on clinical laboratory parameters. The reviewer noticed that ALT and AST were elevated mildly in one patient with YM905 and the drug was discontinued, and later the ALT and AST returned to normal. The QTc interval was prolonged by approximately 3 msec compared to placebo. QTc prolongation issues are addressed in the review of Study CL-022 and in the Executive Summary of Clinical Review.

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Appendix B

Clinical Trials 905-CL-014: A randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, multicenter study to assess efficacy and safety of daily oral administration of 10 mg YM905 (solifenacin succinate) versus placebo in male and female patients with overactive bladder (in the US)

B.1 Design

Study 905-CL-014 was a randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, multicenter study of 10 mg solifenacin succinate versus placebo, administered orally once daily for 12 weeks. Patients were evaluated at baseline and at 4, 8 and 12 weeks. The objective of the study was to confirm the efficacy of YM905 versus placebo in reducing the number of micturitions per 24h in patients with OAB and evaluate the safety and tolerability of YM905 in patients with OAB.

Inclusion criteria:

Symptoms of OAB (urinary frequency with urgency and/or incontinence), age ≥ 18 years, an average of ≥ 8 micturitions/24h, and either an average of ≥ 1 urinary incontinence episode/24h or an average of ≥ 1 urinary urgency episode/24h, documented in a 3-day diary in the screening phase.

Exclusion criteria:

Stress incontinence, mixed incontinence with a predominant stress component, or neurological cause for detrusor overactivity. Urinary retention as demonstrated by post-void residual urine volume > 150 mL as evidenced by bladder scan.

Methodology:

This is a Phase 3, randomized, double-blind, parallel-group, fixed-dose, multicenter study of 10 mg YM905 versus placebo in the treatment of OAB (frequency, urgency, and/or urge incontinence). The study consisted of a 2-week screening/washout period, a 12-week double-blind treatment period, and a 2-week post-treatment follow-up period. Patients who completed the study had the option to enter an open-label extension study. Patients visited the clinic at screening (Visit 1); baseline (Visit 2); after 4 weeks (Visit 3); 8 weeks (Visit 4); and 12 weeks (Visit 5) of the double-blind treatment; and at the end of the follow-up period (for those who did not enter the extension study) (Visit 6).

Study drug regimen: Solifenacin succinate 10 mg tablet or identical placebo tablet once daily.

Primary efficacy endpoint: the primary endpoint was "mean change from baseline to endpoint in number of micturitions/24h." Micturition was defined as any voiding episode recorded by the patient in the 3-day diary as either "urinated" with or without "incontinence".

Secondary efficacy endpoints: mean change from baseline to endpoint in number of incontinence episode/24h, number of urgency episodes/24h, mean volume voided/micturition, number of nocturnal voids/24h, and number of nocturia episodes/24h.

Safety was assessed via adverse events, clinical laboratory values (hematology, clinical chemistry, and urinalysis), vital signs, physical examination findings, 12-lead ECG, and post-void residual volume.

The study was initiated in January, 2001, and the final study report reflects all available efficacy and safety data from all patients through January, 2002. The final observation was on January 23, 2002. Study visits occurred at screening (1) baseline (2) after 4 weeks (3) 8 weeks (4) 12 weeks (5, at the end of follow-up (6) or withdrawal from the study.

B.2 Study Population

A total of 634 patients from 33 centers randomized (316 placebo and 318 solifenacin succinate) took study drug and were included in the safety population. Of the 634 patients, 41 (21 for placebo and 20 for YM905) were excluded from the efficacy analysis for lack of on-treatment diary data, so that, the full-analysis set (FAS: all patients who were randomized, received at least one dose of double-blind treatment, had baseline diary data available and on-treatment diary data available) included 593 patients (295 placebo and 298 solifenacin succinate). The per protocol set (PPS: all patients who were randomized, received at least one dose of double-blind treatment, had baseline diary data available, had at least 8-weeks of on-treatment diary data available, had overall treatment compliance of at least 70%, and had no major protocol violation) included 535 patients (266 placebo and 269 YM905). The safety population (SAF: all patients who were randomized and received at least one dose of double-blind treatment) included all 634 randomized patients. There were no notable imbalances between treatment groups in demographic characteristics including age, gender, race, weight, and height. The study population was predominantly Caucasian (90%) and female (82%) with mean age of 60 years. 40% of the study population was 65 years or older, and 90 patients (14%) were 75 years or older. The median time since start of OAB symptoms was approximately 5-6 years in both the placebo and YM905 groups (mean 9 years for placebo and 10 years for YM905).

Table B1 Number of patients in study population

Patient groups	Placebo	YM905 10 mg	Total
Randomized	316	318	634
Treated	316	318	634
FAS	295	298	593
Completed	272	269 ^a	541 ^a
Dropouts	23	29	52
PPS ^b	266	269	535

^a one patient completed the study but had no baseline diary data and was thus not included in the FAS

^b PPS: per protocol set

Reviewer's comment: The treatment groups appeared to be well-balanced at the baseline with respect to the important demographic characteristics.

The percentage of patients at each visit during the treatment period (Weeks 4, 8, and 12) was similar between the placebo and YM905 groups ranging from 96% to 100% for Week 4, 86% to 100% for Week 8, and 80% to 97% for Week 12 (Table B2). The small percentage of patients at the follow-up visit (10% to 12% for the 3 populations) was due to the fact that the majority of patients entered the open-label extension study (905-CL-016) and only patients who did not go on to the extension had the follow-up visit.

Table B2 Number of patients in each population by treatment group and study visit

Visit	SAF Population: n (%)		FAS population: n (%)		PPS population: n (%)	
	Placebo (N=316)	YM905 10 mg (N=318)	Placebo (N=295)	YM905 10 mg (N=298)	Placebo (N=266)	YM905 10 mg (N=269)
Screening/washout (Visit 1)	316 (100)	318 (100)	295 (100)	298 (100)	266 (100)	269 (100)
Baseline (Visit 2)	316 (100)	318 (100)	295 (100)	298 (100)	266 (100)	269 (100)
Week 4 (Visit 3)	308 (98)	314 (99)	295 (100)	298 (100)	266 (100)	269 (100)
Week 8 (Visit 4)	285 (90)	290 (91)	285 (97)	290 (97)	266 (100)	269 (100)
Week 12 (Visit 5)	276 (87)	275 (87)	276 (94)	275 (92)	262 (99)	262 (97)
Follow-up (Visit 6) ^a	37 (12)	43 (14)	31 (11)	97 (33)	28 (11)	31 (12)

^a Follow-up (Visit 6) visit reflects the number of patients who had a follow-up assessment (2 weeks post-treatment completion) regardless of study completion.

Reviewer's comment: The treatment groups were thus reasonably balanced in terms of numbers of patients available for analysis at each visit.

The majority (58%) of patients in the safety population reported no prior anticholinergic agent use and no history of non-drug treatment. Slightly less than half of the patients reported having a history of mixed

incontinence with urge as predominant factor. Approximately 38% of all patients in the placebo group and 43% of all patients in the YM905 group took previous OAB medications with the most common medications were tolterodine tartrate (23% of placebo and 22% of YM905) and oxybutynin (17% and 19%, respectively). Also, the two treatment groups were balanced in terms of medical history. Most patients in the safety population had no history of biofeedback, exercises, electrical stimulation, behavioral therapy, pessaries, or implants. There were no notable differences between treatment groups in terms of previous treatments of OAB. There were no clinically relevant differences between the two treatment groups in the incidence or severity of baseline signs and symptoms.

Extent of study drug exposure: Mean exposure to study medication was 78 days in the placebo group and 75 days in the YM905 group. The frequency distribution for the number of days of exposure was similar between treatment groups, with the majority of patients in each treatment group exposed to study medication for at least 12 weeks.

Table B3 Study medication exposure (safety population, N=634)

Study Medication Exposure (days) ^a	Placebo (N=316) N (%)	YM905 10 mg (N=318) N (%)
1 to 13 days	8 (3)	13 (4)
14 to 27 days	9 (3)	9 (3)
28 to 55 days	14 (4)	12 (4)
56 to 83 days	48 (15)	50 (16)
≥ 84 days	233 (74)	234 (74)
Unknown	4(1)	0 (0)
Mean exposure	80 days	79 days

^a Length of treatment exposure is defined as the last day of treatment minus the first day of treatment plus one day. Last visit date is used if the date of last dose of study drug is unknown.

B.3 Withdrawals and compliance

Patients who discontinued prematurely from the treatment period could have been more than one reason specified as the cause of discontinuation. The percentage of patients who prematurely discontinued from the treatment period was similar in the placebo (14%) and YM905 (15%) groups. In both treatment groups, the most common primary reason for discontinuation was adverse event (5% for placebo and 11% for YM905).

Table B4 Summary of study drug discontinuation by primary reason (safety population, N=634)

Disposition	Placebo ^a n (%)	YM905 10 mg ^a n (%)	Total ^a n (%)
Primary reason for discontinuation			
Number of patients randomized	316	3318	634
Number of patients who received study drug	316 (100)	318 (100)	634 (100)
Number of patients who completed the study ^b	272 (86)	269 (84.6)	541 (85)
Number of patients who prematurely discontinued from the treatment period	44 (13.9)	49 (15.4)	93 (15)
Primary reason for discontinuation			
Adverse event ^c	15 (4.7)	28 (8.8)	43 (6.8)
Withdrawal of consent	10 (3.2)	8 (2.5)	18 (2.8)
Patient lost to follow-up	7 (2.2)	2 (0.6)	9 (1.4)
Protocol violation	5 (1.6)	5 (1.6)	10 (1.6)
Insufficient therapeutic response	3 (0.9)	2 (0.6)	5(0.8)
Other	4 (1.3)	4 (1.3)	8 (1.3)

^a Percentage are based on the total number of patients randomized in each treatment group

^b Study completion was defined as having completed the Week 12 (Visit 5) visit

^c Patients for whom adverse event was listed as reason for discontinuation on discontinuation page of the CRF.

In addition to the primary reason for discontinuation summary in above table, 4 patients in the placebo group and 7 patients in the YM905 group had secondary reason for discontinuation specified by the investigator.

As shown in Table B5, 233 of 316 patients in the placebo group and 224 of 318 patients in the YM905 group were at least 100% compliant with the dosing schedule. Mean overall compliance was approximately 99% in both the placebo and YM905 groups.

Overall compliance to Dosing schedule (%) ^a	Placebo (N=316)	YM905 10 mg (N=318)
	n	n
<50%	0	0
50 to <60%	0	0
60 to <70%	1	1
70 to <80%	3	2
80 to <90%	3	7
90 to <100%	70	79
≥100%	233	224
Unknown	5	5

^a Overall compliance (%) is calculated using visits with study drug information: [(total number of tablets taken between treatment visits) / (total number of days between visits)] x 100

Protocol violation: 41 patients (21 in the placebo and 20 in the YM905) who violated study protocol were not included in the FAS because they did not have baseline data and/or did not have any on-treatment diary data.

Table B6 Summary of protocol violations for the 57 patients not included in the FAS (Safety population, N=672)

Protocol violation ^a	Placebo (N=332)	YM905 10 mg (N=340)	Total (N=672)
	n (%)	n (%)	n (%)
Number of patients not evaluable for efficacy	21 (6.6)	20 (6.3)	41 (6.5)
Did not have on-treatment diary data	26 (6.9)	20 (6.3)	41 (6.5)

^a Patients may have more than one protocol violation leading to exclusion from FSA and are counted once under each violation

Excluded visits: For 5 patients in each group, part or all data from a visit were excluded because the patients were taking prohibited medications.

Reviewer's comment: The withdrawal rates for both placebo and YM905 10 mg groups are acceptable and the overall compliance was > 95% in both treatment groups.

B.4 Efficacy analysis

Summary of efficacy

92.5% of both placebo and 90.9% solifenacin 10 mg patients had their final endpoint efficacy evaluation at Week 12.

Table B7 Study 905-CL-013: Number (%) of patients with endpoint representation of Efficacy data by week (FAS population N=593)

Week of assessment used as Endpoint	Placebo n (%)	YM905 10 mg n (%)
Week 4	14 (4.8)	15 (5.03)
Week 8	8 (2.7)	12 (4.03)
Week 12	273 (92.5)	271 (90.94)

Table B8 Efficacy results of Study 905-CL-013 at endpoint^a (FAS N=593)

Efficacy endpoint	Placebo		YM905 10 mg		P value
	Baseline Mean	Mean change from baseline (Mean±SE)	Baseline Mean	Mean change from baseline (Mean±SE)	
Primary efficacy endpoint					
Number of micturitions/24h	N = 295 11.8	N = 295 -1.3±0.16	N = 298 11.5	N = 298 -2.4±0.15	<0.001
Secondary efficacy endpoints					
Number of incontinence episodes/24h	N = 238 2.9	N = 238 -1.2±0.15	N = 230 2.9	N = 230 -2.0±0.15	<0.001
Number of urgency episodes/24h	N = 292 6.8	N = 292 -1.8±0.22	N = 296 6.3	N = 296 -3.3±0.23	<0.001
Volume voided per micturition	N = 293 175.7	N = 293 13.0±3.45	N = 298 174.2	N = 298 46.4±3.73	<0.001
Number of nocturnal void episodes/24h	N = 281 2.0	N = 281 -0.4±0.06	N = 283 2.1	N = 283 -0.5±0.06	0.251
Number of nocturia episodes/24h	N = 267 1.6	N = 267 -0.3±0.06	N = 274 1.7	N = 274 -0.5±0.06	0.158

^a Endpoint is the last available on-treatment visit on or before Week 12 (Visit 5).

As shown in the above table, compared with placebo, YM905 10 mg significantly reduced the number of micturitions/24hr, the number of incontinence episodes/24h, urgency episodes/24hr, and also significantly increased volume voided per micturition. The significant effect of YM905 10 mg over placebo in reduction from baseline in micturitions per 24 hr was first observed at the Week 4 assessment, and was maintained throughout the remainder of the double blind treatment period.

Primary endpoint (Table B9, Figure B2)

Table B9 Summary of change from baseline to endpoint in number of micturitions^a/24 h (FAS, N^a=593)

Statistic	Placebo (N=295)	YM905 10 mg (N=298)	p value ^b
Baseline mean	11.8	11.5	
Mean change±SE	-1.3±0.16	-2.4±0.15	<0.001
Median change (min, max)	-1.3 (-11.0, 5.3)	-2.3 (-16.0, 10.3)	
95% confidence interval	-1.5 to -0.9	-2.6 to -2.0	
p value^c	<0.001	<0.001	

^a n = number of patients with baseline and visit mean

^b p value for testing the treatment difference, based Van Elteren's method for treatment comparisons

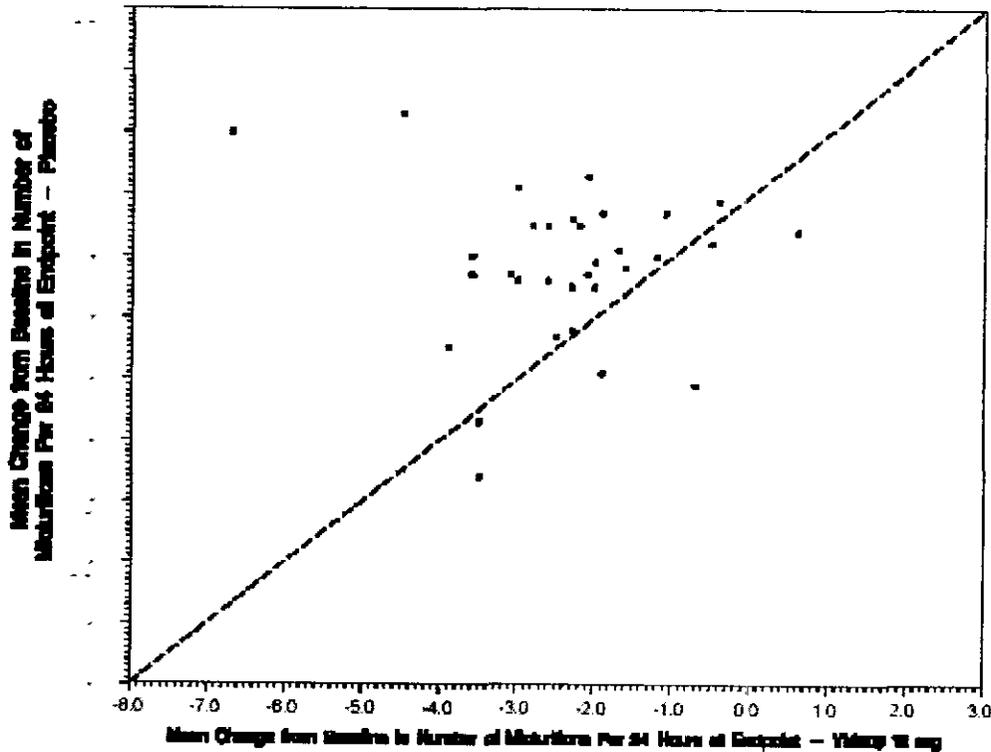
^c p value for within-treatment testing of the change from baseline using a paired t-test

Treatment-by-center interaction

As shown in the Figure B1, of the total 33 centers, 27 favored YM905, and 6 (#2, #5, #11, #13, #24, and #33) favored placebo. Center 35 with 23 patients had a small difference favoring placebo (0.3 micturition/24 h) and Center #33 with 24 patients had a small difference favoring placebo (0.2 micturition/24 h). The remaining 4 centers favoring placebo had few patients (sample sizes of 10, 6, 12 and 8, respectively).

Within-center analyses were carried out using three models: Wilcoxon test, ANCOVA, and 2-sample t-test.

Figure B1 Mean changes from baseline in number of Micturitions / 24 hr at endpoint by center (N=593)



Influence of dropouts

The dropout rate was balanced between treatment groups. To ensure that the conclusions of the primary analyses on the FAS were not unduly influenced by dropouts or missing data, analyses were done on the 2 partitions of the FAS: completers and dropouts. As shown in Table , dropouts tended to have higher baselines than completers and the FAS, but the effect size (the difference between YM905 and placebo in the change from baseline to endpoint in micturitions per 24 hrs) is similar among the groups.

Table B10 Summary of mean change from baseline to endpoint in micturitions / 24 h for FAS, completers, and dropouts

Treatment Group	FAS			Completers			Dropouts		
	Baseline Mean (n)	Mean Change From baseline	Effect size (P-Y)	Baseline Mean (n)	Mean Change From baseline	Effect size (P-Y)	Baseline Mean (n)	Mean Change From baseline	Effect size (P-Y)
Placebo	11.8 (n=295)	-1.3	1.1	11.8 (n=272)	-1.3	1.1	11.9 (n=23)	-1.4	0.6
YM905	11.5 (n=298)	-2.4		11.5 (n=269)	-2.4		12.2 (n=29)	-2.0	

Secondary efficacy analysis

Mean change from baseline to visit in the number of micturitions per 24 hrs: As shown in Figure B2, YM905 statistically significantly decreased the number of micturitions per 24 hrs at Weeks 4, 8, and 12 when compared with placebo. Among the FAS patients, 60 placebo patients (20%) and 119 YM905 patients (40%) had a mean of fewer than 8 micturitions per 24 hrs at endpoint. The difference was statistically significant (p<0.001)

Mean change from baseline in number of incontinence episodes per 24 hrs: As shown in the Figure B3, at the endpoint and at all study visits (Week 4, 8, and 12), YM905 statistically significantly decreased the number of incontinence episodes per 24 hrs when compared with placebo. Significantly more YM905 than placebo patients became continent during the course of the study. Among the FAS patients who had at least one episode of incontinence during the baseline period, 69 placebo (29%) and 122 YM905 patients (53%) became continent at endpoint ($p < 0.001$).

Table B11 Summary of change from baseline to endpoint in number of incontinence episodes/24 h (FAS, N^a=593)

Statistic	Placebo (N=238)	YM905 10 mg (N=230)	p value ^b
Baseline mean	2.9	2.9	
Mean change±SE	-1.2±0.15	-2.0±0.15	<0.001
Median change (min, max)	-1.0 (-10.3, 8.0)	-1.7 (-15.5, 6.0)	
95% confidence interval	-1.5 to -0.8	-2.2 to -1.5	
p value ^c	<0.001	<0.001	

^a n = number of patients with baseline and visit mean

^b p value for testing the treatment difference, based Van Elteren's method for treatment comparisons

^c p value for within-treatment testing of the change from baseline using a paired t-test

Mean change from baseline in number of urgency episodes per 24 hrs: As shown in the Figure B4, at the endpoint and at all study visits (Week 4, 8, and 12), YM905 statistically significantly decreased the number of urgency episodes per 24 hrs when compared with placebo.

Table B12 Summary of change from baseline to endpoint in number of urgency episodes/24 h (FAS, N^a=593)

Statistic	Placebo (N=292)	YM905 10 mg (N=296)	p value ^b
Baseline mean	6.8	6.3	
Mean change±SE	-1.8±0.22	-3.3±0.23	<0.001
Median change (min, max)	-1.7 (-23.7, 9.7)	-3.0 (-16.7, 12.7)	
95% confidence interval	-2.2 to -1.2	-3.7 to -2.7	
p value ^c	<0.001	<0.001	

^a n = number of patients with baseline and visit mean

^b p value for testing the treatment difference, based Van Elteren's method for treatment comparisons

^c p value for within-treatment testing of the change from baseline using a paired t-test

Mean change from baseline in volume voided per micturition: As shown in the Figure B5, at the endpoint and at all study visits (Week 4, 8, and 12), YM905 statistically significantly increased volume voided per micturition when compared with placebo. After excluding patients with large volumes, additional analyses did not change the study conclusions.

Table B13 Summary of change from baseline to endpoint in volume voided (mL) /24 h (FAS, N^a=593)

Statistic	Placebo (N=308)	YM905 10 mg (N=305)	p value ^b
Baseline mean	175.7	174.1	
Mean change±SE	13.0±34.15	46.4±3.73	<0.001
Median change (min, max)	7.8 (-208.7, 400.0)	42.6 (-252.8, 331.7)	
95% confidence interval	1.0 to 16.9	34.3 to 50.0	
p value ^c	<0.001	<0.001	

^a n = number of patients with baseline and visit mean

^b p value for testing the treatment difference, based Van Elteren's method for treatment comparisons

^c p value for within-treatment testing of the change from baseline using a paired t-test

Mean change from baseline in number of nocturnal void episodes per 24 hrs: A total of 281 patients in the placebo group and 283 patients in the YM905 group with both baseline and endpoint results were evaluated.

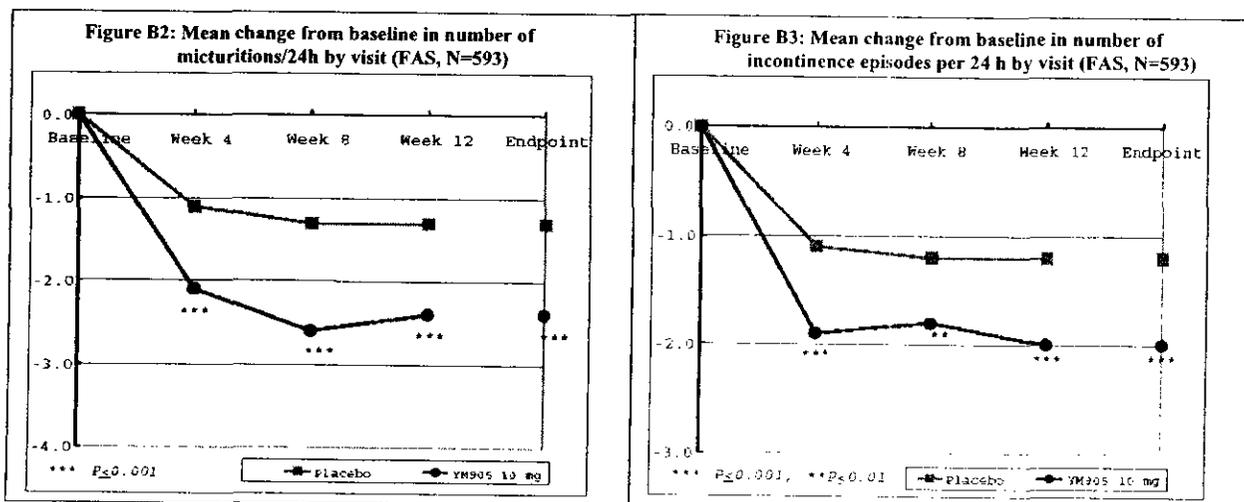
As shown in the Figure B6, at the endpoint, the mean change from baseline in the number of nocturnal void episodes per 24 hrs was -0.4 for the placebo and -0.5 for the YM905 group. The difference between treatment groups was not statistically significant at any time point. Among the FAS patients who had at least one episode of nocturnal void during the baseline period, 26 placebo patients (9%) and 34 YM905 patients (12%) had no episode of nocturnal void at endpoint. This difference was not statistically significant.

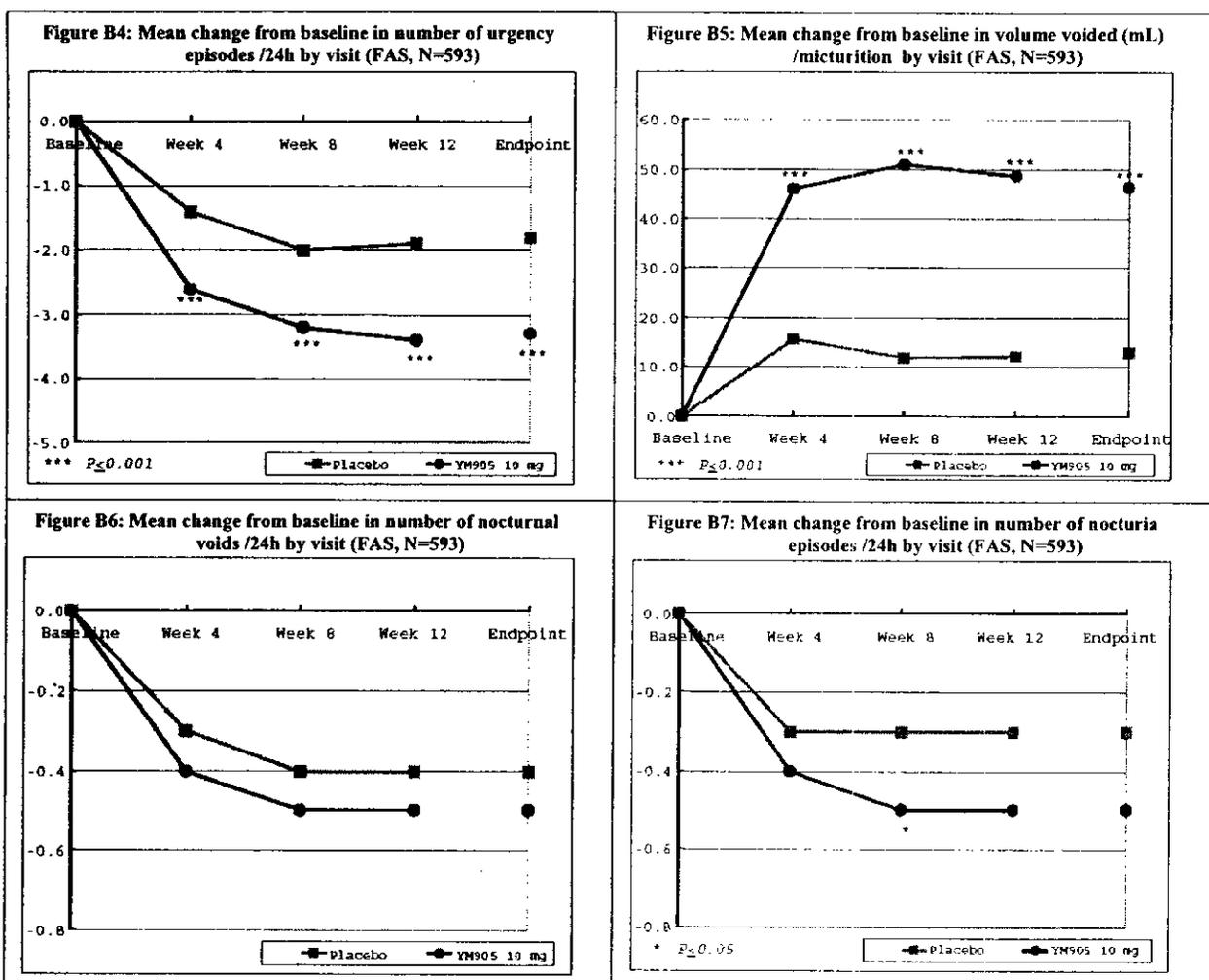
Mean change from baseline in number of nocturia episodes per 24 hrs: A total of 267 patients in the placebo group and 274 patients in the YM905 group with both baseline and endpoint results were evaluated. As shown in the Figure B7, at endpoint, the mean change from baseline in the number of nocturia episodes per 24 hrs was -0.3 for the placebo group and -0.5 for the YM905 group. The difference between treatment groups was statistically significant only at Week 8. Among the FAS patients who had at least one nocturia episode during the baseline period, 30 placebo patients (11%) and 49 YM905 patients (18%) had no episode of nocturia at endpoint. This difference was statistically significant ($p = 0.038$) at endpoint.

Efficacy conclusions

- YM905 statistically significantly reduced the number of micturitions per 24 hours at endpoint when compared to the placebo (primary efficacy endpoint). The statistically significant reduction in the number of micturitions per 24 hours with YM905 was observed at the Week 4 assessment and was maintained through Week 12 (end of double-blind treatment period).
- YM905 statistically significantly reduced the number of incontinence episodes per 24 hours compared to the placebo.
- YM905 statistically significantly reduced the number of urgency episodes per 24 hours compared to placebo.
- YM905 statistically significantly increased volume voided per micturition compared to placebo.
- The efficacy of YM905 over placebo in reducing the number of incontinence and urgency episodes and in increasing volume voided was observed at the Week 4 assessment and was maintained through Week 12 and at endpoint.
- YM905 did not reduce the number of nocturnal voids and did not significantly lower the number of nocturia episodes compared to placebo.

In summary, YM905 was effective in treating the symptoms of overactive bladder including frequency, urgency, and urge incontinence. With YM905, 53% of patients (vs. 29% for the placebo) became continent at endpoint with increased bladder capacity (demonstrated by the increase in the volume voided per micturition).





B.5 Safety analyses

Extent of study drug exposure

Mean exposure to study medication was 80 days in the placebo group and 79 days in the YM905 group. The frequency distribution for the number of days of exposure was similar between treatment groups, with the majority of patients (74%) in both treatment groups exposed to study medication for at least 12 weeks. Placebo patients were exposed for a total of 820 person-months and YM905 patients were exposed for a total of 828 person-months.

Table B14 Study medication exposure (safety population, N=634)

Study Medication Exposure (days) ^a	Placebo (N=316)	YM905 10 mg (N=318)
	n (%)	n (%)
1 to 13 days	8 (2.5)	13 (4.1)
14 to 27 days	9 (2.9)	9 (2.8)
28 to 55 days	14 (4.4)	12 (3.8)
56 to 83 days	48 (15.2)	50 (15.7)
≥ 84 days	233 (73.7)	234 (73.6)
Unknown	4 (1.3)	0 (0)
Mean exposure	80 days	79 days

^a Length of treatment exposure is defined as the last day of treatment minus the first day of treatment plus one day. Last visit date is used if the date of last dose of study drug is unknown.

Reviewer's comment: The extent of exposure in this trial was adequate to make an assessment of safety.

Deaths: No patients died during the study.

Serious adverse events (SAEs):

Serious adverse events (SAE) were reported for two patients in the placebo group and ten patients in the YM905 group during the 12-week treatment period.

Table B15 Patients with serious adverse events (SAE's) (safety population, N = 672)

Patient #	MedDRA preferred term/Verbatim term	Start day ^a	Relationship to study medication	Action taken/ Outcome
Placebo				
5014	Myocardial infarction/myocardial infarction	14	Unrelated	Discontinued/recovered
17027	Pneumonia nos/pneumonia	12	Unrelated	Interrupt/recovered
YM905 10 mg				
1002	Hyponatremia/hyponatremia secondary to polydypsia	17	Possibly	Discontinued/recovered
5009	Hyponatramia/myocardial infarction	4 (+1)	Unrelated	Discontinued/recovered
	Atelectasis/left lower lobes atelectasis	10 (+7)	Unrelated	None/recovered
5013	Transient ischemic attack/transient ischemic attack	29	Unrelated	None/recovered
5024	Fecal impaction/fecal impaction	44	Probably	None/recovered
6012	Angina pectoris/angina	70	Unrelated	None/recovered
	Abdominal pain upper/epigastric pain	70	Unrelated	None/recovered
8021	Upper limb fracture nos/grade 2 displaced right distal radius fracture	61	Unrelated	Interrupt/not recovered
10007	Cellulites/infected right leg	29	Unrelated	Discontinued/unknown
10026	Cerebro-vascular accident nos/stroke	89	Unrelated	Discontinued/recovered with sequelae
14003	Hypotension nos/hypotension	54 (+1)	Possibly	Discontinued/recovered
16032	Suicidal ideation/worsening of bipolar disorder	10	Unrelated	None/recovered

nos = not otherwise specified

^a Relative to day of first dose of study drug, (post-treatment day relative to first day after the last dose is indicated with a + sign)

Of the SAE's with YM905, three were judged related to study drug: two (hyponatremia secondary to polydypsia and hypotension) were judged possibly related to study drug and another (fecal impaction following several days of constipation) was judged probably related to study drug.

Narratives of SAE's (YM905 group):

Patient #1002: This 46-year-old woman had a history of schizoaffective disorder. On Day 17 of treatment, she was taken to the emergency room after experiencing intense thirst and ingesting a very large volume of water. Study drug was discontinued on that day because of this event. She was admitted to the hospital and was diagnosed with hyponatremia secondary to polydypsia. Her serum sodium was 118 and her serum potassium was 3.0. A urine osmolality was 5. She diuresed 11 liters. Two days after her last dose of study drug, she recovered from the event and was discharged from the hospital. The investigator assessed the relationship between the hyponatremia and the study drug to be possibly related.

Reviewer's comment: The reviewer believes that this event is possibly related to study drug.

Patient #5009: This 73-year-old man had a medical history of cardiomegaly, hypertension, diabetes, obesity, decrease in peripheral pulses, and edema in the extremities. Four days after starting study drug, he was hospitalized for a myocardial infarction, which resulted in premature discontinuation of study drug. Earlier that day, the patient had collapsed at home after complaining of feeling weak and dizzy. Cardiac enzymes and ECGs were suggestive of a small non-Q myocardial infarction. A cardiac catheterization revealed severe triple vessel coronary artery disease and an ejection fraction of 60%. Five days after admission, he underwent triple bypass surgery. A pulmonary consult was requested on post-operative Day 1 because the patient was experiencing hypoxemia and respiratory distress. An adverse event of left lower lobe atelectasis was reported. This event was serious because it resulted in prolongation of the patient's hospitalization. A bronchoscopy revealed mild to moderate mucous plugging in the left lung, which was suctioned and sent for microbiology. Bronchial washings were positive for *Candida albicans*. Under antibiotic therapy and therapy for airway obstruction, the patient recovered from both events and was discharged from the hospital 10 days after surgery. The investigator assessed the relationship to the study drug to be unrelated for both the myocardial infarction and left lower lobe atelectasis.

Reviewer's comment: The reviewer agrees that these events were not related to study drug.

Patient #5013: This 70-year-old woman had a medical history of hypercholesterolemia and palpitations. On Day 29 of treatment, she experienced a sudden onset of slurred speech, clumsiness in the right arm and hand when reaching for an object, and mild dragging of the right lower extremity. No drooping of the face was noted and she had no palpitations, chest pain, edema, or shortness of breath. The patient was hospitalized the next day for evaluation. The weakness of the extremities had resolved, but the patient still had some mild residual slurring of speech. A CT scan of the brain performed on Day 30 revealed a small lacunar infarct on the right in the area of the internal capsule. The patient was discharged after 2 days in the hospital and recovered without sequelae 5 days later. She went on to complete the double-blind treatment period on Day 82 of treatment and indicated her intention to enter the open-label extension study. The investigator assessed the relationship between the transient ischemic attack and the study drug to be unrelated.

Reviewer's comment: The reviewer believes that the relationship to study drug is unlikely.

Patient #5024: This 71-year-old man had a history of hypercholesterolemia, environmental allergies, and obesity. He had no history of chronic constipation. He experienced mild constipation beginning at an unspecified time following the start of study drug. This event was judged by the investigator to be mild and probably related to study drug. On Day 44 of treatment, the patient experienced fecal impaction. He had not had a bowel movement in several days and was experiencing cramping and leakage of stools. After taking two docusate tablets advised by the investigator but without relief, he was admitted to the hospital with increasing abdominal distention and discomfort. There was solid hard stool in the rectal vault and tenderness in the anal canal. He underwent a gastrografin enema, which revealed a large amount of stool and no obvious obstruction. The event resolved the following day and the patient was discharged. He completed the double-blind treatment period on Day 85 of treatment, at which time the constipation was ongoing. He indicated his intention to enter the open-label extension study. The investigator assessed the fecal impaction as probably related to study drug.

Reviewer's comment: The reviewer believes that the event was probably related with study drug.

Patient #6012: This 84-year-old woman had a medical history of hyperlipidemia, arthritis, and muscle spasms. On Day 70 of treatment, the patient developed chest discomfort, epigastric pain, and constipation. An ECG on the following day showed evidence of an old myocardial infarction, and the patient was hospitalized to determine the cause of the chest pain. The patient had a CPK of 400 with an MB band that was positive and troponin of 30. Cardiac catheterization showed no evidence of significant coronary artery disease, and an ultrasound of the abdomen was normal. The investigator diagnosed the epigastric and chest pain as angina. The patient was treated with various medications. She was discharged after 3 days in the hospital. Five days later, the patient recovered from the epigastric pain/angina, but the constipation continued. On Day 82 of treatment, the patient complained of dry eyes, blurred vision, and dry mouth. The following day, the patient

was discontinued from the study because of these four ongoing events. The dry eyes, blurred vision, and dry mouth resolved within four days, and the constipation was ongoing at the time of the patient's last assessment nine days later. The investigator assessed the relationship of the epigastric pain/angina to be unrelated to study drug.

Reviewer's comment: The reviewer agrees that this event was not related to study drug.

Patient #8021: This 85-year-old woman had no relevant medical history and reported no risk factors. On Day 61 of treatment, she fell off a ladder and experienced a right arm fracture, for which she was hospitalized the same day. An x-ray revealed a Grade 2, open, displaced right radius fracture of the right wrist. The following day, she underwent reconstructive surgery to repair the fracture. Study medication was interrupted the day of and the day following her surgery, but was then resumed. The patient was discharged the day after the surgery. She went on to complete the double-blind treatment period 86 days after starting study drug and indicated her intention to enter the open-label extension study. The adverse event was not resolved as of her last protocol-associated assessment on the day of her last dose. Additional information received approximately 2 months later indicated that the fracture resolved 55 days after her discontinuation. The fracture was judged by the investigator to be unrelated to study drug.

Reviewer's comment: The reviewer agrees that the relationship of this event to study drug was unlikely.

Patient #10007: This 84-year-old woman had a medical history of easy bruising and bleeding and was taking warfarin as a concomitant medication. On Day 29 of treatment, she hit her leg on the car door. One week later, she went to the ER because her right leg was ecchymotic and swollen. She was hospitalized for what was initially thought to be a blood clot in the right leg. A duplex ultrasound of the right lower leg revealed no evidence of deep venous thrombosis and an ill-defined hypoechoic mass in the deep tissue that may have represented a hematoma. The patient's warfarin was withheld on the day of the ultrasound. She was diagnosed with cellulitis and administered hydrocodone/APAP and acetaminophen. She discontinued study drug because of this event 35 days after the first dose. She was discharged from the hospital 4 days later. The outcome of the adverse event is unknown. The investigator assessed the patient's cellulitis to be unrelated to study drug.

Reviewer's comment: The reviewer believes that the event was not related to study drug.

Patient #10026: This 64-year-old woman had a medical history of high blood pressure, depression, and arthritis. In addition, her familial history was positive for CVA and MI. On an unspecified day after approximately 2 ½ months of study drug treatment, the patient developed constipation. On Day 89 of treatment, she experienced a cerebrovascular accident. Paramedics found her on the floor experiencing right-sided hemiparesis, slurred speech, and left sided visual gaze and took her to the emergency room. She reported being in good health before this incident and denied any prior similar episodes. Her initial ER blood pressure was 182/93 mmHg and increased to 225/116 mmHg after admission to the hospital the same day. She was given anti-hypertension medicine, and her blood pressure returned to 166/90 mmHg. A CT scan of the head revealed a left parietal demarcation that was consistent with an infarct; there was no evidence of acute intra- or extra-axial hemorrhagic bleed. The same day, she discontinued study drug because of the constipation and cerebrovascular accident. The investigator judged the patient's stroke to be unrelated to study drug.

Reviewer's comment: The reviewer believes that the relationship to study drug is unlikely.

Patient #14003: This 76-year-old man had a history of hypertension, atrial fibrillation, and exertional dyspnea. The patient was a former smoker. On Day 25 of treatment, the patient experienced an episode of shortness of breath and chest pain. He underwent a cardiac catheterization on Day 39 of treatment, which revealed no significant coronary disease. Three days later, the patient went to the emergency room complaining of shortness of breath. All tests done in the ER on that day were negative and the patient was released. At his Visit 4 evaluation (Day 54), he was sweating; his blood pressure was 80/50 mmHg and his

heart rate was 82 bpm and irregular. An ECG was done, and the patient was sent to the emergency room for evaluation of hypotension. His chief complaints upon arrival at the emergency room were recorded as shortness of breath and diaphoresis; emergency room notes indicated that these symptoms began while blood was being drawn at the investigator's office and that the patient had been intermittently short of breath for 1 year. While in the ER, the patient was asymptomatic; his blood pressure was 129/91 mmHg and his pulse was irregular at 76 bpm. CXR was normal. ECG showed atrial fibrillation, poor R wave progression, and T wave changes in leads II and III, which were unchanged from baseline. His PT was 27.7 and INR was 4.5. Warfarin was withheld for 2 days. The patient was released from the ER with instructions to repeat his PT and INR. The adverse events resolved that same day. The patient was contacted 3 days later and reported feeling well. The study drug was prematurely discontinued because of the dyspnea and hypotension. The patient took his last dose of study drug on Day 53, the day prior to his Visit 4 evaluation. The investigator assessed the hypotension to be possibly related to study drug.

Reviewer's comment: the reviewer believes that the event was possibly related to study drug.

Patient #16032: This 52-year-old post-menopausal woman had a history of bipolar disorder since 1997, for which she received treatment with clonazepam, lamotrigine, lithium, and risperidone, and a history of hyperlipidemia since 1999. On Day 10 of treatment, the patient was hospitalized due to a depressive crisis, especially suicidal thoughts over the past 3 months. She was severely affected by her mother's recent death. The dosage of risperidone was increased and lamotrigine and clonazepam were discontinued. The patient was started on valproic acid which stabilized her mood and she stopped having suicidal ideation and became more optimistic. The patient was discharged from the hospital on Day 13 of study medication treatment and recovered from the event 3 days later. It was recommended that she attend a grief and loss support group. She continued to take the study medication while hospitalized and went on to complete the double-blind period 84 days after starting study drug. She subsequently entered the open-label study. The investigator assessed the patient's suicidal ideation to be unrelated to study drug.

Reviewer's comment: The reviewer believes that this event is unlikely to have been related to study drug.

Overall adverse events

Table B16 Summary of treat-emergent adverse events (TEAEs) (safety population, N = 634)

	Placebo (N = 316)	YM905 10 mg (N = 318)
Number of TEAEs reported	436	677
Number of patients with TEAEs [n (%)]	199 (63)	251 (79)
Number of SAE's	2	12
Number of patients with SAE's [n (%)]	2 (0.6)	10 (3.1)
Patients with AE's by severity [n (%)]		
Mild	82 (26)	98 (31)
Moderate	103 (33)	123 (39)
Severe	14 (4.4)	30 (9.4)
Number of patients discontinued because of AE's [n (%)]	18 (5.7)	28 (8.8)
Number of patients with drug-related AE's [n (%)]	95 (30)	197 (62)
Number of deaths	0	0

More than 60% of the patients in both groups reported adverse events (63% for placebo and 79% for YM905). Most of the patients experienced AE's that were mild or moderate, but more patients experienced AE's that were rated severe in the YM905 group (9.4%) than did patients in the placebo group (4.4%). Also the number of patients with AE's judged possibly or probably related to study drug was much higher for YM905 patients (62%) than for placebo patients (30%). The differences in frequency and severity of AE's between placebo and YM905 were largely due to the anticholinergic effects of YM905, i.e. dry mouth (6% for placebo vs. 38% for YM905), constipation (4% for placebo vs. 19% for YM905), and blurred vision (1.3% for placebo vs. 4% for YM905).

Table B17 Most common (≥2%) TEAEs by system organ class (safety population, N = 634)

System organ class MedDRA preferred term	Placebo (N=316) n (%)	YM905 10 mg (N=318) n (%)
Gastrointestinal disorders	61 (19)	165 (52)
Dry mouth	18 (6)	121 (38)
Constipation	13 (4)	59 (19)
Nausea	6 (2)	15 (5)
Diarrhea	6 (2)	9 (3)
Dyspepsia	5 (1.6)	16 (5)
Infection and infestations	65 (21)	63 (20)
Urinary tract infection nos	16 (5)	26 (8)
Nasopharyngitis	14 (4)	7 (2.2)
Upper respiratory tract infection	12 (4)	6 (1.9)
Sinusitis nos	8 (2.5)	8 (2.5)
Nervous system disorders	34 (11)	41 (13)
Headache nos	11 (4)	16 (5)
Dizziness (excluding vertigo)	8 (3)	5 (1.6)
Musculoskeletal, connective tissue & bone disorders	38 (12)	25 (8)
Arthralgia	13 (4)	8 (2.5)
Back pain	10 (3)	4 (1.3)
General disorders & administration center conditions	20 (6.3)	40 (12.6)
Fatigue	7 (2.2)	11 (3.5)
Oedema lower limb	4 (1.3)	9 (2.8)
Eye disorders	12 (3.8)	30 (9.4)
Vision blurred	4 (1.3)	13 (4.1)
Dry eye nec	4 (1.3)	12 (3.8)
Skin & subcutaneous tissue disorders	17 (5.4)	31 (9.8)
Pruritus nos	0	7 (2.2)
Renal and urinary disorders	18 (5.7)	27 (8.5)
Urinary retention	4 (1.3)	10 (3.1)

The incidences for both dry mouth and constipation were significantly greater with YM905 than with placebo ($p < 0.001$). Another relatively commonly reported AE was urinary tract infection (UTI), with an incidence of 3% for placebo and 6% for YM905. There is no evidence that the higher incidence of UTI in YM905 patients was due to urinary retention.

The most common drug-related AE's, as expected, were dry mouth and constipation shown in Table B18.

Table B18 Most common (≥2%) drug-related TEAEs by system organ class (safety population, N = 634)

System organ class MedDRA preferred term	Placebo (N=316) n (%)	YM905 10 mg (N=318) n (%)
Gastrointestinal disorders	48 (15)	151 (48)
Dry mouth	18 (5.7)	118 (37)
Constipation	12 (3.8)	56 (17.6)
Nausea	4 (1.3)	13 (4.1)
Dyspepsia	3 (0.9)	13 (4.1)
General disorders & administration center conditions	8 (2.5)	29 (9.1)
Fatigue	2 (0.6)	10 (3.1)
Nervous system disorders	19 (6)	18 (5.7)
Headache nos (not otherwise specified)	7 (2.2)	6 (1.9)
Dizziness (excluding vertigo)	7 (2.2)	1 (0.3)
Eye disorders	9 (2.8)	23 (7.2)
Dry eye nec (not else classified)	4 (1.3)	12 (3.8)
Vision blurred	4 (1.3)	10 (3.1)
Renal and urinary disorders	5 (1.6)	15 (4.7)
Urinary retention	3 (0.9)	9 (2.8)

Other AE's of interest included urinary retention and QT prolongation.

Urinary retention: 5 patients (1.6%) in the placebo group and 10 patients (3.1%) in the YM905 group experienced shifts in post-void residual volume from ≤ 150 mL at baseline to > 150 mL at Week 12. An AE of urinary retention was documented for 4 of the 5 placebo patients and 9 of the 10 YM905 patients with shifts from ≤ 150 mL at baseline to > 150 mL at Week 12. All of the events were of mild to moderate severity and with the exception of one patient in the placebo group and one in the YM905 group, were considered related to study drug. Post-void residual volumes for the patients who experienced shifts from baseline to > 150 mL at the last available visit, ranged from 166 mL to 268 mL in the placebo group and from 151 mL to 368 mL in the YM905 group.

Table B19 Number of patients with shift from baseline to Week 12 in post-void residual volume (mL) (safety population, N=634)

Shift of post-void residual volume	Placebo (N=316)		YM905 10 mg (N=318)	
	Male	Female	Male	Female
≤ 150 mL \rightarrow >150 mL	1	4	2	8

QT prolongation:

The mean increase in QT interval (calculated using Bazett's formula) of 3.3 msec relative to placebo reflects a small but statistically significant ($p=0.044$) treatment difference. Similar results are obtained when QTc is calculated using Fridericia's formula (because Bazett's formula is not linear with heart rate).

For the analysis of changes from baseline in QTc intervals, patients were categorized as follows:

- Patients with normal QTc (men, ≤ 430 msec; women, ≤ 450 msec)
- Patients with borderline QTc (men, >430 to ≤ 450 msec; women, >450 to ≤ 470 msec)
- Patients with prolonged QTc (men, >450 to ≤ 500 msec; women, >470 to ≤ 500 msec)
- Patients with prolonged QTc of clinical concern (>500 msec)

The changes from baseline in QTc interval were categorized by the sponsor as follows:

- <30 msec; within normal limits
- Between 30 and 60 msec: borderline
- >60 msec: clinical concern

Table B20 Summary of changes of QT interval values from baseline to endpoint (safety population, N=634)

QT prolongation evaluation	Placebo (N=316)	YM905 10mg (N=318)	P values
QT interval (msec)			
N	220	229	
Baseline mean	397.2	397.9	
Mean change \pm SE	2.1 \pm 1.60	7.6 \pm 1.75	0.043
P value	0.182	<0.001	
QTc interval (msec) (Bazett's)			
N	220	229	
Baseline mean	421.5	423.5	
Mean change \pm SE	1.1 \pm 1.25	4.4 \pm 1.30	0.044
P value	0.385	<0.001	

Among the female patients, 12 on placebo (4%) and 30 on YM905 (9%) had a borderline to prolonged QTc (>450 msec) at one or more observations during the study, including baseline. Of these, two YM905 patients (#27003 and #5011) had a QTc >500 msec at one point during double-blind treatment. Of the patients with a QTc >450 msec, 9 on placebo and 26 on YM905 had a QTc increase <30 msec. 3 on placebo and 12 on YM905 had a QTc increase between 30 and 60 msec, and 2 on YM905 had an QTc increase of >60 msec at any time point (#27003 and #5011).

Among the male patients, 15 on placebo and 22 on YM905 had a QTc >430 msec at one or more observations during the study, including baseline. Of these, 13 on placebo and 14 on YM905 had a QTc increase <30 msec, while 2 on the placebo and 8 on YM905 had a QTc increase between 30 and 60 msec. No patient had a QTc increase >60 msec.

Three female patients in the YM905 group had a QTc >450 msec at any time during the study with narratives below.

Patient #23010: This 54-year-old Caucasian woman had a baseline QTc of 470 msec with a heart rate of 86 bpm. Her QTc was 450 msec at Week 4 and 8 and 510 msec at Week 12, with a heart rate of 76 bpm. The patient remained on the study drug and completed the study. She subsequently went on to the extension study and at Month 3 of the open-label extension study, her QTc was 480 msec.

Patient #27003: A 77-year-old white woman had a QTc of 450 msec at screening with a hear rate of 72 bpm and QTc of 420 msec at baseline with a HR of 76 bpm. Her QTc was 500 msec at Week 4 with a HR of 76 bpm and 520 msec at Week 8 with a HR of 74 bpm. At Week 12, her QTc was 450 msec with a HR of 80 bpm. She continued in the extension study. At Month 3, her QTc was 470 msec and at Month 6, her QTc was 460 msec.

Patient #5011: A 69-year-old white woman had a QTc of 440 msec at screening, 390 msec at baseline, and 460 msec at Week 4, with a HR of 60 bpm each time. Treatment with YM905 was discontinued after 18 days of treatment because of depression which began after 8 days of treatment.

Table B21 Number of patients with changes of clinical importance from baseline to Week 12 and endpoint in QTc interval (safety population, N=634)

Visit: change from baseline (msec)	Placebo (N=316)	YM905 10 mg (N=318)
Week 12	195	203
Increase > 60	0	0
Increase ≥ 30 to ≤ 60	19	28
Increase or decrease < 30	164	160
Endpoint	220	229
Increase > 60	0	1
Increase ≥ 30 to ≤ 60	23	29
Increase or decrease < 30	184	182

Endpoint is the last available on-treatment visit on or before Week 12 (Visit 5).

One patient in YM905 group had a change in QTc > 60 msec at endpoint. An increase in QTc between 30 and 60 msec was found in 19 (10%) placebo vs. 28 (14%) YM905 patients at 12 weeks and in 23 (11%) placebo vs. 29 (13%) YM905 patients at endpoint. Decreases in QTc also occurred with both placebo and YM905

Discontinuations due to adverse events

A total of 18 patients in the placebo group (6%) (with a total of 23 AE's) and 28 patients in the YM905 group (9%) (with a total of 49 AE's) had adverse events during the 12-week treatment period that led to discontinuation of study drug. The events causing the highest rates of discontinuations for YM905 were dry mouth (1.9%) and constipation (1.6%). In addition, nausea led to discontinuation in 3 YM905 patients (0.9%) vs. 2 (0.6%) for placebo; dry eye led to discontinuation of YM905 treatment in 3 patients (0.9% vs. 0 for placebo); and blurred vision led to discontinuation in 1 YM905 and 1 placebo patient (0.3% for each group). No other AE's led to discontinuation for more than 1% of patients in either treatment group.

In the 18 placebo patients who discontinued treatment because of an adverse event, 17 of the 23 events were mild or moderate and 6 were severe. In the 28 YM905 patients who discontinued treatment because of an adverse event, 33 of the 49 adverse events were mild or moderate and 16 were severe.

Other important AE's leading to discontinuation: Elevated ALT and AST in three (0.9%) YM905 patients (patients #29003, #33009 and #34021) (vs. none in the placebo group).

Table B22 3 YM905 patients with abnormal liver function tests led to discontinuation (AST & ALT: U/L)

Patient	#29003				#33009				#34021			
	Base	WK 4	WK 8	WK 12	Base	WK 4	WK 8	WK 12	Base	WK 4	WK 8	WK 12
AST	65	51	234	297	54	79	81	52	27	61		
ALT	104	52	254	304	97	140	141	88	60	115		
γ-GT	62	51	130	145	30	30	30	27	107	91		

#29003: Discontinued Day 62. 105 days after, AST, ALT and γ-GT remained high (161, 143, 259, respectively), with Hepatitis A history as well as suggesting auto immune hepatitis

#33009: Discontinued Day 35. 56 days after, AST and ALT returned to baseline; γ-GT was normal all the time.

#34021: Discontinued Day 43. 40 days after, AST and ALT and γ-GT returned to normal

Normal range for #29003: AST 9-34 U/L, ALT 6-32 U/L and γ-GT 5-50 U/L; for #33009 and #34021: ALT 11-36 U/L, ALT 6-43 U/L., and γ-GT 10-61 U/L. All were with normal bilirubin.

Expected AE's:

The overall incidences of both dry mouth and constipation were significantly greater in YM905 group than in the placebo group ($p < 0.001$). All AE's of dry mouth and constipation reported in placebo group had maximum severity of mild or moderate, while in the YM905 group 8 patients (2.5%) had severe dry mouth and 5 patients (1.6%) had severe constipation. Four of the 8 with severe dry mouth and 1 of the 5 with severe constipation discontinued study because of these AE's. For all of these patients except one case of constipation in the YM905 group, the investigator judged the dry mouth or constipation probably related to the study medication.

Blurred vision and other related visual AE's: Vision blurred was also greater in the YM905 group (4%) than in the placebo group (1.3%). Other types of visual disturbances (e.g. visual acuity reduced, dry eye, and vision abnormal) were also more common with YM905 (13 patients, 4%) than with placebo (5 patients, 1.6%). They were mild or moderate in all 5 placebo patients and in 10 of the 13 YM905 patients, and severe in 3 YM905 patients.

In addition to dry mouth, several patients in each group reported other AE's that may be related to anticholinergics, including dry eye nec (not else where classified), and nasal dryness. As expected, these events were reported for more YM905 patients (18 patients) than placebo (4 patients). They were mild or moderate for all patients with the exception of 2 patients in the YM905 group with severe dry eye and 1 patient in the YM905 group who had severe nasal dryness. All of the events of dry skin, dry eye, and nasal dryness were judged by the investigator to be related to study drug for all patients. In the YM905 group, dry eye led to discontinuation of treatment in 3 patients.

In summary, most occurrences of expected anticholinergic AE's in both groups were considered by the investigator to be treatment-related. All severe AE's of dry mouth, constipation, and blurred vision in the YM905 group were considered possibly or probably related to study drug. The incidences of treatment-related dry mouth and constipation were significantly greater in the YM905 group than in the placebo group ($p < 0.001$). However, the difference between the 2 groups in the incidence of treatment-related blurred vision was not significant.

Clinical laboratory evaluation: YM905 10mg had no influence on clinical laboratory parameters or vital signs.

Safety conclusions

- In this study, YM905 10 mg was tolerated
- The most common AE's with YM905 were consistent with the pharmacologic effects of the drug, namely dry mouth, constipation, and visual disturbances
- YM905 did not have clinically relevant influence on clinical laboratory parameters or vital signs
- YM905 had a small (3.3 msec) but statistically significant effect on the QTc interval relative to placebo (Bazett's correction).

B.6 Reviewer's assessment of safety and efficacy in Clinical Trial CL-905-014

The reviewer believes that YM905 10 mg daily does reduce the number of micturitions per 24 hrs (-2.4 ± 0.15) in the majority of patients with OAB when compared with placebo (-1.3 ± 0.16).

In terms of secondary endpoints, the reviewer agrees that the reduction of incontinence episodes (53% of patients in YM905 group became continent), and the increase of volume voided per micturition (+46 mL in volume voided for YM905) appeared to support the efficacy of YM905.

The reviewer believes that the positive effects of YM905 on various symptoms of OAB, along with the improvement in incontinence and volume voided are evidence that treatment with YM905 10 mg provides a clinically meaningful benefit to patients with OAB.

In terms of safety, the reviewer believes that overall, YM905, at daily dose of 10 mg, was safe and tolerated. The most common adverse events in the active drug group were anticholinergic events, including dry mouth, constipation, and blurred vision. The reviewer agrees that these AE's are expected and were mild to moderate in severity in majority of patients. The reviewer agrees that YM905 had no influence on clinical laboratory parameters. The reviewer notes that ALT and AST elevated in three patients with YM905 and the treatment was discontinued. The QTc interval was prolonged by approximately 3 msec compared to placebo. QTc prolongation issues are addressed in the review of Study CL-022 and in the Executive Summary of Clinical Review.

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Appendix C

Clinical Trials 905-CL-015: A randomized, double-blind, placebo and active controlled, multi-center study solifenacin succinate 5 mg and 10 mg in patients with overactive bladder (in the Europe)

C.1 Design

Study 905-CL-015 was a randomized, double-blind, parallel-group, placebo- and active-controlled, fixed-dose, multi-center study of 5 mg 10 mg solifenacin succinate administered orally once daily for 12 weeks. Patients were evaluated at baseline and at 4, 8 and 12 weeks. The study had a placebo and an active (tolterodine 2 mg BID) control. The primary aim of the study was to assess the efficacy of YM905 (solifenacin succinate) 5 mg and 10 mg in patients with OAB. The secondary aims were to assess the safety and the tolerability of 5 mg and 10 mg solifenacin, and to compare the efficacy and safety of solifenacin with tolteradine 2 mg bid.

Inclusion criteria:

Symptoms of OAB (urinary frequency with urgency and/or incontinence) for ≥ 3 months, age ≥ 18 years, an average of ≥ 8 micturitions/24h, and either an average of ≥ 3 urinary incontinence episodes per 3-day or an average of ≥ 3 urinary urgency episodes per 3-day, documented in a 3-day diary in the screening phase.

Exclusion criteria:

Stress incontinence, mixed incontinence with a predominant stress component, or neurological cause for detrusor overactivity. Urinary retention as demonstrated by post-void residual urine volume (PVR) > 200 mL as evidenced by bladder scan.

Methodology:

This is a Phase 3, randomized, double-blind, parallel-group, fixed-dose, placebo- and active-controlled, multicenter study. The study comprised of a single-blind, 2-week placebo run-in period, followed by a randomized, double-blind, placebo- and active-controlled, 12-week treatment period. Patients visited the clinic at screening (Visit 1); at the end of the placebo run-in period (Visit 2); after 4, 8 and 12 weeks of double-blind treatment (Visits 3, 4, and 5).

Study drug regimen:

Table C1 Study regimen in Study CL-015

Randomization	Solifenacin 5 mg qd		Solifenacin 10 mg qd		Tolterodine 2 mg bid		Placebo	
	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.
YM905 5 mg tablet	1							
YM905 10 mg tablet			1					
Placebo tablet	1		1		2		2	
Tolterodine 2 mg capsule					1	1		
Placebo capsule	1	1	1	1			1	1

Primary efficacy endpoint: Change from baseline in mean number of micturition/24h." Micturition was defined as any voiding episode recorded by the patient in the 3-day diary as either "urinated" with or without "incontinence".

Secondary efficacy endpoints:

- Change from baseline in mean volume voided per micturition
- Change from baseline in mean number of incontinence episodes / 24 hrs
- Change from baseline in mean number of urge incontinence episodes / 24 hrs
- Change from baseline in mean number of urgency episodes / 24 hrs
- Change from baseline in mean number of nocturnal voided / 24 hrs
- Change from baseline in mean number of nocturia episodes / 24 hrs
- Change from baseline in mean number of pads used
- Change from baseline in quality of life scores as assessed by King's Health Questionnaire

Safety was assessed by: incidence and severity of adverse events, clinical laboratory values (hematology, clinical chemistry, and urinalysis), vital signs, ECG, and post-void residual volume.

The study was initiated in February 22, 2001 and the final study report reflects all available efficacy and safety data from all patients through January, 2002. The final observation was on January 21, 2002. Study visits occurred at screening (1) placebo run-in period (2) after 4 weeks (3) 8 weeks (4) 12 weeks (5).

C.2 Study Population

Safety population (SAF): All patients who had been randomized and had taken at least 1 dose of double-blind study medication

Full analysis set (FAS): All patients who had been randomized, and had taken at least 1 dose of double-blind study medication, and provided efficacy data at baseline (Visit 2) and endpoint visit (on treatment)

Per protocol set (PPS): All patients who were included in the FAS and completed the study without major violations of the protocol.

Pharmacokinetic set (PKS): All patients of whom a blood sample was collected within the range of 22 to 26 hours after the last dose of double-blind treatment.

A total of 1281 patients from 98 centers were enrolled in the study, of which 1081 were randomized.

Table C2 Number and percentage of patients randomized, treated, discontinued and completed the study

	Placebo n (%)	Solifenacin succinate		Tolterodine 2 mg bid n (%)	Total n (%)
		5 mg qd n (%)	10 mg qd n (%)		
Randomized	267 (100)	279 (100)	269 (100)	266 (100)	1081 (100)
Treated	267 (100)	279 (100)	268 (99.6)	263 (98.9)	1077 (99.6)
Discontinued	32 (12)	28 (10)	20 (7.4)	29 (10.9)	109 (10.1)
Completed	235 (88)	251 (90)	249 (92.6)	237 (89.1)	972 (89.9)

Out of 972 patients who completed the study, 892 (92%) stated they were willing to participate in the open-label extension study (905-CL-019).

316 placebo patients and 318 solifenacin patients took study drug and were included in the safety population. Of the 634 patients, 41 (21 for placebo and 20 for YM905) were excluded from the efficacy analysis, so that, the full-analysis set (FAS: all patients who were randomized, received at least one dose of double-blind treatment, had baseline diary data available and on-treatment diary data available) included 593 patients (295 placebo and 298 solifenacin succinate). The per protocol set (PPS: all patients who were randomized, received at least one dose of double-blind treatment, had baseline diary data available, had at least 8-weeks of on-treatment diary data available, had overall treatment compliance of at least 70%, and had no major protocol violation) included 535 patients (266 placebo and 269 YM905). The safety population (SAF: all patients who were randomized and received at least one dose of double-blind treatment) included all 634

randomized patients. There were no notable imbalances between treatment groups in demographic characteristics including age, gender, race, weight, and height. The study population was predominantly Caucasian (90%) and female (82%) with mean age of 60 years. 40% of the study population was 65 years or older, and 90 patients (14%) were 75 years or older. The median time since the beginning of symptoms of OAB was approximately 5-6 years in both the placebo and YM905 groups (mean 9 years for placebo and 10 years for YM905).

Table C3 Number of randomized patients in the SAF, FAS, and PPS population at each visit patients in study population

Patient groups	Placebo	Solifenacin		Tolterodine 2 mg bid	Total n (%)
		5 mg qd	10 mg qd		
Randomized	267	279	269	266	1081 (100)
Treated	267	279	268	263	1077 (99.6)
SAF Baseline	267	279	268	263	1077 (99.6)
Visit 3	266	277	267	259	1069 (98.9)
Visit 4	249	262	260	245	1016 (94)
Visit 5	239	252	253	238	982 (90.8)
FAS Baseline	253	266	264	250	1033 (95.6)
Visit 3	253	266	264	250	1033 (95.6)
Visit 4	244	259	257	241	1001 (92.6)
Visit 5	235	249	250	235	969 (89.6)
PPS Baseline	225	243	242	232	942 (87.1)
Visit 3	225	243	242	232	942 (87.1)
Visit 4	225	243	242	231	941 (87)
Visit 5	220	234	236	227	917 (84.8)

PKS population: 319 patients, which is about 60% of all patients treated with 5 mg (158) or 10 mg (161) solifenacin succinate.

Reviewer's comment: The treatment groups appeared to be balanced at baseline with respect to the three different populations. The proportion of patients excluded from each population was low. The treatment groups were thus reasonably balanced in terms of numbers of patients available for analysis at each visit.

Demographic and other baseline characteristics The treatment groups were balanced for all demographic characteristics with the mean age between 56.9 and 58.1 years. The overall female:male ratio was 3:1 with a slightly higher proportion of women in the tolterodine 2 mg bid treatment group (4:1 ratio females:males). 98% of patients were Caucasians. Medical history of the patients appeared to be balanced with no relevant differences between treatment groups.

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Disease and therapeutic history

Table C4 Number (%) of patients with incontinence and prior OAB therapy at baseline (FAS, N=1033)

Patient groups	Placebo N=253	Solifenacin		Tolterodine 2 mg bid N=250
		5 mg qd N=266	10 mg qd N=264	
Type of incontinence n (%)				
Urge incontinence only	177 (70.0)	172 (64.7)	162 (61.4)	142 (56.8)
Mixed stress/urge incontinence	59 (23.3)	79 (29.7)	81 (30.7)	90 (36.0)
Without incontinence	17 (6.7)	15 (5.6)	20 (7.6)	18 (7.2)
Time since start of symptoms (month)				
N	108	120	113	96
Mean±SD	61.0±83.9	57.4±60.5	72.6±105.4	62.9±82.5
Median	30.5	35.0	37.0	34.0
Range	4-551	5-333	1-746	5-503
Prior drug therapy n (%)				
Yes, at least one effective	46 (18.2)	45 (16.9)	56 (21.2)	32 (12.8)
Yes, none effective	37 (14.6)	48 (18.0)	50 (18.9)	45 (18.0)
No	169 (66.8)	172 (64.7)	157 (59.5)	172 (68.8)
Any non-drug therapy n (%)	76 (30.0)	92 (34.6)	92 (34.8)	88 (35.2)

The time since onset of OAB symptoms ranged between 1 month and approximately 62 years. The median time since onset was comparable across treatment groups (30.5 to 37.0 months). Approximately one-third of the patients had previously received non-drug therapy with no relevant differences between treatment groups. Approximately one-third of the patients had had previous drug therapy. The most commonly used medications before start of the study were oxybutynin and tolterodine.

Extent of study drug exposure

The mean and median duration of exposure was comparable among treatment groups. The median treatment duration was 84 days for each treatment group. The mean treatment duration ranged between 80.3 and 82.1 days. Almost two thirds of the patients were treated for 12 weeks or longer. Less than 10 % of the patients prematurely discontinued during the first 8 weeks of the study.

Table C5 Duration (days) of exposure to study medication (SAF, N=1077)

Characteristics	Placebo N=267	Solifenacin succinate		Tolterodine 2 mg bid N=263
		5 mg qd N=279	10 mg qd N=268	
Duration of exposure (days)				
N	261	270	265	258
Mean±SD	80.3±16.4	81.7±14.4	82.1±12.2	81.3±15.8
Median	84.0	84.0	84.0	84.0
Range	6-111	3-112	18-105	7-105
Number (%) of patients treated for:				
Unknown n (%)	6 (2.2)	9 (3.2)	3 (1.1)	5 (1.9)
1-6 days n (%)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
7-13 days n (%)	1 (0.4)	0 (0.0)	0 (0.0)	3 (1.1)
14-27 days n (%)	7 (2.6)	4 (1.4)	2 (0.7)	2 (0.8)
28-55 days n (%)	11 (4.1)	11 (3.9)	8 (3.0)	11 (4.2)
56-83 days n (%)	86 (32.2)	89 (31.9)	99 (36.9)	78 (29.7)
84-90 days n (%)	125 (46.8)	124 (44.4)	115 (42.9)	115 (43.7)
≥91 days n (%)	30 (11.2)	41 (14.7)	41 (15.3)	49 (18.6)

C.3 Withdrawals and compliance

The main reasons for discontinuation were adverse events (2.9% of all patients) and withdrawal of consent (3.3%). The highest overall discontinuation rate was found in the placebo group (12%). There were no major differences between the active treatment groups, although the discontinuation rate in the solifenacin 10 mg group (7.1%) was slightly lower compared to the other active treatment groups (solifenacin 5 mg 10% and tolterodine 9.9%). Two patients (one each on solifenacin 10 mg and on tolterodine) died during the course of the study.

Table C6 Number (%) of patients prematurely discontinuing from the study by primary reason for discontinuation (SAF, N=1077)

	Placebo (N=267) n (%)	Solifenacin succinate		Tolterodine 2 mg bid (N=263)	Total (N=1077) n (%)
		5 mg qd (N=279)	10 mg qd (N=268)		
Adverse events	10 (3.7)	9 (3.2)	7 (2.6)	5 (1.9)	31 (2.9)
Consent withdrawal	10 (3.7)	11 (3.9)	7 (2.6)	8 (3.0)	36 (3.3)
Lost to follow-up	2 (0.7)	1 (0.4)	2 (0.7)	6 (2.3)	11 (1.0)
Protocol violation	5 (1.9)	4 (1.4)	0 (0.0)	3 (1.1)	12 (1.1)
Insufficient response	2 (0.7)	2 (0.7)	1 (0.4)	3 (1.1)	8 (0.7)
Patient died	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.2)
Other	3 (1.1)	1 (0.4)	1 (0.4)	0 (0.0)	5 (0.5)
Total	32 (12.0)	28 (10.0)	19 (7.1)	26 (9.9)	105 (9.7)

Treatment compliance: The mean compliance was similar across treatment groups, and ranged between 99.1% and 99.4%. Median compliance was 100.0% in all treatment groups.

Protocol violation:

Table C7 Number (%) of patients with protocol violations leading to exclusion from the PPS (FAS, N=1033)

	Placebo (N=253) n (%)	Solifenacin succinate		Tolterodine 2 mg bid (N=255)	Total (N=1033) n (%)
		5 mg qd (N=266)	10 mg qd (N=264)		
Violation in/ex criteria	6 (2.4)	3 (1.1)	6 (2.3)	3 (1.2)	18 (1.7)
Forbidden concomitant med.	7 (2.8)	2 (0.8)	3 (1.1)	3 (1.2)	15 (1.5)
Non-compliance	2 (0.8)	3 (1.1)	3 (1.1)	0 (0.0)	8 (0.8)
Treatment duration too short	17 (6.7)	14 (5.3)	11 (4.2)	12 (4.8)	54 (5.2)
Diary > 3days after last med.	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.2)
Incorrect medication	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
ICH GCP non-compliance	1 (0.4)	2 (0.8)	1 (0.4)	1 (0.4)	5 (0.5)
Total	28 (11.1)	23 (8.6)	22 (8.3)	18 (7.2)	91 (8.8)

Patients with more than 1 protocol violation are included more than once.

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Patients excluded from the study:

Table C8 Number (%) of patients excluded from the SAF/FAS

	Placebo n (%)	Solifenacin succinate		Tolterodine 2 mg bid n (%)	Total n (%)
		5 mg qd n (%)	10 mg qd n (%)		
Not randomized					200
Number of randomized	267	279	269	266	1081
Excluded from SAF					
Randomized but no double blind medication taken	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.1)	4 (0.4)
Excluded from FAS					
No baseline or no endpoint data for primary efficacy variable	11 (4.1)	10 (3.6)	1 (0.4)	11 (4.1)	33 (3.1)
ICH GCP non-compliance	3 (1.1)	3 (1.1)	3 (1.1)	2 (0.8)	11 (1.0)

Excluded visits: For 5 patients in each group, part or all data from a visit were excluded because the patients were taking prohibited medications.

Reviewer's comment: The withdrawal rates for the groups of placebo, solifenacin 5 mg and 10 mg, and tolterodine are acceptable and the overall compliance was > 95% in all treatment groups.

C.4 Efficacy analysis

Summary of efficacy

Over 90% of patients from each treatment group had their final endpoint efficacy evaluation at Week 12.

Table C9 Study 905-CL-015: Number (%) of patients with endpoint representation of Efficacy data by week (FAS population N=1033)

Week of assessment Used as Endpoint	Placebo (N=253) n (%)	Solifenacin succinate		Tolterodine 2 mg bid (N=250) n (%)
		5 mg (N=266) n (%)	10 mg (N=264) n (%)	
Week 4	16 (6.3)	12 (4.5)	10 (3.8)	11 (4.4)
Week 8	6 (2.4)	6 (2.3)	8 (3.0)	6 (2.4)
Week 12	231 (91.3)	248 (93.2)	246 (93.2)	233 (93.2)

**APPEARS THIS WAY
ON ORIGINAL**

Overall efficacy:

Table C10 Study 905-CL-015 Overview of efficacy results at endpoint^a (FAS, N=1033)

	Placebo	Solifenacin succinate		Tolterodine
		5 mg qd	10 mg qd	2 mg bid
Micturitions/24 h	n = 253	n = 266	n = 264	n = 250
Baseline	12.20	12.08	12.32	12.08
Endpoint change from baseline	-1.20	-2.19	-2.61	-1.88
Estimate difference to placebo		-0.98	-1.41	-0.67
(p value)		(0.0003)	(0.0001)	(0.0145)
Mean volume voided	n = 253	n = 266	n = 264	n = 250
Baseline	143.8	149.6	147.2	147.0
Endpoint change from baseline	7.4	32.9	39.2	24.4
Estimate difference to placebo		25.4	31.8	17.0
(p value)		(0.0001)	(0.0001)	(0.0001)
Incontinence episodes/24 h	n = 153	n = 141	n = 158	n = 157
Baseline	2.71	2.64	2.59	2.32
Endpoint change from baseline	-0.76	-1.42	-1.45	-1.14
Estimate difference to placebo		-0.66	-0.70	-0.38
(p value)		(0.0080)	(0.0038)	(0.1122)
Urge incontinence episodes/24 h	n = 127	n = 113	n = 127	n = 119
Baseline	2.02	2.33	2.14	1.86
Endpoint change from baseline	-0.62	-1.41	-1.36	-0.91
Estimate difference to placebo		-0.78	-0.70	-0.29
(p value)		(0.0020)	(0.0028)	(0.2390)
Urgency episodes/24 h	n = 248	n = 264	n = 261	n = 250
Baseline	5.30	5.77	5.82	5.45
Endpoint change from baseline	-1.41	-2.85	-3.07	-2.05
Estimate difference to placebo		-1.44	-1.67	-0.65
(p value)		(0.0001)	(0.0001)	(0.0511)
Nocturia episodes/24 h	n = 219	n = 240	n = 235	n = 232
Baseline	2.04	1.94	2.03	1.92
Endpoint change from baseline	-0.41	-0.57	-0.51	-0.48
Estimate difference to placebo		-0.16	-0.11	-0.08
(p value)		(-)	(0.2798)	(0.4110)
Nocturnal voids/24 h	n = 232	n = 253	n = 247	n = 242
Baseline	2.38	2.23	2.25	2.21
Endpoint change from baseline	-0.45	-0.65	-0.51	-0.55
Estimate difference to placebo		-0.19	-0.06	-0.10
(p value)		(-)	(0.5457)	(0.3210)

^a Endpoint is the last available on-treatment visit on or before Week 12 (Visit 5).

As shown in the above table, compared with placebo, YM905 10 mg significantly reduced the number of micturitions per 24hr, the number of incontinence episodes, urgency episodes per 24 hr, and also significantly increased volume voided per micturition. The significant effect of YM905 10 mg over placebo in reduction from baseline in micturitions per 24 hr was first observed at the Week 4 assessment, and was maintained throughout the remainder of the double blind treatment period.

Primary endpoint

Table C11 Study 905-CL-015 Mean number of micturitions/24 h at endpoint (FAS, N=1033)

	Placebo N =253	Solifenacin succinate		Tolterodine
		5 mg qd N = 266	10 mg qd N = 264	2 mg bid N = 250
Baseline (Mean±SD)	12.20±4.11	12.08±3.86	12.32±3.95	12.08±3.43
Endpoint (Mean±SD)	10.99±4.21	9.88±3.75	9.70±3.52	10.20±3.71
Change from baseline	-1.20±3.26	-2.19±2.87	-2.61±3.24	-1.88±3.00
% change from baseline	-8.1%	-17.0%	-19.5%	-14.5%

For FAS population: ANOVA

Table C12 ANOVA results: change in mean number of micturition/24 h at endpoint (FAS, N=1033)

	Solifenacin succinate		Tolterodine
	5 mg qd N = 266	10 mg qd N = 264	2 mg bid N = 250
Primary analysis			
Adjusted mean change from baseline	-2.19	-2.61	-1.87
Estimated difference to placebo	-0.98	-1.41	-0.67
95% CI	-1.51, -0.45	-1.94, -0.88	-1.21, -0.13
P value hierarchical test	0.0003	0.0001	(0.0145)

Adjusted mean change for placebo in primary analysis = -1.20, N=253.

For PPS population: ANOVA

Table C13 ANOVA results: change in mean number of micturition/24 h at endpoint (PPS, N=942)

	Solifenacin succinate		Tolterodine
	5 mg qd N = 243	10 mg qd N = 242	2 mg bid N = 232
Primary analysis			
Adjusted mean change from baseline	-2.20	-2.67	-1.95
Estimated difference to placebo	-0.89	-1.36	-0.64
95% CI	-1.44, -0.34	-1.91, -0.81	-1.19, -0.08
P value hierarchical test	0.0016	0.0001	(0.0251)

Adjusted mean change for placebo in primary analysis = -1.31, N=225.

Reviewer's comment: The results of ANOVA test in PPS population also confirm the significance of primary endpoint in FAS population.

Treatment-by-center interaction: The treatment by center interaction was tested and the interaction term was not statistically significant (p=0.58). The same holds for the center effect (p=0.39). Potential region effects were investigated and no statistically significant region by treatment interaction was found (p=0.11), nor as region effect (p=0.078).

Reviewer's comment: In the placebo group, a large effect in the region "Russia" was found as compared to the other regions.

Proportion of patients showing response: For the FAS endpoint, 19.4% of the placebo patients have <8 micturitions/24 h at endpoint, compared with 28.2% in the 5 mg solifenacin qd group, 32.6% in the 10 mg solifenacin group, and 26.0% in the tolterodine 2 mg bid group.

Influence of dropouts: The dropout rate was balanced between treatment groups. To ensure that the conclusions of the primary analyses of the FAS were not unduly influenced by dropouts or missing data, analyses were done on the 2 partitions of the FAS: completers and dropouts. As shown in Table C14, dropouts tended to have higher baselines than completers in the FAS, but the effect size (the difference between YM905 and placebo in the change from baseline to endpoint in micturitions per 24 hrs) is similar among the groups.

Table C14 Mean number of micturition/24 h at endpoint, FAS, completers and dropouts

Treatment Group	FAS			Completers			Dropouts		
	Baseline Mean (n)	Mean Change From baseline	Effect Size [#]	Baseline Mean (n)	Mean Change From baseline	Effect size (P-Y)	Baseline Mean (n)	Mean Change From baseline	Effect Size [#]
Placebo	12.20 (n=253)	-1.20		12.16 (n=231)	-1.36		12.61 (n=22)	0.47	
Solifenacin 5 mg qd	12.08 (n=266)	-2.19	0.99	12.12 (n=248)	-2.29	0.93	11.57 (n=18)	-0.89	1.36
Solifenacin 10 mg qd	12.32 (n=264)	-2.61	1.41	12.43 (n=246)	-2.73	1.37	10.78 (n=18)	-1.02	1.49
tolterodine 2 mg bid	12.08 (n=250)	-1.88	0.68	12.13 (n=234)	-2.00	0.64	11.35 (n=16)	-0.07	0.54

[#] Effect size is defined as the mean change from baseline from the placebo group minus the mean change from baseline for the active treatment group.

Mean change from baseline to visit in the number of micturitions per 24 hrs: As shown in Figure C1, two thirds of the effect obtained after 12 weeks is already achieved after 4 weeks. Further improvement is achieved in the subsequent periods for all groups including placebo.

Secondary efficacy analysis

Mean volume voided per micturition: As shown in the Figure C2, at the endpoint and at all study visits (Week 4, 8, and 12), YM905 statistically significantly increased volume voided per micturition when compared with placebo. After excluding patients with large volumes, additional analyses did not change the study conclusions.

Table C15 Study 015 Mean volume voided per micturition (mL) at endpoint (FAS, N=1033)

	Placebo N =253	Solifenacin succinate		Tolterodine
		5 mg qd N = 266	10 mg qd N = 264	2 mg bid N = 250
Baseline (Mean±SD)	143.8±53.6	149.6±54.6	147.2±51.2	147.0±50.3
Endpoint (Mean±SD)	151.2±55.9	182.6±71.7	186.4±76.6	171.4±67.6
Change from baseline	7.4±36.3	32.9±47.7	39.2±50.5	24.4±49.2
% change from baseline	+9.3%	+25.1%	+29.0%	+20.3%

Table C16 ANOVA: change in mean volume voided per micturition (mL) at endpoint (FAS, N=1033)

	Solifenacin succinate		Tolterodine
	5 mg qd N = 266	10 mg qd N = 264	2 mg bid N = 250
Primary analysis			
Adjusted mean change from baseline	33.03	39.41	24.62
Estimated difference to placebo	25.40	31.78	16.99
95% CI	17.51, 33.30	23.87, 39.69	8.97, 25.01
P value hierarchical test	0.0001	0.0001	(0.0001)

Adjusted mean change for placebo in primary analysis = 7.63, N=253. Compared to baseline the largest mean increase relative to placebo is seen in the 10 mg group (adjusted mean difference: 31.8 mL) and the lowest in the tolterodine group (17.0 mL, p=0.0001)

Figure C2 shows that two thirds of the effect obtained after 12 weeks of treatment is already achieved after 4 weeks. For tolterodine and placebo the numbers show no further improvement after 8 weeks (Visit 4) but there is some improvement in both solifenacin groups.

Mean number of incontinence episodes per 24 hrs: As shown in the Figure C3, and in the following tables.

Table C17 Study 015 Mean number of incontinence episodes/24 h at endpoint (FAS, N=1033)

	Placebo N=153	Solifenacin succinate		Tolterodine
		5 mg qd N = 141	10 mg qd N = 158	2 mg bid N = 157
Baseline (Mean±SD)	2.71±2.83	2.64±2.55	2.59±2.88	2.32±1.94
Endpoint (Mean±SD)	1.96±3.24	1.22±2.17	1.14±2.22	1.18±2.38
Change from baseline	-0.76±2.26	-1.42±1.82	-1.45±2.24	-1.14±2.15

For FAS population: ANOVA

Table C18 ANOVA: change in mean number of incontinence episodes/24 h at endpoint (FAS, N=1033)

	Solifenacin succinate		Tolterodine
	5 mg qd N = 141	10 mg qd N = 158	2 mg bid N = 157
Primary analysis			
Adjusted mean change from baseline	-1.41	-1.45	-1.14
Estimated difference to placebo	-0.66	-0.70	-0.38
95% CI	-1.15, -0.17	-1.17, -0.23	-0.86, 0.09
Analysis with baseline as covariate			
Adjusted mean change from baseline	-1.39	-1.44	-1.22
Estimated difference to placebo	-0.69	-0.74	-0.52
95% CI	-1.13, -0.25	-1.17, -0.31	-0.95, 0.09

Adjusted mean change for placebo in primary analysis = -0.75, N=153.

Reviewer's comment: The study was not designed to make comparison between solifenacin 5 mg and 10 mg, or comparison between 5 mg, 10 mg solifenacin and tolterodine.

Among the FAS patients who had at least one episode of incontinence at baseline, 37.3% of the patients in the placebo group had no incontinence at endpoint, compared to 51.1% of the 5mg solifenacin group, 50.6% of the 10 mg solifenacin group, and 48.4% of the tolterodine group.

The three quarters of the effect obtained after 12 weeks of treatment is already achieved after 4 weeks. Further improvement is achieved in subsequent periods for all treatment groups, except for the placebo group.

Mean number of urge incontinence episodes per 24 hrs: As shown in the Figure C4, and in the following tables.

Table C19 Study 015 Mean number of urge incontinence episodes/24 h at endpoint (FAS, N=1033)

	Placebo N =127	Solifenacin succinate		Tolterodine
		5 mg qd N = 113	10 mg qd N = 127	2 mg bid N = 119
Baseline (Mean±SD)	2.02±2.50	2.33±2.42	2.14±2.44	1.86±1.54
Endpoint (Mean±SD)	1.40±2.59	0.92±1.99	0.77±1.82	0.94±2.20
Change from baseline	-0.62±1.96	-1.41±1.74	-1.36±2.13	-0.91±2.01

For FAS population: ANOVA

Table C20 ANOVA: change in mean number of urge incontinence episodes/24 h at endpoint (FAS, N=1033)

	Solifenacin succinate		Tolterodine
	5 mg qd N = 113	10 mg qd N = 127	2 mg bid N = 119
Primary analysis			
Adjusted mean change from baseline	-1.37	-1.32	-0.88
Estimated difference to placebo	-0.78	-0.73	-0.29
95% CI	-1.27, -0.29	-1.20, -0.25	-0.78, 0.19
P value hierarchical test	0.0020	0.0028	(0.2390)

Adjusted mean change for placebo in primary analysis = -0.59, N=127.

The conclusions for the analysis with baseline as covariate did not change from the above.

The effect (change from the baseline) in mean number of urge incontinence episodes per 24 hrs (FAS) is fully achieved within the first 4 weeks for all treatment groups except for solifenacin 5 mg, for which a further improvement is obtained between 4 and 8 weeks of treatment.

Mean number of urgency episodes per 24 hrs: shown in the Figure C5, and in the following tables.

Table C21 Study 015 Mean number of urgency episodes/24 h at endpoint (FAS, N=1033)

	Placebo N =248	Solifenacin succinate		Tolterodine
		5 mg qd N = 264	10 mg qd N = 261	2 mg bid N = 250
Baseline (Mean±SD)	5.30±3.92	5.77±4.89	5.82±4.45	5.45±3.87
Endpoint (Mean±SD)	3.89±4.64	2.93±4.40	2.75±3.80	3.40±4.29
Change from baseline	-1.41±3.67	-2.85±3.74	-3.07±3.90	-2.05±3.58
% change from baseline (Mean)	-32.7%	-51.9%	-54.7%	-37.9%

For FAS population: ANOVA

Table C22 ANOVA: change in mean number of urgency episodes/24 h at endpoint (FAS, N=1033)

	Solifenacin succinate		Tolterodine
	5 mg qd N = 264	10 mg qd N = 261	2 mg bid N = 250
Primary analysis			
Adjusted mean change from baseline	-2.83	-3.06	-2.04
Estimated difference to placebo	-1.44	-1.67	-0.65
95% CI	-2.09, -0.80	-2.31, -1.02	-1.30, 0.00
P value hierarchical test	0.0001	0.0001	(0.0511)

Adjusted mean change for placebo in primary analysis = -1.39, N=248.

The conclusions for the analysis with baseline as covariate did not change from the above.

Two thirds of the effect (change from the baseline) obtained after 12 weeks of treatment already achieved after 4 weeks. Further improvement is achieved in subsequent periods for all treatment groups, including placebo.

Among patient who had at least one urgency episode at baseline, 21.4% of the patients in placebo group had no urgency at endpoint, compared to 31.1% of the 5 mg solifenacin group, 31.4% of the solifenacin 10 mg group and 24.8% in the tolterodine group.

Mean number of nocturnal void episodes per 24 hrs: As shown in the Figure C6, and in the following tables.

Table C23 Study 015 Mean number of nocturia episodes/24 h at endpoint (FAS, N=1033)				
	Placebo N =219	Solifenacin succinate		Tolterodine
		5 mg qd N = 240	10 mg qd N = 235	2 mg bid N = 232
Baseline (Mean±SD)	2.04±1.47	1.94±1.18	2.03±1.36	1.92±1.17
Endpoint (Mean±SD)	1.63±1.53	1.38±1.20	1.51±1.33	1.43±1.40
Change from baseline	-0.41±1.12	-0.57±1.01	-0.51±0.98	-0.48±1.07

For FAS population: ANOVA

Table C24 ANOVA: change in mean number of nocturia episodes/24 h at endpoint (FAS, N=1033)			
	Solifenacin succinate		Tolterodine
	5 mg qd N = 240	10 mg qd N = 235	2 mg bid N = 232
Primary analysis			
Adjusted mean change from baseline	-0.55	-0.50	-0.47
Estimated difference to placebo	-0.16	-0.11	-0.08
95% CI	-0.35, 0.03	-0.30, 0.09	-0.27, 0.11

Adjusted mean change for placebo in primary analysis = -0.39, N=219.

The conclusions for the analysis with baseline as covariate did not change from the above.

Figure C6 shows no relevant effect of active treatment vs. placebo was observed. Among the FAS patients who had at least one episode of noturia at baseline, 11.9% of the patients in the placebo group had no noturia at the endpoint, compared to 18.3% in the solifenacin 5 mg group, 14.9% in the solifenacin 10 mg group, and 15.1% in the tolterodine 2 mg bid group.

Mean number of nocturnal voids per 24 hrs: As shown in the Figure C7, and in the following tables.

Table C25 Study 015 Mean number of nocturnal voids/24 h at endpoint (FAS, N=1033)				
	Placebo N =232	Solifenacin succinate		Tolterodine
		5 mg qd N = 253	10 mg qd N = 247	2 mg bid N = 242
Baseline (Mean±SD)	2.38±1.62	2.23±1.30	2.25±1.43	2.21±1.32
Endpoint (Mean±SD)	1.92±1.61	1.58±1.27	1.73±1.42	1.66±1.43
Change from baseline	-0.45±1.19	-0.65±1.02	-0.51±1.10	-0.55±1.18

For FAS population: ANOVA

Table 26 ANOVA: change in mean number of nocturia episodes/24 h at endpoint (FAS, N=1033)

	Solifenacin succinate		Tolterodine
	5 mg qd N = 253	10 mg qd N = 247	2 mg bid N = 242
Primary analysis			
Adjusted mean change from baseline	-0.64	-0.51	-0.55
Estimated difference to placebo	-0.19	-0.06	-0.10
95% CI	-0.39, 0.01	-0.26, 0.14	-0.30, 0.10

Adjusted mean change for placebo in primary analysis = -0.44, N=232.

The conclusions for the analysis with baseline as covariate did not change from the above.

Figure C7 shows that no relevant effect of active treatment vs. placebo was observed.

Mean number of pads used per 24 hrs: As shown in the following table.

	Placebo N=118	Solifenacin succinate		Tolterodine
		5 mg qd N = 106	10 mg qd N = 115	2 mg bid N = 105
Baseline (Mean±SD)	2.86±2.37	2.71±2.17	2.75±2.17	2.70±2.03
Endpoint (Mean±SD)	2.31±2.45	1.47±2.22	1.31±1.82	1.68±2.24
Change from baseline	-0.55±2.06	-1.24±1.65	-1.44±1.85	-1.02±1.76
% change from baseline	-5.48%	-49.71%	-49.15%	-39.70%

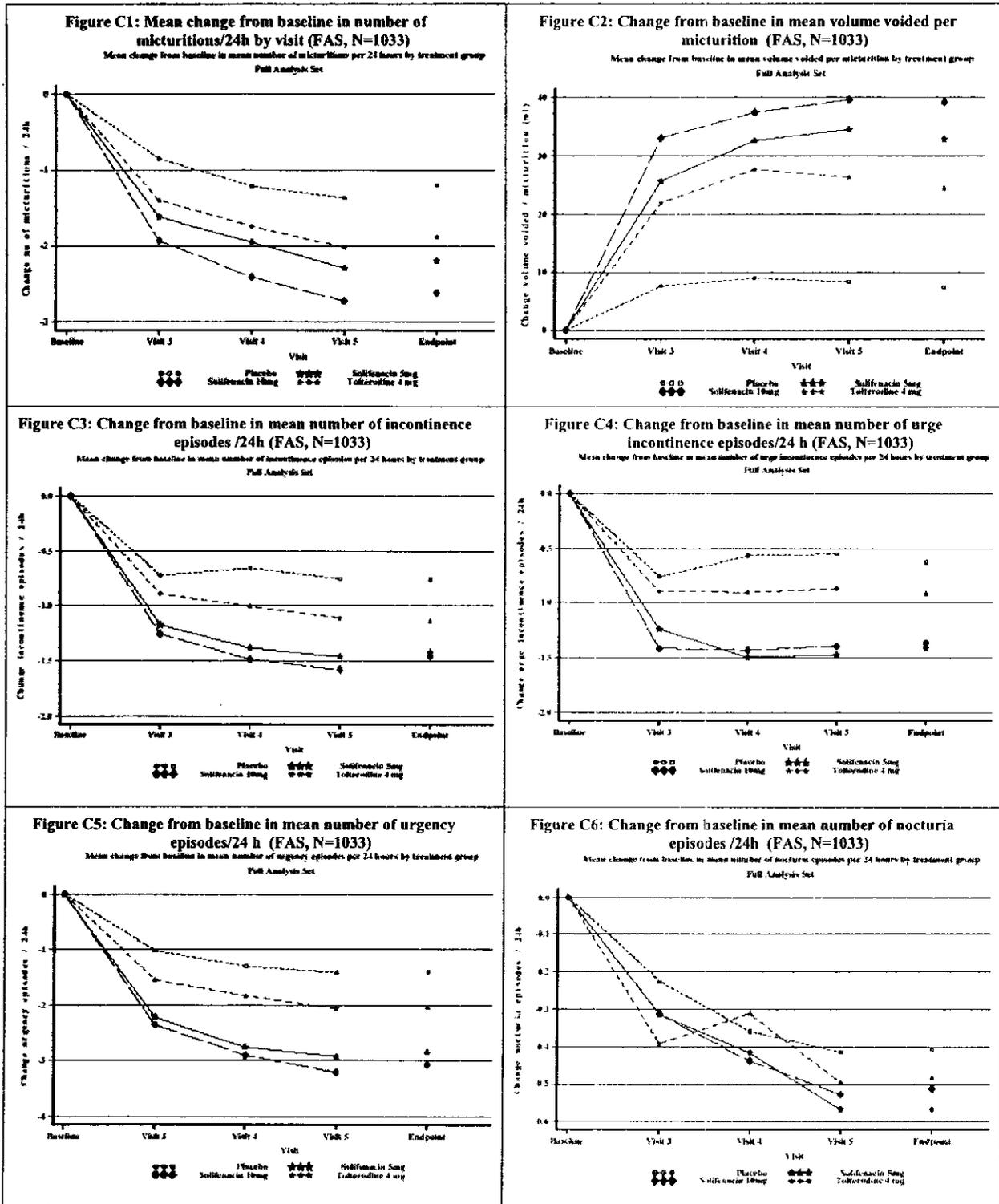
Quality of life (QoL) questionnaire: The QoL questionnaire showed that solifenacin 5 mg was statistically significantly better than placebo for the following domains: role limitations, physical limitations, emotions, severity measures, and symptom severity. Solifenacin 10 mg was statistically significantly better for these domains plus for the domains: incontinence impact and emotions. The estimated differences from placebo were very similar for all active treatment groups.

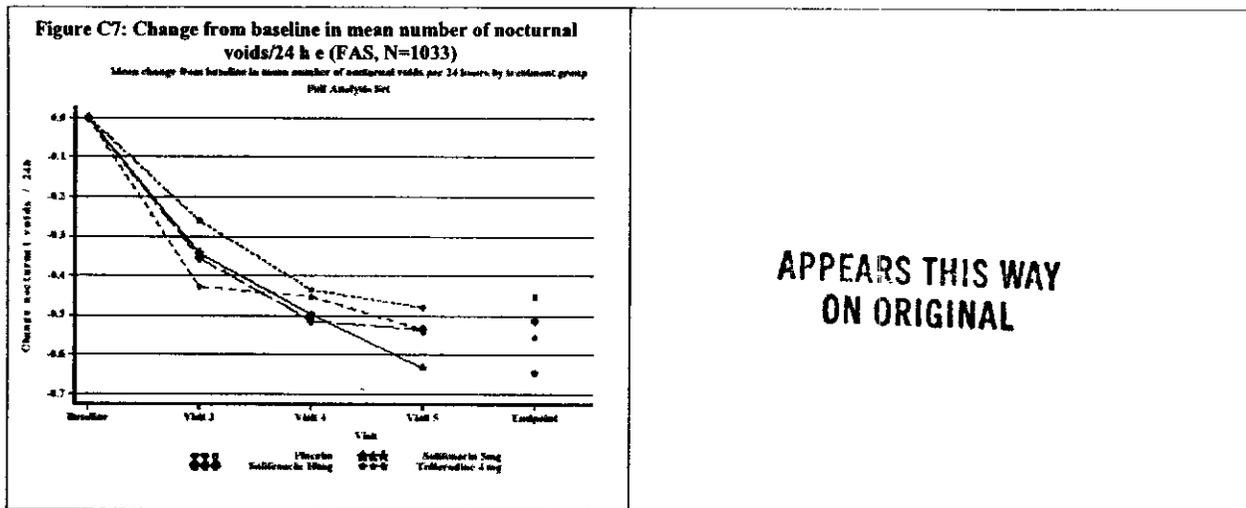
Efficacy conclusions

- Solifenacin 5 mg and 10 mg once daily were statistically significantly better in reducing the number of micturitions per 24 hours at endpoint when compared to the placebo (primary efficacy endpoint). Two thirds of the efficacy obtained after 12 weeks was achieved after 4 weeks.
- Treatment with 5 mg and 10 mg solifenacin once daily was statistically significantly better than placebo with respect to increasing mean volume voided per micturition, reduce the mean number of incontinence episodes, urge incontinence episodes and urgency episodes per 24 hrs (secondary efficacy variables).
- With respect to the other two secondary efficacy variables (mean number of nocturia episodes and nocturnal voids), no relevant effects were found for the solifenacin treatment groups vs. placebo
- Treatment with solifenacin 5 mg and 10 mg, more patients became continent than in the placebo group.
- There were no relevant differences between the two solifenacin dose groups, except for the mean number of micturitions per 24 hrs and the mean volume voided per micturition, where a small difference was found in favor of the 10 mg group.
- The results from the primary analyses were confirmed in additional exploratory analyses (FAS or PPS).

In summary, solifenacin 5 mg and 10 mg were effective in treating the symptoms of OAB including frequency, incontinence, urge incontinence and urgency. With solifenacin 5 mg and 10 mg, 51% of patients in each group (vs. 37% for the placebo) became continent at endpoint with increased bladder capacity

(demonstrated by the increase in the volume voided per micturition, +33 mL for 5 mg, +39 mL for 10 mg, vs. +7.6 mL for placebo).





C.5 Safety analyses

Extent of study drug exposure

The mean and median duration of exposure was comparable among treatment groups. The median treatment duration was 84 days for each treatment group. The mean treatment duration ranged between 80.3 and 82.1 days. Almost two thirds of the patients were treated for 12 weeks or longer. Less than 10 % of the patients prematurely discontinued during the first 8 weeks of the study.

Table C28 Duration (days) of exposure to study medication (SAF, N=1077)

Characteristics	Placebo N=267	Solifenacin succinate		Tolterodine 2 mg bid N=263
		5 mg qd N=279	10 mg qd N=268	
Duration of exposure (days)				
N	261	270	265	258
Mean±SD	80.3±16.4	81.7±14.4	82.1±12.2	81.3±15.8
Median	84.0	84.0	84.0	84.0
Range	6-111	3-112	18-105	7-105
Number (%) of patients treated for:				
Unknown n (%)	6 (2.2)	9 (3.2)	3 (1.1)	5 (1.9)
1-6 days n (%)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
7-13 days n (%)	1 (0.4)	0 (0.0)	0 (0.0)	3 (1.1)
14-27 days n (%)	7 (2.6)	4 (1.4)	2 (0.7)	2 (0.8)
28-55 days n (%)	11 (4.1)	11 (3.9)	8 (3.0)	11 (4.2)
56-83 days n (%)	86 (32.2)	89 (31.9)	99 (36.9)	78 (29.7)
84-90 days n (%)	125 (46.8)	124 (44.4)	115 (42.9)	115 (43.7)
≥91 days n (%)	30 (11.2)	41 (14.7)	41 (15.3)	49 (18.6)

Reviewer's comment: The extent of exposure in this trial was adequate to make an assessment of safety.

Deaths: Two patients died during the course of the study.

Patient #11533: This was a 75-year-old female Caucasian in solifenacin 10 mg group. The investigator was informed that she died on — Presumptive cause of death was indicated as acute heart failure.

Autopsy was not performed. Last contact was on Visit 3 (09/18/2001). No further information could be obtained. The investigator judged the death was not related to the study drug.

Reviewer's comment: The reviewer believes that there was not enough evidence to approve the death was related to study drug.

Patient #11882: This was a 79-year-old female Caucasian in the tolterodine 2 mg bid group who had a medical history of ischemic heart disease, hypertension, and asthma. The investigator was notified by the patient's relative on _____ of the patient's sudden death on _____. She apparently became unconscious and died. No autopsy was performed but the cause of death was thought to be cerebral atherosclerosis.

Reviewer's comment: The reviewer agrees that the relationship of this sudden death to study drug was unlikely.

Serious adverse events (SAEs): Serious adverse events (SAE) were reported in a total of 23 patients with one or more SAE (two patients in the placebo group and ten patients in the YM905 group) during the 12-week treatment period.

Table C29 Patients with serious adverse events (SAE's) (SAF, N = 1077)

Patient #	Age (yrs)	Sex	MedDRA preferred term	Onset day (days ^a)	Relationship to study medication	Intensity	Action taken/ outcome
Placebo							
10219	67	M	Bronchial carcinoma	60	Not related	Severe	None/not RCV
10525	73	F	Abnormal pain NOS	N/A	Not related	Severe	Discontinued/not recovered/died
			Laparotomy	N/A	Not related	Severe	
			Metastases NOS	N/A	Not related	Severe	
10706	80	F	Pulmonary embolism	20	Not Related	Moderate	None/resolved
10728	52	M	Myocardial infarction	74	Not Related	Severe	None/recovered
11035	52	M	Gastrointestinal disorders NOS	80	Not Related	Moderate	None/recovered
11086	74	M	Left ventricular hypertrophy	86	Possible	Moderate	None/recovered
11104	69	F	Colitis NOS	33	Not Related	Severe	Discontinued/RCV
11422	72	F	Syncope	19	Possible	Severe	Discontinued/RCV
11928	75	F	Chondrocalcinosis	86	Not Related	Severe	None/resolved
11950	57	M	Joint dislocation NEC	56	Not Related	Severe	None/recovered
Solifenacin 5 mg qd							
10385	85	F	Confusion	48	Not Related	Moderate	None/recovered
10704	74	M	Infection NOS	22	Not Related	Moderate	None/recovered
10810	76	F	Pneumonia NOS	25	Not Related	Severe	Discontinued/RCV
11024	52	M	Syncope	45	Possible	Severe	None/recovered
11031	75	M	Angina pectoris	71	Not Related	Mild	None/recovered
11268	69	M	Depression NEC	38	Not Related	Mild	None/resolved
11579	74	F	Tachyarrhythmia	16	Possible	Severe	Discontinued/RCV
11661	29	F	Pregnancy NOS	7	Not Related	Severe	Discontinued/RCV
Solifenacin 10 mg qd							
10886	68	M	Myocardial infarction	N/A	Possible	Mild	None/recovered
10969	45	F	Burns NOS	17	Not Related	Severe	None/recovered
11857	64	F	Gastrointestinal hemorrhage	10	Not Related	Severe	None/recovered
Tolterodine 2 mg bid							
10033	20	F	Family stress NOS	49	Not Related	Mild	None/not RCV
11976	58	F	Epilepsy NOS	40	Not Related	Mild	None/recovered

nos = not otherwise specified

* Relative to day of first dose of study drug, (post-treatment day relative to first day after the last dose is indicated with a + sign)

Of the SAE's with solifenacin 5 mg, two were judged to be possibly related to study drug: syncope in one and tachyarrhythmia in another; in the solifenacin 10 mg group, one was assessed as possibly related to study drug (mild myocardial infarction); two in the placebo group were also judged to be possibly related to the study drug (left ventricular hypertrophy in one, syncope in another).

Narratives of SAE's

Solifenacin 5 mg group:

Patient #10385(Belgium): This 85-year-old woman had a history of hypercholesterimia, sleeplessness, and hypertension. On Day 48 of treatment (—), she was hospitalized for mental confusion and the event resolved on —. The investigator assessed the relationship between the confusion and the study drug to be unlikely.

Reviewer's comment: The reviewer believes that this event is not related to study drug.

Patient #10704 (Australia): This 74-year-old man had a medical history of arthritis. Twenty two days after starting study drug, he was hospitalized for a scheduled surgery on his left hand (—) following discharge he had to be re-admitted twice because of fever and not feeling well. He was diagnosed with wound infection and treated. The patient continued the study. The investigator assessed the relationship to the study drug to be unrelated.

Reviewer's comment: The reviewer agrees that these events were not related to study drug.

Patient #10810 (Australia): This 76-year-old woman had a medical history of pneumonia (last episode in 2000). Twenty-five days after enrolling into the study but 3 days after treatment discontinuation, she was hospitalized on — with fever, cough, breathlessness and confusion. Her white blood cell counts were elevated and CXR confirmed left lower lobe consolidation. After 3 days, she developed hypotension, pneumothorax and was transferred to the ICU. Her pneumonic illness improved slowly and was she discharged —. The investigator assessed the relationship between the pneumonia and the study drug to be unrelated.

Reviewer's comment: The reviewer believes that the relationship to study drug is unlikely.

Patient #11024 (Poland): This 52-year-old man had a history of meningoencephalitis in childhood, headaches, vertigo and 3 syncopal episodes. 45 days after starting study medication with 5 mg solifenacin he was found unconscious in the morning and was hospitalized and regained consciousness by noon. During 3 days of hospitalization the study medication was interrupted. A CT scan and EEG confirmed epilepsy status post meningoencephalitis in childhood. The patient completed the study. The investigator assessed the syncope as possibly related to study drug.

Reviewer's comment: The reviewer believes that the event was possibly related with study drug.

Patient #11031 (Poland): This 75-year-old man had a medical history including LBBB for 40 years. He was admitted to the hospital 71 days after starting solifenacin 5 mg with thorax pain and a pain radiating to the shoulder blade. An ECG and laboratory studies excluded an infarct. Patient recovered and was discharged with diagnoses of ischaemic heart disease, unstable angina, hypertension grade II, arteriosclerosis and emphysema. He completed the study. The investigator assessed the relationship of the angina to be unrelated to study drug.

Reviewer's comment: The reviewer agrees that this event was not related to study drug.

Patient #11268 (Hungary): This 69 year-old man was hospitalized 38 days after starting study medication (solifenacin 5 mg) for depression. Patient completed the study. The event was judged by the investigator to be unrelated to study drug.

Reviewer's comment: The reviewer agrees that the relationship of this event to study drug was unlikely.

Patient #11579 (Germany): This 74-year-old woman had a medical history of recurrent thoracic complaints and arrhythmia, which required previous cardioconversion. On Day 16 of treatment with solifenacin 5 mg, she was hospitalized because of tachyarrhythmia and required cardioconversion. The ECG at screening was normal, while the ECG at the end of the study was abnormal but not clinically significant. The study medication was discontinued. The investigator assessed the event to be possibly related to study drug.

Reviewer's comment: The reviewer believes that the event was possibly related to study drug.

Patient #11661 (Poland): This 29-year-old woman was confirmed to be pregnant for 4 weeks, 7 days after the start of double-blind treatment of solifenacin 5 mg. Two days after the start of double-blind treatment study medication was discontinued. She was withdrawn from the study. The patient gave birth to a healthy child in the — . The patient recovered without sequelae. The investigator judged the event to be unrelated to study drug.

Reviewer's comment: The reviewer believes that there is no relationship to study drug is unlikely.

Narratives of SAE's

Solifenacin 10 mg qd

Patient #10886 (UK): This 68-year-old man had an ECG at the baseline showing abnormal but not clinically significance. Upon completing the study (solifenacin 10 mg), he had another ECG, which was consistent with a possible inferior myocardial infarction (MI) of unknown age. The patient had been asymptomatic during the trial. The investigator assessed the MI to be possibly related to study drug.

Reviewer's comment: the reviewer believes that the event was possibly related to study drug.

Patient #10969 (South Africa): On — , this 45-year-old woman had 1st and 2nd degree burns to her face, both arms and hands during a barbecue 17 days after starting study drug. She was admitted to the hospital, where she was treated and discharged — . The study medication was continued and she completed the study. The investigator assessed the patient's burns to be unrelated to study drug.

Reviewer's comment: The reviewer agrees that this event is not related to study drug.

Patient #11857 (Russia): This 64-year-old woman had a medical history of a duodenal ulcer for which vagotomy was carried out (1991). She informed the investigator that she had been hospitalized for duodenal ulcer haemorrhage beginning 10 days after starting the study medication solifenacin 10 mg. Study drug was interrupted during hospitalisation. Endoscopy results confirmed the presence of a chronic duodenal ulcer. She was further confirmed to have ischaemic heart disease. Study drug was re-started and the patient completed the study. The investigator assessed that the event was not related to the study drug.

Reviewer's comment: The reviewer agrees that this event is not related to study drug.

Narratives of SAE's

Tolterodine 2 mg bid group

Patient #10033: This 20-year-old woman had a history of psychiatric problems in 2000. She was admitted to a psychiatric center on Day 49 of the study — , for psychological support because of severe family problems at home. She completed the study. Patient recovered — . The investigator assessed the relationship between the psychiatric problem and the study drug to be unrelated.

Reviewer's comment: The reviewer agrees that these events were not related to study drug.

Patient #11976 (South Africa): This 58-year-old woman suffered a "blackout" while driving 40 days after starting the study medication tolterodine 2 mg bid. The patient recovered on admission to hospital without intervention. Diagnosis of epilepsy petit mal was made. She completed the study. The investigator assessed that the event was not related to the study drug.

Reviewer's comment: The reviewer agrees that this event is not related to study drug.

Overall adverse events

Almost 50% of all patients had 1 or more adverse events (AE's) with no differences across treatment groups in the incidence.

Table C30 Study 015 Summary of adverse events (FAS, N=1077)

	Placebo N =267	Solifenacin succinate		Tolterodine 2 mg bid N = 263
		5 mg qd N = 279	10 mg qd N = 268	
N (%) with AE's	121 (45.3%)	135 (48.4%)	139 (51.9%)	127 (48.3%)
Total number of AE's	247	257	315	248
N (%) with SAEs	10 (3.7%)	8 (2.9%)	5 (1.9%)	3 (1.1%)
Total number of SAEs	12	8	5	3
N (%) with AEs by severity				
Mild	65 (24.3%)	82 (29.4%)	80 (29.9%)	72 (27.4%)
Moderate	44 (16.5%)	43 (15.4%)	47 (17.5%)	47 (17.9%)
Severe	12 (4.5%)	9 (3.2%)	12 (4.5%)	7 (2.7%)
N (%) who discontinued because of AEs (including deaths)	9 (3.4%)	8 (2.9%)	7 (2.6%)	5 (1.9%)
N (%) with treatment-related AEs	50 (18.7%)	90 (32.3%)	102 (38.1%)	74 (28.1%)
N (%) deaths	0	0	1 (0.4%)	1 (0.4%)

Most common TEAEs that were considered possibly or probably related to treatment by the investigator were GI AEs in all treatment groups including placebo. The incidences in the active treatment groups were higher than that in the placebo groups, especially pronounced for dry mouth (14% in solifenacin 5 mg, 21.3% in solifenacin 10 mg, and 18.6% in tolterodine 2 mg, bid vs. 4.9% in placebo), constipation (7.2% in solifenacin 5 mg, 7.8% in solifenacin 10 mg, vs. 1.9% in placebo and 2.7% in tolterodine 2 mg bid). Blurred vision was also more often reported by patients with solifenacin (3.6% in 5 mg and 5.6% in 10 mg) than by those with tolterodine (1.5%) or placebo (2.6%).

Table C31 Treatment-related (groups of) TEAEs (≥2%) (safety population, N = 1077)

	Placebo N =267	Solifenacin succinate		Tolterodine 2 mg bid N = 263
		5 mg qd N = 279	10 mg qd N = 268	
Cardiac disorders	5 (1.9%)	5 (1.8%)	7 (2.6%)	3 (1.1%)
Eyes disorders	11 (4.1%)	13 (4.7%)	21 (7.8%)	5 (1.9%)
<i>Vision blurred</i>	7 (2.6%)	10 (3.6%)	15 (5.6%)	4 (1.5%)
Gastrointestinal disorders	24 (9.0%)	61 (21.9%)	79 (29.5%)	59 (22.4%)
<i>Abnormal pain upper</i>	4 (1.5%)	2 (0.7%)	7 (2.6%)	4 (1.5%)
<i>Constipation</i>	5 (1.9%)	20 (7.2%)	21 (7.8%)	7 (2.7%)
<i>Dry mouth</i>	13 (4.9%)	39 (14.0%)	57 (21.3%)	49 (18.6%)
<i>Dyspepsia</i>	1 (0.4%)	4 (1.4%)	6 (2.2%)	3 (1.1%)
Investigations	3 (1.1%)	10 (3.6%)	8 (3.0%)	5 (1.9%)
Nerve system disorders	8 (3.0%)	8 (2.9%)	13 (4.9%)	6 (2.3%)
<i>Headache NOS</i>	4 (1.5%)	3 (1.1%)	6 (2.2%)	4 (1.5%)
General disorders	5 (1.9%)	4 (1.4%)	6 (2.2%)	4 (1.5%)

Other AE's of interest included urinary retention and QT prolongation.

Urinary retention (evaluated by post-void residual volume, PVR): None of the patients developed clinically relevant urinary retention.. There was a small mean increase in PVR volume after treatment with solifenacin 5 and 10 mg, whereas a mean decrease was observed with placebo treatment and for patients treated with tolterodine 2 mg bid. However, inter-patient variability was very high, and the largest mean increase (4.9 mL) was observed at the 5 mg dose. Only 2 patients (1 on 5 mg and 10 mg solifenacin each) had a PVR volume that exceeded 200 mL at the end of the study. There were no clinically relevant differences between treatment groups.

Table C32 PVR: mean values and mean changes from baseline at the end of the study (SAF, N = 1077)

Post-void residual (PVR)	Volume (mL)	Placebo N = 267	Solifenacin succinate		Tolterodine 2 mg bid N = 263
			5 mg qd N = 279	10 mg qd N = 268	
Baseline	Mean±SD	15.5±29.5	15.0±25.9	16.5±30.3	15.7±31.5
	Range		—		
End of the study	Mean±SD	14.6±26.0	19.4±36.0	18.4±34.9	13.1±22.8
	Range		—		
Change	Mean±SD	-0.9±22.9	4.9±36.4	1.9±34.3	-3.2±31.8

QT prolongation:

Overall, the effect of solifenacin treatment on QT and QTc (corrected by Bazett's formula) was evaluated. In accordance with the protocol and the CPMP guidelines, all ECGs where less than 3 intervals were measured were excluded. Two sets were defined: Set A reporting the results based on all available data and Set B reporting the results with exclusion of ECGs that are inappropriate for QTc measurements.

Table C33 Changes from the baseline for QT and QTc interval (safety population, N = 1077)

		Placebo N = 267	Solifenacin succinate		Tolterodine 2 mg bid N = 263
			5 mg qd N = 279	10 mg qd N = 268	
Set A					
QT interval (msec)	Screening	377.0±29.8	380.4±37.6	378.5±33.3	380.0±30.6
	End of the study	376.0±30.0	382.0±33.3	382.5±35.7	377.0±30.4
	Change	-1.1±22.4	0.6±27.8	3.1±26.5	-4.5±25.5
QTc interval (msec)	Screening	407.9±27.5	405.1±29.5	401.5±28.0	406.2±27.2
	End of the study	404.4±27.7	407.0±26.7	407.7±31.0	410.5±27.2
	Change	-4.0±24.4	1.9±27.3	4.7±26.1	2.1±23.9
Set B					
QT interval (msec)	Screening	375.3±28.4	377.9±35.3	376.1±31.5	379.5±31.0
	End of the study	375.4±29.3	380.6±33.1	378.4±34.0	377.5±30.1
	Change	-0.0±22.0	1.0±29.1	2.2±25.9	-4.2±25.6
QTc interval (msec)	Screening	407.6±25.8	403.8±27.3	401.0±26.9	406.5±26.8
	End of the study	402.2±26.7	406.9±27.0	405.6±29.4	411.3±26.0
	Change	-5.2±24.6	1.9±26.7	4.5±24.5	2.5±23.7

Table C34 ANOVA: Mean change from baseline of the QTc at the end of study (central reading data)

	Placebo	Solifenacin succinate		Tolterodine 2 mg bid
		5 mg qd	10 mg qd	
Set A	n=219	n=237	n=229	n=222
Adjusted mean change from baseline	-2.7	1.6	3.4	3.0
Estimated difference to placebo		4.3	6.1	5.7
95 % CI		0.19, 8.35	1.95, 10.19	1.56, 9.84
P value		0.040	0.004	0.007
Set B	n=174	n=193	n=172	n=188
Adjusted mean change from baseline	-3.9	1.8	2.8	4.1
Estimated difference to placebo		5.6	6.7	8.0
95 % CI		1.25, 10.02	2.16, 11.21	3.57, 12.39
P value		0.012	0.004	0.0004

The mean increase in QTc interval of 5.6 msec and 6.7 msec for solifenacin 5 mg and 10 mg relative to placebo is a statistically significant (p=0.012, 0.004, respectively) treatment difference.

For the analysis of changes from baseline in QTc intervals, patients were categorized by the sponsor as follows:

- Patients with normal QTc (men, ≤430 msec; women, ≤450 msec)
- Patients with borderline QTc (men, >430 to ≤450 msec; women, >450 to ≤470 msec)
- Patients with prolonged QTc (men, >450 to ≤500 msec; women, >470 to ≤500 msec)
- Patients with prolonged QTc of clinical concern (>500 msec)

Table C35 Patients with normal screening QTc and prolonged QTc at the end of the study (SAF, N=1077)

Patient #	Sex	Ventricular rate		QT (msec)		QTc (msec)		Δ QTc (msec)	Remarks / cardiac adverse events
		Screen	End	Screen	End	Screen	End		
Placebo									
#10400	M	63	81	399	389	408	452	44	
#10114	F	69	88	389	396	418	480	62	
#10142	F	70	77	388	420	418	480	62	
#10204 ^A	M	56	74	439	407	423	452	29	Right bundle branch block (RBBB)
Solifenacin 5 mg									
#10998	F	71	70	396	439	429	475	46	
#10569	M	69	78	352	396	378	453	75	
#11987	M	73	73	375	409	415	452	37	
Solifenacin 10 mg									
#10010	M	54	56	400	468	379	453	74	
#11923	M	69	80	393	410	420	472	52	Old inferior MI
#10769	M		67		442		466		Screening could not be calibrated
#10276	F	78	87	390	413	446	498	52	Mild atrial hypertrophy-not related
#10158	F	59	76	400	450	397	507	110	Pathologically prolonged
#10125 ^A	M		66		449		471		Only 2 complexes measured,
#11424 ^A	F	64	75	422	423	435	472	37	Left bundle branch block (LBBB)
#10962 ^A	M	65	62	390	464	405	471	66	Old MI, measured in V2 as mild AE, Possibly treatment related.
Tolterodine 2 mg bid									
#10123	F		66		476		497		Screening couldn't be calibrated

^A excluded from set B.

There was one patient with QTc interval at the end of the study >500 msec:

Patient #10158 of solifenacin 10 mg group was a 44-year-old female who had a QTc of 397 msec at screening that increased to 507 msec at the end of the study (increase of 110 msec). She had no abnormalities in her medical history, and had no adverse events were reported during the study.

For set A the number of patients with QTc increases of 30-60 msec from baseline in the 5 mg and 10 mg solifenacin groups (11.8% and 14%, respectively) was somewhat higher than the placebo (6.4%) or tolterodine 2 mg bid group (7.2%). A similar result was found with set B.

The changes from baseline in QTc interval were categorized by the sponsor as follows:

- <30 msec; within normal limits
- Between 30 and 60 msec: borderline
- >60 msec: clinical concern

Table C36 Patients with Δ QTc > 60 msec from baseline (SAF, N=1077)

Patient #	Sex	Ventricular rate		QT (msec)		QTc (msec)		Δ QTc (msec)	Remarks / cardiac adverse events
		Screen	End	Screen	End	Screen	End		
Placebo									
#10813	F	57	85	379	375	368	445	77	
#10285	F	57	93	368	337	358	419	61	OL [*] : QTc = 413 msec
#10114	F	69	88	389	396	418	480	62	Prolonged; OL [*] : QTc=416 msec
Solifenacin 5 mg									
#10569	M	69	78	352	396	378	453	75	Prolonged; OL [*] : QTc=386 msec
#10282	F	62	99	382	359	387	461	74	AE: mild tachycardia; unrelated to treatment; OL [*] : QTc=408 msec
#10107	F	101	61	273	423	354	427	73	OL8: QTc=422 msec
#11886	M	58	79	379	384	374	441	67	
#11460 ^A	F	82	107	300	340	350	454	104	Mild AE, Possibly treatment-related
Solifenacin 10 mg									
#10010	M	54	56	400	468	379	453	74	Prolonged
#10158	F	59	76	400	450	397	507	110	Pathologically prolonged
#10396	F	63	72	343	377	350	412	62	
#10962 ^A	M	65	62	390	464	405	471	66	Old MI, measured in V2 as mild AE, Possibly treatment related.
Tolterodine 2 mg bid									
#11477	F	53	76	396	393	372	442	70	
#11195	M	76	78	320	380	360	433	73	

^A excluded from set B.

^{*} OL: after 16 weeks in open-label extension study.

Reviewer's comment: Overall, there was a slight mean increase of the QTc interval with solifenacin in comparison with placebo. Nine of the 14 patients with QTc increase >60 msec were from solifenacin 5 mg or 10 mg treatment. In these nine patients, two were assessed as possibly related to the treatment (#11460 and #10962), and one as pathologically prolonged (#10158).

Discontinuations due to adverse events

The proportions of patients that discontinued because of AEs were similar. 9 patients in the placebo (3.4%), 8 patients in the solifenacin 5 mg (2.9%), 7 patients in solifenacin 10 mg (2.6%) and 5 in tolterodine 2 mg bid (1.9%) groups had adverse events during the 12-week treatment period that led to permanent discontinuation of study drug. The most frequent treatment emergent AEs (TEAE) leading to discontinuation were of gastrointestinal (GI) origin, especially in the 10 mg solifenacin group, where 5 out of 6 patients discontinued because of constipation, dyspepsia, nausea and/or abdominal pain. For 6 patients the AEs leading to

discontinuation were serious (#10525, #10706 and #11422 in placebo, #10385, #10810 and #11661 in the solifenacin 5 mg group).

In 6 of the 9 placebo patients, 4 of the 8 in the solifenacin 5 mg group, 6 all in the solifenacin 10 mg group, and 3 of the 4 in the tolterodine group, who discontinued because of AEs, the adverse events were thought by the investigator to be possibly or probably related to study drugs.

Table C37 Patients with AEs as primary reason for discontinuation from the study (FAS, N=1077)

Relationship with the Study medication	Placebo N=9	Solifenacin succinate		Tolterodine
		5 mg qd N=8	10 mg qd N=6	2 mg bid N=4
Probably related	0	1	1	2
Possibly related	6	3	5	1
Not related	3	4	0	1

Treatment-related laboratory abnormalities: There was no clinically relevant effect of treatment on laboratory safety parameters. Elevated liver function tests which were assessed by the investigator as treatment-related AEs were in 3 (#11427, #10626, #11088) in the solifenacin 5 mg, 1 (#10969) in the solifenacin 10 mg, and 1 (#11984) in the tolterodine group.

Table C38 Abnormal liver function tests in five patients treated with Solifenacin

Liver function	#11427		#10626		#11088		#10969		#11984	
	Screen	End	Screen	End	Screen	End	Screen	End	Screen	End
AST	109	183	14	91						
ALT	101	127	12	179					33	69
r-GT	256	705	25	149			59	133	89	170
Bilirubin					9.1	24.9				

Expected AE's:

Constipation, dry mouth, and blurred vision are all expected AEs with this class of anticholinergics.

Table C39 Number (%) of patients with expected adverse events by severity (FAS, N=1077)

	Placebo N=267 n (%)	Solifenacin succinate		Tolterodine
		5 mg qd (N=279) n (%)	10 mg qd (N=268) n (%)	2 mg bid (N=263) n (%)
Dry mouth	13 (4.9)	40 (14.3)	57 (21.3)	51 (19.4)
Mild	11 (4.1)	32 (11.5)	38 (14.2)	35 (13.3)
Moderate	2 (0.7)	7 (2.5)	16 (6.0)	12 (4.6)
Severe	0 (0)	1 (0.4)	3 (1.1)	4 (1.5)
Constipation	5 (1.9)	20 (7.2)	21 (7.8)	8 (3.0)
Mild	3 (1.1)	13 (4.7)	10 (3.7)	7 (2.7)
Moderate	2 (0.7)	6 (2.2)	9 (3.4)	1 (0.4)
Severe	0 (0)	1 (0.4)	2 (0.7)	0 (0)
Vision blurred	7 (2.6)	10 (3.6)	16 (6.0)	4 (1.5)
Mild	6 (2.2)	8 (2.9)	14 (5.2)	4 (1.5)
Moderate	1 (0.4)	2 (0.7)	1 (0.4)	0 (0)
Severe	0 (0)	0 (0)	1 (0.4)	0 (0)

Dry mouth and blurred vision tended to be more often reported at the higher doses of solifenacin. In the group of patients with plasma solifenacin levels of ≥ 60 ng/mL, dry mouth was found in 7/28 (38.9%) and blurred vision in 4/28 (14.3%) patients.

Safety conclusions

- Treatment with 5 mg and 10 mg solifenacin qd was tolerated
- The most common AE's with solifenacin were consistent with the pharmacologic effects of the drug, including dry mouth, constipation, and blurred vision. The incidence of these AEs was lower in the 5 mg solifenacin treatment group than in the 10 mg solifenacin treatment group
- The discontinuation rate because of AEs was low and comparable between treatment groups
- Solifenacin did not have clinically relevant influence on clinical laboratory parameters or vital signs
- The QTc change from baseline relative to placebo was 4.3 msec for 5 mg and 6.0 msec for 10 mg solifenacin. A slightly higher proportion of patients on 5 mg or 10 mg solifenacin had an increase of 30-60 msec in QTc at endpoint compared to placebo. The number of patients with a QTc increase of >60 msec was comparable among the treatment groups.

C.6 Reviewer's assessment of safety and efficacy in Clinical Trial CL-905-015

Reviewer's assessment:

The reviewer believes that solifenacin 5 mg and 10 mg daily does reduce the number of micturitions per 24 hrs (-2.19 ± 2.87 , -2.61 ± 3.24 , respectively) in the majority of patients with OAB when compared with placebo (-1.20 ± 3.26). In terms of secondary endpoints, the reviewer agrees that the reduction of incontinence episodes (51.1% and 50.6% of patients in solifenacin 5 mg and 10 mg, respectively, became continent vs. 37.3% in placebo, and 48.4% in tolterodine group), and the increase of volume voided per micturition ($+32.9$ mL and $+39.2$ mL, respectively, for solifenacin 5 mg and 10 mg, vs. $+7.4$ mL for placebo and $+24.4$ mL for tolterodine) appear to support the efficacy of solifenacin.

The reviewer agrees that the important benefit of solifenacin for patients is that the effect was observed at the first assessment at 4 weeks and was maintained throughout the remainder of the treatment period. The reviewer further agrees that the strength of the study results is confirmed by the fact that the efficacy was consistent in various primary analyses, regardless of the choice of model, method or population (FAS or PPS). The reviewer believes that the positive effects of solifenacin on various symptoms of OAB, along with the improvement in incontinence, volume voided, are evidence that treatment with solifenacin 5 mg and 10 mg provides a clinically meaningful benefit to patients with OAB.

In terms of safety, the reviewer believes that overall, YM905, at daily doses of 5 mg and 10 mg, is safe and well tolerated. The most common adverse events in the active drug group were anticholinergic events, including dry mouth, constipation, and blurred vision. The reviewer agrees that these AE's are expected. The reviewer agrees that solifenacin had no influence on clinical laboratory parameters. The reviewer noticed that ALT and AST elevated in five patients with solifenacin.

The effect of solifenacin on QTc interval prolongation was statistically significant. One patient had an end of treatment QTc interval of 507 msec (increase of 110 msec). QT prolongation issues are addressed in the review of Study CL-022 and in the Executive Summary and Clinical Review.

Appendix D

Clinical Trials 905-CL-015: A randomized, double-blind, parallel group, placebo-controlled, multi-center study solifenacin succinate 5 mg and 10 mg in patients with overactive bladder (in the Europe)

D.1 Design

Study 905-CL-018 was a randomized, double-blind, parallel-group, placebo-controlled, fixed-dose, multinational, multi-center study of 5 mg 10 mg solifenacin succinate administered orally once daily for 12 weeks. Patients were evaluated at baseline and at 4, 8 and 12 weeks. The study had a placebo control. The primary aim of the study was to assess the efficacy of solifenacin succinate 5 mg and 10 mg in patients with OAB. The secondary aims were to assess the safety and the tolerability of 5 mg and 10 mg solifenacin.

Inclusion criteria: Symptoms of OAB (urinary frequency with urgency and/or incontinence) for ≥ 3 months, age ≥ 18 years, an average of ≥ 8 micturitions/24h, and either an average of ≥ 3 urinary incontinence episodes/3-day or an average of ≥ 3 urinary urgency episodes/3-day, documented during a 3-day diary in the screening phase.

Exclusion criteria: Stress incontinence, mixed incontinence with a predominant stress component, or neurological cause for detrusor overactivity. Urinary retention as demonstrated by post-void residual urine volume (PVR) > 200 mL as evidenced by bladder scan.

Methodology: This is a Phase 3, randomized, double-blind, parallel-group, fixed-dose, placebo-controlled, multinational, multicenter study. The study was comprised of a single-blind, 2-week placebo run-in period, followed by a randomized, double-blind, placebo-controlled, 12-week treatment period. Patients visited the clinic at screening (Visit 1); at the end of the placebo run-in period (Visit 2); after 4, 8 and 12 weeks of double-blind treatment (Visit 3, 4, and 5).

Study drug regimen:

Table D1 Study drug regimen in Study 018

Placebo run-in 2 weeks (daily A.M)	Randomization	Double-blind treatment (daily A.M)		
		Solifenacin 5 mg qd	Solifenacin 10 mg qd	Placebo
	solifenacin 5 mg tablet	1		
	solifenacin 10 mg tablet		1	
2	Placebo tablet	1	1	2

Primary efficacy endpoint: Change from baseline in mean number of micturitions/24h." Micturition was defined as any voiding episode recorded by the patient in the 3-day diary as either "urinated" with or without "incontinence" (episodes of incontinence only, not included).

Secondary efficacy endpoints:

- Change from baseline in mean volume voided per micturition
- Change from baseline in mean number of incontinence episodes / 24 hrs
- Change from baseline in mean number of urge incontinence episodes / 24 hrs
- Change from baseline in mean number of urgency episodes / 24 hrs
- Change from baseline in mean number of nocturnal voided / 24 hrs
- Change from baseline in mean number of nocturia episodes / 24 hrs
- Change from baseline in mean number of pads used
- Change from baseline in quality of life scores as assessed by King's Health Questionnaire

Safety was assessed by: incidence and severity of adverse events, clinical laboratory values (hematology, clinical chemistry, and urinalysis), vital signs, ECG, and post-void residual volume.

The study was initiated in May 14, 2001, and the final study report reflects all available efficacy and safety data from all patients through June, 2002. The final observation was on March 4, 2002. Study visits occurred at screening (1) placebo run-in period (2) after 4 weeks (3) 8 weeks (4) 12 weeks (5).

D.2 Study Population

Safety population (SAF): All patients who had been randomized and had taken at least 1 dose of double-blind study medication

Full analysis set (FAS): All patients who had been randomized, and had taken at least 1 dose of double-blind study medication, and provided efficacy data at baseline (Visit 2) and endpoint visit (on treatment)

Per protocol set (PPS): All patients who were included in the FAS and completed the study without major violations of the protocol.

Pharmacokinetic set (PKS) All patients of whom a blood sample was collected within the range of 22 to 26 hours after the last dose of double-blind treatment.

A total of 1281 patients from 98 centers were enrolled in the study, of which 1081 were randomized.

Table D2 Number and percentage of patients randomized, treated, discontinued and completed the study

	Placebo n (%)	Solifenacin succinate		Total n (%)
		5 mg qd n (%)	10 mg qd n (%)	
Randomized	302 (100)	301 (100)	308 (100)	911 (100)
Treated	301 (99.7)	299 (99.3)	307 (99.6)	907 (99.6)
Discontinued	32 (10.6)	24 (8.0)	25 (8.1)	181 (8.9)
Completed	270 (89.4)	277 (92.0)	283 (91.9)	830 (91.1)

Out of 830 patients who completed the study, 743 (89.5%) stated they were willing to participate in the open-label extension study (905-CL-019)

Table D3 Number of randomized patients in the SAF, FAS, and PPS population at each visit/patients in study population

Patient groups	Placebo	Solifenacin		Total n (%)
		5 mg qd	10 mg qd	
Randomized	302	301	308	911 (100.0)
Treated	301	299	307	907 (99.6)
SAF Baseline	301	299	307	907 (99.6)
Visit 3	298	298	306	902 (99.0)
Visit 4	286	287	294	867 (95.2)
Visit 5	275	280	283	838 (92.0)
FAS Baseline	281	286	290	857 (94.1)
Visit 3	281	286	290	857 (94.1)
Visit 4	274	278	283	835 (91.7)
Visit 5	264	271	274	809 (88.8)
PPS Baseline	260	257	264	781 (85.7)
Visit 3	260	257	264	781 (85.7)
Visit 4	260	257	264	781 (85.7)
Visit 5	253	248	256	757 (83.1)

PKS population: 309 patients, which is about 50% of all patients treated with 5 mg (154) or 10 mg (155) solifenacin succinate.

Demographic and other baseline characteristics There were no notable imbalances between treatment groups in demographic characteristics including age, gender, race, weight, and height. The study population was predominantly Caucasian (>96%) and female (80%) with mean age between 55.4 and 56.1 years. About 30% of the study population was 65 years or older, and 63 patients (7.4%) were 75 years or older. The median time since the start of OAB symptoms was approximately 27-29 months in the placebo and 2 solifenacin groups (mean 58.1 months for placebo and 52.6, 48.2 months for solifenacin 5 mg and 10 mg, respectively).

Reviewer's comment: The treatment groups appear to be balanced at the baseline with respect to the three different treatment groups. The treatment groups were reasonably balanced in terms of numbers of patients available for analysis at each visit.

Medical history of the patients appeared to be balanced with no relevant differences between treatment groups.

Disease and therapeutic history

Table D4 Number (%) of patients with incontinence and prior OAB therapy at baseline (FAS, N=857)

Patient groups	Placebo N=281	Solifenacin	
		5 mg qd N=286	10 mg qd N=290
Type of incontinence n (%)			
Urge incontinence only	165 (58.7)	180 (62.9)	194 (66.9)
Mixed stress/urge incontinence	77 (27.4)	80 (28.0)	69 (23.8)
Without incontinence	39 (13.9)	26 (9.1)	27 (9.3)
Time since start of symptoms (month)			
N	85	109	103
Mean±SD	58.1±68.1	52.6±71.9	48.2±60.0
Median	29.0	27.0	28.0
Range	5-327	4-383	4-314
Prior drug therapy n (%)			
Yes, at least one effective	52 (18.5)	50 (17.5)	48 (16.6)
Yes, none effective	43 (15.3)	51 (17.8)	46 (15.9)
No	186 (66.2)	184 (64.3)	196 (67.6)
Any non-drug therapy n (%)	94 (33.5)	64 (22.4)	77 (26.6)

The time since onset of symptoms ranged between 4 months and approximately 32 years. The median time since onset was comparable across treatment groups (27.0 to 29.0 months). Approximately one third of the patients had previously received non-drug therapy. The percentage was lower in the active treatment groups (22.4% for 5 mg and 26.6% for 10 mg in solifenacin) compared with placebo (33.5%). And approximately one-third of the patients had a history of previous drug therapy. The most commonly used medications before start of the study were oxybutynin and tolterodine.

Extent of study drug exposure

The mean and median duration of exposure were comparable among treatment groups. The median treatment duration was 84 days for each treatment group. The mean treatment duration ranged between 80.3 and 82.1 days. Almost two thirds of the patients were treated for 12 weeks or longer. Less than 10 % of the patients prematurely discontinued during the first 8 weeks of the study.

Table D5 Duration (days) of exposure to study medication (SAF, N=907)

Characteristics	Placebo N=301	Solifenacin succinate	
		5 mg qd N=299	10 mg qd N=307
Duration of exposure: days			
N	293	296	306
Mean±SD	82.4±15.1	83.0±12.7	81.8±14.5
Median	84.0	84.0	83.0
Range	2-111	11-104	2-101
Number (%) of patients treated for			
Unknown n (%)	8 (2.7)	9 (3.2)	3 (1.1)
1-6 days n (%)	1 (0.3)	1 (0.4)	0 (0.0)
7-13 days n (%)	2 (0.7)	0 (0.0)	0 (0.0)
14-27 days n (%)	4 (1.3)	4 (1.4)	2 (0.7)
28-55 days n (%)	11 (4.1)	11 (3.9)	8 (3.0)
56-83 days n (%)	86 (32.2)	89 (31.9)	99 (36.9)
84-90 days n (%)	125 (46.8)	124 (44.4)	115 (42.9)
≥91 days n (%)	30 (11.2)	41 (14.7)	41 (15.3)

D.3 Withdrawals and compliance

The main reasons for discontinuation were adverse events (3.2% of all patients) and withdrawal of consent (2.5%). The highest overall discontinuation rate was found in the placebo group (10.3%). There were no major differences between the active treatment groups. One patient in the placebo group died during the course of the study. One other patient in the 10 mg solifenacin group died after discontinuation of the study medication; the primary reason for discontinuation was "adverse event".

Table D6 Number (%) of patients prematurely discontinuing from the study by primary reason for discontinuation (SAF, N=907)

	Placebo (N=301) n (%)	Solifenacin succinate		Total (N=907) n (%)
		5 mg qd (N=299)	10 mg qd (N=307)	
Adverse events	10 (3.3)	7 (2.3)	12 (3.9)	29 (3.2)
Consent withdrawal	9 (3.0)	8 (2.7)	6 (2.0)	23 (2.5)
Lost to follow-up	4 (1.3)	2 (0.7)	2 (0.7)	8 (0.9)
Protocol violation	2 (0.7)	2 (0.7)	2 (0.7)	6 (0.7)
Insufficient response	2 (0.7)	2 (0.7)	2 (0.7)	6 (0.7)
Patient died	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Other	3 (1.0)	1 (0.3)	0 (0.0)	4 (0.4)
Total	31 (10.3)	22 (7.4)	24 (7.9)	77 (8.5)

Treatment compliance: The mean compliance was similar across treatment groups, and ranged between 98.9% and 99.8%. Median compliance was 100.0% in all treatment groups.

Protocol violation:

Table D7 Number (%) of patients with protocol violations leading to exclusion from the PPS (FAS, N=857)

	Placebo (N=281) n (%)	Solifenacin succinate		Total (N=1033) n (%)
		5 mg qd (N=286) n (%)	10 mg qd (N=290) n (%)	
Violation in/ex criteria	7 (2.5)	13 (4.5)	15 (5.2)	35 (4.1)
Forbidden concomitant med.	3 (1.1)	4 (1.4)	2 (0.7)	9 (1.1)
Non-compliance	1 (0.4)	3 (1.0)	0 (0.0)	4 (0.5)
Treatment duration too short	12 (4.3)	12 (4.2)	8 (2.8)	32 (3.7)
Diary > 3days after last med.	1 (0.4)	2 (0.7)	2 (0.7)	5 (0.6)
Incorrect medication	0(0.0)	0(0.0)	1 (0.3)	1 (0.1)
Total	21 (7.5)	29 (10.1)	26 (9.0)	76 (8.9)

Patients with more than 1 protocol violation are included more than once.

Patients excluded from the study:

Table D8 Number (%) of patients excluded from the SAF/FAS

	Placebo n (%)	Solifenacin succinate		Total n (%)
		5 mg qd n (%)	10 mg qd n (%)	
Not randomized				180
Number of randomized	302	301	308	911
Excluded from SAF				
Randomized but no double blind medication taken	1 (0.3)	2 (0.7)	1 (0.3)	4 (0.4)
Excluded from FAS				
No baseline or no endpoint data for primary efficacy variable	12 (4.0)	5 (1.7)	9 (2.9)	26 (2.9)
ICH GCP non-compliance	8 (2.6)	8 (2.7)	8 (2.6)	24 (2.6)

Based on audit findings, all patients from centre #624 were excluded from the FAS and PPS, indicated as "ICH GCP non-compliance".

Reviewer's comment: The withdrawal rates for the groups of placebo, solifenacin 5 mg and 10 mg , are acceptable and the overall compliance was > 95% in all treatment groups.

D.4 Efficacy analysis

Summary of efficacy

Over 90% of patients from each treatment group had their final endpoint efficacy evaluation at Week 12.

Table D9 Study 905-CL-018: Number (%) of patients with endpoint representation of Efficacy data by week (FAS population N=857)

Week of assessment Used as Endpoint	Placebo (N=281) n (%)	Solifenacin succinate	
		5 mg (N=286) n (%)	10 mg (N=290) n (%)
Week 4	13 (4.6)	12 (4.2)	9 (3.1)
Week 8	9 (3.2)	5 (1.7)	8 (2.8)
Week 12	259 (92.2)	269 (94.1)	273 (94.1)

Overall efficacy:

Table D10 Study 905-CL-015 Overview of efficacy results at endpoint^a (FAS, N=857)

	Placebo	Solifenacin succinate	
		5 mg qd	10 mg qd
Micturitions/24 h	n = 281	n = 286	n = 290
Baseline	12.31	12.05	12.12
Endpoint change from baseline	-1.66	-2.45	-2.88
Estimate difference to placebo		-0.78	-1.22
(p value)		(0.0018)	(0.0001)
Mean volume voided	n = 281	n = 286	n = 290
Baseline	147.21	148.52	145.85
Endpoint change from baseline	11.32	31.76	36.55
Estimate difference to placebo		20.07	25.32
(p value)		(0.0001)	(0.0001)
Incontinence episodes/24 h	n = 153	n = 173	n = 165
Baseline	3.21	2.65	2.82
Endpoint change from baseline	-1.25	-1.63	-1.57
Estimate difference to placebo		-0.39	-0.30
(p value)		(-)	(0.22)
Urge incontinence episodes/24 h	n = 126	n = 141	n = 138
Baseline	2.34	2.02	2.02
Endpoint change from baseline	-0.91	-1.30	-1.21
Estimate difference to placebo		-0.38	-0.29
(p value)		(-)	(0.23)
Urgency episodes/24 h	n = 278	n = 284	n = 289
Baseline	5.62	6.04	5.52
Endpoint change from baseline	-2.05	-2.98	-3.00
Estimate difference to placebo		-0.86	-0.92
(p value)		(0.003)	(0.002)
Nocturia episodes/24 h	n = 240	n = 254	n = 259
Baseline	2.05	1.96	1.89
Endpoint change from baseline	-0.53	-0.60	-0.73
Estimate difference to placebo		-0.07	-0.19
(p value)		(0.48)	(0.038)
Nocturnal voids/24 h	n = 257	n = 261	n = 269
Baseline	2.31	2.21	2.17
Endpoint change from baseline	-0.62	-0.61	-0.78
Estimate difference to placebo		0.01	-0.15
(p value)		(-)	(0.13)

^a Endpoint is the last available on-treatment visit on or before Week 12 (Visit 5).

As shown in the above table, compared with placebo, solifenacin 5 mg and 10 mg significantly reduced the number of micturitions per 24hr, and also significantly increased volume voided per micturition. The significant effect of solifenacin 5 mg and 10 mg over placebo in reduction from baseline in micturitions per 24 hr was first observed at the Week 4 assessment, and was maintained throughout the remainder of the double blind treatment period.

Reviewer's comment: Solifenacin 10 mg dose seems to be more effective than 5 mg dose in reducing micturition numbers, reducing urgency episode numbers, but not in increasing volume voided and reducing incontinence episodes.

Primary endpoint

Table D11 Study 905-CL-018 Mean number of micturitions/24 h at endpoint (FAS, N=857)

	Placebo N =281	Solifenacin succinate	
		5 mg qd N = 286	10 mg qd N = 290
Baseline (Mean±SD)	12.31±3.81	12.05±3.89	12.12±3.59
Endpoint (Mean±SD)	10.65±4.70	9.60±3.88	9.24±2.96
Change from baseline	-1.66±3.21	-2.45±2.86	-2.88±3.08
% change from baseline	-12.8±23.5%	-19.6±21.0%	-21.9±20.5%

For FAS population: ANOVA

Table D12 ANOVA results: change in mean number of micturition/24 h at endpoint (FAS, N=857)

	Placebo (N=281)	Solifenacin succinate	
		5 mg qd N = 286	10 mg qd N = 290
Primary analysis			
Adjusted mean change from baseline	-1.59	-2.37	-2.81
Estimated difference to placebo		-0.78	-1.22
95% CI		-1.27,	-1.71,
		-0.29	-0.72

Adjusted mean change for placebo in primary analysis = -1.20, N=253.

For PPS population: ANOVA

Table D13 ANOVA results: change in mean number of micturition/24 h at endpoint (PPS, N=781)

	Placebo (N=260)	Solifenacin succinate	
		5 mg qd N = 257	10 mg qd N = 264
Primary analysis			
Adjusted mean change from baseline	-1.63	-2.49	-2.83
Estimated difference to placebo		-0.86	-1.20
95% CI		-1.38,	-1.71,
		-0.34	-0.68

Reviewer's comment: The results of AVONA test in PPS population further confirmed the primary endpoint in FAS population. In the placebo group, a large effect in the region "Russia" and "Central Europe" was found as compared to the other regions.

Proportion of patients showing response: For the FAS endpoint, 22.4% of the placebo patients have <8 micturitions/24 h at endpoint, compared with 37.4% in the 5 mg solifenacin qd group, and 31.4% in the 10 mg solifenacin qd group.

Influence of dropouts: The dropout rate was low and balanced between treatment groups. To ensure that the conclusions of the primary analyses on the FAS were not unduly influenced by dropouts or missing data, analyses were done on the two partitions of the FAS: completers and dropouts. As shown in Table D14, the effect sizes in the completers group are comparable to the FAS.

Table D14 Mean number of micturition/24 h at endpoint, FAS, completers and dropouts

Treatment Group	FAS			Completers			Dropouts		
	Baseline Mean (n)	Mean Change From baseline	Effect Size*	Baseline Mean (n)	Mean Change From baseline	Effect Size (P-Y)	Baseline Mean (n)	Mean Change From baseline	Effect Size*
Placebo	12.31 (n=281)	-1.66		12.30 (n=262)	-1.75		12.43 (n=19)	0.45	
Solifenacin 5 mg qd	12.05 (n=286)	-2.45	0.79	11.88 (n=248)	-2.57	0.82	14.76 (n=17)	-0.59	0.14
Solifenacin 10 mg qd	12.12 (n=290)	-2.88	1.22	12.21 (n=273)	-2.96	1.21	10.76 (n=17)	-1.65	1.20

* Effect size is defined as the mean change from baseline from the placebo group minus the mean change from baseline for the active treatment group.

Mean change from baseline to visit in the number of micturitions per 24 hrs: As shown in Figure D1, two thirds of the effect obtained after 12 weeks is achieved after 4 weeks. Further improvement is achieved in the subsequent periods for all groups including placebo.

Secondary efficacy analysis

Mean volume voided per micturition: As shown in the Figure D2, at the endpoint and at all study visits (Week 4, 8, and 12), solifenacin statistically significantly increased volume voided per micturition when compared with placebo. After excluding patients with large volumes, additional analyses did not change the study conclusions.

Table D15 Study 018 Mean volume voided per micturition (mL) at endpoint (FAS, N=857)

	Placebo N = 281	Solifenacin succinate	
		5 mg qd N = 286	10 mg qd N = 290
Baseline (Mean±SD)	147.21±53.3	148.52±53.4	145.85±58.2
Endpoint (Mean±SD)	158.54±60.9	180.28±68.2	182.41±76.8
Change from baseline	11.32±42.3	31.76±49.6	36.55±51.7
% change from baseline	+11.0±31.2%	+25.4±35.3%	+29.7±40.5%

Table D16 ANOVA: change in mean volume voided per micturition (mL) at endpoint (FAS, N=857)

	Placebo N=281)	Solifenacin succinate	
		5 mg qd N = 286	10 mg qd N = 290
Primary analysis			
Adjusted mean change from baseline	10.67	30.75	35.99
Estimated difference to placebo		20.07	25.21
95% CI		12.67, 27.88	17.63, 32.78

Figure D2 shows that >75% of the effect obtained after 12 weeks of treatment was already achieved after 4 weeks. Further improvement was achieved in subsequent periods for all treatment groups.

Mean number of incontinence episodes per 24 hrs: As shown in the Figure D3, and in the following tables.

Table D17 Study 018 Mean number of incontinence episodes/24 h at endpoint (FAS, N=857)

	Placebo N =153	Solifenacin succinate	
		5 mg qd N = 173	10 mg qd N = 165
Baseline (Mean±SD)	3.21±3.03	2.65±2.41	2.82±2.55
Endpoint (Mean±SD)	1.96±2.87	1.01±1.90	1.25±2.12
Change from baseline	-1.25±2.38	-1.63±2.12	-1.57±2.33
% change from baseline	-27.9±151.4%	-60.7±70.4%	-51.9±92.3%

For FAS population: ANOVA

Table D18 ANOVA: change in mean number of incontinence episodes/24 h at endpoint (FAS, N=857)

	Placebo (N=153)	Solifenacin succinate	
		5 mg qd N = 173	10 mg qd N = 165
Primary analysis			
Adjusted mean change from baseline	-1.23	-1.62	-1.53
Estimated difference to placebo		-0.39	-0.30
95% CI		-0.87, 0.1	-0.79, 0.19
Analysis with baseline as covariate			
Adjusted mean change from baseline	-1.08	-1.73	-1.58
Estimated difference to placebo		-0.66	-0.50
95% CI		-1.07, -0.25	-0.92, -0.09

From the above table, the results from the primary analysis show that the difference from placebo was not statistically significant for solifenacin 10 mg group ($p=0.22$); the secondary analysis with baseline included as covariate might be considered as being more appropriate in this case because of the baseline differences between placebo and the 2 active treatment groups.

Among the FAS patients who had at least one episode of incontinence at baseline, 39.2% of the patients in the placebo group had no incontinence at endpoint, compared to 50.3% of the 5mg solifenacin group, and 49.7% of the 10 mg solifenacin group.

As seen in Figure D3, more than 70% of the effect obtained after 12 weeks of treatment is already achieved after 4 weeks. Further improvement is achieved in subsequent periods for all treatment groups, including placebo.

Mean number of urge incontinence episodes per 24 hrs: As shown in the Figure D4, and in the following tables.

Table D19 Study 018 Mean number of urge incontinence episodes/24 h at endpoint (FAS, N=857)

	Placebo N =126	Solifenacin succinate	
		5 mg qd N = 141	10 mg qd N = 138
Baseline (Mean±SD)	2.34±2.70	2.02±1.97	2.02±2.20
Endpoint (Mean±SD)	1.43±2.76	0.73±1.83	0.81±1.85
Change from baseline	-0.91±1.91	-1.30±1.84	-1.21±2.13
% change from baseline	-42.5±110.5%	-62.7±88.8%	-57.1±106.8%

For FAS population: ANOVA

Table D20 ANOVA: change in mean of urge incontinence episodes/24 h at endpoint (FAS, N=857)

	Placebo (N=126)	Solifenacin succinate	
		5 mg qd N = 141	10 mg qd N = 138
Primary analysis			
Adjusted mean change from baseline	-0.90	-1.28	-1.18
Estimated difference to placebo		-0.38	-0.29
95% CI		-0.85, 0.09	-0.76, 0.19
Analysis with baseline as covariate			
Adjusted mean change from baseline	-0.81	-1.33	-1.24
Estimated difference to placebo		-0.52	-0.43
95% CI		-0.93, -0.10	-0.85, -0.01

From the above table, the results from the primary analysis showed that the difference from placebo was not statistically significant for solifenacin 10 mg group ($p=0.23$); the secondary analysis with baseline included as covariate might be considered as being more appropriate in this case because of the baseline differences between placebo and the 2 active treatment groups.

As seen in Figure D4, more than 80% of the effect obtained after 12 weeks of treatment is already achieved after 4 weeks. Further improvement is achieved in subsequent periods for all treatment groups, but especially for the placebo.

Mean number of urgency episodes per 24 hrs: shown in the Figure D5, and in the following tables.

Table D21 Study 015 Mean number of urgency episodes/24 h at endpoint (FAS, N=857)

	Placebo N =278	Solifenacin succinate	
		5 mg qd N = 284	10 mg qd N = 289
Baseline (Mean±SD)	5.62±3.97	6.04±4.70	5.52±4.06
Endpoint (Mean±SD)	3.57±4.29	3.06±4.22	2.52±3.39
Change from baseline	-2.05±3.71	-2.98±3.66	-3.00±3.67
% change from baseline (Mean)	-33.0±104.9%	-51.4±57.1%	-52.0±77.0%

For FAS population: ANOVA

Table D22 ANOVA: change in mean of urge incontinence episodes/24 h at endpoint (FAS, N=857)

	Placebo (N=278)	Solifenacin succinate	
		5 mg qd N = 284	10 mg qd N = 289
Primary analysis			
Adjusted mean change from baseline	-1.98	-2.84	-2.90
Estimated difference to placebo		-0.86	-0.92
95% CI		-1.44, -0.28	-1.49, -0.35

The primary analysis results showed that the differences from placebo were statistically significant for both solifenacin 5 mg and 10 mg ($p=0.003$, 0.002 , respectively).

As seen in Figure D5, more than 80% of the effect obtained after 12 weeks of treatment is already achieved after 4 weeks. Further improvement is achieved in subsequent periods for all treatment groups, including placebo.

Among patients who had at least one urgency episode at baseline, 24.9% of the patients in placebo group had no urgency at endpoint, compared to 26.2% of the 5 mg solifenacin group, 32.8% of the solifenacin 10 mg group and 24.8% in the tolterodine group.

Mean number of nocturnal void episodes per 24 hrs: As shown in the Figure D6, and in the following tables.

Table D23 Study 018 Mean number of nocturia episodes/24 h at endpoint (FAS, N=857)

	Placebo N =240	Solifenacin succinate	
		5 mg qd N = 254	10 mg qd N = 259
Baseline (Mean±SD)	2.05±1.37	1.96±1.14	1.89±1.24
Endpoint (Mean±SD)	1.52±1.47	1.36±1.28	1.17±1.16
Change from baseline	-0.53±1.07	-0.60±1.05	-0.73±1.00
% change from baseline (Mean)	-16.4±100.3%	-25.3±69.2%	-38.5±51.8%

For FAS population: ANOVA

Table D24 ANOVA: change in mean number of noctria episodes/24 h at endpoint (FAS, N=857)

	Placebo (N=240)	Solifenacin succinate	
		5 mg qd N = 254	10 mg qd N = 259
Primary analysis			
Adjusted mean change from baseline	-0.52	-0.58	-0.71
Estimated difference to placebo		-0.07	-0.19
95% CI		-0.25, 0.12	-0.38, 0.02

The primary analysis results showed that the difference from placebo was statistically significant for solifenacin 10 mg (p=0.036) but not for solifenacin 5 mg (p= 0.48).

As seen in Figure D6, the results for nocturia per visit, no relevant effect of active treatment versus placebo was seen.

Among patient who had at least one urgency episode at baseline, 17.5% of the patients in placebo group had no urgency at endpoint, compared to 14.2% of the 5 mg solifenacin group, 21.2% of the solifenacin 10 mg group and 24.8% in the tolterodine group.

Mean number of nocturnal voids per 24 hrs: As shown in the Figure D7, and in the following tables.

Table D25 Study 018 Mean number of nocturnal voids/24 h at endpoint (FAS, N=857)

	Placebo N =257	Solifenacin succinate	
		5 mg qd N = 261	10 mg qd N = 269
Baseline (Mean±SD)	2.31±1.46	2.21±1.30	2.17±1.39
Endpoint (Mean±SD)	1.69±1.50	1.60±1.41	1.39±1.26
Change from baseline	-0.62±1.13	-0.61±1.25	-0.78±1.14
% change from baseline (Mean)	-23.3±65.0%	-22.4±65.6%	-34.0±52.5%

For FAS population: ANOVA

Table D26 ANOVA: change in mean number of nocturnal voids/24 h at endpoint (FAS, N=857)

	Placebo (N=257)	Solifenacin succinate	
		5 mg qd N = 261	10 mg qd N = 269
Primary analysis			
Adjusted mean change from baseline	-0.62	-0.61	-0.77
Estimated difference to placebo		0.01	-0.15
95% CI		-0.20, 0.22	-0.36, 0.05

The primary analysis results showed that the difference from placebo was not statistically significant for solifenacin 10 mg (p=0.13). Therefore, the solifenacin 5 mg group was not statistically tested.

Figure D7 shows no relevant effect of active treatment vs. placebo was observed.

Mean number of pads used per 24 hrs: As shown in the following table.

Table D27 Study 015 Mean number of pads used/24 h at endpoint (FAS, N=857)

	Placebo N=120	Solifenacin succinate	
		5 mg qd N = 130	10 mg qd N = 127
Baseline (Mean±SD)	3.23±2.43	2.79±1.99	2.67±2.02
Endpoint (Mean±SD)	2.16±2.36	1.47±1.81	1.51±2.10
Change from baseline	-1.06±2.08	-1.33±1.96	-1.16±1.88
% change from baseline	-13.9±210.2%	-45.7±67.8%	-42.3±87.4%

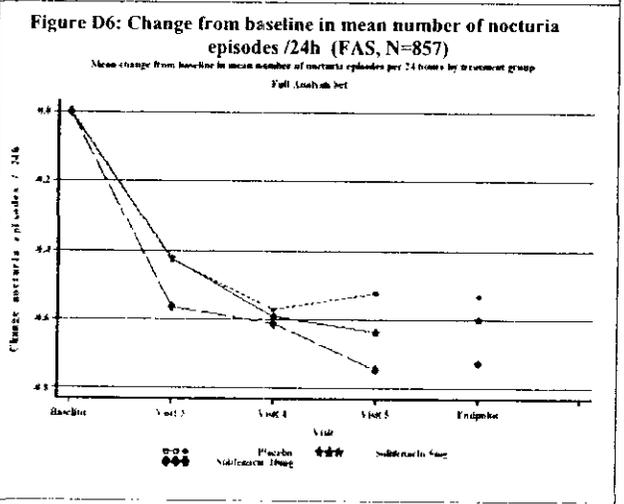
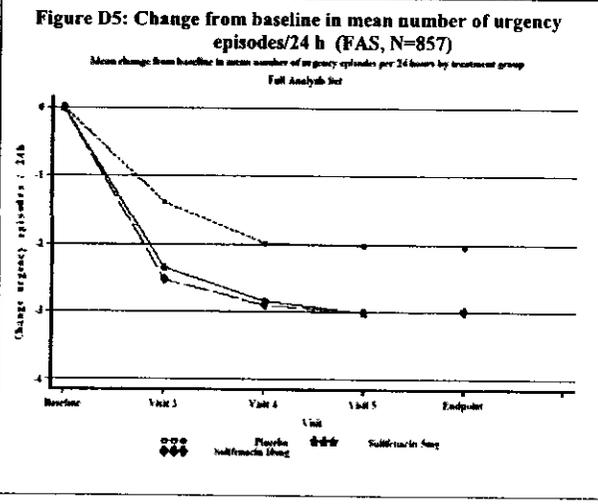
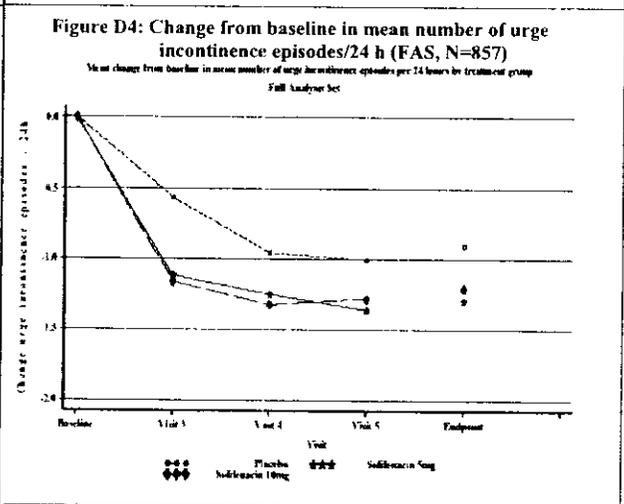
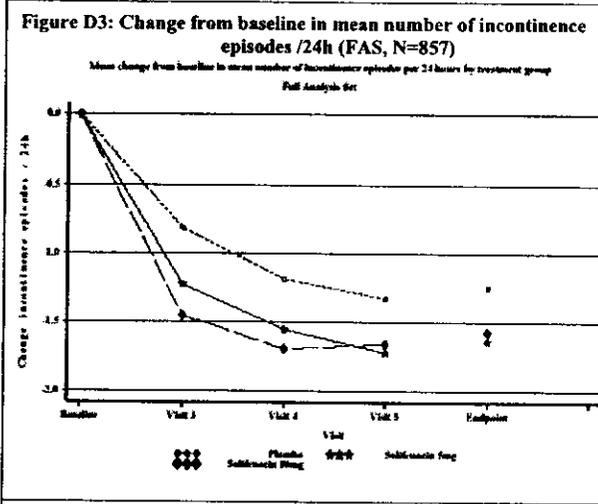
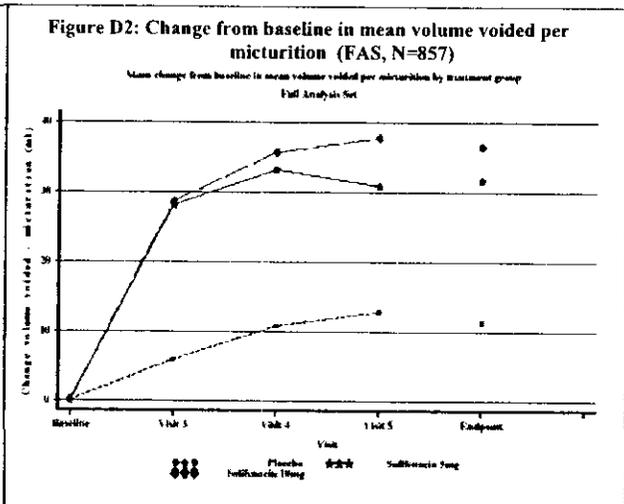
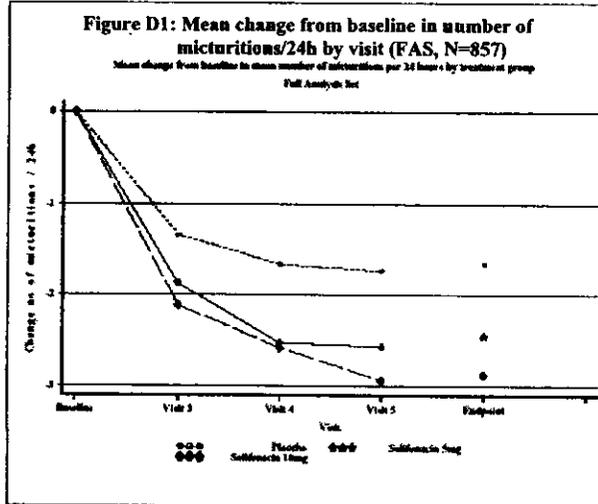
Quality of life (QoL) questionnaire: The QoL questionnaire showed that both solifenacin 5 mg group and 10 mg group were statistically significantly better than placebo for five of ten domains: incontinence impact, role limitations, emotions, sleep/energy and symptom severity. For physical limitations and severity measures, only solifenacin 10 mg was statistically significantly different from placebo.

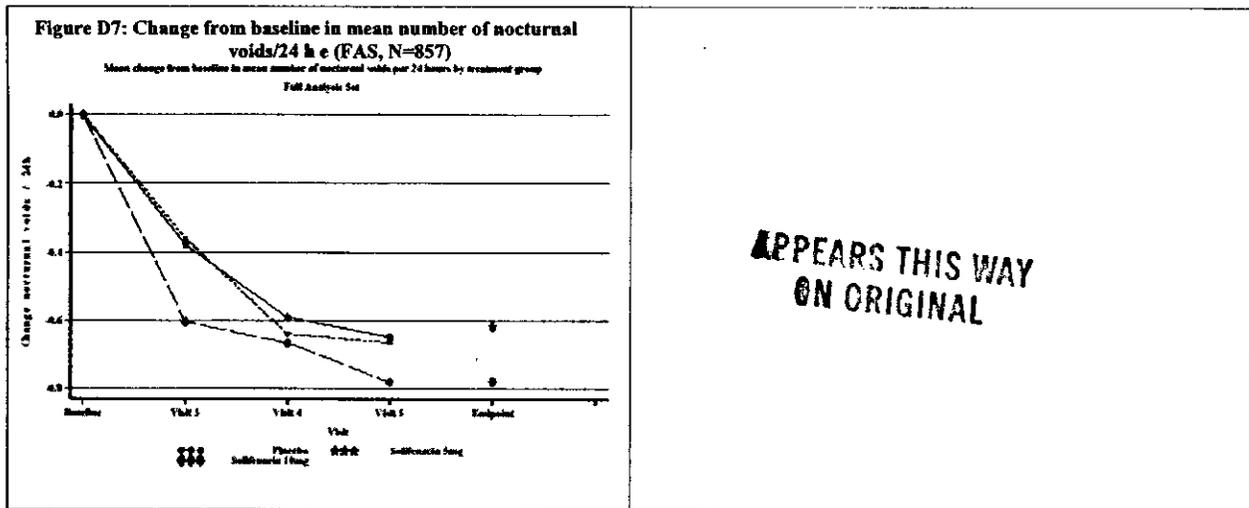
Efficacy conclusions

- Solifenacin 5 mg and 10 mg once daily were statistically significantly better in reducing the number of micturitions per 24 hours at endpoint when compared to the placebo (primary efficacy endpoint). About 70% of the efficacy was obtained after 12 weeks was achieved after 4 weeks.
- Treatment with 5 mg and 10 mg solifenacin once daily was statistically significantly better than placebo with respect to increase in mean volume voided per micturition, and to reduce mean number of urgency episodes per 24 hrs (secondary efficacy variables). The analysis with baseline included as covariate showed a statistically significant effect of solifenacin treatment over placebo for reducing the mean number of incontinence episodes, and urge incontinence episodes.
- With respect to the other two secondary efficacy variables (mean number of nocturia episodes and nocturnal voids), no benefit was demonstrated for solifenacin treatment compared to placebo
- Treatment with solifenacin 5 mg and 10 mg, resulted in more patients becoming continent than the placebo group.
- There were no relevant differences between the two solifenacin dose groups, except for the mean number of micturitions per 24 hrs and the mean volume voided per micturition, where a small difference was found in favor of the 10 mg group.
- The results from the primary analyses were confirmed in additional exploratory analyses (FAS or PPS).

In summary, solifenacin 5 mg and 10 mg were effective in treating the symptoms of OAB. With solifenacin 5 mg and 10 mg, about 50% of patients in each group (vs. 39% for placebo) became continent at endpoint with

increased bladder capacity (demonstrated by the increase in the volume voided per micturition (+31.8 mL for 5 mg, +36.6 mL for 10 mg, vs. +11.3 mL for placebo).





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D.5 Safety analyses

Extent of study drug exposure

The mean and median duration of exposure was comparable among treatment groups. The median treatment duration was 84 days for patients treated with placebo and with solifenacin 5 mg, and 83 days in patients treated with solifenacin 10 mg. The mean treatment duration ranged between 81.8 and 83.0 days. Less than 10 % of the patients prematurely discontinued during the first 8 weeks of the study.

Table D28 Duration (days) of exposure to study medication (SAF, N=907)

Characteristics	Placebo N=301	Solifenacin succinate	
		5 mg qd N=299	10 mg qd N=307
Duration of exposure: days			
N	293	296	306
Mean±SD	82.4±15.1	83.0±12.7	81.8±14.5
Median	84.0	84.0	83.0
Range	2-111	11-104	2-101
Number (%) of patients treated for			
Unknown n (%)	8 (2.7)	9 (3.2)	3 (1.1)
1-6 days n (%)	1 (0.3)	1 (0.4)	0 (0.0)
7-13 days n (%)	2 (0.7)	0 (0.0)	0 (0.0)
14-27 days n (%)	4 (1.3)	4 (1.4)	2 (0.7)
28-55 days n (%)	11 (4.1)	11 (3.9)	8 (3.0)
56-83 days n (%)	86 (32.2)	89 (31.9)	99 (36.9)
84-90 days n (%)	125 (46.8)	124 (44.4)	115 (42.9)
≥91 days n (%)	30 (11.2)	41 (14.7)	41 (15.3)

Reviewer's comment: The extent of exposure in this trial was adequate to make an assessment of safety.

Deaths: Two patients died during the course of the study.

Patient #21316: This 72-year-old male Caucasian had a medical history of arterial hypertension and was treated with placebo. He died of hypertensive crisis and stroke 42 days after starting the double-blind

treatment period. Sixteen day after the patient died, the investigator was informed of the cause of death. No autopsy was performed. The investigator judged the death was not related to the study drug.

Reviewer's comment: This patient was randomized to placebo.

Patient #20638: This 68-year-old female Caucasian had a medical history of myocardial infarction, arterial hypertension, ischemic heart disease and diabetes mellitus type II. She was treated with solifenacin 10 mg. The patient missed Visit 5 and the investigator was later informed that the patient suffered a right sided hemiparesis due to an insult 81 days after starting the double-blind treatment period. Study medication was stopped immediately and the patient died 17 days later. The cause of the death was pulmonary thromboembolism. The investigator assessed the death was not related to the study drug.

Reviewer's comment: The reviewer agrees that the relationship of this death to study drug was unlikely.

Serious adverse events (SAEs): Serious adverse events (SAE) were reported in a total of 22 patients with one or more SAF: ten patients in the placebo group, four in the solifenacin 5 mg group and eight in the solifenacin 10 mg group during the 12-week treatment period. Treatment-related SAEs were reported in 7 patients.

Table D29 Patients with serious adverse events (SAE's) (SAF, N = 907)

Patient #	Age (yrs)	Sex	MedDRA preferred term	Onset Day (days ^a)	Relationship to study medication	Intensity	Action taken/outcome
Placebo							
20071	69	F	Angina pectoris	40	Possible	Severe	None/recovered
20098	50	F	Acute myocardial infarction	36	Not related	Severe	Discontinued/RCV
20347	57	F	Depression NOS	66	Not related	Moderate	None/resolved
20404	62	F	Myocardial infarction	88	Possible	Moderate	None/not yet RCV
20659	34	F	Mood disorder NOS	36	Not related	Severe	Discontinued/
20688	74	M	Myasthenia gravis	55	Possible	Moderate	Discontinued/
20868	55	F	Vision blurred	50	Possible	Moderate	Discontinued/resumed
			Headache NOS	50	Not related	Moderate	Recovered
20909	71	M	Tachycardi paroxysmal NOS	31	Not related	Moderate	None/recovered
21010	76	M	Chest pain	25	Not related	Severe	Discontinued/RCV
21528	45	F	Bartholin's abscess	41	Not related	Severe	None/recovered
Solifenacin 5 mg qd							
20020	78	F	Upper limb fracture NOS	32	Not related	Severe	Discontinued/recovered
20034	70	M	Peripher. vascular disorder NOS	14	Not related	Moderate	Discontinued/RCV
20399	74	F	Deep venous thrombosis NOS	83	Not related	Moderate	None/recovered
20815	45	F	Menometrorrhagia	59	Possible	Mild	None/recovered
Solifenacin 10 mg qd							
20007	64	M	Chest pain	40	Not related	Mild	None/recovered
			Dizziness postural	39	Not related	Mild	
20605	56	F	Femur fracture NOS	57	Not related	Severe	None/recovered
20638	68	F	Cerebral circulatory failure	81	Not related	Severe	Discontinued/
20723	66	F	Intestinal obstruction NOS	76	Not related	Severe	Discontinued/RCV
21391	65	F	Hernia repair NOS	15	Not related	Severe	None/recovered
21449	56	F	Nausea & vomiting NOS	12	Possible	Moderate	None/recovered
			Abdominal pain upper	12	Not related	Mild	
21454	72	F	Syncope	7	Possible	Moderate	None/recovered
21502	58	F	Ovarian cyst	12	Not related	Moderate	None/recovered

nos = not otherwise specified; RCV: recovered;

^a Relative to day of first dose of study drug, (post-treatment day relative to first day after the last dose is indicated with a + sign)

Of the SAE's with solifenacin 5 mg, one with menometrorrhagia was judged to be possibly related to study drug; in the solifenacin 10 mg group, two were assessed as possibly related to study drug: one with nausea and vomiting and the other with syncope; four in the placebo group were also judged to be possibly related to the study drug: angina pectoris, myocardial infarction, myasthenia gravis and blurred vision each.

Narratives of SAE's: Group of Solifenacin 5 mg qd:

Patient #20020 (The Netherlands): This 78-year-old Caucasian woman was hospitalized after 32 days of double-blind treatment due to a broken shoulder when she fell from the side walk. She was unable to take care of herself and was admitted to a care centre. Patient discontinued double-blind treatment. She recovered 32 days later. The investigator assessed the relationship between the upper limb fracture and the study drug to be unlikely.

Reviewer's comment: The reviewer believes that this event is not related to study drug.

Patient #20034 (The Netherland): This 70-year-old man had a medical history of hip surgery (left and right), gastric perforation and had hypertension that was still active at the start of the trial, had a small wound on the right toe, that was noticed after 14 days of double-blind treatment and which would not heal. He was admitted to the hospital for Doppler ultrasound, X-ray and surgery. Patient underwent right lower leg amputation due to arterial insufficiency of the right leg. He discontinued treatment after 63 days of double blind study treatment. The patient recovered with sequelae. The patient continued the study. The investigator assessed the relationship to the study drug to be unrelated.

Reviewer's comment: The reviewer agrees that these events were not related to study drug.

Patient #20399 (Czech Republic): This 74-year-old Caucasian woman was hospitalized 83 days after start of the double-blind treatment period due to thrombosis of deep vein of her left leg. She was discharged 8 days later and was fully mobile again a month later. The investigator assessed the relationship between the deep venous thrombosis and the study drug to be unrelated.

Reviewer's comment: The reviewer believes that the relationship to study drug is unlikely.

Patient #20815 (Czech Republic): This 45-year-old Caucasian woman underwent diagnostic curettage in the hospital. She had had metrorrhagia for 6 days from Day 59 after start of the double-blind treatment period. There were no pathological findings and the patient recovered. She continued the study. The investigator assessed this mild event was possibly related to study drug.

Reviewer's comment: The reviewer agrees that the event was possibly related with study drug.

Narratives of SAE's: Group of Solifenacin 10 mg qd

Patient #20007 (The Netherlands): This 64-year-old man had a history of atrial fibrillation, angina pectoris and high cholesterol levels and was given solifenacin 10 mg qd. He developed dizziness on standing up and chest pain between the shoulder blades after 39 and 40 days of double-blind treatment, respectively. Patient was hospitalised for observation but no evidence of ischaemia was found. Patient recovered the next day and was discharged. The investigator assessed the relationship between the chest pain, dizziness postural and the study drug to be unlikely.

Reviewer's comment: the reviewer believes that the event was unlikely related to study drug.

Patient #20605 (Russia): This 56-year-old Caucasian woman was hospitalised 57 days after start of the double-blind treatment period due to fractured femur. She was discharged later. Patient completed the study. No concomitant medication was given. The investigator assessed the patient's femur fracture to be unrelated to study drug.

Reviewer's comment: The reviewer agrees that this event is not related to study drug.

Patient #20638 (Russia): This 68-year-old Caucasian woman had a medical history of myocardial infarction, arterial hypertension, ischaemic heart disease and diabetes mellitus type II. The patient missed her Study Visit 5. Patient's daughter reported her mother suffered a right sided hemiparesis due to an insult on Day 81 after start of the double-blind treatment period. The patient died later (Day 98) from pulmonary embolism. The investigator assessed that the death due to cerebral circulatory failure was not related to the study drug.

Reviewer's comment: The reviewer agrees that the relationship of this death to study drug was unlikely.

Patient #20723 (France): This 66-year-old Caucasian woman had a history of intestinal motility dysfunction (on medication) and surgery for occlusion (ileal resection). The patient underwent further surgical treatment 76 days after start of the double-blind treatment period, for an unspecified intestinal occlusion (without ileal resection). On the day the intestinal obstruction was diagnosed, the study medication was temporarily discontinued, no concomitant medication was given and the patient recovered. The investigator assessed the relationship between the intestinal obstruction and the study drug to be unrelated.

Reviewer's comment: The reviewer agrees that the event was unlikely related to study drug.

Patient #21391 (South Africa): This 65-year-old Caucasian woman had a medical a history of spinal fusion. She developed acute left inguinal pain and swelling 15 days after start of the double-blind treatment period. The next day she was operated and a Richter's hernia. No bowel resection was done. She recovered 6 days later. She continued the study. The investigator assessed that the event was not related to the study drug.

Reviewer's comment: The reviewer believes that this event is not related to study drug.

Patient #21449 (South Africa): This 56-year-old Caucasian woman had a medical history of irritable bowel syndrome at the start of the study. After 12 days of double-blind treatment she developed nausea, vomiting and epigastric pain (mild severity) diagnosed as resulting from known reflux, and was hospitalized and treated. She was discharged 3 days later and recovered with sequelae. She completed the study. The investigator assessed that the nausea and vomiting were possibly related to the study drug and her upper abdominal pain was not related to the study drug.

Reviewer's comment: The reviewer believes that the nausea and vomiting was possibly related to study drug.

Patient #21449 (South Africa): This 72-year-old Caucasian woman had hypertension and hypercholesterolaemia at the start of the study, and had a history of myocardial infarct. She was hospitalized for atrial fibrillation with syncope 7 days after start of the double-blind treatment period. According to the investigator the occurrence of intermittent syncope started after initiation of Atenolol, which was therefore discontinued the first day in the hospital. She was discharged from the hospital 4 days after the start of the AE but readmitted 2 days later due to recurrence of syncopal episodes. The presence of atrial fibrillation could not be confirmed. Pulse and other vital signs were normal. She was discharged and completed the study. The ECG at the end of study showed U-waves, but this was considered not clinically relevant. QTc values at screening and at the end of the study were 422 ms and 407 ms, respectively. The investigator considered the syncope was possibly related to the study drug.

Reviewer's comment: The reviewer believes that the event was possibly related to study drug.

Patient #21502 (South Africa): This 58-year-old Caucasian woman had a medical history of vaginal hysterectomy and ovarian cystectomy. She was hospitalized for surgical excision of a benign pelvic cyst 12 days after the start of the double-blind treatment period. Investigator was aware of the cyst prior to her entry into the study, but a gynecologist advised excision of cyst after study entry. While hospitalized, patient continued to take study medication and recovered completely. The investigator assessed the ovarian cyst was not related to the study drug.

Reviewer's comment: The reviewer agrees that the event was not related to study drug.

Overall adverse events

Approximately 40-50% of all patients had 1 or more adverse events (AE's) with no differences across treatment groups in the incidence.

Table D30 Study 018 Summary of adverse events (FAS, N=1907)

	Placebo N = 301	Solifenacin succinate	
		5 mg qd N = 299	10 mg qd N = 307
N (%) with AE's	117 (38.9%)	130 (43.3%)	148 (48.2%)
Total number of AE's	210	229	318
N (%) with SAEs	11 (3.7%)	4 (1.3%)	8 (2.6%)
Total number of SAEs	12	4	12
N (%) with AEs by severity			
Mild	64 (21.3%)	75 (25.1%)	87 (28.3%)
Moderate	40 (13.3%)	50 (16.7%)	52 (16.9%)
Severe	13 (4.3%)	5 (1.7%)	9 (2.9%)
N (%) who discontinued because of AEs (including deaths)	9 (3.0%)	7 (2.3%)	12 (3.9%)
N (%) with treatment-related AEs	45 (15.0%)	81 (27.1%)	114 (37.1%)
N (%) deaths	1 (0.3%)	0	1 (0.3%)

Most common TEAEs that were considered possibly or probably related to treatment by the investigator were gastro-intestinal AEs in both active treatment groups and placebo (16.7% and 29.6% in the 5 mg and 10 mg solifenacin group, respectively, compared with 9.6% in the placebo group). The incidences in the active treatment groups were higher than that in the placebo groups, especially pronounced for dry mouth (7.7% in solifenacin 5 mg, 23.1% in solifenacin 10 mg, vs. 2.3% in placebo), constipation (3.7% in solifenacin 5 mg, 9.1% in solifenacin 10 mg, vs. 2.3% in placebo), dyspepsia (1.3% and 2.3% in the 5 mg and 10 mg solifenacin groups, respectively, vs. 1.0% in the placebo). Constipation and dry mouth were more often reported in the 10 mg solifenacin group than in the 5 mg group. Most gastro-intestinal AEs were considered treatment-related by the investigator (see table below).

Blurred vision was also more often reported by patients with solifenacin (4.0% in 5 mg and 5.9% in 10 mg) than by those on placebo (2.3%). Nearly all reports of blurred vision were considered treatment-related (see table below).

Table D31 Treatment (T)-related (groups of) TEAEs (≥2%) (safety population, N = 907)

	Placebo		Solifenacin succinate			
	TEAEs	T-related	5 mg qd		10 mg qd	
			TEAEs	T-related	TEAEs	T-related
Cardiac disorders	12 (4.0%)	7 (2.3%)	5 (1.7%)	4 (1.3%)	7 (2.3%)	2 (0.7%)
Eye disorders	12 (4.0%)	9 (3.0%)	19 (6.4%)	16 (5.4%)	22 (7.2%)	21 (6.8%)
<i>Vision blurred</i>	7 (2.3%)	7 (2.3%)	12 (4.0%)	11 (3.7%)	18 (5.9%)	17 (5.5%)
Gastrointestinal disorders	29 (9.6%)	20 (6.6%)	50 (16.7%)	41 (13.7%)	91 (29.6%)	88 (28.7%)
<i>Constipation</i>	6 (2.0%)	6 (2.0%)	11 (3.7%)	10 (3.3%)	28 (9.1%)	27 (8.8%)
<i>Dry mouth</i>	7 (2.3%)	7 (2.3%)	23 (7.7%)	22 (7.4%)	71 (23.1%)	71 (23.1%)
<i>Dyspepsia</i>	3 (1.0%)	2 (0.7%)	3 (1.3%)	4 (1.3%)	7 (2.3%)	6 (2.0%)
Infections & infestations	40 (13.3%)	2 (0.7%)	38 (12.7%)	7 (2.3%)	34 (11.1%)	5 (1.6%)
Investigations	4 (1.3%)	0 (0.0%)	15 (5.0%)	8 (2.7%)	10 (3.3%)	3 (1.0%)
Nerve system disorders	15 (5.0%)	5 (1.7%)	17 (5.7%)	11 (2.7%)	19 (6.2%)	11 (3.6%)

Other AE's of interest included urinary retention and QT prolongation.

Urinary retention (evaluated by post-void residual volume, PVR): None of the patients developed clinically relevant urinary retention. There was a small mean increase in PVR volume after treatment with solifenacin 10 mg, whereas a mean decrease was observed with placebo and for patients on solifenacin 5 mg. However, inter-patient variability was very high, and only 3 patients (one male: #20243, two female: #20070, #20581, all on 10 mg solifenacin) had a PVR that was > 200 mL at the end of the study. Most cases were considered to be unrelated to the treatment by the investigator.

Table D32 PVR: mean values and mean changes from baseline at the end of the study (SAF, N = 907)

Post-void residual (PVR)	Volume (mL)	Placebo N =301	Solifenacin succinate	
			5 mg qd N = 299	10 mg qd N = 307
Baseline	Mean±SD	18.5±28.5	15.9±23.2	20.0±32.3
	Range	0-169	0-117	0-178
End of the study	Mean±SD	15.4±25.5	15.5±26.2	22.4±39.6
	Range	0-155	0-191	0-259
Change	Mean±SD	-3.5±27.1	-0.1±29.0	2.3±34.6

QT prolongation:

Overall, the effect of solifenacin treatment on QT and QTc (corrected by Bazett's formula) was evaluated. In accordance with the protocol and the CPMP guidelines, all ECGs where less than 3 intervals were measured were excluded. Two sets were defined: Set A reporting the results based on all available data and Set B reporting the results with exclusion of ECGs that are inappropriate for QTc measurements.

Table D33 Changes from the baseline for QT and QTc interval (safety population, N = 907)

		Placebo N =301	Solifenacin succinate	
			5 mg qd N = 299	10 mg qd N = 307
Set A				
QT interval (msec)	Screening	379.5±32.8	380.7±30.2	381.2±33.5
	End of the study	375.3±31.9	380.0±31.3	380.4±29.3
	Change	-3.0±21.9	0.4±26.1	0.1±25.1
QTc interval (msec)	Screening	404.8±26.8	406.1±26.5	406.6±30.5
	End of the study	404.2±25.1	407.3±27.0	408.5±26.1
	Change	-0.5±22.8	1.6±22.6	1.4±22.5
Set B				
QT interval (msec)	Screening	377.5±29.8	377.9±30.2	378.3±30.2
	End of the study	374.9±31.4	377.7±30.2	378.9±28.1
	Change	-1.4±20.7	0.0±27.2	0.9±24.2
QTc interval (msec)	Screening	404.6±25.8	405.0±26.5	404.7±25.7
	End of the study	403.6±25.5	404.5±25.7	408.1±24.9
	Change	-0.2±21.7	1.2±23.1	2.8±22.5

Table D34 ANOVA: Mean change from baseline of the QTc at the end of study (central reading data)

	Placebo	Solifenacin succinate	
		5 mg qd	10 mg qd
Set A	n=202	n=203	n=199
Adjusted mean change from baseline	-1.1	1.9	1.7
Estimated difference to placebo		2.9	2.8
95 % CI		-1.0, 6.8	-1.1, 6.7
P value		0.13	0.16
Set B	n=153	n=158	n=158
Adjusted mean change from baseline	-0.5	0.9	3.4
Estimated difference to placebo		1.4	3.9
95 % CI		-3.0, 5.7	-0.5, 8.3
P value		0.54	0.08

The mean increase in QTc interval was 1.4 msec and 3.9 msec for solifenacin 5 mg and 10 mg relative to placebo. These differences with placebo were statistically not significant (p=0.535, 0.076, respectively).

For the analysis of changes from baseline in QTc intervals, patients were categorized by the sponsor as follows:

- Patients with normal QTc (men, ≤430 msec; women, ≤450 msec)
- Patients with borderline QTc (men, >430 to ≤450 msec; women, >450 to ≤470 msec)
- Patients with prolonged QTc (men, >450 to ≤500 msec; women, >470 to ≤500 msec)
- Patients with prolonged QTc of clinical concern (>500 msec)

Table D35 Patients with normal screening QTc and prolonged QTc at the end of the study (SAF, N=1077)

Patient #	Sex	Ventricular rate		QT (msec)		QTc (msec)		Δ QTc (msec)	Remarks / cardiac adverse events
		Screen	End	Screen	End	Screen	End		
Placebo									
#20659	F		131		353		522		No screening data due to no grid
#20663	M		83		384		452		No screening data: poor trace
Solifenacin 5 mg									
#21136	M		95		358		451		No screening data due to no grid
#20345	F	80	132	350	323	405	480	75	Screening: inferior ischemia
#20182	F	71	85	411	399	448	474	26	Measurements in V2
Solifenacin 10 mg									
#21191	F		83		401		471		No scm data: poor trace; Measure in V4
#20343	F	87	105	370	366	444	484	40	
#21727 ⁴	M		64	470	446		461		RBBB: not able to calculate RR

⁴ excluded from set B.

There was one patient with QTc interval at the end of the study >500 msec:

Patient #10158 of solifenacin 10 mg group was a 44-year-old female who had a QTc of 397 msec at the screening that increased to 507 msec at the end of the study (increase of 110 msec). She had no abnormalities in her medical history, and no adverse events were reported during the study.

For set A the number of patients with QTc increases of 30-60 msec from baseline in the 5 mg and 10 mg solifenacin groups (11.8% and 14%, respectively) was higher than the placebo (6.4%) or tolterodine 2 mg bid group (7.2%). A similar result was found with set B.

The changes from baseline in QTc interval were categorized as follows:

- <30 msec; within normal limits
- Between 30 and 60 msec: borderline

- >60 msec: clinical concern

There were no relevant differences between treatment groups with regard to prolonged or borderline prolonged QTc interval. The number of patients with QTc increases of 30-60 msec from baseline was comparable for all treatment groups in both set A and set B.

The number of patients with QTc increases >60 msec from baseline was 2 in the placebo group for set A and 1 for set B, compared with 1 in the 5 mg (both sets) and 3 in the 10 mg (both sets) solifenacin group.

Table D36 Patients with Δ QTc > 60 msec from baseline (SAF, N=907)

Patient #	Sex	Ventricular rate		QT (msec)		QTc (msec)		Δ QTc (msec)	Remarks / cardiac adverse events
		Screen	End	Screen	End	Screen	End		
Placebo									
#20347	F	63	81	332	354	339	411	72	
#21108 ⁴	F	72	80	364	400	397	462	63	Measurement on 2 complexes only
Solifenacin 5 mg									
#20345	M	80	132	350	323	405	480	75	Screening: inferior ischemia
Solifenacin 10 mg									
#20598	F	65	97	344	330	358	420	62	
#20107	F	76	81	333	377	376	439	63	
#21640	F	45	64	445	437	383	453	68	

⁴ excluded from set B.

Reviewer's comment: Overall, there was a slight mean increase of the QTc interval with solifenacin in comparison with placebo. Four of the 6 patients with QTc increase >60 msec were taking solifenacin 5 mg (1) or 10 mg (3).

Discontinuations due to adverse events

A total of 29 patients discontinued during the course of the study because of adverse events. The proportions of patients that discontinued because of AEs were similar: 10 patients in the placebo (3.3%), 7 patients in the solifenacin 5 mg (2.3%), and 12 patients in solifenacin 10 mg (3.9%), respectively. The most frequent treatment emergent AEs (TEAEs) leading to discontinuation were gastrointestinal (GI), especially in the 10 mg solifenacin group, where 5 out of 12 patients discontinued because of dry mouth, and 1 patient due to constipation. For 6 patients the AEs leading to discontinuation were serious (#20098, #20659 and #21010 in placebo, #20010 and #20034 in the solifenacin 5 mg group, and #20638 in the 10 mg solifenacin group).

In the patients who discontinued treatment because of an adverse event, 6 of the 10 placebo patients, 4 of the 7 in the solifenacin 5 mg group, and 11 of the 12 in the solifenacin 10 mg group, had AEs which were possibly or probably related to the study drug as judged by investigator.

Table D37 Patients with AEs as primary reason for discontinuation from the study (FAS, N=907)

Relationship with the Study medication	Placebo N = 10	Solifenacin succinate	
		5 mg qd N = 7	10 mg qd N = 12
Probably related	3	1	4
Possibly related	3	3	7
Not related	4	3	1

Treatment-related laboratory abnormalities: There was no clinically relevant effect of treatment on laboratory safety parameters. Elevated liver function tests which were assessed by the investigator as treatment-related

AEs were seen in 2 (#20563, #21095) of the solifenacin 5 mg group, and 2 (#20817, #21130) of the solifenacin 10 mg group.

Table D38 Abnormal liver function tests in four patients treated with Solifenacin

Liver function	#20563		#21095		#20817		#21130	
	Screen	End	Screen	End	Screen	End	Screen	End
γ -GT	147	213	41	84	32	222	34	107

Expected AE's:

Constipation, dry mouth, and blurred vision are all expected AEs with this class of anticholinergics. Nausea was reported by <2% of all patients in each treatment group. Few patients in the active treatment groups had expected AEs of severe intensity. Mild and moderate constipation and dry mouth, and mild blurred vision, occurred more frequently in the 10 mg solifenacin group than in the other 2 groups. Dry mouth was statistically significantly more often reported at the 10 mg solifenacin dose than with 5 mg dose ($p < 0.001$). A similar effect was also seen for constipation ($p = 0.010$), but not for blurred vision.

Table D39 Number (%) of patients with expected adverse events by severity (FAS, N=907)

	Placebo N =301 n (%)	Solifenacin succinate	
		5 mg qd (N = 299) n (%)	10 mg qd (N = 307) n (%)
Dry mouth	7 (2.3)	23 (7.7)	71 (23.1)
Mild	5 (1.7)	18 (6.0)	55 (17.9)
Moderate	1 (0.3)	5 (1.7)	16 (5.2)
Severe	1 (0.3)	0 (0.0)	0 (0.0)
Constipation	6 (2.0)	11 (3.7)	28 (9.1)
Mild	5 (1.7)	9 (3.0)	16 (5.2)
Moderate	1 (0.3)	2 (0.7)	10 (3.3)
Severe	0 (0)	0 (0.0)	2 (0.7)
Vision blurred	7 (2.3)	12 (4.0)	18 (5.9)
Mild	6 (2.0)	7 (2.3)	14 (4.6)
Moderate	1 (0.3)	4 (1.3)	4 (1.3)
Severe	0 (0)	1 (0.3)	0 (0.0)

Dry mouth tended to be more often reported at the higher plasma levels of solifenacin, by 9 out of 26 patients (34.6%) with plasma levels ≥ 60 ng/mL.

Eye disorders other than blurred vision reported more often (>1 patient) by patients treated with 5 mg and 10 mg solifenacin than the placebo included dry eye NOS (2 patients on 5 mg solifenacin) and reduced vision acuity (2 patients on 10 mg solifenacin).

Safety conclusions

- Treatment with 5 mg and 10 mg solifenacin qd was tolerated
- The most common AE's with solifenacin were consistent with the pharmacologic effects of the drug, including dry mouth, constipation, and blurred vision. The incidence of these AEs was lower in the 5 mg solifenacin treatment group than in the 10 mg solifenacin treatment group
- The discontinuation rate because of AEs was low and comparable between treatment groups
- Solifenacin did not have clinically relevant influence on clinical laboratory parameters or vital signs
- In comparison with placebo, a small increase in QTc was detected for 5 mg and 10 mg solifenacin with the mean prolongation of 1.4 msec for 5 mg and 3.9 msec for 10 mg solifenacin, relative to placebo, respectively. The number of patients with a QTc increase of 30-60 msec or >60 msec was comparable among the treatment groups.

D.6 Reviewer's assessment of safety and efficacy in Clinical Trial CL-905-014**Reviewer's assessment:**

The reviewer believes that solifenacin 5 mg and 10 mg daily does reduce the number of micturitions per 24 hrs (-2.45 ± 2.86 , -2.88 ± 3.08 , respectively) in the majority of patients with OAB when compared with placebo (-1.66 ± 3.21). In terms of secondary endpoints, the reviewer agrees that the reduction of incontinence episodes (50.3% and 49.7% of patients in solifenacin 5 mg and 10 mg, respectively, became continent vs. 39.2% in placebo group), and the increase of volume voided per micturition ($+31.76$ mL and $+36.55$ mL, respectively, for solifenacin 5 mg and 10 mg, vs. $+11.32$ mL for placebo) appear to support the efficacy of solifenacin.

The reviewer agrees that the important benefit of solifenacin for patients is that the effect was observed at the first assessment at 4 weeks and was maintained throughout the remainder of the treatment period. The reviewer further agrees that the strength of the study results is confirmed by the fact that the efficacy was consistent in various primary and secondary analyses, regardless of the choice of model, method or population (FAS or PPS). The reviewer believes that the positive effects of solifenacin on various symptoms of OAB, along with the improvement in incontinence, and volume voided, are evidence that treatment with solifenacin 5 mg and 10 mg provides a clinically meaningful benefit to patients with OAB.

In terms of safety, the reviewer believes that, overall, solifenacin at daily doses of 5 mg and 10 mg, were safe and tolerated. The most common adverse events in active drug group were anticholinergic events, including dry mouth, constipation, and blurred vision. The reviewer agrees that these AE's are expected with mild to moderate severity in the majority of patients. The reviewer agrees that solifenacin had no influence on clinical laboratory parameters.

The increase in QTc interval is discussed in the review of trial CL-022 and in the Executive Summary and Clinical Review portions of this memorandum.

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/s/

Guodong Fang
10/17/03 04:05:37 PM
MEDICAL OFFICER

George Benson
10/17/03 04:23:04 PM
MEDICAL OFFICER



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-518 (solifenacin)

Sponsor: Yamanouchi Pharma America

Submission: Original NDA submission dated 19 December 2002, seeking approval for treatment of overactive bladder.

Review date: 21 February 2003

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Concurrence: Doug Throckmorton, M.D., Division Director, HFD-110

The Division of Cardio-Renal Drug Products is asked to comment on the results of a 'definitive' QT study, submitted as part of the NDA. Cardio-Renal performed two consultative reviews of the protocol for this study, under IND 58,135; these reviews were performed 6 August 2001 and (revised protocol) 20 November 2001.

Study 905-CL-022 is entitled "Clinical pharmacology study to evaluate the effect on QTc of escalating multiple doses of YM905 administered orally qd in male, premenopausal female, and postmenopausal female healthy volunteers". The description of the study and its results are based on the sponsor's final study report dated 19 November 2002, and all analyses are derived from this report unless otherwise specified.

This was a single-center, open-label study conducted by Dr. Ken Lasseter, Miami, FL. ECG data were interpreted and analyzed by a central lab, blinded to treatment. QT measurement methodology was carefully specified.

Subjects were healthy volunteers, men between the age of 18 and 75 (n=20), premenopausal women between 18 and 49 (n=20), and postmenopausal women age 50 to 75 (n=20).

Subjects received placebo on days 1-2, and then, as tolerated, solifenacin 10 mg for 14 days, 20 mg for 14 days, 30 mg for 14 days, 40 mg for 14 days, and 50 mg for 14 days. Subjects remained in the clinic for the duration of the study. Twelve-lead ECGs were obtained at 0, 1, 2, 4, 6, 8, 12, 16, and 24 hours after dosing on the last day at each dose level. PK samples for parent and metabolites were collected at times of ECGs.

Because of protocol changes and tolerance problems, not all subjects received all doses of study drug. Actual disposition is shown in Table 1.

Table 1. Disposition of subjects

	Placebo N=60	Solifenacin				
		10 mg N=60	20 mg N=60	30 mg N=58	40 mg N=42	50 mg N=16
Completed treatment	60	60	58	56	42	0
Withdrew—total	0	0	2	2	0	16
For adverse event			1	1		2
For withdrawn consent			0	1		0
For other reasons			1	0		14

Subjects in the prespecified subgroups remained evenly distributed at all exposure levels. The ethnic mix was somewhat unusual—Caucasian 23%, Black 13%, Hispanic 60%, and Asian 3%.

The distribution in time of the maximum QTc is different in placebo and active treatment periods, as shown in Figure 1, giving some indication that there is an effect of treatment. However, since this analysis is based on Bazett's correction, the effect shown in Figure 1 may be an effect on heart rate rather than repolarization.

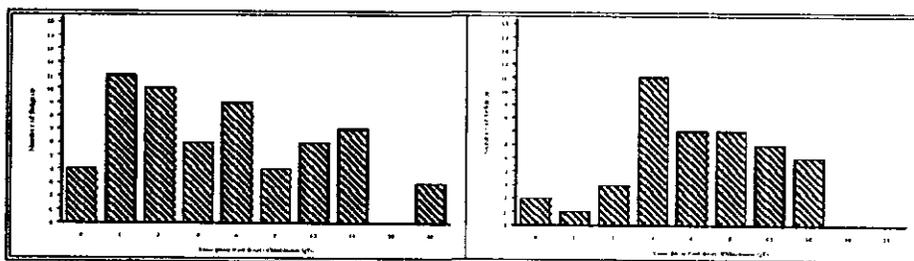


Figure 1. Distribution of time of maximum QTc

From sponsor's Figure 8.1.13. This is a histogram of the number of subjects having the maximum QTc reported by time after dosing for placebo (LEFT) and 40 mg (RIGHT). All 5 active treatment periods look much like the right panel.

Heart rate does appear to be affected by solifenacin, as shown in Figure 2.

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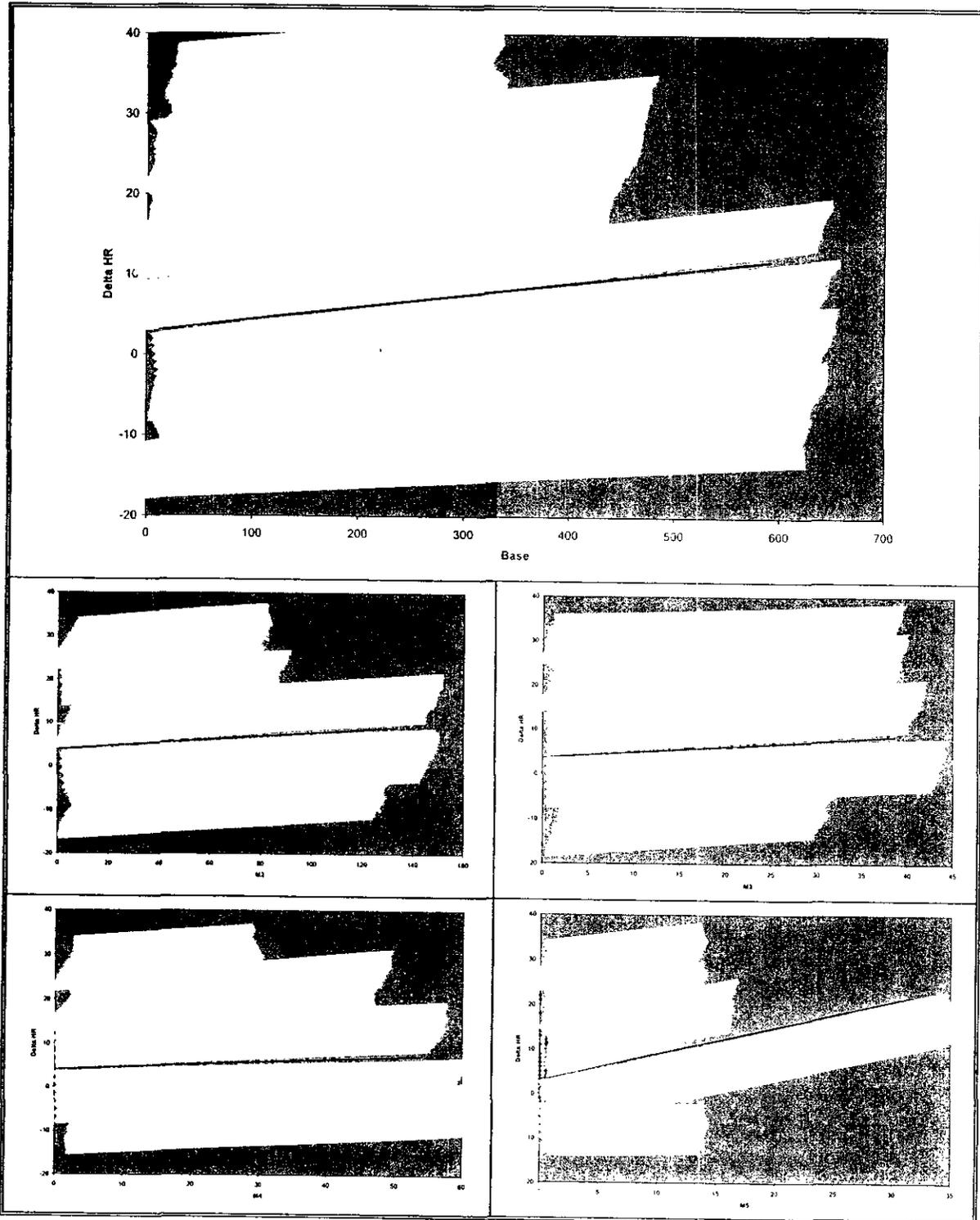


Figure 2. Change in heart rate vs. plasma levels

Reviewer's analyses of change in heart rate from dataset ECG and plasma levels of solifenacin (top) and metabolites M2-M5 from dataset META. Linear trend lines are shown.

The strongest relationship to change in heart rate is with plasma levels of solifenacin and the M5 metabolite.

Figure 3 shows the timing for the maximum effects on heart rate and QTcF on day 2 (placebo) and 58 (after 2 weeks on 40 mg).

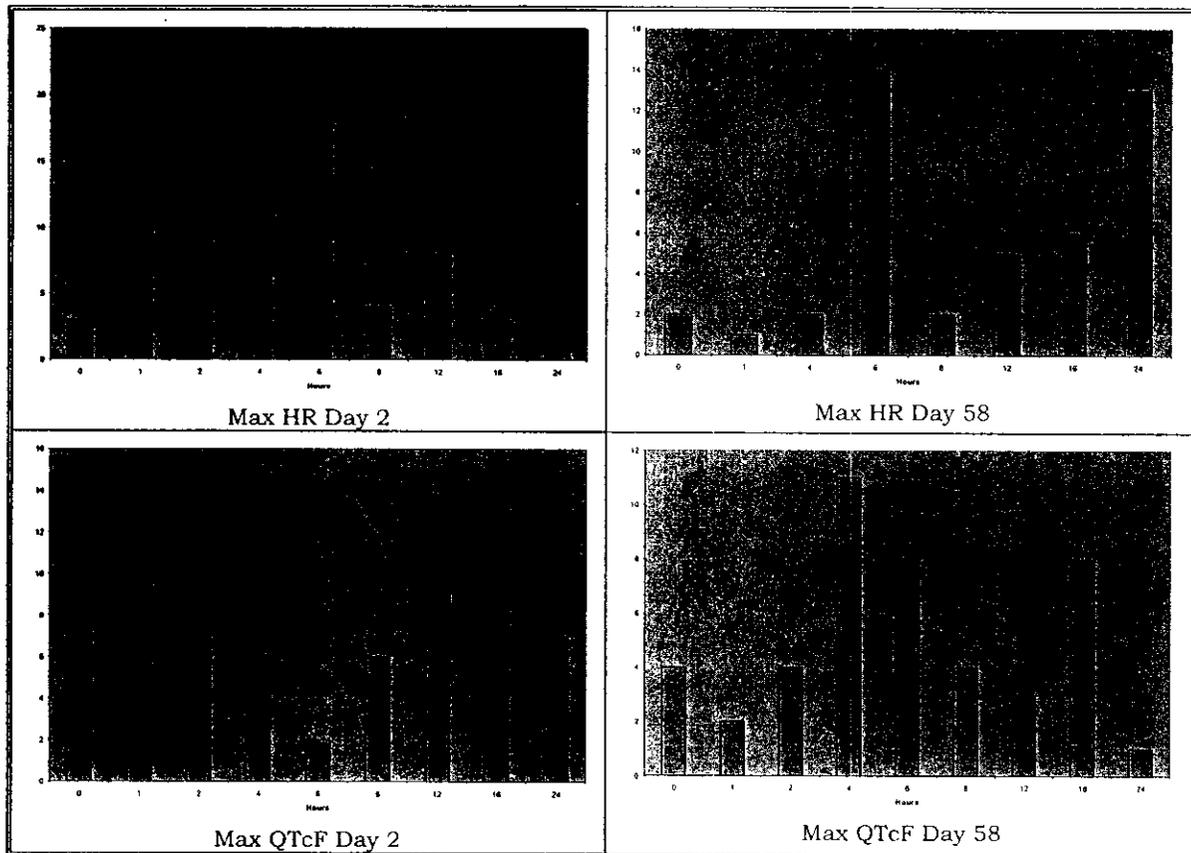


Figure 3. Timing of peak effects on heart rate and QTcF

Reviewer's analysis of dataset ECG for day 2 (placebo) and day 58 (after 2 weeks on 40 mg).

These data do not show a clearly defined time course for effects on heart rate or QTcF.

The sponsor's mixed-effects modeling looked at QTc (Bazett corrected) effects by dose, time, and gender. It is not clear why they did not model QT and include heart rate as a factor. Figure 4 was done as part of this review to look for relationships between QTcF and plasma levels of the parent drug and available metabolites.

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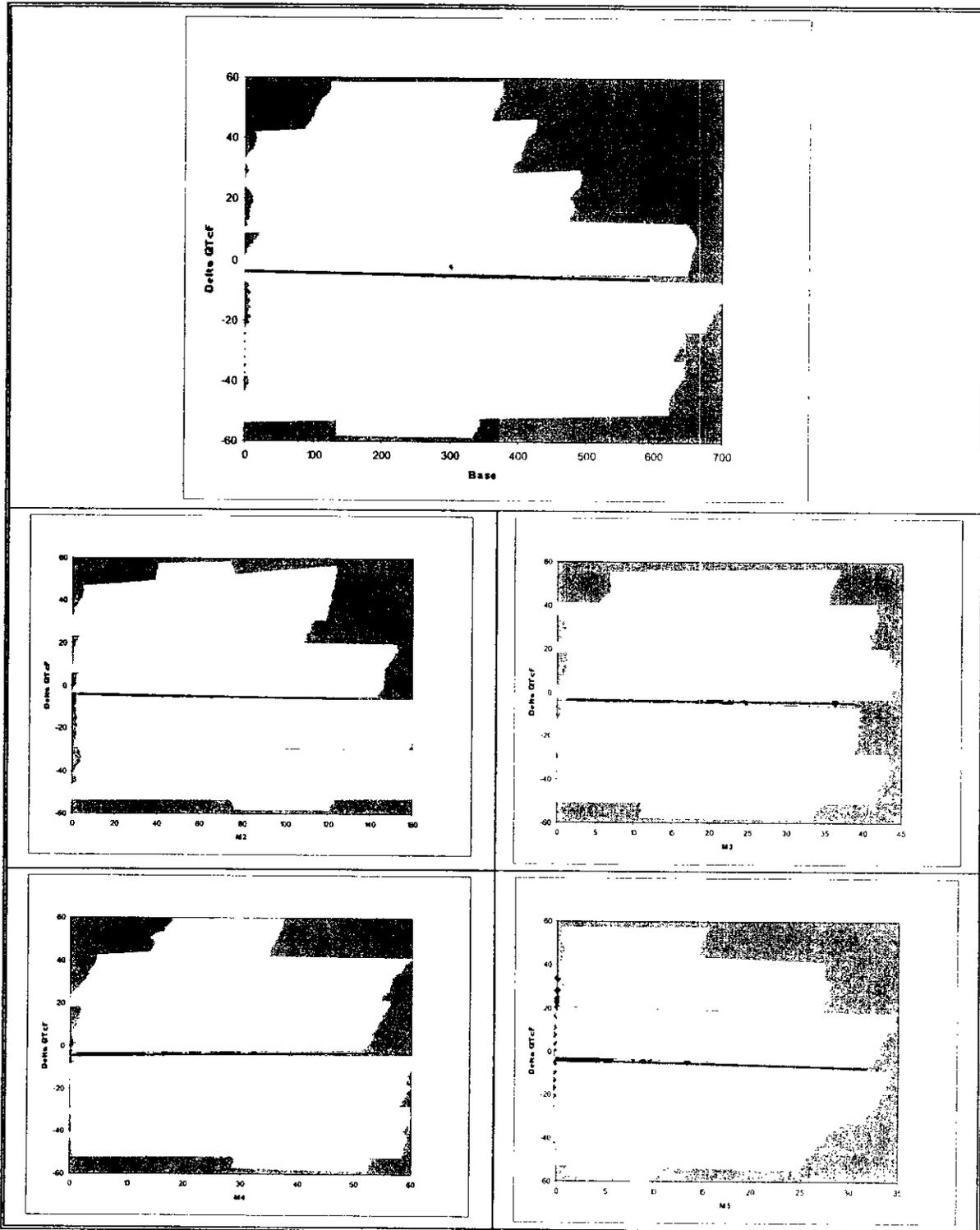


Figure 4. Change in QTcF vs. plasma levels of solifenacin and metabolites.

Reviewer analysis, based on QTcF computed from data in ECG dataset and plasma levels of base (top) and metabolites M2-M5 from META dataset. Baseline data were from Day 2, 0 Hour.

For base solifenacin and metabolites M2-M5, there does not appear to be any relationship to QTcF.

To explore further possible temporal effects, as part of this review, changes in QTcF were analyzed as a function of time, as shown in Figure 5.

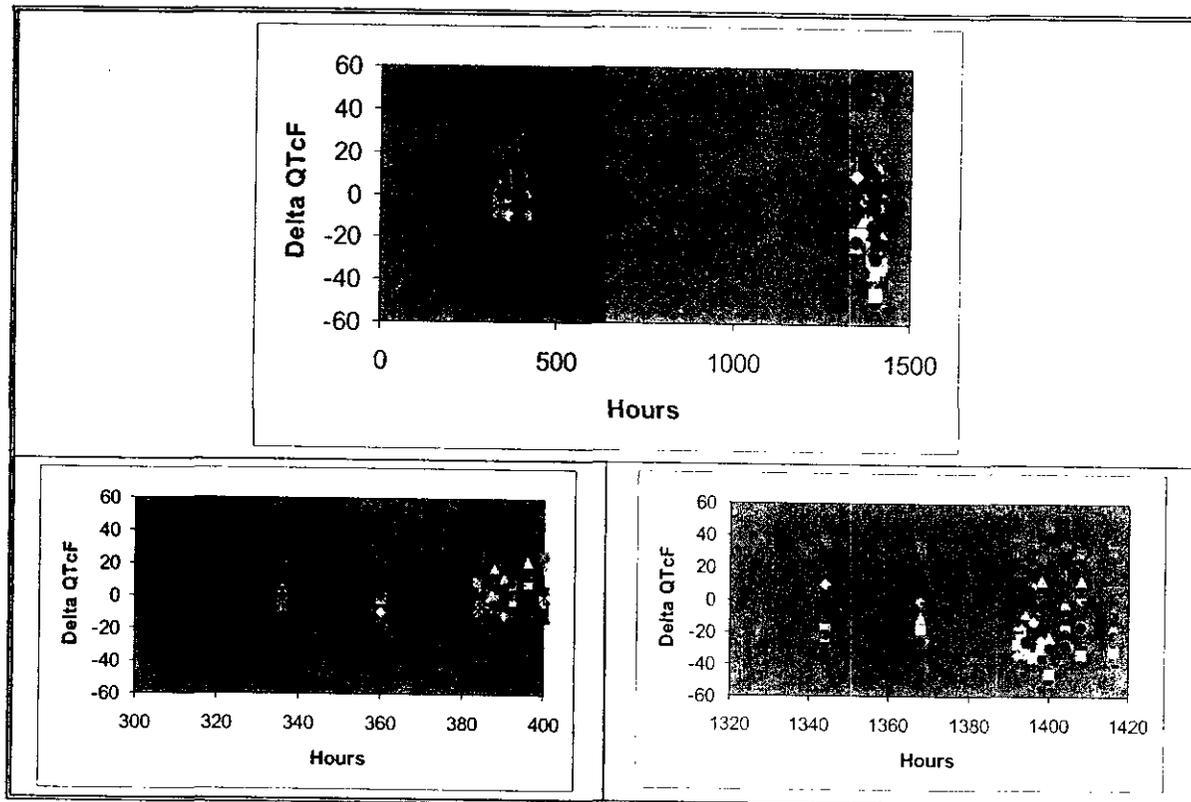


Figure 5. Change in QTcF as a function of time.

Reviewer's analysis. Upper panel shows change from baseline (Day 2, hour 0) in QTcF from ECG dataset. Lower panels show expanded time scale views of the same data. Individual subjects are represented by different symbols. Every third subject's data (out of 60) are plotted. Lower left pane shows the end of treatment period for 10 mg and the lower right pane shows the end of treatment for 40 mg.

These data do not appear to show an effect of time.

There were no deaths and one serious urologic adverse event. None of the more than 500 reported adverse events appear to be cardiac.

Comments. There are important limitations to these data.

Although the Division's consultative review of November 2001 recommended an assay-validating positive control, there is none in this study. The small diurnal variation in QTc, an effect that appears to be a few milliseconds difference between awake and asleep, might be exploited to show the study had the ability to resolve a small QT effect, but all of the data in this study are presumably from awake subjects, so this effect cannot be used to show assay sensitivity either. Consequently, one cannot be certain that a small QT effect would have been detected by this study.

Suboptimal correction of QT for heart rate can mask or mislead one with respect to effects on repolarization.

A Malik-style individualized QT correction is probably not feasible with these data, because there are not enough measurements off treatment.

The sponsor performed mixed effects modeling on Bazett-corrected QT. It would have been more interesting had they included heart rate in the modeling of uncorrected QT data, as a way of doing individualized QT correction. This might still be feasible.

Acknowledging these limitations, the available data do not indicate an obvious problem.

The safety database has no events likely to represent arrhythmias.

This review examines some effects of time and pharmacokinetic data on Fridericia-corrected QT, and the trend, if there is one, is that QTcF is smaller at higher plasma levels of parent and 4 metabolites. These analyses find no hint of an effect of time.

The distribution in changes in QTcF appears to be fairly symmetric with respect to outliers high and low.

This study provided limited data beyond 40 mg, but this dose is a factor of four over the proposed maximum dose, providing some reassurance. This dose appears to be close to the maximum tolerated, which probably means that higher doses or the plasma levels associated with higher doses, will not pose much risk, even if repolarization were affected. Solifenacin is 90% bioavailable, so one source of idiosyncratic increases in plasma levels is not a problem. Solifenacin is predominantly metabolized by CYP 3A4, but ketoconazole only produced a 40% increase in plasma levels, so metabolic inhibition is not as large a factor as it might be.

Thus, for the most part, the setting—dose multiple, tolerance-limiting, pharmacokinetic insensitivity, lack of likely arrhythmia events—and the ECG data—lack of upward trend or high-end outliers—are reassuring. However, given the uncertainties in the discriminatory power, is that reassurance enough? The answer has to depend somewhat on the nature of the benefit achieved with treatment. For a small and unimportant symptomatic benefit, the degree of comfort is probably less than one might expect. Treatments for erectile dysfunction, for example, are being held to a higher standard; one could justify asking for a positive-controlled study of QT effects of solifenacin, too.

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/s/

Norman Stockbridge
2/21/03 07:53:25 AM
MEDICAL OFFICER

Doug Throckmorton
2/21/03 12:03:01 PM
MEDICAL OFFICER

I concur with Dr. Stockbridge's review, and reinforce his
comments on the limited adequacy of this trial
to exclude an effect on QT interval without
the use of an active control or other
means of assessing assay sensitivity.

Medical Officer's NDA Filing Review
Prepared for 45-day Filing Meeting on February 3, 2003

NDA 21,518
Generic Name: Solifenacin Succinate
Proposed Trade Name: Vesicare®
Internal development name: YM905
Chemical name: (+)-(1*S*,3'*R*)-quinuclidin-3-yl 1-phenyl-1,2,3,4-Tetrahydro-isoquinoline-2-carboxylate monosuccinate
Empirical formula: C₂₃H₂₆N₂O₂·C₄H₆O₄
Sponsor: Yamanouchi Pharma America, Inc., Paratus, NJ
[Mr. Rudolph W. Lucek at (201) 909-3041]
Primary Goal Date: October 19, 2003

I. SUMMARY

Purpose:

This review is conducted to fulfill a regulatory requirement of reviewing a NDA to determine its eligibility for filing under 21 CFR 314.101. This document will also serve as the basis for communicating to the sponsor the potential review issues identified during the initial filing review period as required by CDER manual of policies and procedure (MaPP 6010).

Conclusion:

After preliminary review of the clinical section of NDA 21,518 submission, this reviewer has not identified any major deficiencies that would constitute the basis for a Refusal-to-file (RTF) action as described in the FDA guidance consistent with 21 CFR 314.101(d)(3). **This reviewer concludes that the NDA 21,518 application submitted is sufficiently complete to permit a substantive clinical review, and that it is fileable.**

II. NDA FILING REVIEW

Drug Product:

Solifenacin succinate, with a proposed trade name of VESICARE®, is a M₃ muscarinic receptor antagonist, which is proposed for

Maximum and steady-state plasma levels are reached approximately 5 hours after dosing (with a range of 3-8 h) and by 10-12th day of dosing respectively. Due to its large volume of distribution and low clearance, solifenacin has a long terminal plasma elimination half-life, average ~ 50 h in young and up to 75 h in elderly. Metabolism is mediated primarily by CYP3A4. Solifenacin and its metabolites are excreted in urine and feces, which account for approximately 70% and 23% of dose-related material respectively.

After a pre-IND meeting in December 1998, the IND 58,135 for this indication was initially filed in April, 1999, and the EOPII and pre-NDA meetings were held in September, 2000, and July, 2002, respectively. The proposed doses for the marketing registration are 5 mg and 10 mg once daily with a recommended starting dose of 5 mg daily. This NDA contains a total of 3,583 patients from two Phase 2 and four pivotal Phase 3 clinical studies in the US and Europe, of whom 2,069 received solifenacin, 287 received comparative agent (Tolterodine), and 1,227

received placebo. Of those who received solifenacin, 359 patients were dosed for 4 weeks with doses up to 20 mg and 1710 patients for 12 weeks with a dose of 5 or 10 mg. The safety database contains 2,621 patients with OAB exposed to solifenacin succinate once daily in pivotal Phase 3 as well as Phase 2 studies, including 667 patients who were exposed to 5 mg, 1,768 patients to 10 mg, and the remainder were exposed to either 2.5 mg or 20 mg. Among them, 718 patients were exposed to solifenacin succinate 10 mg once daily for at least 6 months with 308 of this 718 had completed at least 1 year of treatment.

Other drugs that have been approved for this indication are oxybutynin (Ditropan), tolterodine (Detrol) and Trospium (being marketed in Europe).

Methods of RTF Review:

The review is based on three crucial criteria proposed in FDA guidance for the filing review that represents FDA's interpretation of 21 CFR314.101 (d)(3):

- Omission of a section of the NDA required under 21 CFR 314.50, or presentation of a section in so haphazard a manner as to render it incomplete on its face
- Clear failure to include evidence of effectiveness compatible with the statute and regulations
- Omission of critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use

Results of Filing Review:

1. Does the NDA 21,518 omit a section required under 21 CFR 314.50, or was any of the sections of the NDA presented in so haphazard a manner as to render it incomplete on its face for a sufficient clinical review?

Answer: No. The NDA contains critical sections in sufficient detail as demonstrated in Table 1. Certification (Form 3454) and an attachment of investigator list are provided for a total of 838 investigators in eight covered studies in the US and Europe. Among them, the sponsor included a detailed financial disclosure with Form 3455 from one particular investigator who had incorrectly filed a financial disclosure form and later corrected.

Table 1. Checklist for the critical sections of NDA for a sufficient clinical review

Required Sections (21 CFR 314.50)	Location
The proposed text of the labeling (c)(2)(i)	Module 1
A summary of the data (c)(2)(viii)	2.3, 2.4, 2.5 & 2.6
The technical sections and integrated summaries (d)	Module 2, 3, 4 & 5
Controlled clinical studies (d)(5)(ii)	2.7.6 and 5.3.5.1
Integrated summary of efficacy (d)(5)(v)	2.7.3
Integrated summary of safety (d)(5)(vi)	2.7.4
Integrated summary of the benefits and risks (d)(5)(viii)	2.5.6
Required case report forms and tabulations (f)	5.3.7
Financial certification or disclosure statement (k)	Module 1

2. Does the NDA clearly fail to include evidence of effectiveness compatible with the statute and regulations, for example:

- a. **lack of any adequate and well-controlled studies (21 CFR 314.126), including use of obviously inappropriate or clinically irrelevant study endpoints**
- b. **presentation of what appears to be only a single adequate and well-controlled trial without adequate explanation of why the trial should be regarded as fulfilling the legal requirement for adequate and well-controlled investigations**
- c. **use of a study design clearly inappropriate (as reflected in regulations or well-established agency interpretation) for the particular claim**

Answer: No. The sponsor provides data from 4 pivotal Phase 3 studies, which are controlled, multi-center, double blind, randomized, parallel group, placebo controlled studies. Supportive evidence of effectiveness is provided by 2 Phase 2 studies. In addition, 2 open-labeled long-term extension studies provide support to the proposed indication and dosage (both 5 mg and 10 mg). One of the Phase 3 placebo-controlled studies also included an active comparative arm (tolterodine). The data presented in this NDA were derived from a total of 2,621 OAB patients who were treated with Vesicare® for periods of one day to 52 weeks. Additionally, 423 subjects were treated with Vesicare® in the clinical pharmacology studies (Appendix A). All above studies appear to be adequate and well controlled. The primary endpoint used in the NDA is mean change from baseline to endpoint in number of micturitions / 24 h. This is consistent with the standard established during the pre-NDA meeting with the Division. Secondary efficacy endpoints used in this NDA are mean change from baseline to endpoint in number of incontinence episodes / 24 h, number of urgency episode / 24 h, mean volume voided / micturition, number of nocturia voids / 24 h, and number of nocturia episode / 24 h. All these were addressed during the pre-NDA meeting with the Division.

Comment: This reviewer believes that some review issues will be raised in further detailed review but won't constitute the basis for a RTF action. Two pivotal studies conducted in Europe were performed outside the IND. In addition, this reviewer has concerns about the fact that the patients are predominantly female in all studies and predominantly Caucasian in 2 European studies.

3. **Does the NDA omit critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use, for example:**
 - a. **total patients exposure at relevant doses that is clearly inadequate to evaluate safety**
 - b. **clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age and racial subsets:**
 - c. **absence of a comprehensive analysis of safety data**
 - d. **absence of an analysis of data supporting the proposed dose and dose interval**

Answer: No. The patients enrolled in the 4 pivotal studies exhibited frequency of micturition, urinary incontinence, and urinary urgency, which is consistent with the division's standard for the selection of the target population. The majority of study subjects are female (77-82%) with mean age of 57-59 years of age, which is consistent with the disease distribution in the general population. The potential limitation is under-representation of a non-white population, especially in studies from Europe. The limitation, in the opinion of this reviewer, could be treated as a review issue and be addressed through the labeling negotiation — if it is deemed to be necessary.

The NDA contains the analysis of data supporting proposed doses (5 mg and 10 mg). It appears that the sponsor has achieved the pre-defined level of statistical significance for the

primary endpoint in all pivotal studies (Appendix B1 and B2) and the secondary endpoints in most of pivotal studies.

Comment: This reviewer has concern over some treat-emergent adverse events (Table 2) and serious adverse events (Appendix C) identified during this filing review. A number of the SAEs were complications or exacerbations of expected antimuscarinic side effects including fecal impaction and intestinal obstruction.

Table 2. Summary (% of patients) of common treatment-emergent adverse events (frequency \geq 1.5%) in 4 Phase 3 pivotal studies

System organ class MedDRA preferred term	Treatment		
	Placebo (N=1216)	YM905 5 mg (N=578)	YM905 10 mg (N=1233)
Gastrointestinal disorders			
Dry mouth	4.2	10.9	27.6
Constipation	2.9	5.4	13.4
Nausea	2.0	1.7	3.3
Dyspepsia	1.0	1.4	3.9
Abdominal pain upper	1.0	1.9	1.2
Infections & infestations			
UTI NOS	2.8	2.8	4.8
Influenza	1.3	2.2	0.9
Eye disorders			
Vision blurred	1.8	3.8	4.8
Dry eyes NOS	0.6	0.3	1.6
General disorders			
Fatigue	1.1	1.0	2.1

NOS = not otherwise specified

Comment: This reviewer has concerns with urinary retention, which did not appear as one of the SAEs. This occurred in 1.5% patients on solifenacin succinate 10 mg vs. 0.6% of patients on placebo. In addition, in the dose-rising QTc study, at the 30 mg dose level, one patient required hospitalization and catheterization for urinary retention.

Special concern about potential effects of solifenacin succinate on myocardial repolarization as shown on ECG and QTc interval: The QTc increase of 1.2 to 1.9 msec at 5 mg solifenacin succinate and 2.8 to 4.9 msec at 10 mg were observed in 4 Phase 3 pivotal studies. The changes were statistically significant in 3 of the 4 studies. This reviewer has concerns about these results even if there were no cases of serious ventricular arrhythmias recorded. The sponsor has included the results of a dose-escalating QTc study (#905-CL-022). This protocol was reviewed by the Cardio-renal Division and will be a review issue. The results of this particular study have been sent to Cardio-renal for consultation. The relationship between dose of solifenacin succinate and change from baseline in QTc is included in this NDA submission.

III. Recommendation:

- **Participation of Office of Drug Safety (ODS):** This is a NME and ODS participation is required by MaPP 6010. ODS will be consulted with regard to the development of risk management program

- **Proposed Site for DSI Auditing:** Appendix D showed the mean and median improvement among study subjects by the study investigators. A negative sign indicates the improvement. It appears that sites of Drs. [redacted], Richard Harris [redacted] (Study 905-CL-013), and Drs. Joel Kaufman [redacted] (Study 905-CL-014) are good candidates for the DSI auditing based upon fairly large sample size of randomization and full analysis set.

Reviewer's comments: From the clinical point of view, the following comments should be communicated to the sponsor in a regulatory letter:

- Safety concerns pertaining to QTc prolongation, hepatic toxicity, and drug-drug interactions as well as adverse events are major ongoing review issues.
- It has been noted that (1) a non-white patient population is not well represented in the 2 European clinical studies that were conducted outside the IND; (2) none of the data supporting the use of 5 mg dose comes from pivotal trials in US sites. This will be a review issue.

Reviewed by:

Guodong Fang, MD
Medical Officer

George Benson, MD
Medical Team Leader

Appendix A – Summary of Pivotal and Supportive Studies

Study #	Study Design	Treatment Group	Patients Randomized	Duration of Treatment	Region
Pivotal Studies					
905-CL-013	Phase 3, randomized, DB, placebo-controlled, parallel group, fixed-dose study	YM905: 10 mg	306	12 wks	USA
		Placebo	309		
905-CL-014	Phase 3, randomized, DB, placebo-controlled, parallel group, fixed-dose study	YM905: 10 mg	298	12 wks	USA
		Placebo	295		
905-CL-015	Phase 3, randomized, DB, placebo-controlled, active-controlled, parallel group study	YM905: 5 mg	266	12 wks	Europe
		YM905: 10 mg	264		
		Tolter: 2 mg, bid	250		
		Placebo	253		
905-CL-018	Phase 3, randomized, DB, placebo-controlled, parallel group study	YM905: 5 mg	286	12 wks	Europe
		YM905: 10 mg	290		
		Placebo	281		
Supportive Studies					
905-CL-005	Phase 2, randomized, DB, placebo-controlled, active-controlled, parallel group, dose-response study	YM905: 2.5 mg	40	4 wks	Europe
		YM905: 5 mg	37		
		YM905: 10 mg	33		
		YM905: 20 mg	34		
		Placebo	36		
		Tolter: 2 mg bid	37		
905-CL-006	Phase 2, randomized, DB, placebo-controlled, parallel group, fixed-dose, dose ranging study	YM905: 2.5 mg	54	4 wks	USA
		YM905: 5 mg	52		
		YM905: 10 mg	51		
		YM905: 20 mg	54		
		Placebo	53		

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Appendix B1 – Summary of P values: Comparison with placebo in mean change from baseline to endpoint for primary and secondary efficacy parameters in European and US Phase 3 pivotal studies

Efficacy Parameter	Study 015 ^a			Study 018 ^a		Study 013 ^a	Study 014 ^a	Studies 015, 018, 013, 014 ^b	
	YM905		Tolter [*]	YM905		YM905	YM905	YM905	
	5 mg	10 mg	4 mg	5 mg	10 mg	10 mg	10 mg	5 mg	10 mg
Primary efficacy endpoint									
Micturition/24 h	0.0003	0.0001	0.0145	0.0018	0.0001	<0.001	<0.001	<0.001	<0.001
Secondary efficacy endpoints									
Incontinence/24 h	0.0080	0.0038	NS	NS	NS	<0.001	<0.001	<0.001	<0.001
Urgency/24 h	0.0001	0.0001	NS	0.003	0.002	<0.001	<0.001	<0.001	<0.001
Volume voided per micturition	0.0001	0.0001	0.0001	0.0001	0.0001	<0.001	<0.001	<0.001	<0.001
Nocturia/24 h	NS	NS	NS	NS	0.036	NS	NS	0.025	<0.001

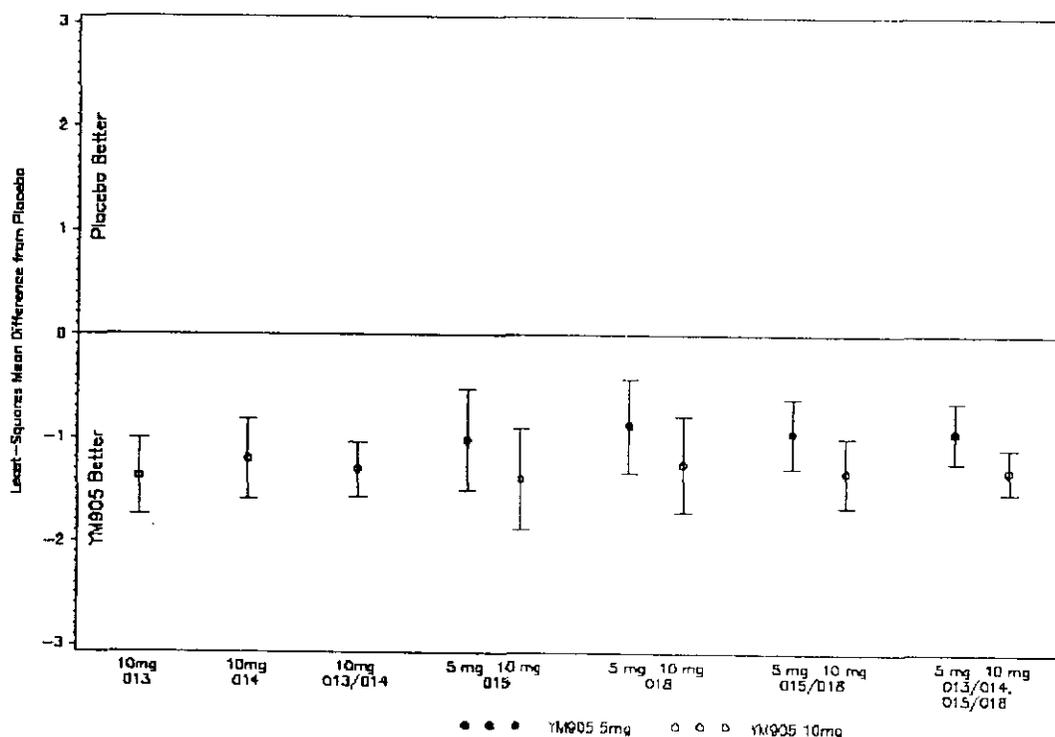
NS – Not statistically significant (p>0.05)

* Tolterodine 2 mg BID

^a P values from analysis in individual clinical study report

^b P values from analysis in integrated Analysis of Efficacy

Appendix B2 – 95% Confidence intervals for micturition / 24 h change from baseline means for individual studies, combined US, combined EU and combined US/EU studies



Appendix C – Selected serious adverse events (SAE) reported in pivotal Phase 3 studies

System organ class MedDRA preferred term	Combined studies (013/014, 015/018)			
	Placebo N (%)	YM905 5 mg N (%)	YM905 10 mg N (%)	Tolter 4 mg N (%)
No. of patients	1216	578	1233	263
No of pts with any SAE	27 (2.2)	13 (2.2)	30 (2.4)	3 (1.1)
Cardiac disorders	8 (0.70)	3 (0.5)	3 (0.2)	0
Nervous system disorders	4 (0.3)	1 (0.20)	4 (0.3)	1 (0.4)
GI disorders	3 (0.2)	0	6 (0.5)	0
Abdominal pain upper	0	0	2 (0.2)	0
Colonic obstruction	0	0	1 (0.1)	0
Fecal impaction	0	0	1 (0.1)	0
GI hemorrhage NOS	0	0	1 (0.1)	0
Intestinal obstruction	0	0	1 (0.1)	0
Nausea	0	0	1 (0.1)	0
Vomiting NOS	0	0	1 (0.1)	0
General disorders	2 (0.2)	0	5 (0.4)	1 (0.4)
Chest pain	2 (0.2)	0	3 (0.2)	0
Death NOS	0	0	1 (0.1)	0
Pain NOS	0	0	1 (0.1)	0
Sudden death unexplained	0	0	0	1 (0.4)
Infections & infestations	3 (0.2)	2 (0.3)	2 (0.2)	0
Vascular disorders	2 (0.2)	2 (0.3)	3 (0.2)	0
Cerebrovascular accident	1 (0.1)	0	1 (0.1)	0
Pulmonary embolism	1 (0.1)	0	1 (0.1)	0
DVT NOS	0	1 (0.2)	0	0
Hypotension NOS	0	0	1 (0.1)	0
Peripheral vas. dis. NOS	0	1 (0.2)	1	0
Metabolism & nutrition dis.	0	0	2 (0.2)	0
Dehydration	0	0	1 (0.1)	0
Hyponatraemia	0	0	1 (0.1)	0
Reproductive syst. & breast	0	1 (0.2)	1 (0.1)	0
Menometrorrhagia	0	1 (0.2)	0	0
Ovarian cyst	0	0	1 (0.1)	0
Eye disorders	1 (0.1)	0	0	0
Vision blurred	1 (0.1)	0	0	0
Respiratory disorders	0	0	1 (0.1)	0
Atelectasis	0	0	1 (0.1)	0

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/s/

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George Benson
2/4/03 07:57:19 AM
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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

IND: 58,135 (YM 905)
Sponsor: Yamanouchi/Covance
Submission: Proposed study of QTc.

Review date: August 6, 2001

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110 _____

Concur: R. Lipicky, M.D., Division Director, HFD-110 _____

Distribution: IND 58,135

HFD-580/Division Director

HFD-580/Farinas

HFD-110/Stockbridge

Background

The Division of Cardio-Renal Drug Products is asked to comment upon the adequacy of draft protocol 905-CL-022 to address concerns about QT prolongation with YM905, a muscarinic receptor antagonist being developed to treat overactive bladder.

Response

One subject in a food-effect study was previously thought to have exhibited an increased QT (on some unspecified dose), but expert re-evaluation of study indicated that (a) this subject's QT measurement was affected by inclusion of the U-wave, and (b) the entire study was uninterpretable because it failed to obtain ECGs with a reasonable number of beats. There are no other data suggesting a QT-prolonging effect.

Although the data are not provided, the descriptions indicate that concentrations of YM905 well above what is likely to be encountered clinically produced no measurable effects on dog cardiac Purkinje fibers (not an optimal choice) or in HERG potassium channels.

The useful dose range is expected to be 5 to 20 mg/day. Doses above 20 mg per day are not well tolerated, apparently because of anti-muscarinic effects (dry mouth, blurred vision, and constipation).

Plasma levels are linearly related to dose up to 20 mg/day. Steady-state is reached after about 10 days. The CYP3A4 inhibitor ketoconazole roughly doubled plasma levels of YM905. Little YM905 is excreted unchanged, but little is said about the activity of the metabolites.

It is not clear what is the range of doses the sponsor expects to get approved, nor if the dose needs to be adjusted based on body size, hepatic impairment, renal impairment, or for other factors.

The proposed study is an open-label, forced-titration study (improperly characterized as a cross-over study), in which 40 normal male and female subjects will have 12-lead ECGs at baseline, on placebo (2 days), and on YM905 10, 20, and 30 mg (14 days each). ECGs are to be obtained several times before the first dose of active drug, then 8 times in the first 24 hours after each dose transition. The methodologies for measuring QT and for applying Bazett's correction are carefully specified.

The data provided suggest that the risk of QT-related arrhythmias is small with this compound. The animal and in vitro data are said to be clean. Presumably there are no concerns from the exposure in man (sudden death or syncope). Given the setting, the proposed study seems entirely adequate, except perhaps with respect to establishing a safety margin in dose.

If the only recommended dose is 5 mg, then studying 30 mg allows some small cushion against inter-subject variability in plasma levels, but 30 mg is clearly no safety margin for, say, the 20-mg dose. Unless there are other safety or tolerance issues, higher doses should be evaluated.

The Division of Cardio-Renal Drug Products appreciates the opportunity to consult on this drug. DRUDP is welcome to contact DCRDP for further clarification or follow-up.

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Norman Stockbridge
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Raymond Lipicky
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