

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-518

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics Review

NDA	21,518
Submission Date	June 18, 2004
Brand Name	Vesicare
Generic Name	Solifenacin succinate
Reviewer	Stephan R. Ortiz, R.Ph., Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
Pharmacometric Reviewer	He Sun, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Reproductive & Urologic Drug Products
Sponsor	Yamanouchi
Dosing regimen	Once daily
Indication	Treatment of —

1	Table of Contents	1
2	Executive Summary	2
	A. Recommendations	2
	B. Phase IV Commitments (if necessary)	2
3	Question Based Review	2
	A. General Clinical Pharmacology	2
	1. Pharmacokinetics/Bioavailability	4
	2. Exposure-Response	6

An optional inter-division briefing, dated November 17, 2004 was attended by Shiew Mei Huang, Hank Malinowski, John Hunt, He Sun, Ameeta Parekh, Dhruba J. Chatterjee, Myong Jin Kim, Leslie Kenna, Sandhya Apparaju, Julie Bullock, George Benson and Guodong Fang.

2. Executive Summary

On 17 October 2003, Yamanouchi Pharma America, Inc (YPA) received an Approvable Letter for New Drug Application (NDA) 21-518 (submitted 19 December 2002). In response to the issues raised in this Approvable letter, the sponsor submitted an NDA amendment addressing these issues, and updating the safety profile of solifenacin succinate since the submission of the 4-month Safety Update.

In its Approvable Letter to YPA, the Agency made the following request regarding performing an additional QT study: *Conduct an additional QT study (095-CL-043) using both placebo and positive controls to confirm that solifenacin succinate is not associated with clinically relevant QT interval prolongation. FDA noted that the labeling for solifenacin succinate would remain unresolved until data from a positive-controlled QT study were provided.*

Due to the relatively long half life and dose limiting side effect profile of this compound, the submitted study design was more complex than most QT study designs. While reviewing this submission, a significant period effect was detected which precluded the per protocol analysis. This led to alternate analyses, as laid out in the review, which attempted to determine the true QT prolongation of the drug by accurately correcting for the observed period effect. Ultimately, the mean baseline- and placebo-corrected (treatment arm B) QTcF at T_{max} is reported in the label.

A. Recommendations

While the study design makes it difficult to precisely determine the needed QT prolongation values, it is felt that an adequate determination can be derived. The QT response to the therapeutic dose of solifenacin (10mg) appears to be small (approximately 2 msec) while the response to solifenacin 30mg appears similar to, though less than, that seen with moxifloxacin (approximately 8 msec). The QT response to several moxifloxacin 400mg doses was between 10-15 msec. These responses are the mean baseline-corrected QTcF at PK T_{max} corrected for the parallel groups time-matched baseline-corrected placebo QTcF.

It should be noted that there is no 30 mg dose of solifenacin. This dose was studied as the exposure resulting from 30 mg exceeds the "worst case" exposure, when 10 mg solifenacin is administered concomitantly with a potent CYP 3A4 inhibitor or in those patients with hepatic or renal impairment. In those cases where a patient is concomitantly administered a potent CYP 3A4 inhibitor or has renal or hepatic impairment, prescribers are recommended (see DOSING in label) to administer 5mg of solifenacin to account for the increased exposure.

This submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. The labeling comments have been finalized.

B. Phase IV Commitments (if necessary)

None.

3. Question Based Review

C. General Clinical Pharmacology

The sponsor has submitted a study whose primary objective is to estimate the effect of steady state oral dosing of solifenacin (10 mg qd and 30 mg qd) and single dose moxifloxacin (400 mg) on QTc interval as measured by the time-matched QTc effect at the time of maximum concentration (Tmax) on each active regimen relative to placebo with adjustment for baseline. Additionally, secondary objectives, as listed by the sponsor are:

1. To estimate the effect of steady state solifenacin (10 mg qd and 30 mg qd) and single dose moxifloxacin (400 mg) on other summary measures of the QTc interval on each active regimen relative to placebo.
2. To estimate the effect of steady state solifenacin (10 mg qd and 30 mg qd) and single dose moxifloxacin (400 mg) on QT interval and HR relative to placebo.
3. To characterize the pharmacokinetics of solifenacin and moxifloxacin.

Briefly, this study was a five-session, sequential, crossover study. Subjects were randomized to one of two treatment groups (Treatment Group A or Treatment Group B) according to a randomization schedule prepared prior to the start of the study. 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 three day washout between sessions 1 and 2. There was no washout between Session 2 and the start of dosing in Session 3. Subjects were blindfolded during the administration of study medication in both sessions in order to maintain the blind.

Dosing was **double-blind** in Sessions 3 to 5. Subjects randomized to Treatment Group A received increasing doses of oral solifenacin. Subjects randomized to Treatment Group B received matching placebo on each corresponding study day, except for Session 3, Day 14 and Session 5 Day 14 when they received a 400 mg dose of moxifloxacin. There was no washout between any of the treatment sessions. Study medication was provided in blinded subject kits containing the same number of tablets in all kits for a given dosing day (moxifloxacin was added to kits for treatment group B by an unblinded pharmacist), and subjects were blindfolded during the administration of study medication on Session 3, Day 14 and Session 5, Day 14 in order to maintain the study blind. In Sessions 1, 2 and 3, there was a one day baseline (no drug) prior to the start of dosing. Treatment descriptions are summarized in the following table.

Table 1. Treatment Description

	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 UID x 14 days	1-day baseline (no drug) placebo UID x 13 days; moxifloxacin (400 mg) on Day 14
Session 4	solifenacin 20 mg UID x 5 days	placebo UID x 5 days
Session 5	solifenacin 30 mg UID x 14 days	placebo UID x 13 days; moxifloxacin (400 mg) on Day 14

Demographics

Subjects in this study were adult women with a mean age of 51 years (Table 2). 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 2. Demographic Characteristics of Study Population

Group	Parameter	Age (years)	Height (m)	Weight (kg)
All Subjects n = 86	Mean	51	1.60	67.0
	SD	13.3	0.07	9.9
	Range	19 - 79	1.47 - 1.77	40.4 - 97.7

Source Data: Section 12. Table 12.2

100% Female; 48% White, 34% American Hispanic, 6% Black, 6% Oriental, 7% Other

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.

Table 3. Study Population

Disposition	Number of subjects
Total screened	129
Total screened but not used	38
-Alternate not needed	11
-Abnormal labs	10
-did not meet criteria	4
-Abnormal ECG	3
-Decided not to participate	2
-Schedule conflict	2
-Unable to obtain IV access	2
-Positive urine drug screen	1
-Other	3
Total randomized to treatment	91

-withdrawn prior to dosing	5		
	Group A: Solifenacin	Group B: Placebo/Moxi	Total
Total Dosed	58	28	86
Total withdrawn after dosing	7	3	10
-Adverse event	4	3	7
-Schedule conflict	2	0	2
-Withdrew consent	1	0	1
Total Completed	51	25	76

1. Pharmacokinetics/Bioavailability

Blood samples for pharmacokinetic analysis of moxifloxacin were obtained at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours postdose on Session 1, Day 1. To maintain the single-blind across sessions 1 and 2, blood samples were also obtained at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours postdose on Session 2, Day 1. These samples were collected in the same manner as the samples collected for moxifloxacin analysis on Session 1, Day 1.

Blood samples for pharmacokinetic analysis of both moxifloxacin and solifenacin were obtained at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours post-dose on Session 3, Day 14 and Session 5, Day 14. Since Sessions 3 and 5 of this study were double blind, blood samples for pharmacokinetic analysis of both moxifloxacin and solifenacin were obtained *for all subjects* (Treatment Group A and Treatment Group B) at these time points.

For Session 5, Day 14, additional samples were collected at 36, 48, 72, and 96 hours post-dose in order to characterize the terminal phase of solifenacin. Blood samples for trough solifenacin PK levels were also collected on Session 3, Days 5, 10 and 12 and on Session 5, Days 2, 9 and 13. Since Sessions 3 and 5 of this study were double blind, blood samples for pharmacokinetic analysis of solifenacin were obtained *for all subjects* (Treatment Group A and Treatment Group B) at these time points. The maximum number of samples to be collected per subject for pharmacokinetics throughout the entire study did not exceed 48 samples for moxifloxacin (including the 'dummy' samples collected in Session 2) and 34 samples for solifenacin.

Moxifloxacin PK

Overall, peak and total exposure of moxifloxacin were consistent throughout the study. The data between Groups A and B (Session 1) are very consistent, as are the data in Group B between Session 1, 3 and 5. Mean AUC and C_{max} values do not vary by more than 6% from each other in comparisons between Groups A and B in Session 1 or comparisons between Group B in Sessions 1, 3, and 5. The C_{max} and AUC reported by the sponsor are approximately 40% less than the values reported in the moxifloxacin label.

Table 4. Summary of Mean Moxifloxacin Pharmacokinetic Parameters following 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 (0.48-4.10)	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%)

Solifenacin PK

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. The sponsor only reported half-life estimates for Session 5, since this was the last dose of solifenacin given in the study.

Table 5. Summary of Mean Solifenacin Pharmacokinetics following 10 mg and 30 mg QD x 14 days in Healthy Volunteers

Parameter	Solifenacin 10 mg QD Day 14	Solifenacin 30 mg QD 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%)

Reviewer's comments:

- The steady state solifenacin C_{max} achieved in this study in session 5 (30 mg qd X 14 days) well exceeds what would be achieved if a patient took the clinical dose of solifenacin (10 mg qd) along with a potent CYP3A4 inhibitor.

2. Exposure-Response

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

S10	Solifenacin 10mg (Session 3)
S30	Solifenacin 30mg (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)

QT Correction

Population Approaches:

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

Individual Approaches:

3. Individual (linear) correction QTci
4. Individual (non-linear) correction QTciL

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

1. 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 $QT = \alpha \times RR^\beta$ were fit (the latter of which is equivalent to the linear regression model, $\ln QT = \ln \alpha + \beta \times \ln RR$), and the slopes (β) for the above linear regression models were estimated.

2. Individual QT values were corrected to obtain QTci and QTciL values as follows:

$$QTciL = QT / RR^\beta \text{ and}$$

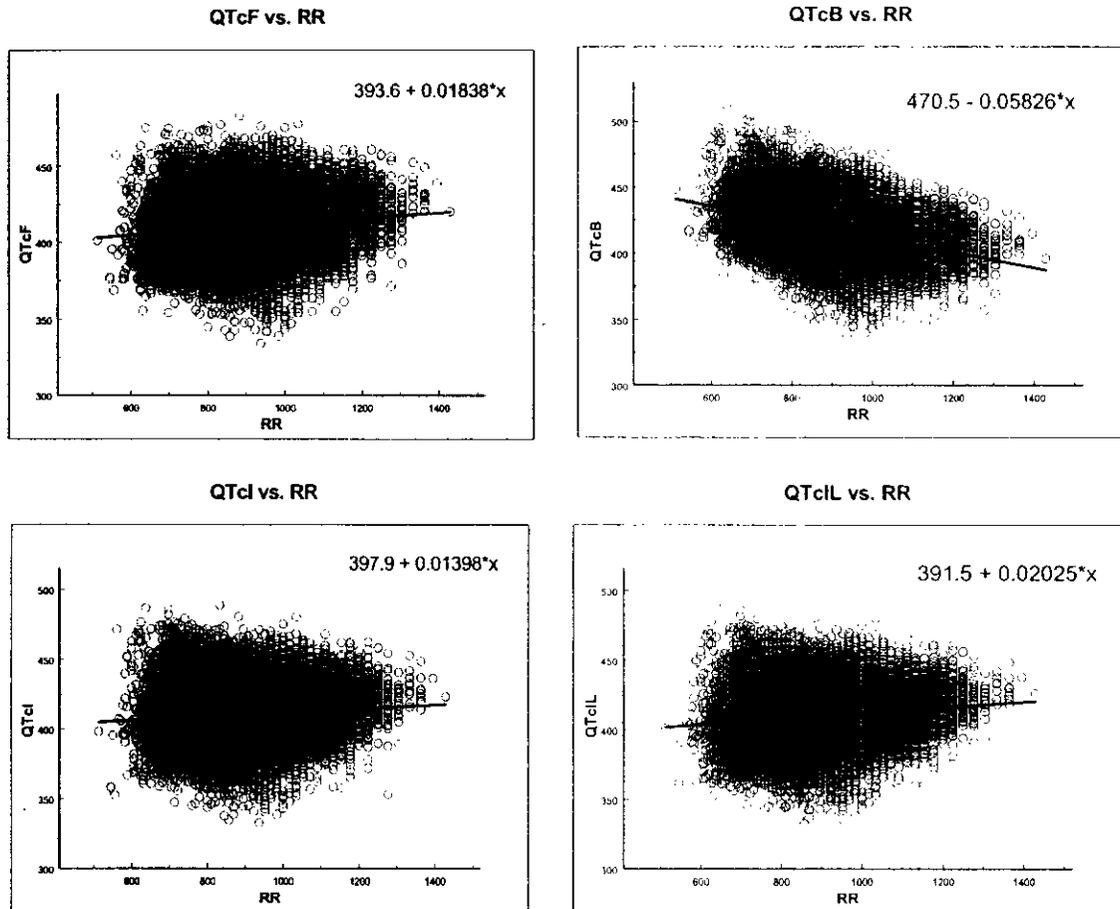
$$QTci = QT + \beta(1-RR)$$

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 check whether the pattern attested to a fairly independent relationship between the two parameters.

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 population. According to these graphs, the best correction for this data is the individual (linear) correction, QTci.

Figure 1. Corrected QT vs. RR



Outlier Measurements

The following table lists the frequency of QTcF measures greater than 450 msec. No QTcF measure was greater than 500 msec.

Table 6. Outlier QTcF > 450 msec; N (%)

Regimen	N(A)	N(B)	N Outliers TRT A	N Outliers TRT B
M	3537	1751	19 (0.54)	31 (1.77)
M3	-	782	-	24 (3.07)
M5	-	750	-	21 (2.80)
P	3423	1667	5 (0.15)	1 (0.06)

P3	-	1563	-	10 (0.64)
P5	-	751	-	3 (0.40)
S10	4957	-	68 (1.37)	-
S30	3060	-	181 (5.92)	-

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table 7. QTcF Change from Baseline Outliers >30 msec and > 60 msec

Regimen	N(A)	N(B)	>30 and < 60 msec		>60 msec	
			TRT A	TRT B	TRT A	TRT B
M	638	289	23 (3.6)	18 (5.9)	0 (0.0)	0 (0.0)
M3	-	232	-	53 (18.5)	-	1 (0.3)
M5	-	232	-	43 (15.6)	-	0 (0.0)
P	625	304	2 (0.3)	0 (0.0)	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_cF and Baseline- and Placebo-corrected QT_cF

Initial analysis will focus on data from Treatment Group A alone as Treatment Group B was proposed for “exploratory purposes only” when the protocol was initially reviewed.

Table 8. Mean Change in Baseline-corrected QT_cF and Baseline- and Placebo- (Treatment A only) 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 ^a (Treatment A)	-0.025 (-0.91 – 0.86)	-
Moxifloxacin 400mg ^b (Treatment A, Session 1)	9.27 (8.37 – 10.17)	9.30 (8.40 – 10.22)
Solifenacin ^c 10 mg	13.30 (11.65 – 14.95)	13.33 (11.69 – 15.00)
Solifenacin ^c 30 mg	17.51 (16.85 – 18.16)	17.53 (16.90 – 18.22)

^aBaseline-corrected with session 1 baseline

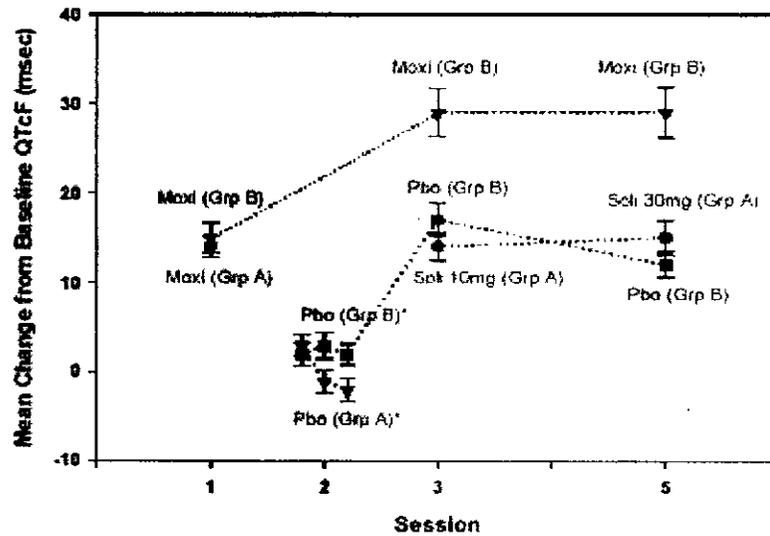
^bBaseline-corrected with session 2 baseline

^cBaseline-corrected with session 3 baseline

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 (possible period effect) and is not captured when placebo correcting with TRT A placebo response. This possible period effect is also seen with the moxifloxacin responses.

The following figure shows the different baseline-corrected means across all sessions for placebo, moxifloxacin and solifenacin.

Figure 2. Mean Change from Baseline QTcF by Group, Session and Regimen



Placebo response in TRT B is measured in a more similar time frame to the Solifenacin measurements in TRT A. Using baseline measures from session 3, those placebo responses, along with session-corrected Moxifloxacin and Solifenacin responses, are presented in the following two tables.

**APPEARS THIS WAY
ON ORIGINAL**

Table 9. Mean Change in Baseline-corrected QT_CF and Baseline- and Placebo- (Treatment B) corrected QT_CF

Treatment Group	Mean Change in Baseline-corrected QT_C (msec)	Mean Change in Baseline- and Placebo-corrected QT_C (msec)
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

APPEARS THIS WAY
ON ORIGINAL

It's important to note the difference in mean baseline readings across session and treatments. As seen in the following two tables, the mean baseline QTc intervals appear to decrease with time with consistently lower baselines in TRT B compared to the same session in TRT A.

Table 10. Mean Baseline QTcF by Treatment Group – (msec (95% CI))

Baseline	Mean QTcF		
	All Subjects	TRT A	TRT 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)

As seen above, the mean baseline reading between groups is significantly different, particularly in Session 3. The Session 3 difference between TRT A and TRT B in QTcF is 3.18 msec. This difference is problematic in that it leads to questions regarding the placebo responses (TRT B) for Sessions 3 and 5. If the mean baseline QTc for each treatment group was identical, the mean change in baseline- and placebo-corrected QTcF for solifenacin 10 and 30mg would be 3.5 and 13.01, respectively.

To better illustrate why such a significant difference exists between subject-corrected and treatment-corrected placebo responses, the following table lists the mean QTc's for moxifloxacin, placebo and solifenacin by treatment group. As seen in the shaded areas, the TRT B subjects showed considerably different placebo responses across sessions.

APPEARS THIS WAY
ON ORIGINAL

Table 12. Mean QTc for Moxifloxacin, Placebo and Solifenacin by Treatment Group (msec (95% CI))

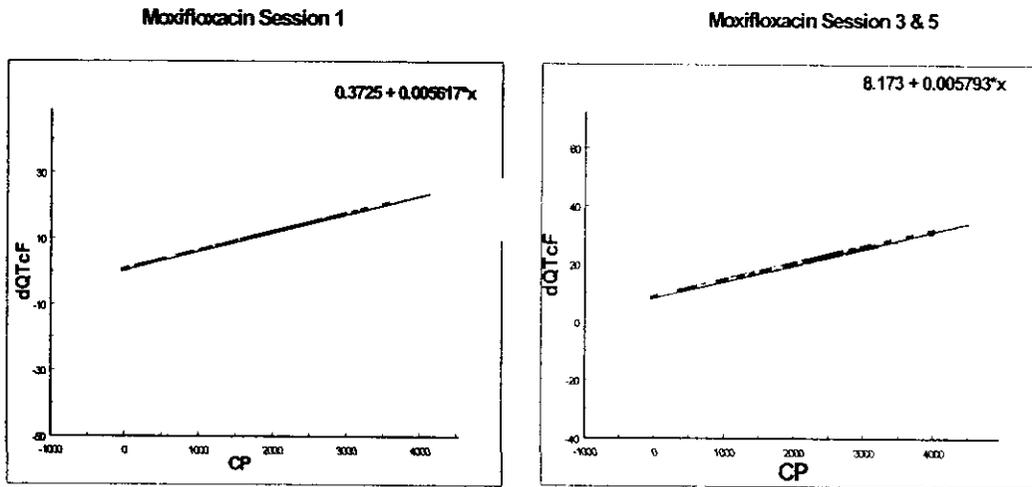
	Mean QTcF		Mean QTcI	
	TRT A	TRT B	TRT A	TRT B
Moxifloxacin, Session 1	414.30 (413.13-415.47)	413.26 (411.32-415.21)	415.00 (413.65-416.35)	412.44 (410.28-414.61)
Moxifloxacin, Session 3	-	416.34 (414.42-418.26)	-	415.67 (413.51-417.83)
Moxifloxacin, Session 5	-	414.30 (412.37-416.22)	-	413.82 (411.70-415.94)
Placebo, Session 2	405.82 (404.75-406.89)	404.16 (402.89-405.43)	406.93 (405.73-408.13)	402.70 (400.28-404.30)
Placebo, Session 3	-	409.32 (407.89-410.75)	-	404.13 (402.01-406.24)
Placebo, Session 5	-	408.21 (406.59-409.83)	-	406.92 (405.02-408.86)
Solifenacin 10mg	415.08 (414.21-415.96)	-	415.75 (414.79-416.71)	-
Solifenacin 30mg	421.34 (420.41-422.26)	-	421.74 (420.72-422.75)	-

Additionally, it should be noted that placebo-correction with TRT B data may not be statistically valid, due to the relatively small sample size (N=26).

In an attempt to make sense of the confounding results, and address questions raised regarding the plausibility of these data, further analysis was performed using the baseline-corrected QTcF and plasma concentration data. The following plots of baseline-corrected QTcF (dQTcF) vs. moxifloxacin concentration in the plasma (Cp) include a linear regression of the points for comparison of slopes and intercepts.

**APPEARS THIS WAY
ON ORIGINAL**

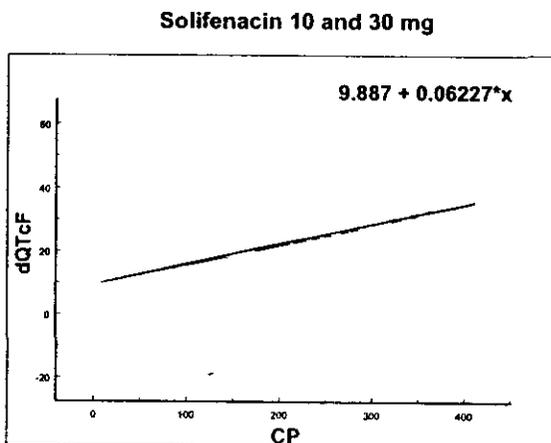
Figure 3. Plasma Concentration vs. Baseline-corrected QTcF for Moxifloxacin



Comparison of these graphs highlights several points. The non-zero intercept seen in the moxifloxacin sessions 3 & 5 regression suggests a potential period effect or temporal distance from baseline effect already seen through alternate analysis of moxifloxacin, solifenacin and placebo data. The similar slopes, however, suggest that even in light of these potential effects, the drug is behaving similarly among the different periods.

The next figure displays the same analysis, but for the sessions 3 and 5 baseline-corrected solifenacin data.

Figure 4. Plasma Concentration vs. Baseline-corrected QTcF for Solifenacin



Using the linear regression equations above along with the mean C_{max} and C_{avg} for moxifloxacin and solifenacin (tables 4 and 5), the following table provides estimates for mean baseline-corrected QTcF are derived.

Table 13. Expected Baseline-Corrected QTcF from Linear Regression Analyses

Drug/Session	Cavg (ng/ml)	dQTcF (msec)		Mean Cmax (ng/ml)	dQTcF (msec)	
		Session Data	Pooled Data*		Session Data	Pooled Data*
Moxifloxacin/1	1654	9.29	-	2700	15.17	-
Moxifloxacin/3	1611	9.95	9.33	2974	18.37	17.23
Moxifloxacin/5	1609	8.60	9.32	2778	14.85	16.09
Solifenacin/3	42.18	3.61	2.63	48.15	4.12	3.00
Solifenacin/5	148.02	8.71	9.22	161.3	9.50	10.04

*Linear regression of both session 3 and 5

These estimates assume that all non-zero intercepts are artifacts of study design, not drug effect, and are not included in determining the estimated dQTcF.

The last two methods of analysis involve use of the current draft ICH guidance. The first analysis proposed by the guidance suggests determining the maximum mean (by timepoint) change from baseline QTcF and subtracting off the time-matched baseline-corrected placebo response. The second analysis suggests determining the mean baseline-corrected QTcF at PK T_{max} and subtracting the subsequent time-matched baseline-corrected placebo response. In the case of Solifenacin, the mean T_{max} was 5.4 hours so the placebo correction used the closest placebo response (6 hours). The results of these analyses are provided in the following table.

Table 14. Alternate Baseline- and Placebo-Corrected QTcF for Moxifloxacin and Solifenacin

Drug	Alternate Correction Method Results – msec (95%CI)	
	A	B
Moxifloxacin 400mg	10.78 (8.00 – 13.56)	10.34 (7.79 – 13.21)
Solifenacin 10mg	5.37 (2.54 – 8.19)	1.30 (-1.47 – 4.07)
Solifenacin 30mg	9.40 (6.29 – 12.51)	8.58 (5.47 – 11.69)

A – Max Mean DQTcF (E_{max}) minus time-matched baseline-corrected placebo

B – Mean DQTcF at PK T_{max} minus time-matched baseline-corrected placebo

For method B, the statistical review led to very similar results of 1.8 and 8.3 msec for Solifenacin 10 and 30 mg, respectively. These estimates were rounded to the nearest whole msec and will be included in the package insert.

Conclusion

Due to the nature of this drug (long half-life, need for dose-ramping), protocol design was complex. The original design was initially intended for TRT B to be used solely for exploratory purposes. However, analysis using just TRT A (Study 905-CL-022) leads to skewed results due

to changing placebo responses with time and different temporal distances from baseline measures as was suggested in the previous solifenacin trial results.

Using TRT B placebo to correct for placebo response yields a mean baseline- and placebo-corrected QTcF for solifenacin 10 and 30 mg of 0.32 and 9.83 msec, respectively. And baseline- and placebo-corrected QTcI means of -0.77 and 8.35 msec, respectively. Using either QTcF or QTcI, the mean QT response for the suprathreshold solifenacin dose is about 2-4 msec greater than the moxifloxacin response (see tables 10, 11). However, analysis of the mean response over all times fails to capture the response seen at either the drug or effect T_{max} , thus leading to further analysis (see table 14).

While the study design makes it difficult to precisely determine the needed QT prolongation values, it is felt that an adequate determination can be derived. The maximum QT response to the therapeutic dose of solifenacin (10mg) appears to be small (approximately 2 msec) while the maximum response to solifenacin 30mg is approximately 8 msec. The maximum response to several moxifloxacin 400mg doses is approximately 10-15 msec. These responses are the mean baseline-corrected QTcF at PK T_{max} corrected for the parallel groups time-matched baseline-corrected placebo QTcF.

It should be noted that there is no 30 mg dose of solifenacin and that the C_{max} achieved with a 30mg dose exceeds the clinically expected "worst-case" C_{max} . Additionally, analysis of the concentration vs. baseline-corrected QTcF allowed for validation of period effects seen in this study and has provided a potentially novel means by which to correct for this effect.

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Stephan Ortiz
11/19/04 09:51:03 AM
BIOPHARMACEUTICS

That's it. No more!!!!

Ameeta Parekh
11/19/04 10:00:21 AM
BIOPHARMACEUTICS
concur

Clinical Pharmacology & Biopharmaceutics Review

NDA: 21-518
Product Trade Name: VERSICARE™
Active Ingredient/s: Solifenacin succinate (5 and 10 mg IR oral tablets daily)
Indication: /
Submission Dates: 12/19/2002 (original NDA)
Sponsor: Yamanouchi Pharma America, Inc.
Submission/Priority Type: Original/1S
Reviewers: Dhruva J. Chatterjee, Ph.D., Stephan Ortiz, Ph.D.
Team Leader: Ameeta Parekh, Ph.D.
Pharmacometrics: He Sun, Ph.D.

Table of Contents

<i>Synopsis</i>	5
<i>Recommendation</i>	5
<i>Comments to the Sponsor</i>	5
<i>Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings</i>	6
<i>Background</i>	7
<i>Clinical Pharmacology</i>	9
<i>Biopharmaceutics</i>	42
<i>Analytical</i>	45
<i>Labeling Comments</i>	47
<i>Appendix 1 (Cardiac Repolarization)</i>	48
<i>Appendix 2 (Pharmacometrics Review)</i>	72

Synopsis

The subject of this submission, Vesicare[®] (solifenacin succinate), is an oral therapy indicated for

Solifenacin is a competitive muscarinic-receptor antagonist. The sponsor is currently seeking approval of 5 and 10-mg immediate-release oral tablets (taken once daily).

RECOMMENDATION

From an OCPB perspective, the application is acceptable. Final decision regarding QT prolongation should be made in the context of the limitations involving the definitive QT study (# R905-CL-022) that was conducted without the use of a positive control for QT determinations (please see details in Appendix 1).

**APPEARS THIS WAY
ON ORIGINAL**

Overall Summary of Clinical Pharmacology and Biopharmaceutics

- **Pharmacokinetic Highlights:** Following administration of solifenacin, C_{max} is achieved in 3 - 6 hrs. The drug eliminates from the body relatively slowly with a half-life ($t_{1/2}$) of around 48 - 60 hours (> 2 days). Solifenacin has 1 major metabolite (M2) with negligible activity and 3 minor metabolites (M3, M4 and M5). M3 has the most muscarinic receptor activity among the metabolites (3 fold lower than the parent), but is significantly lower in plasma levels than solifenacin. Solifenacin is excreted mostly in the urine ($\approx 70\%$ of dose, > 80% as metabolites) and feces ($\approx 23\%$ of dose, mostly as parent). The drug shows linear pharmacokinetics between 5 - 100 mg oral doses (proposed doses - 5 and 10 mg). Solifenacin is > 95% bound to plasma proteins. Absolute bioavailability of solifenacin is high ($\approx 90\%$).
- **Comparative Exposure-Response of 5, 10 and 20 mg:** Based on two phase 2 intensive 'dose-finding' studies, the 5 mg was clearly established as the lowest effective dose in one study, while 10 mg was in the other study. In one of the studies, efficacy was maximized at the 10 mg dose, while in the other, even the 20 mg dose was not at the maximal efficacy. However, based on efficacy and tolerability, 5 and 10 mg doses are acceptable as final doses for the market from an OCPB perspective.
- **Intrinsic Factors:** (i) There was 20 - 25 % increases in C_{max} , AUC and $t_{1/2}$ in the elderly as compared to the young. (ii) There was a 2-fold increase in $t_{1/2}$ and 35% increase in AUC of solifenacin in the moderately hepatic-impaired patients. It is recommended not to exceed a 5 mg daily dose of solifenacin in this group. Severe hepatic impairment was not studied. (iii) Severe renal impairment resulted in a 2-fold increase in AUC. It is recommended not to exceed a 5 mg daily solifenacin dose in patients with severe renal impairment.
- **Extrinsic Factors:**

Metabolic/Pharmacokinetic Drug-Drug Interactions: Solifenacin is metabolized primarily by the CYP 3A4 enzyme system in the liver with minor contributions also from CYP 2C19. 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 results of consequence were that there may be 3 and 1.5 fold increases in solifenacin AUC and C_{max} respectively when 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 in combination with ketoconazole.
- **QT Prolongation:**

Sponsor conducted a study that was prospectively and adequately (based on PK parameters and increased exposure scenarios) designed to determine the effect of solifenacin on cardiac repolarization ("QT prolongation"). Amidst highly variable results from the study and a number of outliers of potential concern, the mean changes in QT_c corrected for baseline and placebo was 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 QT prolonging drug etc). Please see Appendix I for a detailed report on the study. However, clinical significance of the results from this study is beyond the scope of this review, and should be decided by the Clinical Team.

Background

Questions addressed in this section:

- *What are the highlights of chemistry and formulation of the drug and drug product?*
- *What is the mechanism of action, proposed indication and main goal of therapy?*
- *What are the other drugs available in this class?*
- *What are some highlights of claims for this product in the proposed label?*

The subject of this submission, Vesicare® (solifenacin succinate), is an oral therapy indicated for

Solifenacin is a competitive muscarinic-receptor antagonist. According to the sponsor, solifenacin is specific to the M₃ muscarinic receptor and is selective for urinary bladder *in vivo*. The sponsor is currently seeking approval of 5 and 10-mg immediate-release oral tablets (taken once daily).

Solifenacin succinate is a white to pale-yellowish-white crystal or crystalline powder (see Figure 1. For chemical structure). It is freely soluble at room temperature in water, glacial acetic acid, dimethyl sulfoxide, and methanol. The drug products will be provided as round film-coated tablets in dosage strengths of 5 mg and 10 mg. The two tablet strengths are distinguished by color and a strength-specific product code. The following is the composition of the tablets.

Table 1. Composition of Solifenacin succinate (Phase 3 and Commercial formulation)

Components	Function	Unit Formula (mg / tablet)	
		5 mg	10 mg
Tablet Core			
Solifenacin Succinate	Active ingredient	5.0	10.0
Lactose Monohydrate, NF			
Corn Starch, NF			
Hypromellose 2910, USP*			
Magnesium Stearate, NF			
Total		154.0	154.0

* The previous monograph title is Hydroxypropyl Methylcellulose 2910

NF - National Formulary; USP - United States Pharmacopeia

The formulation used in the Phase 3 studies is identical to the formulation proposed for marketing. A change in manufacturing site (Level 3 change as per SUPAC) post phase 3 has been supported with dissolution documentation and the sponsor is seeking a biowaiver.

Urinary incontinence, the involuntary loss of urine, is a clinical problem. Urinary incontinence affects all age groups and is particularly common in the elderly. Overactive bladder is one cause of urinary incontinence. Overactive bladder is a condition characterized by involuntary detrusor contractions during the bladder filling phase, which may be spontaneous or provoked, and which the patient cannot suppress.

The cause of bladder overactivity is not clearly known, but increased afferent activity, decreased inhibitory control, and increased sensitivity of the detrusor to efferent stimulation are some of the

postulated etiologies. It is known that parasympathetic cholinergic nerves innervate the detrusor muscles of the urinary bladder wall. The postganglionic neurotransmitter in the parasympathetic neurons is acetylcholine. As the bladder fills with urine, the stimulated parasympathetic nerves transmit acetylcholine, which causes the detrusor smooth muscle to contract and expel the urine from the bladder. At the molecular level, activation of the muscarinic M₃ receptors that mediate the activity of the urinary bladder, ciliary muscles and salivary glands occurs through binding of acetylcholine to the receptor. Therapeutic treatment for the overactive bladder is based on using anticholinergic agents to inhibit the binding of acetylcholine to the cholinergic receptors and thus suppress involuntary bladder contractions. Solifenacin succinate is a novel muscarinic antagonist possibly with selectivity for M₃ receptors (over M₂ and M₁). Thus, in theory, solifenacin succinate should be effective in the treatment of overactive urinary bladder.

Several drug therapies including antimuscarinics, antispasmodics, tricyclic antidepressants and estrogen are available to treat the disease. Oxybutynin (Ditropan), tolterodine (Detrol) are currently antimuscarinics available in the marketplace for similar indications. More recently extended release formulations for oxybutynin (Ditropan XL) and tolterodine (Detrol LA) have also been approved by the FDA in December, 1998. Common side effects of this class of drugs are dry mouth and constipation.

Information from 45 clinical pharmacology studies (*in vitro* and *in vivo*) have been submitted in support of this NDA. This CPB review follows a 'Question-Based' GRP format, addressing questions only relevant to this application.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Pharmacology

Q. Were appropriate clinical endpoints, surrogate endpoints or pharmacodynamic (PD) biomarkers selected, adequately measured and used to assess efficacy and safety in clinical pharmacology studies?

The efficacy of this drug has been determined in several phase 2 and 3 clinical trials using efficacy endpoints such as mean change from baseline in mean number of micturitions per 24 hours (primary for Phase 3), mean change from baseline in number of incontinence, urgency, and nocturia episodes per 24 hours and in volume of urine voided per micturition. Safety endpoints evaluated in Phase 1, 2 and 3 studies included dry mouth and constipation among others (eg. liver function, cardiovascular events such as QT prolongation etc.). No surrogate endpoints or biomarkers were formally investigated in clinical pharmacology or clinical studies. Considering the indication, the above assessments were acceptable.

Q. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. The parent (solifenacin or YM905), 1 major metabolite (M2) and three minor metabolites (M3, M4 and M5) were monitored in most of the pharmacokinetic studies either in plasma or urine or both.

Q. What are the exposure (pharmacokinetic) characteristics of solifenacin?

What was the mass balance of the parent drug & metabolites following parent administration?

In Study 905-CL-008, the sponsor conducted a mass balance, metabolism and excretion profiling of YM905 and its metabolites following administration 10 mg of an oral solution of radiolabelled [¹⁴C] solifenacin in 4 healthy young male subjects. The following are the results:

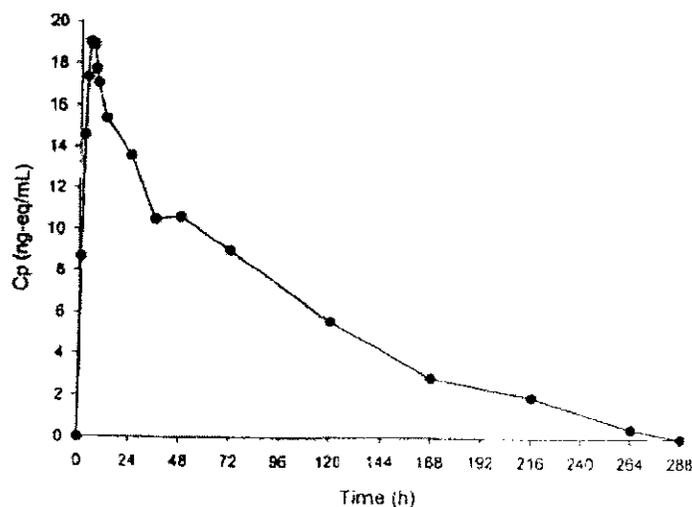


Figure 1: Average radiocarbon plasma concentrations versus time curve.

Table 2: Pharmacokinetic parameters for radiocarbon in plasma (as ng-eq YM905 base)

Parameter	Subject no.				Descriptive statistics			
	1	2	3	4	Mean	SD	Min	Max
C_{max} (ng-eq/mL)					19.8	2.92		
t_{max} (h)					5.25	0.96		
AUC_{0-last} (ng-eq.h/mL)					1543	446		
$AUC_{0-\infty}$ (ng-eq.h/mL)					1794	460		
$t_{1/2}$ (h)					70.1	13.2		

Table 3: Pharmacokinetic parameters for radiocarbon in whole blood (as ng-eq YM905 base)

Parameter	Subject no.				Descriptive statistics			
	1	2	3	4	Mean	SD	Min	Max
C_{max} (ng-eq/mL)					13.1	2.19		
t_{max} (h)					5.25	1.50		
AUC_{0-last} (ng-eq.h/mL)					362	60.2		
$AUC_{0-\infty}$ (ng-eq.h/mL)					770	185		
$t_{1/2}$ (h)				4	41.9	12.3		

Table 4: Cumulative excretion of radiocarbon in urine

Parameter	Subject no.				Descriptive statistics			
	1	2	3	4	Mean	SD	Min	Max
Ae (% dose)					69.2	7.78		
Ae (mg)					5.22	0.587		
Duration*	503 h	480 h	624 h	336 h				

*: post-dose time for collection of the last sample.

Table 5: Cumulative excretion of radiocarbon in faeces

Parameter	Subject no.				Descriptive statistics			
	1	2	3	4	Mean	SD	Min	Max
Ae (% dose)					22.5	3.33		
Ae (mg)					1.70	0.251		
Duration*	503 h	337 h	504 h	312 h				

*: post-dose time for collection of the last sample.

Table 7. Excretion balance for radiocarbon

	Subject no.				Descriptive statistics			
	1	2	3	4	Mean	SD	Min	Max
Urine					69.2	7.78		
Faeces					22.5	3.33		
Expired CO ₂					0.38	0.75		
Total					92.1	7.66		
Duration*	503 h	480 h	624 h	336 h				

*: post-dose time for collection of the last sample.

Table 8: Pharmacokinetic parameters for YM905 in plasma (as ng-eq YM905 base)

Parameter	Subject no.				Descriptive statistics			
	1	2	3	4	Mean	SD	Min	Max
C_{max} (ng/mL)					15.7	3.03		
t_{max} (h)					5.25	0.96		
AUC_{0-last} (ng.h/mL)					1140	462		
$AUC_{0-\infty}$ (ng.h/mL)					1210	474		
$t_{1/2}$ (h)					62.8	20.2		
YM905/radiocarbon ratio (%)								
C_{max}								
AUC_{0-last}								
$AUC_{0-\infty}$								

Table 9: Total excretion of YM905 in urine

Parameter	Subject no.				Descriptive statistics			
	1	2	3	4	Mean	SD	Min	Max
Ae (% dose)					14.7	4.81		
Ae (mg-eq YM905 base)		/			1.11	0.363		/
Duration*	503 h	480 h	624 h	336 h				
YM905/radiocarbon ratio (%)								
Ae			/					

*: post-dose time for collection of the last sample.

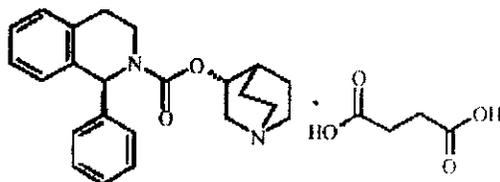
Reviewer's Comments

- Based on Table 7 above, in 3 of the 4 subjects, about 95% of the radioactivity could be recovered (after 21 days of sample collection). In subject 3, even after day 26, only — of the radioactivity was recoverable. No obvious reasons may be attributed to this.
- Based on Table 8 above, about 75% of the plasma radioactivity (based on AUC) could be attributed to the parent YM905 in 3 subjects (indicating the presence of metabolites). Subject 4 (with about — for this value and a shorter half-life) is most likely a faster metabolizer of the drug. This is also indicated by a lower % of dose of YM905 in plasma whereas a higher % of radiocarbon (due to metabolites) in the urine (see Tables 7 and 9).
- Based on Table 7, about 70% of the administered dose was found in urine and 23% in feces.
- Only about 15% of administered dose was excreted unchanged as YM905 in urine (Table 9) accounting for about 12 – 30% of total radioactivity.
- Further metabolite profiling showed radioactivity peaks corresponding to YM905 (10.8%), three major metabolites and 4 minor metabolites in the urine: YM-80264 (8.3%), YM-64250 (17.8%), RT 51 (8.9%), RT 54 (1.8%), RT 55 (2.5%), RT 56 (1.4%), and RT 57 (4.9%).
- For feces, the major radioactivity corresponded to parent YM905. Metabolite YM-80264 was also observed as were traces of RT 64 and RT 55.

Thus, it may be concluded that solifenacin is extensively metabolized and majority of the metabolites are excreted through the urine.

What is the metabolic fate of solifenacin?

The following is the chemical structure of solifenacin succinate:



In vitro studies 905-ME-011 and -060 indicated that of the CYP P450 isoenzymes, CYP3A4 had the greatest potential for metabolizing solifenacin. However, other CYP P450 isoenzymes, in particular 2C19, but also 3A5, 2C8, 2D6 and 1A1 showed the ability to metabolize solifenacin (to a lesser extent). Apart from these phase I reactions, solifenacin is also subject to direct glucuronidation.

Although under normal conditions, CYP3A4 is likely to be the main metabolizing enzyme, these routes may act as salvage pathways in case CYP3A4 is inhibited.

Overall four metabolite peaks corresponding to M2 (solifenacin *N*-oxide), M3 (4*R*-hydroxy solifenacin), M4 (4*R*-hydroxy solifenacin *N*-oxide) and M5 (solifenacin *N*-glucuronide) were found in numerous *in vitro* studies. Three of them were formed by phase 1 metabolism (M2, M3 and M4), while M5 was formed by direct glucuronidation of solifenacin (phase 2 metabolism). *In vitro* experiments showed that M2 was primarily the product of metabolism mediated by CYP3A4, although the isoenzymes 1A1, 2C8, 2C19, 2D6 and 3A5 were also able to convert solifenacin into M2. M3 was extensively formed by 3A4 and to a much lesser extent by 1A1 and 2D6, M4 was formed by 3A4 exclusively. The most important metabolite found in rats was M1 (4*S*-hydroxy solifenacin). This metabolite was also formed in much smaller quantities in mice and dogs, but not in man. Study 905-ME-054 also revealed the formation of a fifth unidentified metabolite. These *in vitro* results were confirmed by the single dose studies 905-CL-008 (mass balance study), 905-CL-009, 905-CL-021 and 905-CL-026 (preliminary data) and the multiple dose studies 905-CL-022 and 905-CL-029 (see table below).

Table 10: Overview of the metabolites found in plasma, urine and feces in clinical pharmacology studies

Metabolite	Single dose studies				Multiple dose studies	
	905-CL-008	905-CL-009	905-CL-021	905-CL-026	905-CL-022	905-CL-029
M2	plasma, urine	not investigated	plasma, urine	plasma, urine	plasma	plasma, urine
M3	urine, feces	urine	plasma, urine	plasma, urine	plasma	plasma, urine
M4	urine	not investigated	plasma, urine	plasma, urine	plasma	plasma, urine
M5	plasma, urine, feces	not investigated	plasma, urine	plasma, urine	plasma	plasma, urine

In plasma samples of the mass balance study 905-CL-008, only M2 and M5 were detected (but not quantified), although all 4 known metabolites were recovered from urine. Plasma samples were collected and analyzed for metabolites up to 48 h post-dose (probably insufficient time for M3 and M4 to reach detectable concentrations). In almost all single and multiple dose studies, all 4 metabolites were found in plasma and urine. According to pharmacology section of this NDA, M3 was the most active among the above metabolites, with a 3-fold lower affinity for the M3 receptor. M3 showed affinity also for muscarinic M1 & M2 receptors and for Na channel site 2. It inhibited the ⁸⁶Rb efflux from the HERG channel with 11-fold less potency than solifenacin and prolonged PR, QRS and QTc intervals in anesthetized dogs. M4 prolonged action potential duration (APD₆₀) in the dog Purkinje fibers.

How much of the drug is bound to plasma proteins?

In the *in vitro* study 905-ME-007, the extent of binding of solifenacin to plasma proteins was investigated. Additionally, in study 905-ME-038, the proteins involved in binding solifenacin were determined. In plasma obtained from Japanese volunteers, *in vitro* protein binding amounted to 96.1% at a solifenacin concentration of 75.4 ng/ml, which is close to the C_{max} values found in steady state after once daily dosing of 10 mg solifenacin succinate (a binding of 96.1% corresponds to an f_u of 0.039).

The primary protein involved in binding appeared to be α 1-acid glycoprotein (AGP). In study 905-CL-029, *in vivo* binding of solifenacin in young and elderly Caucasian men and women was determined. With 5 mg dosing, mean (SD) f_u over all subjects was 0.01920 (0.00450). Although there were some numerical differences between the young and the elderly and between men and women, values in all groups were generally similar. Mean f_u found *in vivo* in Caucasian subjects was about 50% lower compared to the *in vitro* results obtained with plasma from Japanese subjects. For compounds that are highly bound to AGP, ethnic differences in f_u have been observed and consistently lower values have been reported in the Caucasian population. [However, differences in methodologies used in establishing f_u in Japanese and Caucasian subjects cannot be excluded or overlooked as a contributing factor to the observed differences in f_u .]

Based on PK parameters, what is the degree of linearity or non-linearity in the dose-exposure relationship?

Sponsor conducted placebo controlled Phase I PK and PD dose-escalation Study 905-CL-001 in 62 healthy male subjects to determine the PK following single doses of solifenacin from 5 – 100 mg daily.

Results:

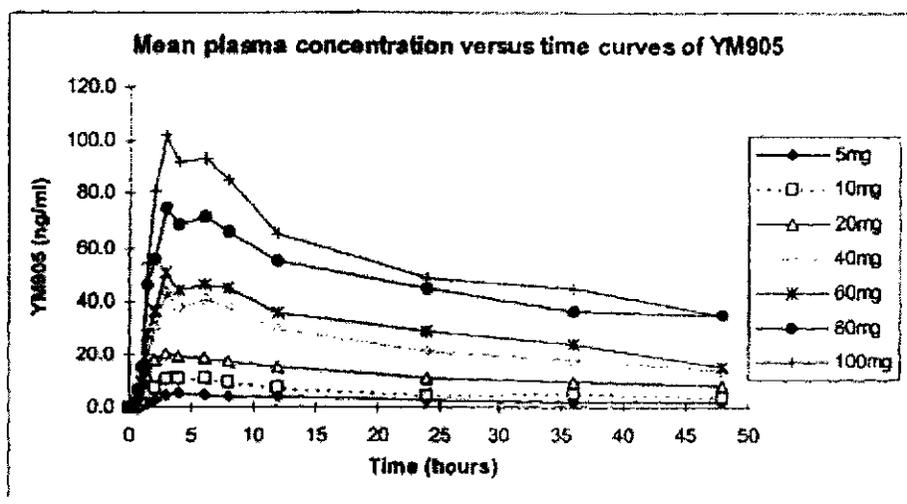


Figure 2. Mean plasma concentrations of parent YM905 after oral administration of single 5 mg to 100 mg doses in healthy male subjects.

Table 11. Summary of selected pharmacokinetic parameters of YM905; in each cell arithmetic mean and standard deviations (between brackets) are shown.

Dose (mg)	t_{max} (h)	C_{max} (ng/ml)	$AUC_{0 \rightarrow \infty}$ (ng.h/ml)	$AUC_{0 \rightarrow \infty}$ extrapolated (%)	AUC_{last} (ng.h/ml)	$t_{1/2, \lambda}$ (h)
5	4.8 (1.4)	6.5 (1.7)	246 (23)	42.2 (7.9)	143 (26)	40.2 (12.5)
10	4.0 (1.6)	11.8 (1.6)	600 (203)	49.4 (8.4)	290 (50)	49.4 (8.7)
20	3.3 (1.5)	22.7 (4.8)	1277 (612)	52.2 (8.34)	576 (196)	55.1 (14.2)
40	3.7 (2.0)	46.5 (10.4)	2249 (1319)	41.6 (20.9)	1116 (279)	49.0 (35.8)
60	3.5 (1.2)	51.4 (12.9)	2658 (1812)	37.5 (23.0)	1379 (487)	49.6 (55.8)
80	4.5 (1.2)	81.4 (14.0)	7952 (5917)	61.9 (20.1)	2200 (596)	102.6 (73.9)
100	3.5 (1.8)	108.5 (17.0)	5433 (1526)	48.6 (15.1)	2613 (375)	55.4 (30.5)

As is clearly noticeable in the above table and figure, the sampling schedule for the drug was not sufficient (till 48 hours post dose) in comparison to its half life (about 50 hours) Hence, AUC_{0-last} is a more dependable parameter than AUC_{∞} . The following figures show the dependency of key PK parameters on dose:

Figure 3A

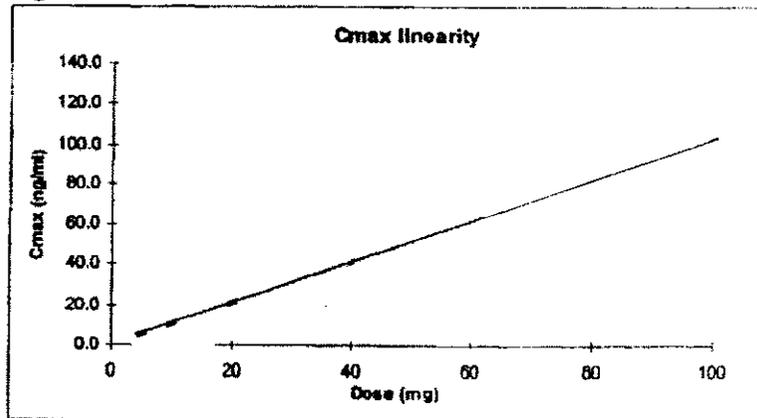


Figure 3B

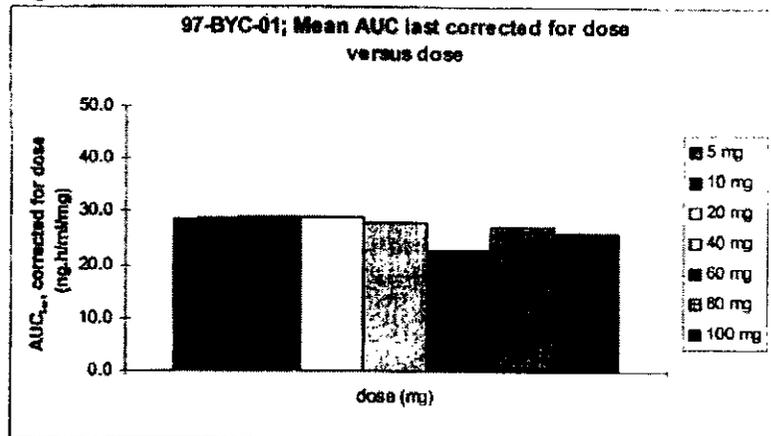
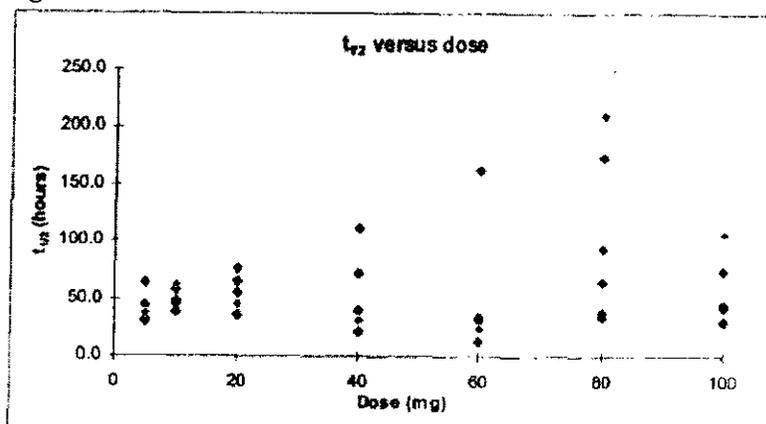


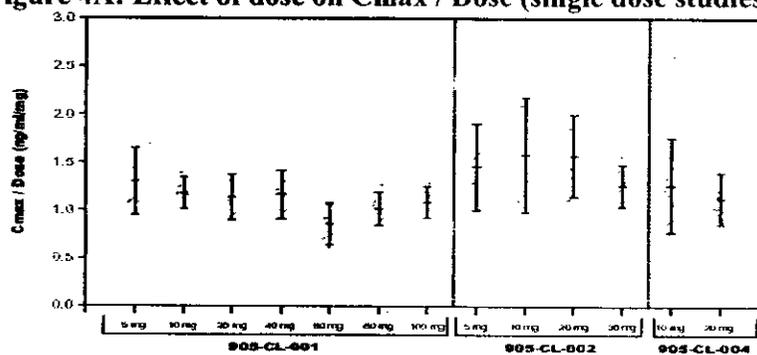
Figure 3C



Reviewer's comments:

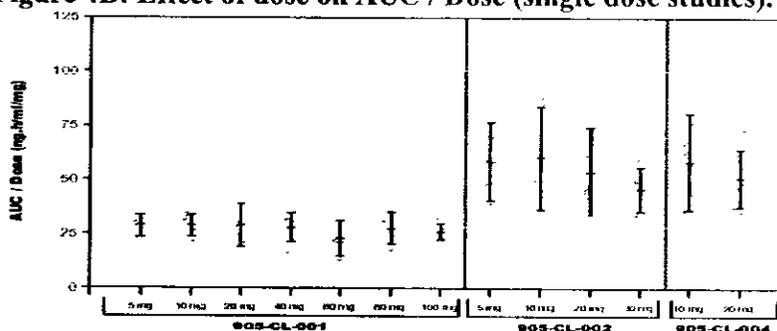
- The exposure (based on AUC_{last} and C_{max}) are generally proportional and linear between the 5 to 100 mg doses
- The half life of solifenacin drug is > 45 hours. The $t_{1/2}$ of the drug is appears to be generally independent of the dose. However, there are some outliers, probably arising from the estimation of the terminal part of the profile when the sampling schedule was incomplete.
- Sponsor has also elegantly presented the dependence of these parameters to dose across several single dose studies (see below):

Figure 4A: Effect of dose on C_{max} / Dose (single dose studies).



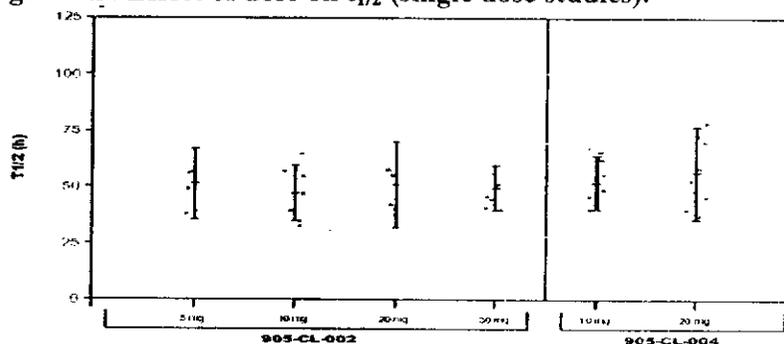
The solid lines represent the arithmetic mean and standard deviation for each dose

Figure 4B: Effect of dose on AUC / Dose (single dose studies).



The solid lines represent the arithmetic mean and standard deviation for each dose. Values of study 905-CL-001 represent the AUC_{last} / Dose values, values of studies 905-CL-002 and 905-CL-004 are $AUC_{0-\infty}$ / Dose values.

Figure 4C: Effect of dose on $t_{1/2}$ (single dose studies).



The solid lines represent the arithmetic mean and standard deviation for each dose

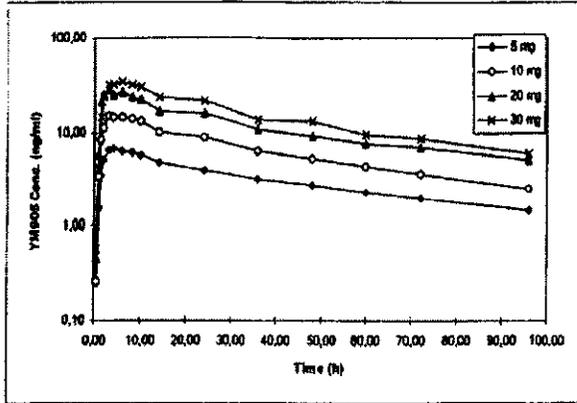
- From the above graphical presentations, it may be concluded that the PK of solifenacin is linear/proportional and that the half-life is independent of dose, certainly in the range of 5 – 10 mg (proposed for market).
- PK information on metabolites was not reported for the single dose study.
- There was a dose dependent increase in antimuscarinic activity (based on adverse events).
- Adverse events (mainly dry mouth) significantly increased beyond 20 mg of daily dosing.

How do PK parameters change with time following chronic dosing?

Study 905-CL-002 was a double blinded, placebo controlled, randomized rising multiple dose study in 4 sequential groups of 10 healthy volunteers each. The dose of solifenacin was 5 – 30 mg daily. The first 4 days was PK characterization following a single dose, while days 5-21 were scheduled for multiple dosing.

Results:

PK after Single Dose



PK after Multiple Doses

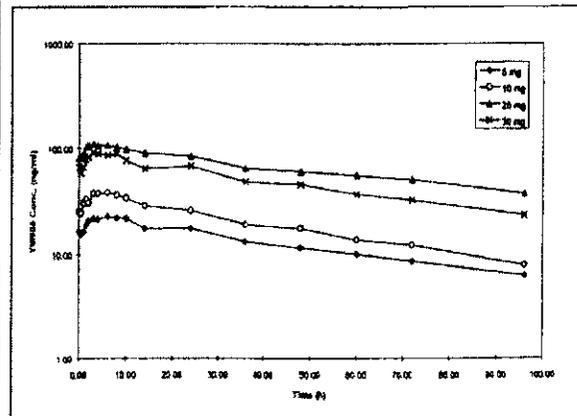


Figure 4. Mean plasma concentration vs. time profiles obtained after the first dose of YM905.

Figure 5. Mean plasma concentration vs. time profiles obtained after the last dose of YM905.

Figure 6. YM905 Mean Trough values vs. Day of Dosing

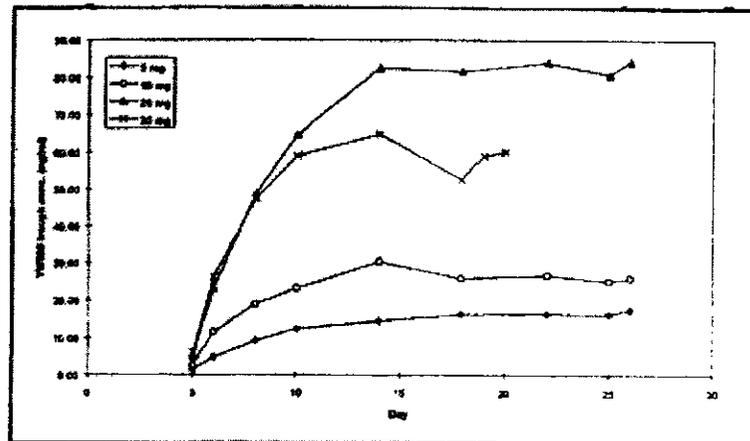


Table 12. Pharmacokinetic parameters of YM905 after the first and after the last dose. Each cell contains the arithmetic mean, the coefficient of variation and the range. For the first dose AUC₀₋₂₄ is tabulated, for the last dose AUC₀₋₂₄.

	5 mg		10 mg		20 mg		30 mg	
	First dose (n = 8)	Last dose (n = 8)	First dose (n = 7)	Last dose (n = 7)	First dose (n = 8)	Last dose (n = 8)	First dose (n = 8)	Last dose (n = 6)
AUC ₀₋₂₄ (ng·h/ml)	294 (31%)		602 (39%)		1075 (38%)		1376 (23%)	
AUC ₀₋₂₄ (ng·h/ml)	411 (44%)	463 (37%)	786 (43%)	749 (22%)	1529 (57%)	2270 (43%)	1839 (25%)	1765 (34%)
t _{max} (h)	3.9 (54%)	5.8 (56%)	4.7 (54%)	4.2 (43%)	2.9 (50%)	3.8 (57%)	5.3 (39%)	4.8 (51%)
C _{max} (ng/ml)	7.29 (31%)	24.01 (30%)	15.82 (38%)	40.61 (21%)	31.44 (27%)	113.86 (42%)	37.83 (18%)	95.22 (27%)
t _{1/2} (h)	51.5 (31%)	55.1 (29%)	47.4 (26%)	45.0 (27%)	50.8 (37%)	64.8 (31%)	49.5 (20%)	51.6 (26%)

Reviewer's comments:

- Assuming that the drug has an effective half-life of 50 h (≈ 2 days), it would take about 14 days for the drug to achieve steady state. According to Figure 6 above, it is about 14 days when steady state is attained from most of the regimens.
- Based on C_{max} and C_{trough} values in Table 12 and Figure 6 respectively, it appears that there is a potential of a 3-5 fold accumulation of the drug following multiple dosing. However, for some unexplainable reason, the C_{trough} values following the 20 mg dose are very high (even higher than that from the 30 mg dose). For that reason, accumulation from the 20 mg dose based on C_{trough} appears higher.
- No mention of solifenacin metabolites are made in the presentation of data or discussion of the study results.

Sponsor conducted another multiple dose (similar design) study with 10 and 20 mg doses in 31 healthy elderly male and female volunteers [Study 905-CL-004]. Results follow:

Figure 7A. Individual PK profile following single dose of 10 mg solifenacin in males and females



Figure 7B. Individual PK profile following single dose of 20 mg solifenacin in males and females

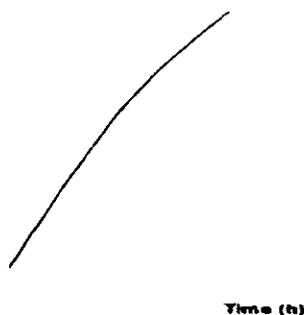


Table 13. Pharmacokinetic parameters of YM905 during the first and last dose.

	10 mg, male		10 mg, female		20 mg, male		20 mg, female	
	First Dose (n = 6)	Last dose (n = 6)	First Dose (n = 6)	Last dose (n = 6)	First dose (n = 6)	Last dose (n = 6)	First dose (n = 6)	Last dose (n = 6)
AUC ₀₋₂₄ (ng.h/ml)	485.2 (25.0%)		685.7 (38.6%)		1194.9 (14.3%)		846.9 (26.6%)	
AUC ₀₋₂₄ (ng.h/ml)	466.0		632.1		1195.4		848.5	
AUC ₀₋₂₄ (ng.h/ml)	672.9 (26.8%)	879.0 (26.4%)	986.2 (43.5%)	1156.8 (30.3%)	1877.6 (22.6%)	1800.5 (41.5%)	1168.9 (39.1%)	1428.1 (37.1%)
t _{max} (h)	721.3 (35.0%)	861.6 (31.6%)	907.6 (41.5%)	1257.2 (12.3%)	1898.5 (43.1%)	2020.4 (56.3%)	1086.4 (34.9%)	1320.8 (14.0%)
C _{max} (ng/ml)	6.00	9.00	6.00	9.00	4.00	8.00	6.02	8.00
C _{max} (ng/ml)	9.72 (21.2%)	41.40 (26.4%)	15.62 (34.3%)	56.03 (27.0%)	24.78 (23.2%)	88.24 (39.2%)	20.07 (20.6%)	72.12 (34.3%)
t _{1/2} (h)	9.00	40.60	14.00	61.70	23.65	91.20	19.65	66.50
t _{1/2} (h)	51.17 (20.8%)	65.30 (20.8%)	52.88 (26.2%)	69.49 (42.1%)	65.33 (31.3%)	82.26 (43.0%)	48.06 (37.6%)	56.90 (30.1%)
	47.67	63.47	55.10	66.91	61.82	69.49	42.58	53.87

Each cell contains the arithmetic mean, the coefficient of variation, the range and the median. For the first dose AUC₀₋₂₄ is tabulated, for the last dose AUC₀₋₂₄.

Reviewer's comments:

- Based on the C_{max} values, a potential of 3-5 fold accumulation of the drug following multiple dosing was also confirmed in this study.
- Based on AUC and C_{max} values, there was a higher exposure in the female subjects. Using the data from the 10 mg dose, there was 30 - 40% higher mean AUC and 40 - 60% higher mean C_{max} in the elderly females as compared to the elderly males based on single & multiple dose data. The t_{1/2}s appeared to be similar in the two groups.
- From the % CV reported in the above studies, it is evident that the PK parameters may be moderately variable for this drug (20 - 40 % CV with most PK parameters).
- There was a clear trend in dose dependence on anti-muscarinic activity (see figures below).
- There were significant adverse events that correlated to dose. There were 40%, 70% and 100% of patients showing digestive system side effects (eg. dry mouth) at 10, 20 and 30 mg doses

respectively. Additionally, there were 14%, 50% and 70% of the patients showing side effects related to the nervous system following the 10, 20 and 30 mg doses respectively. Most of the subjects on the 30 mg dose dropped out of the study due to adverse effects. Side effects from the 5 mg dose were generally lesser.

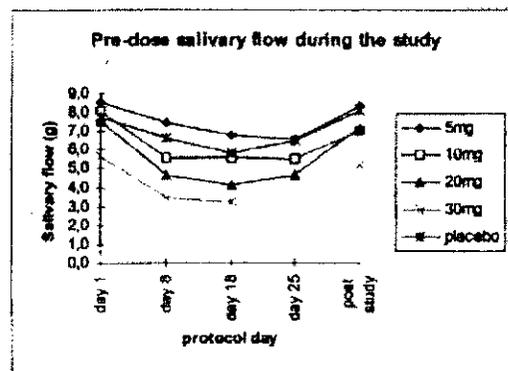
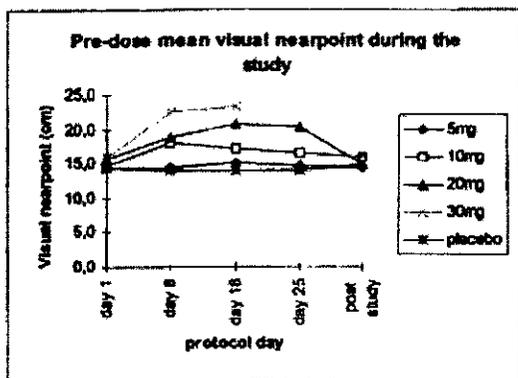


Figure 8A : Mean pre-dose visual nearpoint per dose group during the study; Figure 8B : Mean pre-dose salivary flow per dose group during the study

Q. What are the PK parameters of the metabolites of solifenecin?

An overview of the summary statistics of PK parameters found in the single dose studies 905-CL-021 and -026 and the multiple dose 905-CL-022 is given in Table 14. In the multiple dose study 905-CL-029 only trough samples were collected.

Table 14: Summary of PK parameters of the metabolites of solifenacin after dosing of 10 mg solifenacin succinate to healthy subjects.

Parameter	Design	Study	M2	M3	M4	M5
t_{max} (h)	Single dose	905-CL-021	24.2 (14.9) (N = 6)	43.4 (41.3) (N = 6)	18.7 (6.0) (N = 6)	6.00 (2.00) (N = 3)
		905-CL-026*	21.1 (8.1) (N = 8)	49.0 (32.2) (N = 5)	18.0 (6.4) (N = 8)	4.70 (1.26) (N = 5)
	Multiple dose	905-CL-022	3.75 (1.04) (N = 60)	9.51 (8.65) (N = 60)	6.36 (4.65) (N = 60)	6.13 (2.16) (N = 60)
C_{max} (ng/ml)	Single dose	905-CL-021	1.81 (0.57) (N = 6)	0.872 (0.285) (N = 6)	1.40 (0.33) (N = 6)	0.787 (0.115) (N = 3)
		905-CL-026*	2.81 (0.67) (N = 8)	0.538 (0.030) (N = 5)	1.67 (0.58) (N = 8)	0.872 (0.193) (N = 5)
	Multiple dose	905-CL-022	12.7 (4.8) (N = 60)	4.70 (1.70) (N = 60)	6.21 (2.54) (N = 60)	1.65 (0.70) (N = 60)
$t_{1/2}$ (h)	Single dose	905-CL-021	62.8 (13.0) (N = 6)	183 (114) (N = 4)	96.5 (25.8) (N = 6)	11.5 (4.6) (N = 2)
		905-CL-026*	60.2 (22.0) (N = 8)	90.5 (25.1) (N = 8)	68.2 (25.6) (N = 8)	ND
AUC_{0-24h} (ng.h/ml)	Multiple dose	905-CL-022	239 (89) (N = 60)	95.4 (33.9) (N = 60)	121 (46) (N = 60)	29.1 (14.6) (N = 60)
Ae_{0-168h} (mg)	Single dose	905-CL-026*	1.57 (0.37) (N = 8)	0.412 (0.117) (N = 8)	0.503 (0.127) (N = 8)	0.048 (0.040) (N = 8)

Data are expressed as mean (SD). * Preliminary data

Sponsor's Comments on Metabolite PK:

In each of the studies 905-CL-021, -022, -026 and -029 plasma concentrations of the metabolites were considerably lower than of solifenacin. Of the 4 metabolites the highest concentrations were observed for M2. M5 was lowest in 905-CL-021, -022 and -029, while in -026, M3 was lowest. After a single dose, M3 concentrations were lower than M4 concentrations and close to concentrations observed for M5. Plasma concentrations of M3 and M5 after a single dose were close to the LOQ and in several subjects not quantifiable. This may have biased the estimates of the C_{max} statistics. Results obtained with 5 and 10 mg in study 905-CL-029 and with 10 and 40 mg in study

905-CL-022 indicated that plasma concentrations of the four metabolites increase in proportion to the dose. Although similar after a single dose, plasma concentrations of M3 showed a more pronounced increase than M5 during multiple dosing and became comparable to the concentration of M4. Estimates of the $t_{1/2}$ indicated that the $t_{1/2}$ of M3 might be longer than the $t_{1/2}$ of M4, which may have contributed to its accumulation.

After a single dose, peak concentrations of M2, M3 and M4 occurred later than the C_{max} of solifenacin. However, after multiple dosing resulted in a decrease in t_{max} of M2, M3 and M4, but not M5. In studies 905-CL-021 and -026, $t_{1/2}$ values of the metabolites were determined. However, in a considerable number of subjects an insufficient number of plasma samples were collected to allow an accurate determination of $t_{1/2}$. Instead, in study 905-CL-026 urinary excretion data were used to get estimates for M3 and M4. A value for M5 could not be estimated. In both studies a similar mean $t_{1/2}$ for M2 was obtained. The values were close to the $t_{1/2}$ of solifenacin itself, suggesting that the apparent $t_{1/2}$ of M2 may actually represent the rate of metabolism of solifenacin. In both studies a higher $t_{1/2}$ for M3 was found. In study 905-CL-021 $t_{1/2}$ was based on plasma data and in several subjects $t_{1/2}$ was based on a small number of data, which may have affected the accuracy of the estimate. In study 905-CL-026, a $t_{1/2}$ of 68.2 h for M4 was found based on urinary excretion data. A higher value of 96.5 h, based on plasma data, was found in study 905-CL-021, but in several subjects samples were only quantifiable over a short period of time. This may have affected the accuracy of its estimate. Only in study 905-CL-021 an estimate of the $t_{1/2}$ of M5 was made, but again plasma samples were only quantifiable over a short period of time.

In the urine samples of Study 905-CL-008, the metabolites M2, M3, M4 and M5 were found together with the unidentified peak found in the *in vitro* study 905-ME-054. The highest amounts excreted were found for M2 (17.8%), followed by M4 (8.9%), M3 (8.3%), the unidentified peak (4.9%) and M5 (2.5%); the metabolites M3 and M5 were also found in feces together with solifenacin. Not all metabolites found in 905-CL-008 were detected in the *in vitro* studies. In 3 out of 4 subjects an additional metabolite was found in feces, but not in plasma or urine. This metabolite was not detected in the *in vitro* studies.

Reviewer's Comments

- Solifenacin is extensively metabolized with multiple metabolites having long $t_{1/2}$ s (> 60 hr).
- M2 is the most abundant metabolite. However, its pharmacologic activity is negligible.
- Maximum pharmacologic activity among the metabolites resides with M3 (with 3 fold less affinity for the M3 muscarinic receptor). This metabolite also showed *in vitro* activity in the HERG channel study (however 11 fold lower than solifenacin). The concentrations of M3

producing these effects, according to the sponsor, were mostly lower than those obtained in the *in vivo* studies (eg. the QT prolongation study R905-CL-022).

- There were no obvious reasons (other than inadequate sampling schedule) for metabolite M5 to show low half-lives (much lower than the parent).

Q. What are the exposure-response (PK-PD) characteristics of solifenacin?

Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response?

In this application, the sponsor is seeking approval for 5, and 10 mg doses. Preliminary PD results from the single and multiple dose PK studies (described above), showed 20 mg and higher doses showed significant adverse events. Based on this, the sponsor conducted two phase 2 dose-response studies (905-CL-005 and 905-CL-006) in which OAB patients were treated with 2.5, 5, 10 or 20 mg solifenacin succinate qd for 4 weeks.

Study 905-CL-005

This was a parallel group, multi-centre, multinational study with a single-blind placebo run-in period of 2 weeks followed by a randomized, double-blind, active and placebo-controlled treatment period of 4 weeks. Three hundred patients satisfying all selection criteria at the end of the placebo run-in period (visit 2) were to be randomized to receive one of four doses of YM905 (2.5 mg, 5 mg, 10 mg or 20 mg), placebo or tolterodine 2 mg BID (50 patients per treatment group, 192 completed). Males were 40% and females were 60% of the randomized patients.

The primary efficacy variable was the change from baseline to endpoint in mean number of micturitions per 24 hours (same as the Phase 3 studies) as derived from the urinary diary. There were numerous secondary efficacy variable involving number of micturitions in a day, the volume voided and urgency (also similar to Phase 3 studies). Safety was determined using descriptive statistics of the adverse events reported. Serum PK assessments were performed in this study.

Results:

Figure 9: Mean change from baseline to endpoint in mean number of micturitions/24 h (Primary Efficacy)

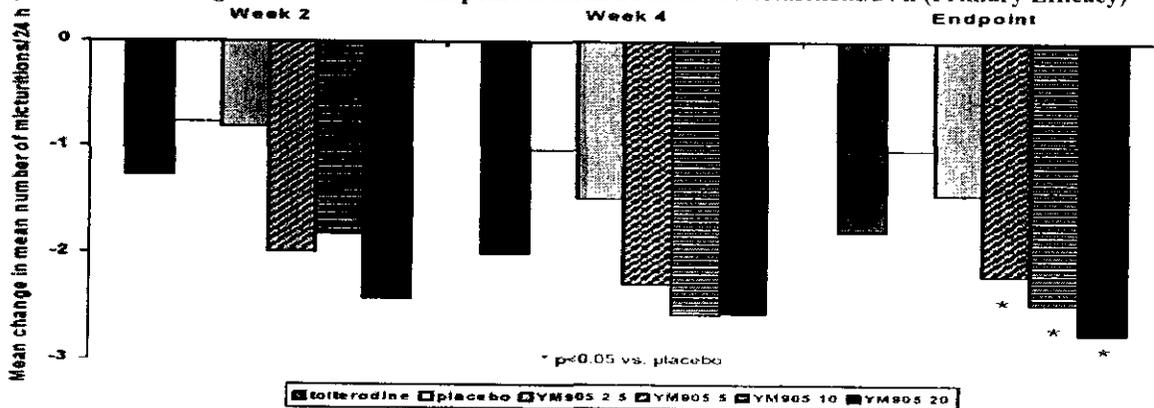


Table 15A: Efficacy Parameters

	Treatment Group					
	Placebo	YM905				Tolterodine
		2.5 mg	5 mg	10 mg	20 mg	
Micturitions/24 h	n=36	n=40	n=37	n=33	n=34	n=37
Baseline mean	11.1	11.9	11.5	11.4	11.7	12.1
Endpoint change from baseline	-1.03	-1.45	-2.21*	-2.47**	-2.75**	-1.79
Incontinence episodes/24 h	n=26	n=31	n=24	n=22	n=24	n=25
Baseline mean	2.3	2.1	2.3	2.5	1.5	2.3
Endpoint change from baseline	-0.46	-0.85	-1.32	-1.18	-0.90	-0.65
Urgency episodes/24 h	n=36	n=40	n=37	n=33	n=34	n=37
Baseline mean	5.2	5.9	5.6	5.3	5.2	5.7
Endpoint change from baseline	-1.03	-1.07	-2.35	-2.46	-2.24	-1.62
Volume voided	n=35	n=40	n=37	n=33	n=34	n=37
Baseline mean (ml)	135	148	162	153	152	160
Endpoint change from baseline	9.7	19.9	38.0**	43.2***	64.7***	14.7

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

Table 15B: **Safety:** Treatment emergent AEs reported by ≥ 3.0% of patients in any treatment group

N (%)	Tolterodine		YM905			
	2 mg bid N=37	Placebo N=38	2.5 mg od N=41	5 mg od N=37	10 mg od N=35	20 mg od N=37
Any AE	23 (62%)	18 (47%)	13 (32%)	16 (43%)	21 (60%)	24 (65%)
Eye disorders	1 (2.7%)	2 (5.3%)	1 (2.4%)	3 (8.1%)	7 (20%)	6 (16%)
Vision blurred	0 (0%)	2 (5.3%)	1 (2.4%)	1 (2.7%)	5 (14%)	5 (14%)
Gastrointestinal disorders	13 (35%)	3 (7.9%)	5 (12%)	9 (24%)	11 (31%)	19 (51%)
Abdominal pain NOS	0 (0%)	0 (0%)	2 (4.9%)	0 (0%)	1 (2.9%)	0 (0%)
Constipation	1 (2.7%)	0 (0%)	2 (4.9%)	5 (14%)	3 (8.6%)	7 (19%)
Dry mouth	9 (24%)	1 (2.6%)	0 (0%)	5 (14%)	5 (14%)	14 (38%)
Dry throat	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5.4%)
Dyspepsia	1 (2.7%)	0 (0%)	0 (0%)	1 (2.7%)	1 (2.9%)	6 (16%)
Nausea	0 (0%)	1 (2.6%)	0 (0%)	3 (8.1%)	1 (2.9%)	1 (2.7%)
Sore throat NOS	2 (5.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
General disorders & administration site conditions	5 (14%)	2 (5.3%)	1 (2.4%)	3 (8.1%)	2 (5.7%)	1 (2.7%)
Influenza like illness	1 (2.7%)	2 (5.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Infections & infestations	5 (14%)	9 (24%)	1 (2.4%)	6 (16%)	8 (23%)	4 (11%)
Bronchitis NOS	1 (2.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5.4%)
Influenza	0 (0%)	1 (2.6%)	1 (2.4%)	0 (0%)	2 (5.7%)	0 (0%)
Nasopharyngitis	1 (2.7%)	4 (11%)	0 (0%)	4 (11%)	3 (8.6%)	0 (0%)
Otitis externa NOS (exc boil of meatus)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5.7%)	0 (0%)
Urinary tract infection NOS	2 (5.4%)	2 (5.3%)	0 (0%)	1 (2.7%)	1 (2.9%)	2 (5.4%)
Investigations	1 (2.7%)	1 (2.6%)	3 (7.3%)	2 (5.4%)	4 (11%)	4 (11%)
ECG T-wave amplitude decreased	1 (2.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5.4%)
Nervous system disorders	2 (5.4%)	3 (7.9%)	4 (9.8%)	5 (14%)	4 (11%)	3 (8.1%)
Dizziness (exc vertigo)	1 (2.7%)	1 (2.6%)	1 (2.4%)	2 (5.4%)	1 (2.9%)	2 (5.4%)
Headache NOS	1 (2.7%)	1 (2.6%)	2 (4.9%)	2 (5.4%)	2 (5.7%)	2 (5.4%)
Renal & urinary disorders	1 (2.7%)	1 (2.6%)	0 (0%)	0 (0%)	1 (2.9%)	5 (14%)
Difficulty in micturition	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (8.1%)
Dysuria	1 (2.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5.4%)
Urinary retention	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5.4%)
Respiratory, thoracic & mediastinal disorders	2 (5.4%)	2 (5.3%)	3 (7.3%)	0 (0%)	0 (0%)	2 (5.4%)
Nasal dryness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5.4%)
Skin & subcutaneous tissue disorders	1 (2.7%)	1 (2.6%)	0 (0%)	2 (5.4%)	2 (5.7%)	1 (2.7%)
Sweating increased	0 (0%)	0 (0%)	0 (0%)	2 (5.4%)	0 (0%)	0 (0%)

Study 905-CL-006

This was a Phase 2 multi-center, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, dose-ranging study of YM905 in 265 male and female patients with overactive bladder. The study was conducted on an outpatient basis and consisted of a 2-week placebo run-in screening period, a 1-day baseline period including randomization, a 4-week treatment period, and a 2-week post-treatment follow-up period. The objective of this Phase 2 study was to determine, over a 4-week period, which of 4 fixed-dose levels of YM905 (2.5, 5, 10, or 20 mg once daily) versus placebo provided the optimum profile of efficacy and safety in reducing symptoms associated with overactive bladder. The primary/secondary efficacy and safety assessments were identical to the Study 905-CL-005 (described above).

Results

Table 16A: Efficacy Parameters

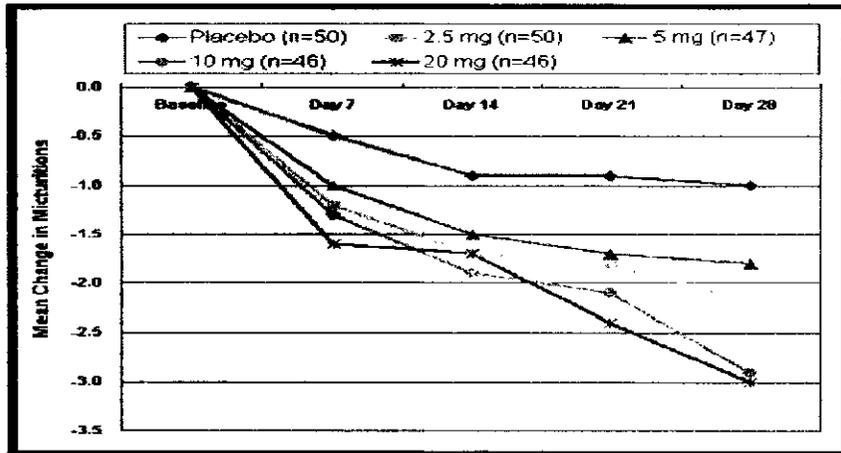
	Treatment Group				
	Placebo	YM905			
		2.5 mg	5 mg	10 mg	20 mg
No. of micturitions/24 h	n=53	n=53	n=52	n=51	n=52
Baseline mean	10.9	11.4	11.1	12.5	11.6
Endpoint ^a	-1.0	-2.0	-1.8	-3.0***	-2.8**
Incontinence episodes/24 h^b	n=43	n=45	n=45	n=39	n=43
Baseline mean ^b	2.3	2.9	2.3	3.7	2.7
Endpoint	-1.3	-1.5	-1.3	-2.5**	-1.4
Nocturia episodes/24 h	n=53	n=53	n=52	n=51	n=52
Baseline mean	2.0	1.8	1.7	2.3	2.5
Endpoint	-0.3	-0.4	-0.3	-0.7	-0.8
Urgency episodes/24 h	n=53	n=53	n=52	n=51	n=52
Baseline mean	6.7	8.0	7.2	7.7	7.3
Endpoint	-2.1	-2.4	-2.0	-3.0	-2.9
Volume voided^c	n=53	n=53	n=50	n=51	n=51
Baseline mean	196	182	170	189	184
Endpoint	6	30	36*	56***	48**

*P < 0.05; **P < 0.01; ***P < 0.001 in pairwise comparisons between treatment groups and placebo
a: Endpoint was the last available on-treatment visit on or before Day 28
b: Patients with a baseline mean of 0 were excluded from the summary
c: Only urine volumes from complete, voluntary micturitions were used in calculations

Table 16B: Safety: # of AEs reported during or post treatment (occurring > 3 patients in each treatment group)

Body System/ Adverse Event	Treatment Group				
	Placebo	YM905			
		2.5 mg	5 mg	10 mg	20 mg
Number of patients	53	54	52	51	54
Total number of patients reporting adverse events	29 (55%)	29 (54%)	33 (63%)	32 (63%)	44 (81%)
Digestive					
Dry mouth	4 (8%)	5 (9%)	6 (12%)	17 (33%)	26 (48%)
Constipation	0 (0%)	7 (13%)	5 (10%)	5 (10%)	7 (13%)
Dyspepsia	1 (2%)	1 (2%)	2 (4%)	1 (2%)	6 (11%)
Body as a whole					
Headache	2 (4%)	3 (6%)	4 (8%)	2 (4%)	2 (4%)
Flu syndrome	1 (2%)	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Pain (back)	0 (0%)	3 (6%)	1 (2%)	0 (0%)	1 (2%)
Urogenital					
Urinary tract infection	0 (0%)	2 (4%)	5 (10%)	2 (4%)	6 (11%)
Urinary retention	1 (2%)	0 (0%)	1 (2%)	0 (0%)	5 (9%)
Respiratory					
Rhinitis	4 (8%)	1 (2%)	2 (4%)	6 (12%)	3 (6%)
Special senses					
Blurred vision	0 (0%)	1 (2%)	2 (4%)	0 (0%)	3 (6%)

Figure 10: Mean change from baseline in the number of micturitions per 24 hours for patients who completed Day 28 of the study (completers subgroup, N=239)



Sponsor also collected limited serum solifenacin PK samples (on Day -1, Day 14, Day 28, and Day 42) submitted an 'Exploratory' PK-PD report from [redacted] using S-Plus software.

Figure 12

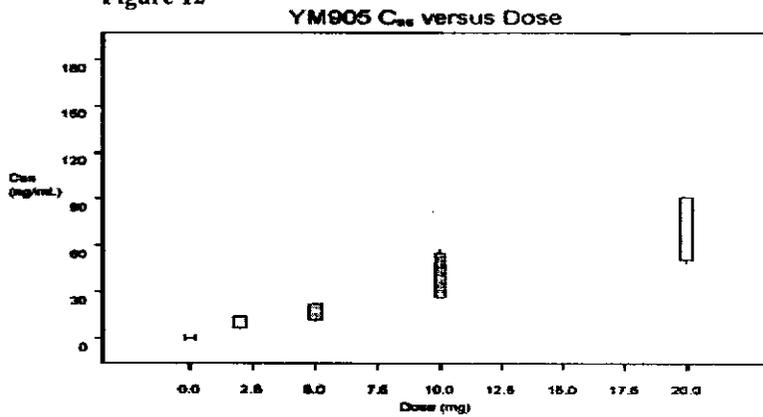


Figure 13A

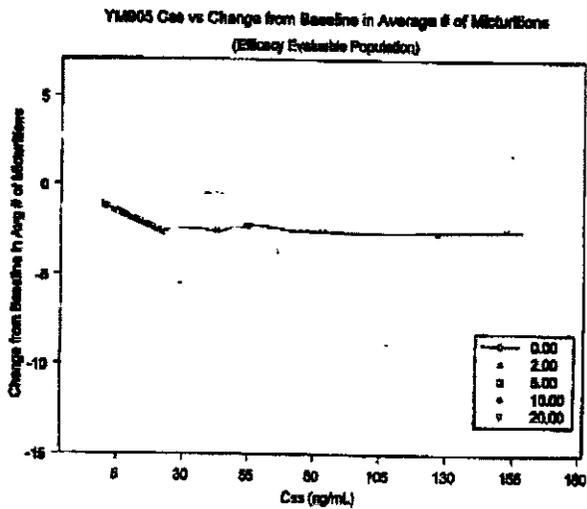


Figure 13B

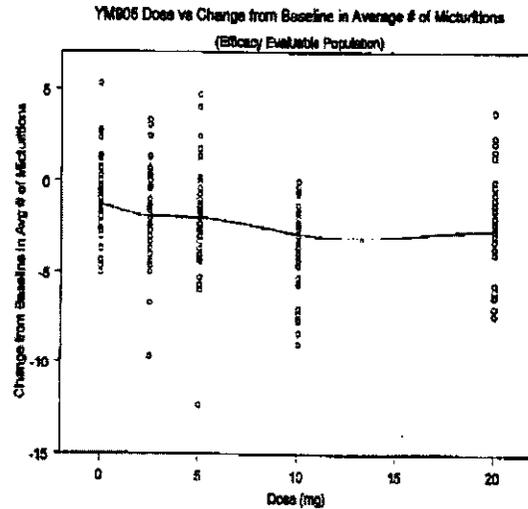
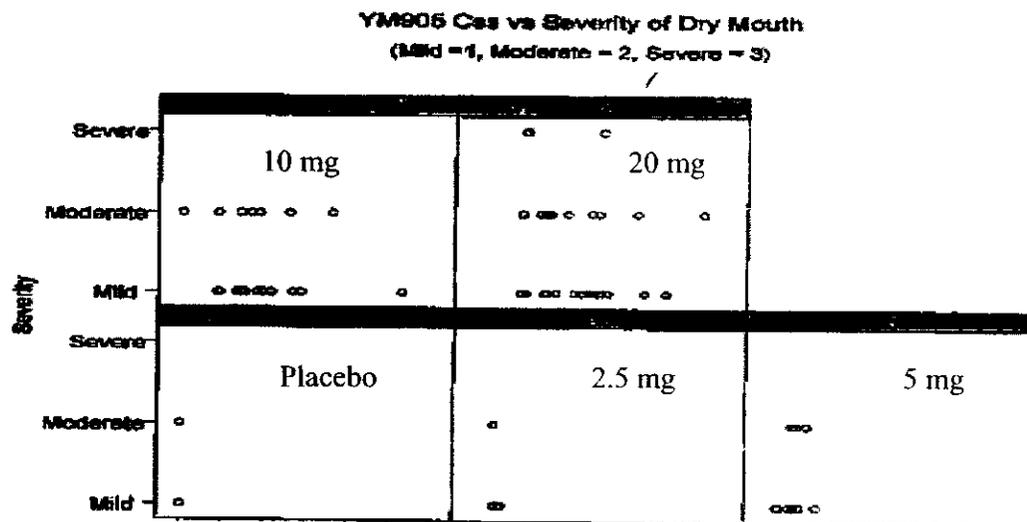


Figure 14. YM905 Cas vs Severity of Dry Mouth – Conditioned on Dose (mg)



Reviewer's Comments:

Efficacy

- From the first study (see Table 15A), the sponsor clearly established 5 mg as the lowest effective dose (since 2.5 mg was not different statistically from placebo). Efficacy (at least based on the primary end point of # of micturitions/24 hours) did not seem to have maximized even at the 20 mg dose (however, some of the secondary end points such as incontinence and urgency showed maximum effect at the 10 mg level).
- Results from the second study were interestingly different. While 10 mg was the lowest effective dose, efficacy had also peaked at that dose (as evident from Table 16A and Figure 13).
- Hence, just from an efficacy standpoint, choice of 5, 10 and probably 20 would be justified (combining results from the 2 dose-finding studies).

Safety

- In first study, as dose increased from 5 – 20 mg, the most commonly expected AEs (dry mouth, constipation etc.) incidences increased (see Table 15B). Expected AEs were similar between the 5 and 10 mg group, but about 2 fold higher for the 20 mg group as compared to the 10 mg. The number of treatment related drop-outs was 2-fold higher for 20 mg as compared to the 10 mg.
- The second study showed a dose dependent increase of % of patients with expected AEs (Table 16B). Similar to the first study, the number of treatment related drop-outs was two-fold for the 20 mg group as compared to 10 mg.
- The dose dependent increase of frequency and severity of dry mouth (the most anticipated common AE of this class of drugs) is elegantly presented in Figure 14 (Study 905-CL-006).

Overall Dose Selection

Based on combination of the results of the two adequate “proof of concept” or dose-finding studies, 5 mg is identified as the lowest effective dose. In the second study, almost 50% patients had dry mouth following the 20 mg dose. Additionally, from the first study, dry mouth from the 10 mg dose was less than a currently approved regimen (Tolterodine 2mg BID) in the same study, but not the 20 mg. Considering these facts, this reviewer supports the sponsor’s decision and believes that it was justified to pursue further development of the 5 and 10 mg doses *only* in the Phase 3 trials.

Q. What is the variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Key PK parameters (C_{max} , AUC and $t_{1/2}$) obtained in the single and multiple dose studies showed % CV values of 10 – 40% in healthy subjects. Not much detailed information on these parameters is available in the OAB patient population (since intensive PK assessments were not performed in the Phase 2 dose finding studies). One might get an idea of the variability in C_{ss} values in patients from different doses from Figure 12 above. The causes of variability may be related to differences in drug metabolism and clearance.

Intrinsic Factors

Q. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Patients with OAB are considered healthy otherwise, unless age and other disease conditions are prevalent. Hence, a significant difference in the PK parameters of the drug and metabolites are not expected between the patients and normal volunteers.

Since intensive PK sampling were not performed in the patient population in the dose finding studies, a direct comparison of the parameters in patients and volunteers is not possible.

Q. What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Gender:

Sponsor compiled information from several CPB studies to compare PK parameters in the two sexes:

Table 17A: Summary of t_{max} values found in men and women.

Study	5 mg, single dose		10 mg, single dose		20 mg, single dose	
	Men	Women	Men	Women	Men	Women
905-CL-004			5.83 (2.04) N = 6	6.17 (2.56) N = 6	5.17 (2.23) N = 6	5.84 (2.04) N = 6
905-CL-010 (-keto)			6.22 (1.10) N = 9	5.38 (0.74) N = 8		
	5 mg, multiple dose		10 mg, multiple dose		20 mg, multiple dose	
905-CL-004			8.00 (2.53) N = 6	9.01 (1.11) N = 6	6.20 (3.49) N = 6	7.34 (1.03) N = 5
905-CL-029	5.32 (4.49) N = 22	4.64 (1.87) N = 22	4.39 (2.11) N = 23	4.86 (1.36) N = 22		

Data are expressed as mean (SD); t_{max} values are in hours; -Keto - in the absence of ketoconazole

Table 17B: Summary of C_{max} values found in men and women.

Study	5 mg, single dose		10 mg, single dose		20 mg, single dose	
	Men	Women	Men	Women	Men	Women
905-CL-004			9.72 (2.06) N = 6	15.6 (5.3) N = 6	24.8 (5.7) N = 6	20.1 (4.1) N = 6
905-CL-010 (-keto)			12.5 (2.8) N = 9	16.7 (3.0) N = 8		
	5 mg, multiple dose		10 mg, multiple dose		20 mg, multiple dose	
905-CL-004			41.4 (10.9) N = 6	56.0 (15.1) N = 6	88.2 (34.6) N = 6	72.1 (24.7) N = 6
905-CL-029	32.3 (13.2) N = 22	32.3 (9.0) N = 22	62.6 (25.8) N = 23	63.2 (20.6) N = 22		

Data are expressed as mean (SD); C_{max} values are in ng/ml; -Keto - in the absence of ketoconazole

Table 17C: Summary of AUC values found in men and women.

Study	5 mg, single dose		10 mg, single dose		20 mg, single dose	
	Men	Women	Men	Women	Men	Women
905-CL-004			673 (180) N = 6	986 (429) N = 6	1878 (424) N = 6	1169 (457) N = 6
905-CL-010 (-keto)			679 (219) N = 9	863 (306) N = 8		
	5 mg, multiple dose		10 mg, multiple dose		20 mg, multiple dose	
905-CL-004			879 (232) N = 6	1157 (351) N = 6	1801 (748) N = 6	1428 (530) N = 6
905-CL-029	646 (273) N = 22	628 (205) N = 22	1248 (525) N = 23	1223 (391) N = 22		

Data are expressed as mean (SD); AUC values are in ng.h/ml, after a single dose $AUC = AUC_{0-inf}$, after multiple dosing $AUC = AUC_{0-72h}$; -Keto - in the absence of ketoconazole

Table 17D: Summary of $t_{1/2}$ values found in men and women.

Study	5 mg, single dose		10 mg, single dose		20 mg, single dose	
	Men	Women	Men	Women	Men	Women
905-CL-004			51.2 (10.7) N = 6	52.9 (13.8) N = 6	65.3 (20.5) N = 6	48.1 (18.1) N = 6
905-CL-010 (-keto)			46.6 (8.6) N = 9	52.2 (13.8) N = 8		
	5 mg, multiple dose		10 mg, multiple dose		20 mg, multiple dose	
905-CL-004			65.3 (13.6) N = 6	69.5 (29.2) N = 6	82.3 (35.4) N = 6	56.9 (17.1) N = 6
905-CL-029	68.0 (18.0) N = 22	60.8 (18.9) N = 22	63.9 (17.7) N = 23	57.7 (16.2) N = 22		

Data are expressed as mean (SD); $t_{1/2}$ values are in hours; -Keto- in the absence of ketoconazole

Reviewer's comments:

- Comparisons of PK parameters with all but one studies show that there are not much differences between males and females. In Study 905-CL-004, both for the single and multiple dose comparisons, the exposure values were 30 – 60% higher in women with the 10 mg dose.
- Values of $t_{1/2}$ s were similar in the two genders in all studies indicating that clearance is probably similar in males and females.
- It is not clear why in Study 905-CL-004 with the 20 mg dose, exposure and $t_{1/2}$ values were longer in men as compared to females.

Age:

Sponsor compared studies 905-CL-004 (elderly subjects) and 905-CL-002 (young subjects), as well as presented data from Study 905-CL-029 (single study involving young and old males and females) to compare the PK parameters in the old (65-80 yrs) vs. the young (18-55 yrs).

Table 18A: Summary of t_{max} values observed in young and elderly subjects.

	Young		Elderly	
	905-CL-002	905-CL-029	905-CL-004	905-CL-029
10 mg, first dose	4.71 (2.56) N = 7		6.00 (2.22) N = 12	
20 mg, first dose	2.94 (1.47) N = 8		5.51 (2.07) N = 12	
5 mg, last dose		4.43 (1.89) N = 21		5.48 (4.36) N = 23
10 mg, last dose	4.21 (1.82) N = 7	4.05 (1.21) N = 22	8.51 (1.94) N = 12	5.17 (2.06) N = 23
20 mg, last dose	3.81 (2.17) N = 8		6.82 (2.40) N = 11	

Data are expressed as mean (SD); t_{max} values are in hours.

Table 18B: Summary of C_{max} values observed in young and elderly subjects.

	Young		Elderly	
	905-CL-002	905-CL-029	905-CL-004	905-CL-029
10 mg, first dose	15.8 (5.9) N = 7		12.7 (4.9) N = 12	
20 mg, first dose	31.4 (8.5) N = 8		22.4 (5.4) N = 12	
5 mg, last dose		29.8 (9.4) N = 21		34.6 (12.4) N = 23
10 mg, last dose	40.6 (8.5) N = 7	57.4 (17.5) N = 22	48.7 (14.7) N = 12	68.2 (26.8) N = 23
20 mg, last dose	114 (48) N = 8		79.4 (29.2) N = 11	

Data are expressed as mean (SD); C_{max} values are in ng/ml

Table 18C: Summary of AUC values observed in young and elderly subjects.

	Young		Elderly	
	905-CL-002	905-CL-029	905-CL-004	905-CL-029
10 mg. first dose	786 (339) N = 7		830 (354) N = 12	
20 mg. first dose	1529 (872) N = 8		1523 (560) N = 12	
5 mg. last dose		574 (204) N = 21		694 (257) N = 23
10 mg. last dose	749 (161) N = 7	1117 (371) N = 22	1018 (319) N = 12	1350 (513) N = 23
20 mg. last dose	2270 (979) N = 8		1597 (634) N = 11	

Data are expressed as mean (SD). AUC values are in ng.h/ml. For single dose results AUC_{0-24h} is reported. In case of multiple dose results AUC_{0-24h} is used.

Table 18D: Summary of $t_{1/2}$ values observed in young and elderly subjects.

	Young		Elderly	
	905-CL-002	905-CL-029	905-CL-004	905-CL-029
10 mg. first dose	47.4 (12.1) N = 7		52.0 (11.8) N = 12	
20 mg. first dose	50.8 (19.0) N = 8		56.7 (20.5) N = 12	
5 mg. last dose		56.2 (11.6) N = 21		71.9 (20.8) N = 23
10 mg. last dose	45.0 (12.3) N = 7	52.5 (8.8) N = 22	67.4 (21.9) N = 12	68.9 (19.3) N = 23
20 mg. last dose	64.8 (19.9) N = 8		68.4 (28.7) N = 11	

Data are expressed as mean (SD). $t_{1/2}$ values are in hours.

Reviewer's comments:

- In Study 905-CL-029, there was a 20 – 25% increase in C_{max} , AUC and $t_{1/2}$ values in the elderly as compared to the young.
- Protein binding was negligibly different in the two groups (results not shown).

Ethnicity:

Sponsor performed PK studies in Caucasian and Japanese populations and obtained the following Comparative results:

Table 19: Comparison of the pharmacokinetic parameters obtained in European and Japanese studies after single and multiple doses of 10 mg solifenacin

Study	Location	Dose no.	t_{max} (h)	C_{max} (ng/ml)	AUC (ng.h/ml)	$t_{1/2}$ (h)
905-CL-001	Europe	Single dose	4.00 (1.55) N = 6	11.8 (1.6) N = 6	*	*
905-CL-002	Europe	Single dose	4.71 (2.56) N = 7	15.8 (5.9) N = 7	786 (339) N = 7	47.4 (12.1) N = 7
905-CL-002	Europe	Steady state	4.21 (1.82) N = 7	40.6 (8.5) N = 7	749 (161) N = 7	45.0 (12.3) N = 7
905-CL-007	Japan	Single dose	5.67 (0.78) N = 12	14.9 (3.4) N = 12	752 (256) N = 12	40.3 (9.2) N = 12
905-CL-012	Japan	Single dose	6.33 (1.58) N = 9	14.2 (3.0) N = 9	699 (227) N = 9	37.8 (7.9) N = 9
905-CL-012	Japan	Steady state	5.89 (2.32) N = 9	42.2 (15.4) N = 9	825 (339) N = 9	46.5 (11.4) N = 9

* Samples were collected over a too short period of time to allow an accurate estimate of AUC_{0-inf} and $t_{1/2}$.

Reviewer's Comments

- From the above data, it does not appear that there was an appreciable difference in the PK parameters of solifenacin between Caucasian and Japanese subjects.
- In the Population PK report involving 2 phase 3 studies, it was mentioned that the proportional variety of ethnicity among Caucasian/African American/Hispanic/Asian/Other was 559/45/25/5/7
- Numerically, sponsor has not adequately compared all representative ethnic groups.

Disease Conditions:

a) *Renal Impairment*

Solifenacin succinate is primarily cleared from the body by way of metabolism through the P450 isoenzyme 3A4. Urinary excretion plays a minor role in solifenacin succinate clearance from the body. While the sponsor believes that decreased renal function will not clinically affect the overall clearance or effects of solifenacin succinate, this question must be evaluated, particularly in light of studies that suggest that both acute renal failure (ARF) and chronic renal failure (CRF) may decrease the *non-renal* clearance of compounds.

The sponsor conducted study R905-CL-021 to determine the effects of mild, moderate and severe renal impairment on the pharmacokinetics of solifenacin succinate following a single 10mg dose. This was a multi-site, open-label study in which 24 patients (6 mild, 6 moderate, and 6 severe renal disease, and 6 weight and age matched healthy volunteers) received a single 10-mg oral dose of YM905 followed by blood draws and urine collections over a 336 hour period. 4 groups were studied (6 subjects/group):

- Group 1: normal renal function (CrCl > 80 ml/min)
- Group 2: mild renal function (CrCl from 50 to 80 ml/min)
- Group 3: moderate renal function (CrCl from 30 to 49 ml/min)
- Group 4: severe renal function (CrCl from 10 to 29 ml/min)

Blood samples for PK analysis of YM905 and metabolites were collected during the clinic confinement period as follows: 0 hour (prior to the YM905 dose on Day 1); and on Day 1 at 1, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours post dose and on Days 3, 4, 5, 7, 9, 11, 13, and 15 post dose. The protein binding samples were assayed from samples taken at Screening/Check-in, 6 hours, and 24 hours post dose. Urine samples for PK analysis of YM905 and metabolites were collected during the clinic confinement period as follows: predose (samples taken from first urine void in the morning), 0 to 12, 12 to 24, 48, 72, 96, 144, 192, 240, 288, and 336 hours postdose. No computations for total fraction excreted can be performed because only spot samples were collected after 24 hours.

Results:

Table 20A. Summary table of PK parameters for Total Solifenacin

Renal Status		C_{max} (ng/mL)	t_{max} ^a (hr)	AUC_{0-t} (ng-hr/mL)	AUC_{0-∞} (ng-hr/mL)	t_{1/2} (hr)	CL/F (L/hr)
Healthy	MEAN	15.7	6.00	1118	1190	68.2	6.92
	SD	3.38	—	378.1	402.8	27.22	2.108
	N	6	6	6	6	6	6
Mild	MEAN	17.5	5.50	1611	1784	89.1	5.06
	SD	3.29	—	664.5	791.9	34.53	2.623
	N	6	6	6	6	6	6

Moderate	MEAN	15.2	5.00	1401	1559	90.6	5.62
	SD	4.41	—	485.7	554.7	27.26	2.670
	N	6	6	6	6	6	6
Severe	MEAN	20.6	3.50	2173	2530	111	3.19
	SD	10.51	—	638.3	699.8	38.3	0.954
	N	6	6	6	6	6	6

*Median (min, max) shown for t_{max}

Figure 15. Mean plasma concentration-time profile for total Solifenacin from healthy, mild, moderate and severe renal disease in the normal scale.

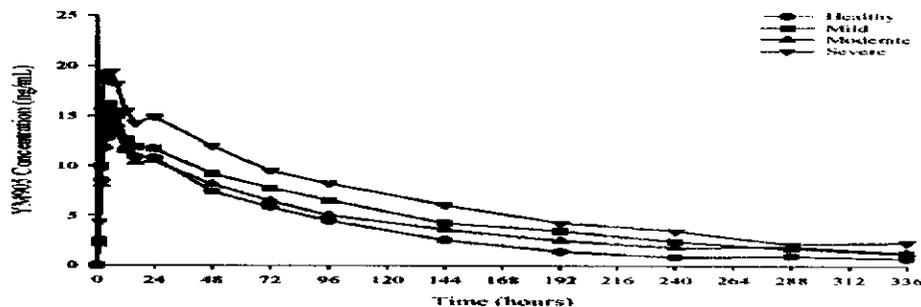


Table 20B. Solifenacin ratios (X 100%) of geometric LS mean of pharmacokinetic parameters between subject groups and corresponding 90 % confidence limits

	Mild/Healthy	Moderate/Health y	Severe/Health y
C_{MAX}	113 (83.5, 152)	96.8 (71.7, 131)	123 (91.3, 166)
AUC_{0-t}	140 (96.2, 203)	123 (84.9, 179)	196 (135, 285)
AUC_{0-inf}	144 (98.3, 211)	128 (87.4, 188)	215 (147, 316)

Table 20C. Summary of C_{max} and AUC_{0-inf} for M2, M3, M4 and M5 in Healthy and Impaired Patients^a

C_{max} (ng/ml)	Healthy	Mild	Moderate	Severe
M2	1.81 (0.57)	2.11 (0.93)	2.08 (0.81)	2.48 (1.11)
M3	0.87 (0.28)	0.873 (0.24)	1.13 (0.25)	1.48 (0.50)
M4	1.40 (0.33)	1.78 (1.07)	1.52 (0.85)	1.42 (0.80)
M5	0.79 (0.12)	0.83 (0.10)	1.09 (0.49)	1.22 (0.69)
AUC_{0-inf} (ng*hr/ml)	Healthy	Mild	Moderate	Severe
M2	224 (92.4)	304 (78.7)	362 (148.1)	539 (197.2)
M3	247 (118.9)	331 (68.9)	404 (105.7)	658 (212.0)
M4	235 (78.2)	360 (100.3)	484 (65.8)	714 (187.0)
M5	14.0 (1.61)	88.1 (112.4)	88.8 (74.9)	278 (116.8)

^aResults reported as mean (SD)

The urinary excretion data indicates that only a small portion of orally administered solifenacin is excreted unchanged in urine for all renally impaired and healthy subject groups. No computations for total fraction excreted in urine were performed due to collection of spot samples only after 24 hours postdose. Mean urinary excretion for metabolites M2, M3, M4, and M5 appeared to decrease in the renally impaired groups relative to corresponding data in the healthy group. This may be a direct result of the renal impairment or as a result of decreased hepatic metabolism as an indirect result of renal impairment, as seen with other compounds.

Reviewer's comments:

- There was a 2.1 fold increase in AUC_{0-inf} of solifenacin in the severely impaired group as compared to the normal group, and marginal increases in drug exposure in the mild and moderate impaired groups
 - There was about a 1.6-fold increase in half-life of solifenacin in the severely impaired group as compared to the healthy and a 1.3-fold increase in the mild and moderately impaired groups as compared to the healthy
 - Greater C_{max} and AUC's are seen in all metabolites with greater levels of renal impairment as seen in Table 3
 - An almost 20-fold increase is seen in M5 in severely impaired patients as compared to healthy
- The results of this study demonstrated that renal impairment influenced the pharmacokinetics of solifenacin succinate (10 mg) and its metabolites, with the greatest increases in exposure occurring in the severely renally impaired group. Based on these results, this reviewer agrees with the sponsor's proposed labeling to

b) Hepatic Impairment

In vitro studies performed by the sponsor have shown that solifenacin is primarily metabolized by cytochrome P450 (CYP450) isoenzyme 3A4 in the liver. Drugs that are primarily metabolized in the liver may have altered pharmacokinetics in patients with hepatic disease. An increase in drug exposure is expected with hepatic impairment.

The sponsor conducted study R905-CL-026 to determine the effects of hepatic impairment on the pharmacokinetics of solifenacin succinate following a single 10mg dose. This was a single center, open-label, parallel study in which 8 patients with moderate hepatic impairment and 8 healthy volunteers received a single 10 mg oral dose of solifenacin succinate. A secondary objective of the study is to evaluate the safety and tolerability of solifenacin succinate in patients with hepatic impairment. 2 subject groups were studied, with 8 subjects per group:

- Group 1: normal hepatic function (Child-Pugh's score of 5)
- Group 2: moderate hepatic impairment (Child-Pugh's score between 7-9)

Results:

Table 21A. Arithmetic Mean and SD for AUC_{0-inf} and C_{max} for Solifenacin

Parameter	Number of subjects	Healthy subjects	Hepatic impaired patients
AUC_{0-inf} (ng*hr/ml)	8	749 (528)	1042 (328)
C_{max} (ng/ml)	8	11.0 (6.0)	10.3 (3.3)

Table 21B. Point estimates and 90% confidence intervals for ratio impaired/healthy

PK parameter	Point estimate of ratio impaired/healthy	90% confidence interval	CV (%) ^a
AUC _{0-inf}	1.596	1.05 - 2.43	50
C _{max}	0.989	0.70 - 1.40	40

^athe variability for AUC_{0-inf} and C_{max} in healthy subjects is much larger than expected and larger than in hepatic impaired patients

Table 21C. Summary statistics of the plasma pharmacokinetic parameters of solifenacin

	t _{max} (h)	C _{max} (ng/ml)	AUC _{last} (ng.h/ml)	AUC _{0-inf} (ng.h/ml)	t _{1/2} (h)	CL/F (l/h)	V _d /F (l)
Healthy subjects (n = 8)	5.96 (0.77, 13%)	11.0 (6.0, 54%)	621 (403, 65%)	749 (528, 71%)	49.9 (19.9, 40%)	13.7 (6.2, 45%)	854 (244, 29%)
Patients (n = 8)	6.50 (2.53, 53%)	9.45 (3.3, 32%)	425 (237, 27%)	460 (328, 31%)	44.1 (48, 45%)	16.4 (2.26, 29%)	877 (1095, 30%)
	6.49	9.39	831	953	106	7.92	1215

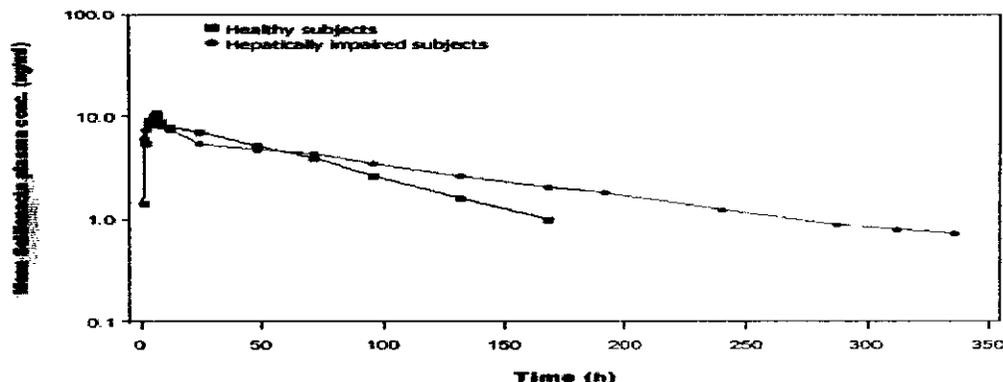
Each cell contains the arithmetic mean, between brackets the SD and CV, the range and the median.

Table 21D. Summary statistics of the plasma pharmacokinetic parameters of the solifenacin metabolites M2, M3, M4 and M5.

Metabolite		T _{max} (h)	C _{max} (ng/ml)	AUC _{last} (ng.hr/ml)	AUC _{0-inf} (ng.hr/ml)	T _{1/2} (h)
M2	Healthy (n=8)	21.2 (8.0, 38%)	2.81 (0.67, 24%)	218 (42, 19%)	282 (35, 12%)	60.5 (21.9, 36%)
	Patients (n=8)	3.90 (8.2, 209%)	1.81 (0.91, 50%)	77.7 (56.6, 73%)	ND	91.1 (37.1, 41%)
M3	Healthy (n=5)	49.0 (32.2, 66%)	0.538 (0.03, 6%)	9.94 (13.5, 136%)	ND	87.4 (25.4, 29%)
	Patients (n=4)	6.52 (1.22, 19%)	0.573 (0.04, 8%)	7.60 (11.8, 156%)	ND	117 (34, 29%)
M4	Healthy (n=8)	18.0 (6.4, 36%)	1.67 (0.58, 35%)	103 (33, 32%)	ND	56.0 (12.3, 22%)
	Patients (n=8)	12.4 (8.1, 65%)	1.15 (0.75, 65%)	63.1 (70.7, 112%)	ND	96.5 (32.5, 34%)
M5	Healthy (n=5)	4.71 (1.27, 27%)	0.872 (0.193, 22%)	4.43 (2.02, 46%)	ND	ND
	Patients (n=7)	5.00 (1.73, 35%)	1.29 (0.78, 61%)	26.4 (53.9, 205%)	ND	ND

Each cell contains the arithmetic mean, between brackets the SD and CV, and the range.

Figure 16. Mean plasma concentration vs. time profiles of solifenacin



Reviewer's comments:

- There was a 2-fold increase in the $t_{1/2}$ of solifenacin in the moderately hepatic impaired group (patients) as compared to the healthy group, with about a 35% increase in AUC_{0-inf} (Table 3).
- C_{max} was similar for both groups (Table 3).
- T_{max} for metabolites M2, M3 and M4 in healthy subjects was considerably longer than in the hepatic impaired group (Table 5). Little difference among the groups for the T_{max} value for metabolite M5.
- AUC_{0-last} for metabolites M2, M3 and M4 was 2.8-, 1.3- and 1.6-fold, respectively, greater in healthy subjects when compared to the moderately hepatic impaired group. However, the AUC_{0-last} for metabolite M5 in the moderately hepatic impaired group was 6-fold higher than in healthy subjects
- Patients with severe hepatic impairment were not studied.

The results of this study demonstrated that moderate hepatic impairment influenced the pharmacokinetics of solifenacin succinate (10 mg) and its metabolites. Based on these results, this reviewer agrees with the sponsor that patients with moderate hepatic impairment receive no more than 5 mg solifenacin succinate once daily.

Extrinsic Factors

Q. What extrinsic factors (drugs, herbals, diet, smoking, alcohol use etc.) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Metabolic Drug-Drug Interactions:

Is there an in vitro basis to suspect in vivo drug-drug interactions?

Sponsor conducted *in vitro* studies incubating solifenacin with cDNA expressed human CYP isoenzymes, used correlation analyses with liver microsomes and performed chemical inhibition studies to determine the *in vitro* capability of other drugs to effect the PK of solifenacin and *vice versa*.

In vitro effect of other drugs on solifenacin:

Based on the results with CYP isoenzymes, only CYP3A4 and CYP2C19 showed potential for metabolism of solifenacin to the major metabolite M2. Enzyme kinetics for this metabolism was similar between the 2 enzymes ($K_m \sim 100 \mu\text{M}$ (36 $\mu\text{g/ml}$ free base) and $V_{max} \sim 0.0135$ nmol/min/pmol CYP). However, correlation analyses results (eg. testosterone 6 β -hydroxylation) and chemical inhibition results (with CYP3A4 and CYP2C19 inhibitors) indicated that CYP3A4 is mostly (if not exclusively) responsible in the metabolism of solifenacin. 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.

An *in vitro* study was also conducted to evaluate the effects of ketoconazole, simvastatin, terfenadine, cyclosporin, erythromycin, cimetidine, acenocoumarole and nifedipine (known inhibitors and/or substrates of CYP3A4) on the metabolism of solifenacin by human liver microsomes. For simvastatin, terfenadine and acenocoumarole the IC_{50} values were > 100 fold higher than the plasma concentrations, and therefore, no K_i values were determined. The ratio of K_i of ketoconazole over the plasma concentration was very low (0.0045-0.018). The ratios of the K_i of cyclosporin, erythromycin and cimetidine over the plasma concentrations were between 2.4 and 59.8. For nifedipine the ratio was higher (27-106). Based on these results it may be concluded that cyclosporin, erythromycin and cimetidine have an intermediate potential to interact with the metabolism of solifenacin succinate *in vivo*. Ketoconazole is anticipated to highly affect solifenacin metabolism *in vivo*.

In vitro effect of solifenacin on other drugs:

Sponsor conducted *in vitro* investigations to determine if solifenacin (YM905) inhibits the major human cytochrome P450 (CYP) isoenzymes. Solifenacin up to 1040 nM did not significantly inhibit human CYP1A1/2, CYP2C9, CYP2D6 and CYP3A4. CYP2C19 was inhibited up to 10% with 1040nM but this was not considered to be of clinical relevance: the clinically observed C_{max} values in steady state after q.d. dosing of 10 mg solifenacin succinate are lower (— ng/ml ~ — nM). Similar tests were also performed with all the detectable metabolites (M2, M3, M4 and M5) and results show that other than very weak inhibition potential of 2C19 and 3A4, other enzymes were unaffected by solifenacin and its metabolites. Thus, the sponsor concluded that solifenacin and its metabolites will not clinically affect the CYP-dependent metabolism of concomitant medication.

Is there a potential for *in vivo* metabolic/pharmacokinetic drug-drug interactions?

With the above *in vitro* information, the sponsor conducted several *in vivo* metabolic PK drug-drug interaction studies with solifenacin, as follows:

Effect of Other Drugs on Solifenacin

DDI: Ketoconazole

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 YM905 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:

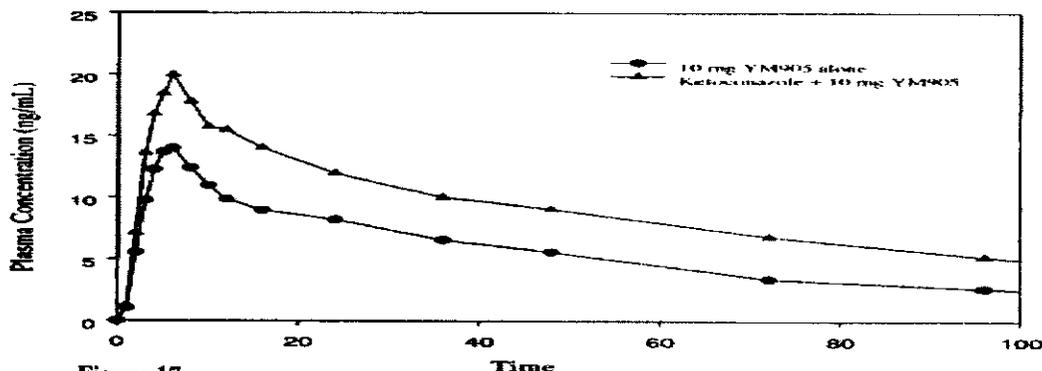


Figure 17 Mean plasma concentration-time profiles for YM905 from Treatments A and B
 Note: For sake of clarity data are shown only up to 100 hours post-dose.

Table 22 Summary table of statistical results for comparison of primary and secondary PK parameters of YM905

Parameter	Units	Test Mean ^a		Point estimate Test/Reference ^b	90% Confidence ^c Interval
		Trt B	Trt A		
C _{max}	ng/mL	20.4	14.5	141	(130 , 152)
ln(C _{max})		20.0	14.1	143	(129 , 157)
AUC _{0-t}	ng·hr/mL	1407	714	197	(180 , 214)
ln(AUC _{0-t})		1360	662	205	(184 , 229)
AUC _{0-∞}	ng·hr/mL	1499	765	196	(179 , 213)
ln(AUC _{0-∞})		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

Note: Treatment A: 1 x 10 mg YM905

Treatment B: 200 mg qd ketoconazole from Days 15 through 34 plus 1 x 10 mg single dose YM905 on Day 21

Since 200 mg QD is not the maximal dose of ketoconazole, OCPB had expressed that a study with 400 mg QD would have been preferable. More recently (6/16/2003), sponsor sent in a completed study report of an exactly 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 folds 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, exposures in females were higher than males. However, the ratios of increases in PK parameters of solifenacin in presence of 400 mg QD ketoconazole were similar.

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% (see later in the BIOPHARMACEUTICS section). 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 solefenacin were not analyzed (or reported) in this study.
- There were sporadic incidences of QT prolongation in both the studies based on individual ECGs in all treatment arms. However, a trend towards increases in QT prolongation in the solifenacin + ketoconazole arm was *not* evident in either study.
- Based on the above information, it not to exceed a 5 mg dose of solifenacin when in combination with ketoconazole.

Effect of Solifenacin on Other Drugs

DDI: Digoxin

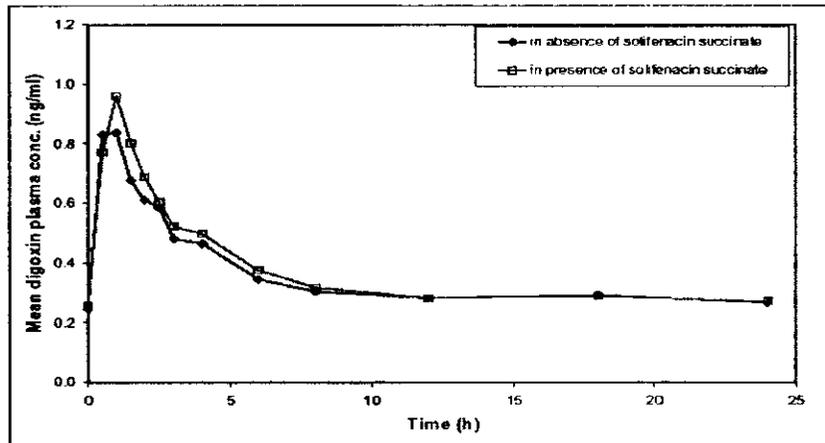
This single center study (905-CL-025) was of an open, one-sequence crossover, multiple dose design. 24 subjects were admitted for 21 days. All subjects were to start treatment with digoxin for 8 days (loading dose of 0.250 mg digoxin on Day 1, followed by 0.125 mg digoxin QD on Days 2 to 8). Consecutively, they were to receive 10 mg solifenacin succinate in combination with 0.125 mg digoxin QD. (from Day 9 to 18). The subjects were to be admitted the day before the first study drug administration (Day 0). The subjects were to be discharged on Day 20. Approximately one week after discharge, the subjects were to return to the unit for a post study visit.

Results:

Table 23. Summary statistics of the plasma PK parameters of digoxin.

			Digoxin + solifenacin succinate
t_{max} (h)	Arithmetic mean	0.81	0.98
	(SD, CV)	(0.39, 49%)	(0.41, 42%)
	Min-Max	—	—
	Median	0.52	1.00
C_{max} (ng/ml)	Arithmetic mean	0.93	1.05
	(SD, CV)	(0.18, 20%)	(0.26, 25%)
	Min-Max	—	—
	Median	0.91	1.03
AUC_{0-24h} (ng.h/ml)	Arithmetic mean	8.43	8.74
	(SD, CV)	(1.66, 20%)	(2.11, 24%)
	Min-Max	—	—
	Median	8.05	8.29
CL/F (l/h)	Arithmetic mean	15.3	15.1
	(SD, CV)	(2.6, 17%)	(3.5, 23%)
	Min-Max	—	—
	Median	15.5	15.1

Figure 18. Mean plasma concentrations vs. time profiles of digoxin in the absence and presence of solifenacin succinate.



Reviewer's comments:

- Study design issue: since it takes about 14 days for achievement of solifenacin steady state, sponsor could have continued concomitant administration of the two drugs from day 9 to at least till day 22 (instead of day 18) to ensure steady state levels of solifenacin.
- There was not much of an effect of solifenacin on digoxin PK. AUC and C_{max} values, when compared with or without solifenacin are within the BE criterion (results not shown).
- Effect of digoxin on solifenacin PK was minimal.
- There is no need to adjust solifenacin dose when in combination with digoxin.

DDI: Warfarin

Sponsor conducted Study 905-CL-028 to evaluate the effect of solifenacin succinate on the pharmacodynamics and pharmacokinetics of warfarin in healthy male subjects.

During two study periods separated by 10 days, subjects received a single oral dose of warfarin (25 mg) on the 10th day of dosing with either solifenacin succinate, 10 mg, or matching placebo once daily for 16 days. The study was double-blind, randomised, placebo-controlled, and crossover with regard to solifenacin succinate administration, and open label with regard to warfarin administration. Blood samples were drawn for measurement of prothrombin time (PT) and plasma concentrations of R- and S-warfarin before and at the following time points after the warfarin dose: 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, 60 h, 72 h, 96 h, 120 h, 144 h and 168 h. Additional samples were collected for measurement of solifenacin concentrations before and at the following time points after dosing on Study Day 10: 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 12 h. Trough concentration of solifenacin was measured on Study Days 8, 9, 11, 12, 14 and 16. A total of 12 subjects completed the study.

Results:

Pharmacodynamics

Table 24A. AUC_{0-inf} and $AUC_{PT; 0-168h}$: ratio of value during warfarin + solifenacin to value during warfarin + placebo.

Variable (unit)	Point estimate of the ratio	90 % confidence interval
$AUC_{PT; 0-168h}$ (s.h)	1.005	0.984 - 1.025
AUC_{0-inf} , R-warfarin (ng.h/ml)	0.967	0.872 - 1.073
AUC_{0-inf} , S-warfarin (ng.h/ml)	0.982	0.879 - 1.097

Table 24B. PT_{max} : ratio of value during warfarin + solifenacin to value during warfarin + placebo.

Variable (unit)	Point estimate of the ratio	90 % confidence interval
PT_{max} (s)	0.997	0.955 - 1.041

Table 24C. t_{PTmax} : value during warfarin + solifenacin minus warfarin + placebo.

Variable (unit)	Point estimate of the difference	90 % confidence interval
t_{PTmax} (h)	0.025	-0.010 - 5.975

Table 24D. Summary statistics of the pharmacodynamic parameters

Parameter	Statistic	Warfarin and placebo	Warfarin and solifenacin succinate
$AUC_{PT; 0-168h}$ (s.h)	Arith. mean	2,427	2,437
	(SD, CV)	(231, 10 %)	(216, 9 %)
	Range	—	—
	Median	2,348	2,364
PT_{max} (s)	Arith. mean	21.5	21.5
	(SD, CV)	(3.0, 14 %)	(3.2, 15 %)
	Range	—	—
	Median	21.8	20.4
$t_{PT; max}$ (h)	Arith. mean	38.0	39.0
	(SD, CV)	(4.7, 12 %)	(5.4, 14 %)
	Range	—	—
	Median	36.0	36.0

Pharmacokinetics

Table 25. Summary statistics of the plasma PK parameters of R- and S-warfarin

Parameter	Statistic	R-warfarin		S-warfarin	
		Warfarin and placebo	Warfarin and solifenacin succinate	Warfarin and placebo	Warfarin and solifenacin succinate
t_{max} (h)	Arith. mean	2.36	2.34	2.36	2.09
	(SD, CV)	(1.48, 63 %)	(2.06, 88 %)	(1.48, 63 %)	(1.57, 75 %)
	Range				
	Median	2.00	1.51	2.00	1.51
C_{max} (ng/ml)	Arith. mean	1,412	1,456	1,402	1,470
	(SD, CV)	(305, 22 %)	(385, 26 %)	(328, 23 %)	(420, 29 %)
	Range				
	Median	1,347	1,320	1,352	1,366
AUC _{last} (ng.h/ml)	Arith. mean	62,418	61,176	42,015	42,581
	(SD, CV)	(13,172, 21 %)	(16,768, 27 %)	(12,999, 31 %)	(17,852, 42 %)
	Range				
	Median	62,568	61,495	42,168	40,515
AUC _{0-inf} (ng.h/ml)	Arith. mean	67,417	65,948	45,114	45,484
	(SD, CV)	(15,611, 23 %)	(18,922, 29 %)	(13,921, 31 %)	(18,800, 41 %)
	Range				
	Median	66,361	65,580	44,891	42,675
CL/F (l/h)	Arith. mean	0.196	0.205	0.300	0.312
	(SD, CV)	(0.052, 27 %)	(0.060, 30 %)	(0.086, 29 %)	(0.109, 35 %)
	Range				
	Median	0.188	0.191	0.279	0.293
$t_{1/2}$ (h)	Arith. mean	41.4	40.9	28.9	28.3
	(SD, CV)	(9.0, 21 %)	(7.9, 19 %)	(8.8, 30 %)	(8.4, 29 %)
	Range				
	Median	41.8	43.4	30.0	26.4

Reviewer's comments:

- There was no detectable PK or PD interaction effect of solifenacin on warfarin.
- No effects of warfarin on solifenacin PK were detectable (results not shown).
- There is no need to adjust the dose of either drug when used concomitantly.

DDI: Combined Oral Contraceptive (COC)

Sponsor conducted a study to determine the effect of solifenacin, if any, on a combined oral contraceptive containing 30 µg ethinyl estradiol (EE) + 150 µg levonorgestrel (LNG). This study may not have been warranted from the *in vitro* metabolic information. However, considering the population of use for solifenacin, this study was conducted for safety reasons.

This was a double blind, placebo-controlled, two-period cross-over study in a group of 24 subjects. Before admission into the study, each subject should have been taking a COC (containing 30 µg EE plus either 125 µg or 150 µg LNG) for at least three cycles. During the study, all subjects were to receive Microgynon®, Schering AG, which contains 30 µg EE plus 150 µg LNG. The 24 subjects were to be studied in three cohorts of eight subjects each. All subjects in each cohort of eight should have received their pre-study COC in such a way that they could start their study COC on the same day. In order to achieve this, some subjects in the cohort might have received their pre-study COC longer than other subjects. Any mention of COC below refers to Microgynon®.

Subjects were to receive 2 cycles of 21 days of COC treatment. In addition to COC, subjects randomly received the following treatments:

- A. 1 tablet of 10 mg of YM905 per day for 10 days, starting on the 12th day of COC treatment.
- B. 1 tablet of YM905-placebo per day for 10 days, starting on the 12th day of COC treatment.

Subjects in each cohort were to start their study COC on the same day (Day 1) and to continue for 21 days in period I. After a 7-day period (without a COC) to allow for a break-through bleeding, they were to re-start the COC for 21 days in period II. In each period, starting from the 12th day of receipt of the COC, subjects were to receive additionally either YM905 (10 mg o.d.) or matching placebo, for 10 days. Thus, the washout for YM905 or placebo between the two cross-over periods was to be at least 17 days. An intermediate cycle with only the COC for 21 days was permitted.

Results:

Table 26A Summary statistics of the plasma pharmacokinetic parameters of ethinyl estradiol (EE).

	COC+placebo* (n=23)	COC+YM905 (n=23)
C _{max} (pg/ml)	110 (30, 27%) — 111	112 (34, 30%) — 104
AUC _{0-10h} (pg.h/ml)	1111 (305, 27%) — 1105	1144 (312, 27%) — 1115

Table 26B Summary statistics of the plasma pharmacokinetic parameters of levonorgestrel (LNG).

	COC+placebo* (n=23)	COC+YM905 (n=23)
C _{max} (ng/ml)	6.98 (1.76, 25%) — 6.41	6.90 (1.67, 24%) — 6.89
AUC _{0-10h} (ng.h/ml)	85.4 (26.6, 31%) — 80.7	84.8 (27.5, 32%) — 79.1

Data presented as mean (SD, CV%), the range and median.

Reviewer's comments:

- Based on the above results and statistical analysis (not shown here), there was no detectable effects of solifenacin on the PK of EE or LNG (or SHBG) and *vice versa*.
- LH and FSH values largely remained below the LOQ (as expected with use of COC).
- No dosage adjustments may be necessary with this combined usage.

Cardiac Repolarization (QT Prolongation)

The sponsor attempted to address the issue whether solifenacin is responsible for clinically relevant prolongation of the QT segment of electrocardiograms, a phenomenon that may lead to serious arrhythmia and has been the reason for the market-withdrawal of several drugs in recent times. 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 orally QD in healthy male and pre- & post-menopausal female volunteers.

This study was reviewed by OCPB reviewers Drs. Stephan Ortiz and He Sun. Their review is attached in Appendix 1. Below are the major conclusions/comments.

Reviewer's Comments

Sponsor conducted a study that was prospectively and adequately (based on PK parameters and increased exposure scenarios) designed to determine the effect of solifenacin on cardiac repolarization ("QT prolongation"). Amidst highly variable results from the study and a number of outliers of potential concern, the mean changes in QT_c corrected for baseline and placebo was 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 QT prolonging drug etc). Please see Appendix 1 for a detailed report on the study. However, clinical significance of the results from this study is beyond the scope of this review, and should be decided by the Clinical Team.

**APPEARS THIS WAY
ON ORIGINAL**

Biopharmaceutics

Is the proposed to-be-marketed formulation identical to the pivotal clinical trial formulation?

The formulation for the commercial tablets is the same formulation used to produce tablets for the Phase 3 clinical studies. The batch size that was used to produce the Phase 3 clinical tablets was

greater than $\frac{1}{10}$ of the batch size to be used in commercial production, and the equipment for producing the Phase 3 tablets and the commercial tablets is of the same design and operating principles, and are categorized in the same subclass according to procedures outlined in the SUPAC-IR guidance. Solifenacin succinate tablets for Phase 3 studies were manufactured at YPT, Palo Alto, CA. The site-specific commercial scale batches were manufactured at YPT, Norman Manufacturing Center, Norman, OK. In support of the equivalence of the Phase 3 and the commercial tablets, the dissolution profiles of Phase 3 tablets and commercial tablets were compared. The results of dissolution tests of Phase 3 tablets and the commercial tablets were analyzed statistically by a multivariate region procedure, and the similarity of those tablets was confirmed. Based on the Phase 3 and commercial formulations being identical, a request for a waiver from the requirement to conduct an in vivo bioequivalence study between the solifenacin succinate Phase 3 clinical trial and the commercial formulations of the drug product was submitted to the Agency on 27 July 2001. A letter was sent from FDA accepting the requested waiver, contingent on the results of the dissolution testing as specified in the waiver request. The following table lists all formulation changes during drug development.

Table 27. Description of solifenacin formulation changes and associated level based on SUPAC

Clinical Studies	Dosage Form	Purpose of PK Study	Change Level in Drug Products			Studies Required	
			Composition	Site of Manufacture	Batch Size	Dissolution	Bioequivalence Study
Phase 1	Capsules	Dose rising	-	-	-	Not performed in this early stage	Not performed in this early stage
	Tablets	Food Effect	Level 3	Not changed (Japan)	-		
Phase 2	Tablets	None	Amount of $\frac{1}{10}$ Level 2	Level 3 (Japan → USA)	-	Case B*	Not necessary
Phase 3	Tablets	Absolute ^b BA					
Commercial	Tablets	None	Not changed	Level 3 (California → Oklahoma)	-	Case B*	Not necessary

*Case B dissolution test conditions: Multipoint profile in $\frac{1}{10}$ as the application medium

^bThis study is classified as Phase 1 study. However, absolute BA study was conducted with Phase 3 tablets whose composition was the same as that of the commercial tablets

Comparative Dissolution Between Phase 3 and Commercial Batches:

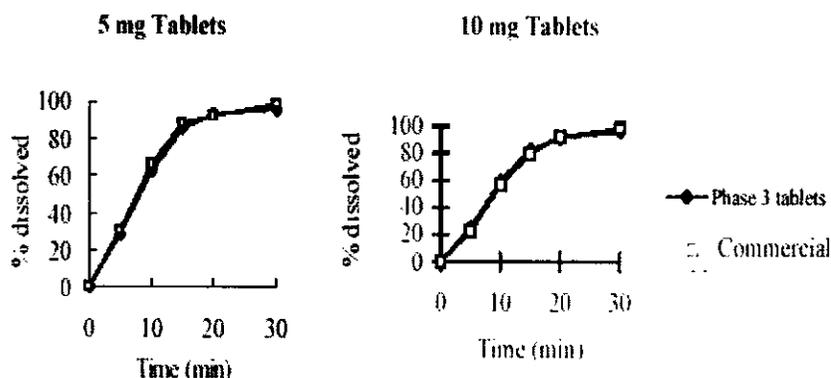
Table 28. Multivariate confidence region values calculated from the dissolution profiles of solifenacin 5 mg and 10 mg tablets (Phase 3 and commercial tablets)**

5 mg Tablet					10 mg Tablet				
Lot No		Results			Lot No		Results		
Reference Product Phase 3 Tablet	Test Products Commercial Tablet	MSD*	Upper 90% Confidence Limit of MSD	Similarity Limit	Reference Product Phase 3 Tablet	Test Products Commercial Tablet	MSD	Upper 90% Confidence Limit of MSD	Similarity Limit
PA00034	B0200099	1.4	2.9	6.2	PA00028	B0200081	1.4	2.9	6.9
	B0200100	1.9	3.4	6.4		B0200082	1.7	3.2	5.6
	B0200101	1.6	3.1	5.1		B0200083	1.3	2.8	6.4

* Multivariate statistical distance

** The dissolution method uses the USP-paddle method, $\frac{1}{10}$ as the medium, and an HPLC assay

Figure 19. Dissolution profiles of 5 mg and 10 mg solifenacin succinate Phase 3 tablets and the commercial tablets



[Test conditions: paddle method, ...]

Values are mean (n = 12)]

Reviewer's Comments

- The Phase 3 and commercial tablets (manufactured at a different site) are identical to each other based on dissolution profiles and similarity analysis.
- A waiver of proof of bioequivalence may be granted and the commercial formulation is deemed bioequivalent to the Phase 3 formulation.

What is the absolute bioavailability of solifenacin?

Sponsor conducted Study 905-CL-009 (randomized, non-blinded, 2-way-crossover) to determine the absolute bioavailability after administration of a single 10 mg oral tablet and a 5 mg i.v. (as 50 ml infusion) of solifenacin in 12 healthy male subjects. Results are below:

Table 29: Key Plasma PK parameters of solifenacin following IV and oral administrations:

	5 mg i.v.	oral 10 mg
t_{max} (h)	0.44	4.78
C_{max} (ng/ml)	19.0	15.2
$t_{1/2}$ (h)	52.4	53.1
$AUC_{0-\infty}$ (ng.h/ml)	386	793
CL (l/h)	9.39	NA
V_z (l)	671	NA
V_{ss} (l)	599	NA

ANOVA resulted in a point estimate of 88.0% for the absolute bioavailability, with a 95% CI of 75.8 - 102.1%.

Reviewer's Comments

- Based on the above study and data analysis, it can be assumed that solifenacin is a highly bioavailable drug (mean F = 0.88).

Is there an effect on food and time of dosing on solifenacin PK?

Study 905-CL-003 was an open study with single doses of YM905 in a two-period cross over design with a washout period of 14 days between treatments. In both study periods, subjects were admitted approximately 24 hours prior to study drug administration. On the morning of study drug administration (Day 1) 12 subjects received solifenacin 10 mg within 5 minutes after completion of a standardized breakfast and 12 subjects received YM905 10 mg in the fasted state. Subjects were discharged 48 hours after solifenacin administration and visited the research unit on Day 5 and Day 7 for the 96h and 144h post dose blood sampling. After a two week washout period subjects were admitted for the second study period. In the second period, subjects who were fasted in the first period received solifenacin immediately after breakfast and subjects who had breakfast before administration in the first period received YM905 in the fasted state. All other procedures were identical to the first period. Results follow:

Fig. 20. Mean plasma concentrations of YM905 after oral administration of a single 10 mg dose in healthy male subjects under fasted or fed condition. The values represent mean \pm SD from 23 subjects.

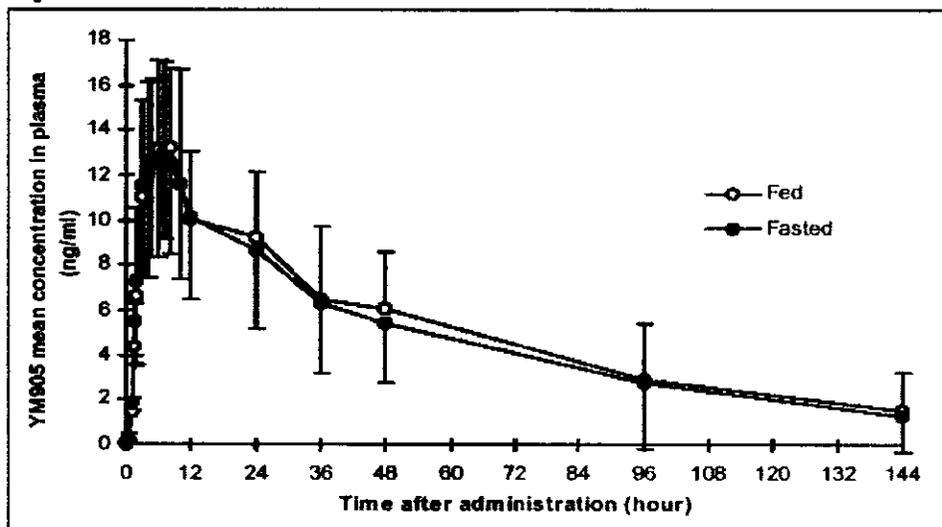


Table 30. Summary statistics of selected PK parameters of solifenacin obtained after oral administration at 10 mg under fasted or fed conditions

Food state	t_{lag}	t_{max} (h)	C_{max} (ng/ml)	AUC_{last}^* (ng.h/ml)	AUC_{0-inf} (ng.h/ml)	AUC_{0-inf} extrapolated (%)	$t_{1/2}$ (h)
Fasted	0.46 (0.33)	6.0 (1.7)	14.1 (4.3)	691 (313)	820 (423)	15.1 (8.0)	50.8 (13.5)
Fed	0.63 (0.48)	5.8 (2.1)	14.7 (4.9)	736 (290)	842 (373)	12.5 (6.3)	46.8 (10.7)

The value represents arithmetic mean and SD (between brackets) from 23 subjects

* Mean and SD from 22 subjects because subjects No. 16 could not be withdrawn the blood sample at final time point.

Reviewer's comments:

- The study and choice of standardized (high fat) breakfast, according to the sponsor, was based on the Agency's Guidance Document on food effect studies.
- There were no detectable effects of food on the absorption or other PK parameters of solifenacin.
- The formulation used for this study was different from that in the Phase 3 and commercial lots. This formulation contained ~ as compared to HPMC in the final formulation (a Level 3 component change). Sponsor assumed that this change should not have an impact on the lack of a food effect for solifenacin.

What are the specifications and methods for dissolution?

The sponsor proposes the acceptance criterion as $Q = \dots$, at 30 minutes. The dissolution method proposed involves USP Apparatus 2 (paddle method).
of dissolution medium:

Sponsor finalized the method based on the fact that the solubility of solifenacin succinate is high, i.e., not less than \dots in \dots and various \dots were investigated as dissolution media, and the dissolution profiles were similar.

Reviewer's Comments:

- It appears that solifenacin succinate has high solubility and high permeability. However, adequate studies to classify this as BCS Class I were not conducted.
- *In vitro* dissolution probably will have minimal effects on the *in vivo* absorption since:
 - The t_{max} of the drug is 5-6 hours
 - $t_{1/2}$ of the drug is approximately 2 days
 - The drug is about 90% bioavailable
- *In vitro* dissolution specification is, in this case, more reflective of product quality than *in vivo* performance
- It is not clear, however, how successful this dissolution medium will be in discriminating subtle changes in the formulation, if there be a need to.

Based on the above, the dissolution release specification is acceptable from an OCPB point of view. CMC Team has finalized the specification as $Q = \dots @ \dots$

Analytical

Q. Which moieties have been selected for analysis and why?

Based on information available from the parent and its metabolic fate, solifenacin and its metabolites M1 – M5 were assayed in many of the studies focused on PK of the drug.

Q. What bioanalytical methods are used to assess concentrations, and how reliable are the methods?

The sponsor developed a HPLC assay method with Mass Spectrometry as detection for determining the concentration of solifenacin and its 5 metabolites in plasma and urine. The method was validated for specificity, linearity, precision and accuracy. The following validation results were obtained with plasma samples.

METHOD VALIDATION CHARACTERISTICS

Correction factor
By multiplication

Method of detection
Sample volume
Extraction method

Regression method
Weighing
Linearity range
LOQ
Matrices tested for selectivity
Stability at
Stability at
Stability processed samples at 4°C
Stability at room temperature
Stability in autosampler
Validated freeze-thaw cycle
Validated dilution factor

Accuracy and Precision YM905 base

Accuracy and Precision BY-348C

Accuracy and Precision YM-64250

/

Accuracy and Precision YM-80264

/

Accuracy and Precision YM-270293

/

Accuracy and Precision YM-277743

/

All recovery values (for solifenacin and the 5 metabolites during the sample preparation) were > 80%.

Reviewer's comments:

- The method of assay and validation are acceptable from an OCPB perspective.

Labeling Comments

Based on the Clinical Team's advise, labeling comments on this product is deferred until later.

Appendix 1

QT Analysis – NDA 21518

Sponsor: Yamanouchi
Drug: YM905 (solifenacin citrate) – selective M₃-receptor antagonist
Indication: Urge urinary incontinence
Reviewer: Stephan R. Ortiz, Ph.D.

The objective of Study R905-CL-022 was to determine the pharmacokinetic/pharmacodynamic (PK/PD) effect interaction of escalating multiple doses of YM905 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 YM905 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 YM905 x 14 days (1 x 10mg tablet/day)
Days 17-30: 20mg YM905 x 14 days (2 x 10mg tablet/day)
Days 31-44: 30mg YM905 x 14 days (3 x 10mg tablet/day)
Days 45-58: 40mg YM905 x 14 days (4 x 10mg tablet/day)
Days 59-72: 50mg YM905 x 14 days (5 x 10mg tablet/day)

Pharmacokinetics (PK) and Pharmacodynamics (PD)

Blood samples for PK analysis of YM905 were collected as follows: 0 hour (prior to dose) and 1, 2, 4, 6, 8, 12, 16, and 24 hours after the YM905 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 YM905 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 1 shows the demographics of the QT study.

Certain issues regarding this study include:

- 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 were performed along with the average of the 2 "true" (not placebo) baseline QT intervals (performed at screening and check-in).
- 2) Only one QT replicate was measured per point. Doesn't account for intra-individual variability in QT interval.
- 3) RR interval was not measured. Instead, RR was determined from HR. Doesn't account for intra-individual variability in RR length. QT correction (Bazzett'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. Considering the sponsor's goal is to rule out a QT effect greater than 10 msec, this is considered a limitation of the study.

Table 1. QT Study Demographics

Demographic	Gender Group			Overall
	Male	Premenopausal female	Postmenopausal female	
Age (years)				
N	20	20	20	60
Mean (Std)	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)

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. A plot of QT_C vs. RR for both methods is presented in figures 1 and 2. Using either the placebo data, which was used by sponsor to define their baseline, or the true baseline data, the graphs suggest that the Fridericia correction is the more appropriate of the two correction methods.

Figure 1. QT_C vs. RR for Fridericia- and Bazett-corrected QT Intervals using Placebo Measures

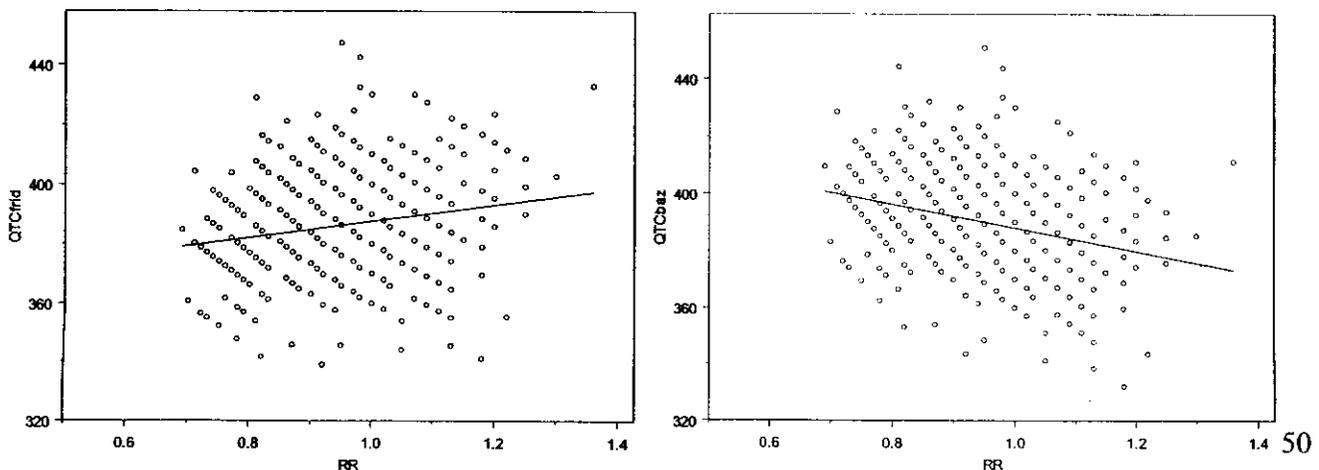
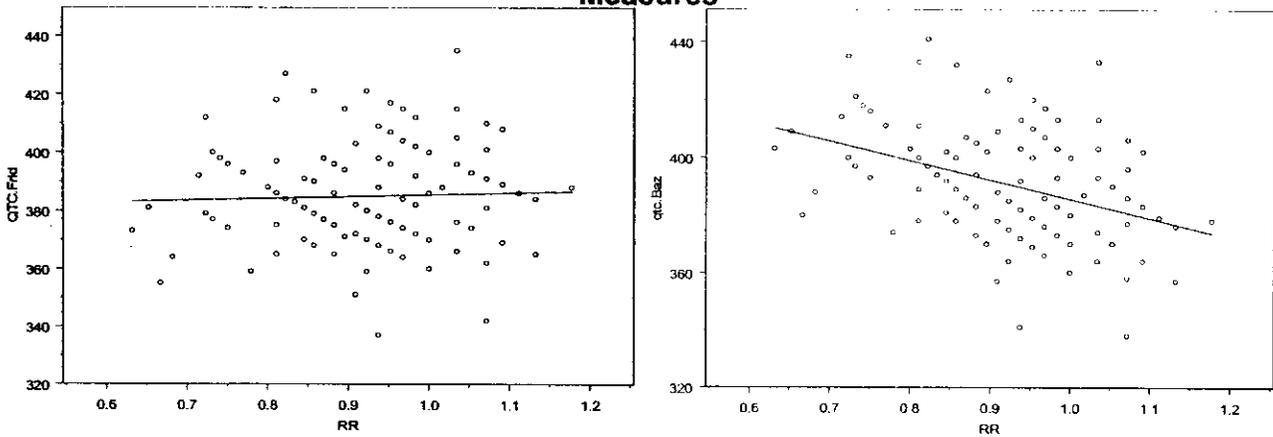


Figure 2. QT_C vs. RR for Fridericia- and Bazett-corrected QT Intervals using Baseline Measures



Mean Baseline-corrected QT_C and Baseline- and Placebo-corrected QT_C

In attempting to analyze mean changes, a problem arises when sorting by a sub-class as it then averages over the remaining sub-class. For example, to know that the average mean baseline- and placebo-corrected QT_C for all 20 mg readings is not helpful as those readings come from all races, sexes and times post-dose administration. However, it is difficult to analyze for these demographics if studies don't provide adequate power for such analysis.

Table 2 summarizes the mean changes in baseline- and placebo-corrected QT_C sorted by treatment group. It should be noted that relying solely on this comparison fails to capture the true risk in QT prolongation associated with this drug due to the very high variability in this data. Figures 3 and 4 however show corrected QT_C values sorted by dose and averaged over time post-dose

**APPEARS THIS WAY
ON ORIGINAL**

Table 2. Mean Change in Baseline-corrected QT_c and Baseline- and Placebo-corrected QT_c by Treatment Group

Treatment Group	Mean Change in HR (bpm)	Mean Change in Baseline-corrected QT _c (msec) ^a	Mean Change in Baseline- and Placebo-corrected QT _c (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)

^aresults reported as mean (95% confidence interval)

Figure 3. Mean Baseline- and Placebo-corrected QT_c sorted by dose and time administered

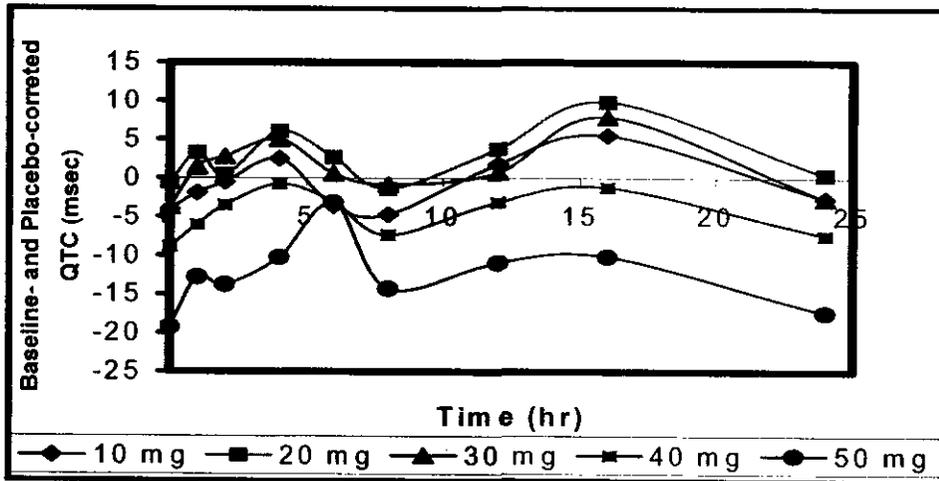
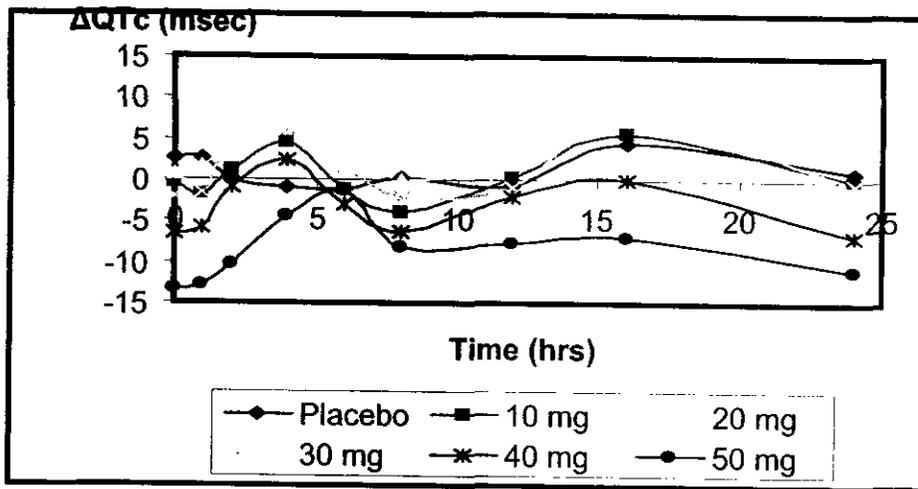


Figure 4. Mean Baseline-corrected QT_c sorted by dose and time administered



From Table 2, little effect on HR is seen with solifenacin administration. Mean baseline-corrected QT_c did not increase with increasing dose. The drug-related changes ranged from -8.46 to 3.46 msec with the maximum change occurring in the 20 mg treatment group. Note however that a positive control was not included in this analysis.

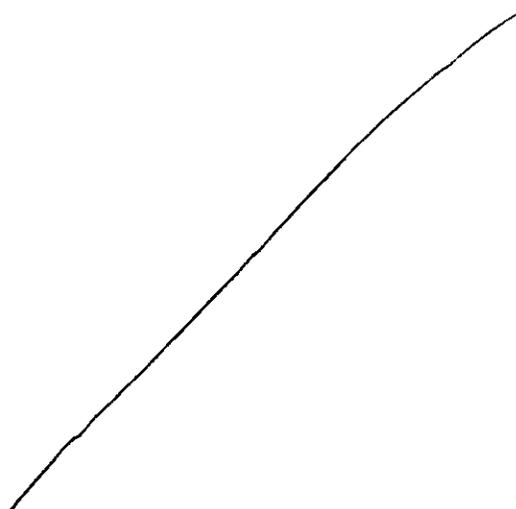
It's interesting to note that Figure 3 shows a drug-related effect that mirrors the parent PK profile at early times. At later times however, we see a secondary peak that in some cases, is larger than the first peak. This secondary peak suggest a lag-effect from the parent compound and/or the presence of a metabolite with pro-arrhythmic potential and/or a diurnal effect. The mean baseline- and placebo-corrected QT_c value at 16 hours for the 20 mg treatment group is 9.82 msec. A diurnal effect can be assumed to contribute to this second peak as it is also present in the placebo, as seen in Figure 4. This pattern also could be an artifact of the means and may not be evident in individual profiles.

Investigation of the individual data, in figure 5, shows no apparent diurnal effect suggesting that evaluating the mean data alone is insufficient

Figure 5. Individual Baseline-corrected Placebo and Dose-related (20mg) Changes in QT over time

APPEARS THIS WAY
ON ORIGINAL

— Placebo.Minus.True.Baseline
— Dose.Minus.True.Baseline

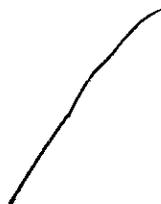


Outlier Analysis

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 figure 6 and table 3.

Figure 6. Fridericia-Corrected QT For Each Subject per Dose Administered

Dose = Placebo



Dose = 50mg

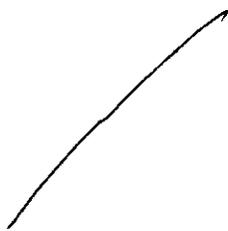


Table 3. Outlier QT_c Measurements > 450msec

	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 figure 5 and table 3, 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, no corrected QT intervals were greater than 500msec.

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

Table 4 and 5 show the results of analyzing the baseline- and placebo-corrected changes in QT_c outliers. These results are further sorted by race, sex, dose administered and time post-dose. Figure 7 sorts these results by dose for each subject. 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, we see a higher incidence of outliers 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 earlier, an unusually high incidence of outliers occur at the 16 hour post-dose reading. This warrants further examination of all metabolite info, particularly those that may have shown any preclinical proarrhythmic potential. According to the Pharmacology Written Summary, metabolite M3 prolonged PR, QRS and QT_c intervals in anesthetized dogs. Additionally, metabolite M4 prolonged action potential duration in the dog Purkinje fibers.

Figure 7. Outlier Values for Baseline- and Placebo-corrected QT_c Changes for Each Subject per Dose Administered

Dose = 10mg



Dose = 20mg



1 Page(s) Withheld

**Table 4. Baseline- and Placebo-corrected QT_C Outliers
(sorted by race and sex)^a**

Category	Baseline- and Placebo-corrected QT _C ^b		N
	> 30msec < 60msec	> 60msec	
African American	27 (8.54)	1 (0.32)	316
Caucasian	37 (5.87)	0 (0)	630
Hispanic	145 (9.86)	1 (0.07)	1470
Asian	4 (4.54)	0 (0)	88
Men	13 (1.64)	0 (0)	794
Postmenopausal Women	103 (11.99)	1 (0.12)	859
Premenopausal Women	97 (11.40)	1 (0.12)	851

^aresults presented as number of QT intervals (% of total)

^bbaseline-corrected dose QT_C minus baseline-corrected, time-matched placebo QT_C

**Table 5. Baseline- and Placebo-corrected QT_C Outliers (sorted by dose and
time post-dose)**

Category	Baseline- and Placebo-corrected QT _C ^b		N
	> 30msec 60msec	< > 60msec	
10mg	48 (7.27)	0 (0)	660
20mg	70 (10.92)	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
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)	230
6 hour	27 (11.74)	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)	230
24 hour	10 (4.37)	0 (0)	229

^aresults presented as number of QT interval outliers (% of total)

^bbaseline-corrected dose QT_C minus baseline-corrected, time-matched placebo QT_C

Again, it is important to note that these studies were not powered to analyze differences among these different demographics. These analyses were performed in order to discern any overt trends but overall, should not be relied on too heavily.

Baseline- and Placebo-corrected QT_C by Individual

In an attempt to discern an effect pattern based on increasing dose, individual data was plotted in Figure 8. No overall pattern is evident. Figure 8 further confirms the great deal of variability in this dataset.

2 Page(s) Withheld

Analysis of Variance

One weakness in this study is that only 1 replicate QT measure was made at each time point. Due to the high intra-subject variability in this measure, it's preferred that the average of multiple QT measures be performed. Additionally, an increase in the number of replicates leads to increased study power. Table 6 shows the mean variability change per dose studied. Alongside is presented the mean maximum drug (parent) concentration achieved at each dose studied.

Table 6. Mean Maximum Concentrations alongside Mean Change in QT_C Range from Placebo

Dose (mg)	Mean Change in QT _C Range (msec)	Mean Maximum Concentration (ng/ml)	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

Mean Maximum Baseline-corrected QT_C and Placebo- and Baseline-corrected QT_C Analysis

Due to highly variable nature of this data, analysis of maximum change in baseline- and placebo-corrected QT_C may give a clearer picture of drug-related effect. When the maximum baseline- and placebo-corrected QT_C value for each subject at any dose was determined, the **mean of these maximums is 31.39 msec** with a mean range of 64.74 msec. However, this fails to discriminate between the different treatment groups. Table 7 shows the average maximum change in baseline- and placebo-corrected QT_C sorted by treatment group.

Table 7. Mean Maximum Baseline-corrected QT_c and Placebo- and Baseline-corrected QT_c per Subject per Treatment Group

Treatment Group	N	Mean Maximum Baseline-corrected QT _c (msec) ^a	Mean Maximum Baseline- and Placebo-corrected QT _c (msec) ^a
Placebo	60	16.72 (11.07, 22.36)	-
10mg	60	14.43 (9.17, 19.69)	19.61 (15.00, 24.23)
20mg	60	18.03 (12.17, 23.88)	23.31 (17.66, 28.95)
30mg	60	20.23 (13.87, 26.59)	25.60 (20.36, 30.85)
40mg	42	14.23 (7.23, 21.23)	18.22 (12.01, 24.49)
50mg	14	7.94 (-4.65, 20.52)	10.40 (-1.57, 23.23)

^aresults reported as mean (95% confidence interval)

This analysis provides insight into the average maximum effect seen for each subject at each dose.

In addition to the previous analysis, QT_c intervals were also corrected for baseline alone. Though analysis baseline- and placebo-corrected QT_c outliers are of the most interest, the following analysis is included for purposes of comparison among the different analyses.

Baseline-corrected QT_c

Before proceeding to display the baseline-corrected data, it should be noted that the sponsor defined baseline QT as the *median* of 9 QT measures while on *placebo*, even though true baseline measurements were performed. Several analyses have shown placebo-related changes in QT interval when compared to baseline. Figure 9 and Table 8 present the outlier values for baseline-corrected QT intervals using the true (average of 1 QT each at screening and check-in) baseline. Table 8 includes analysis with sponsor-defined baseline values for purposes of comparison.

1 Page(s) Withheld

Dose = 40mg

Dose = 50mg

Table 8. Outlier Values for Baseline-Corrected QT Interval Measurements Changes^a

Category	Baseline-corrected QT _{CT} ^b		Baseline-corrected QT _{CS} ^c		Overall N
	>30msec <60msec	>60msec	>30msec <60msec	>60msec	
Placebo	54 (10.00)	1 (0.19)	2 (0.37)	0 (0)	540
10mg	54 (8.18)	0 (0)	4 (0.61)	0 (0)	660
20mg	81 (12.64)	1 (0.16)	14 (2.18)	0 (0)	641
30mg	57 (9.25)	4 (0.65)	28 (4.55)	0 (0)	616
40mg	32 (6.93)	0 (0)	8 (1.73)	0 (0)	462
50mg	3 (2.40)	0 (0)	0 (0)	0 (0)	125
Caucasian	37 (4.89)	0 (0)	9 (1.19)	0 (0)	756
Hispanic	219 (12.21)	6 (0.34)	43 (2.40)	0 (0)	1794

African American	25 (6.44)	0 (0)	4 (1.03)	0 (0)	388
Asian	0 (0)	0 (0)	0 (0)	0 (0)	106
Male	7 (0.72)	0 (0)	6 (0.62)	0 (0)	974
Post-Meno Female	135 (13.00)	4 (0.38)	30 (2.89)	0 (0)	1039
Pre-Meno Female	139 (13.48)	2 (0.19)	20 (1.94)	0 (0)	1031
0 hour	52 (7.17)	0 (0)	5 (0.69)	0 (0)	725
1 hour	23 (7.93)	0 (0)	3 (1.03)	0 (0)	290
2 hour	25 (8.62)	1 (0.34)	6 (2.07)	0 (0)	290
4 hour	36 (12.41)	1 (0.34)	9 (3.10)	0 (0)	290
6 hour	25 (8.62)	1 (0.34)	9 (3.10)	0 (0)	290
8 hour	18 (6.21)	0 (0)	3 (1.03)	0 (0)	290
12 hour	29 (10.00)	1 (0.34)	5 (1.72)	0 (0)	290
16 hour	52 (17.93)	2 (0.69)	14 (4.83)	0 (0)	290
24 hour	21 (7.27)	0 (0)	2 (0.69)	0 (0)	289

^aresults presented as number of QT intervals (% of total)

^bFridericia-corrected QT interval minus Fridericia-corrected true baseline

^cFridericia-corrected QT interval minus Fridericia-corrected sponsor-defined baseline

Table 8 shows the importance of distinguishing between placebo and baseline measurements. The sponsor-defined baseline correction fails to account for the pronounced placebo effect in this study. Additionally, as noted earlier, these studies were not powered to discern differences among assorted demographics.

Time-matched Placebo-corrected QT_c

On days 14, 28, 42, 56 and 66, drug-related ECG's were performed at 0, 1, 2, 4, 6, 8, 12, 16 and 24 hours post-dose for a total of 9 ECG's/subject/dose. Time-matched placebo-related ECG's were also performed for each subject. Time-matched, placebo-

corrected QT_C were calculated and sorted. Table 9 shows all outlier values sorted by dose administered and time post-dose.

In considering only the >60msec outliers, no group contained greater than 1% of QT measurements above this cut-off. When considering the time-point analysis, one sees a response profile that roughly follows the PK of the parent compound. However, as seen with the earlier analysis, another peak in QT outliers occurs at the 16-hour time point. This peak was also seen in both baseline-corrected QT_C data. Again, a diurnal effect is ruled out, as the placebo readings are time-matched. Possible explanations include formation of a pro-arrhythmic metabolite or a lag-effect associated with the parent compound. Further examination of parent and metabolite PK is further warranted. Table 10 shows the same data, this time sorted by race and sex.

Table 9. Time-matched, Placebo-corrected QT_C Intervals (sorted by dose administered and time post-dose)^a

Category	Time-matched, Placebo-corrected QT _C ^b		N
	> 30msec 60msec	< > 60msec	
10mg	9 (1.36)	0 (0)	660
20mg	25 (3.90)	0 (0)	641
30mg	38 (6.17)	1 (0.16)	616
40mg	23 (4.98)	0 (0)	462
50mg	0 (0)	0 (0)	125
0 hour	16 (2.40)	0 (0)	665
1 hour	10 (4.35)	0 (0)	230
2 hour	7 (3.04)	0 (0)	230
4 hour	13 (5.65)	0 (0)	230

6 hour	14 (6.09)	1 (0.43)	230
8 hour	8 (3.48)	0 (0)	230
12 hour	6 (2.61)	0 (0)	230
16 hour	15 (6.52)	0 (0)	230
24 hour	5 (2.18)	0 (0)	229

^aresults presented as number of QT intervals (% of total)

^bFridericia-corrected QT interval minus Fridericia-corrected, time-matched placebo QT interval

**APPEARS THIS WAY
ON ORIGINAL**

Table 10. Time-matched, Placebo-corrected QT_c Intervals (sorted by race and sex)^a

Category	Time-matched, Placebo-corrected QT _c ^b		N
	> 30msec < 60msec	> 60msec	
African American	9 (2.85)	1 (0.32)	316
Caucasian	18 (2.85)	0 (0)	630
Hispanic	67 (4.56)	0 (0)	1470
Asian	0 (0)	0 (0)	88
Men	8 (1.01)	0 (0)	794
Postmenopausal Women	39 (4.54)	1 (0.12)	859
Premenopausal Women	47 (5.52)	0 (0)	851

^aresults presented as number of QT intervals (% of total)

^bFridericia-corrected QT interval minus Fridericia-corrected, time-matched placebo QT interval

In addition to this prospectively designed QT study, QT intervals were measured in 2 Phase III studies (R905-CL-013 and R905-CL-014). Both are randomized, double-blind, parallel-group, fixed-dose, multicenter studies in adult men and women with overactive bladder. They consisted of a 2-week washout/screening period, a 12-week double-blind treatment period and a 2-week post-treatment follow-up period.

Before proceeding with analysis, the following deficiencies are noted:

- 1) As in the previous study, the sponsor recorded uncorrected QT intervals to the nearest ten msec. Considering that these studies are meant to rule out QT interval changes greater than 10 msec, rounding these measures is considered a limitation of the data.
- 2) Unlike the previous study, the sponsor made QT corrections and proceeded to round these to the nearest ten msec. This "double-rounding" error is surprising and leads this reviewer to question the validity of the sponsors analysis. This analysis will use unrounded, corrected QT interval measurements.

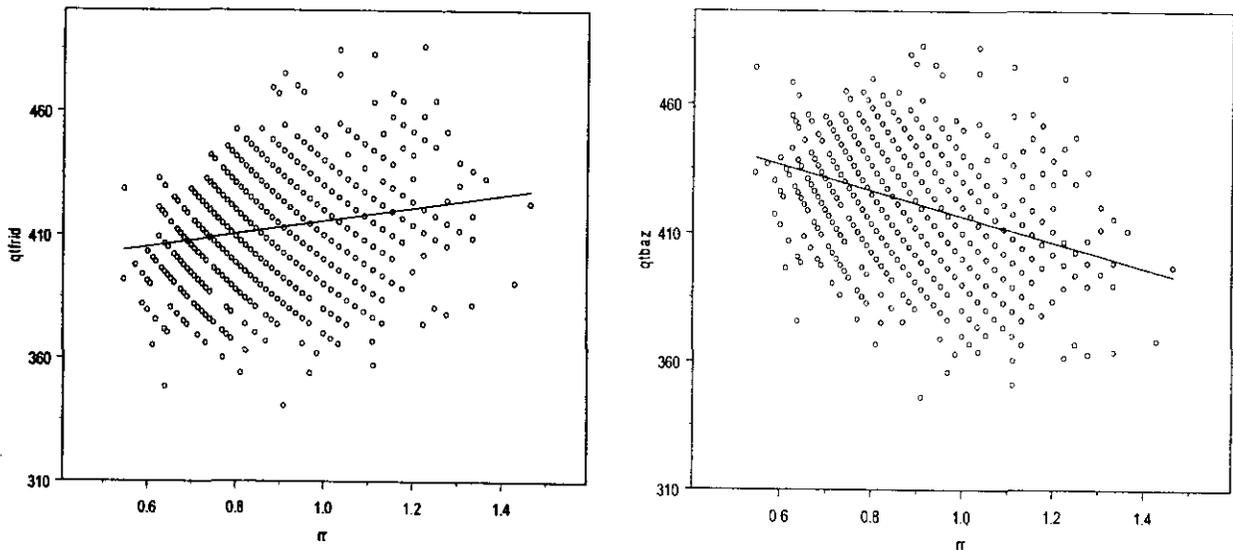
- 3) Only 1 QT measurement per sample as made. Problematic due to high intra-subject variability.
- 4) RR interval was not measured directly. Also, problematic due to high intra-subject variability in this measurement.

Study R905-CL-013

QT-Correction

The sponsor used Bazett's correction in this analysis. Figure 10 shows that the more appropriate correction choice is Fridericia's correction.

Figure 9. QT_C vs. RR for Fridericia- and Bazett-corrected QT Intervals

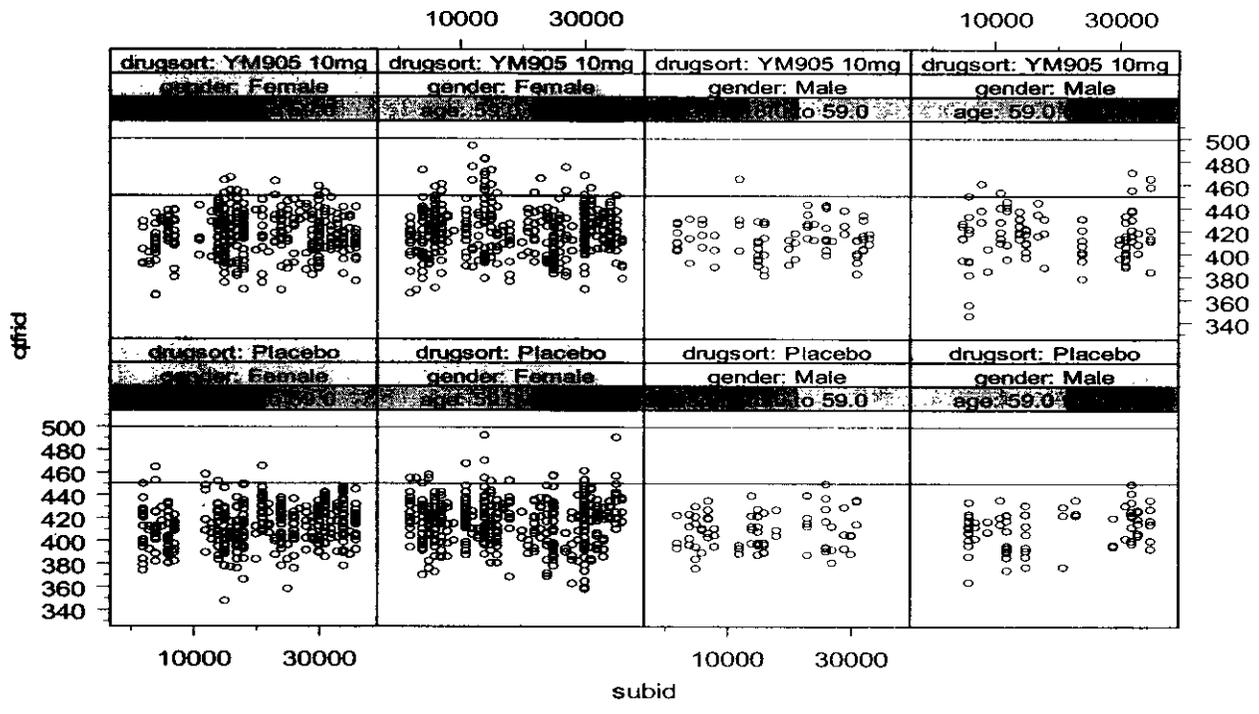


Outlier Analysis

Figure 11 shows a scatter plot of all drug and placebo-related QT_{CF} measures sorted by gender, race and treatment group. As seen in the earlier analysis, women are at higher risk of experiencing a QT_{CF} interval greater than 450 msec, with elderly women at an even higher risk than younger women. However, a very high placebo effect is seen, with the greatest number of outliers greater than 450 msec also in elderly women.

Figure 12 shows a scatter plot of all change from baseline QT_{CF} measures sorted by gender, race and treatment group. Again, the group at the highest apparent risk is elderly women.

Figure 11. Drug and placebo-related QT_{CF} measures sorted by gender, race and treatment group



**APPEARS THIS WAY
ON ORIGINAL**

Figure 12. Change from baseline QT_{CF} measures sorted by gender, race and treatment group

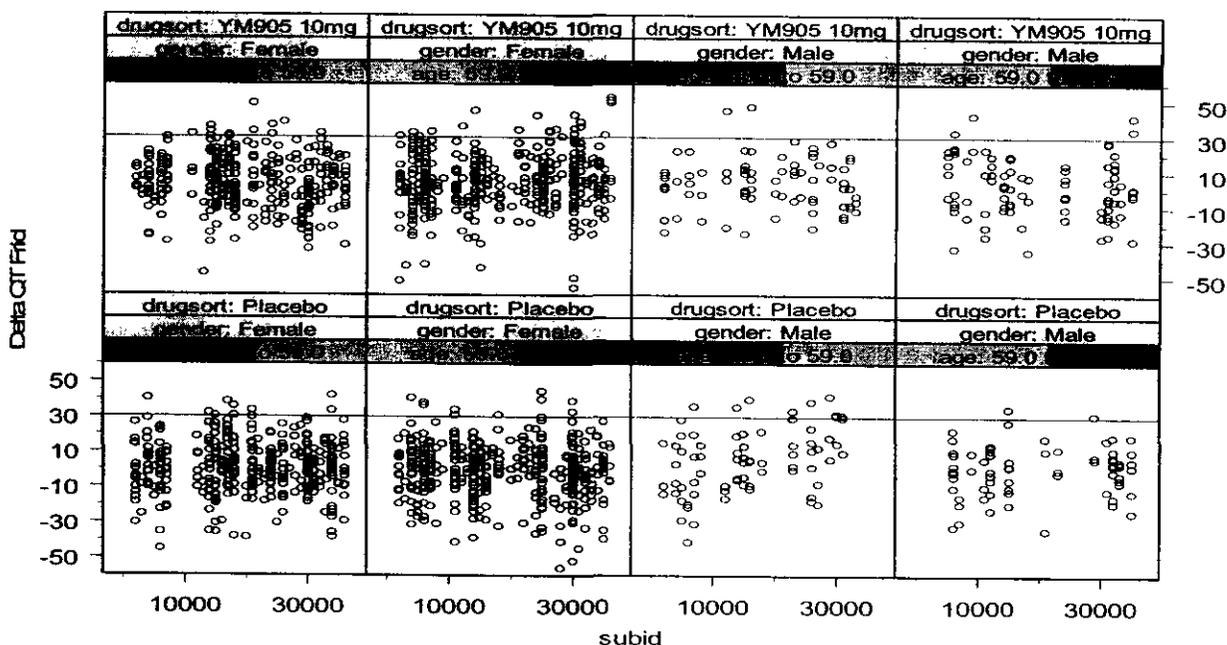


Table 11. Outlier Baseline-corrected QT_C and QT_C for Study 013^a

Treatment Group	Gender	Age	Baseline-corrected QT _C		QT _C	
			>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)

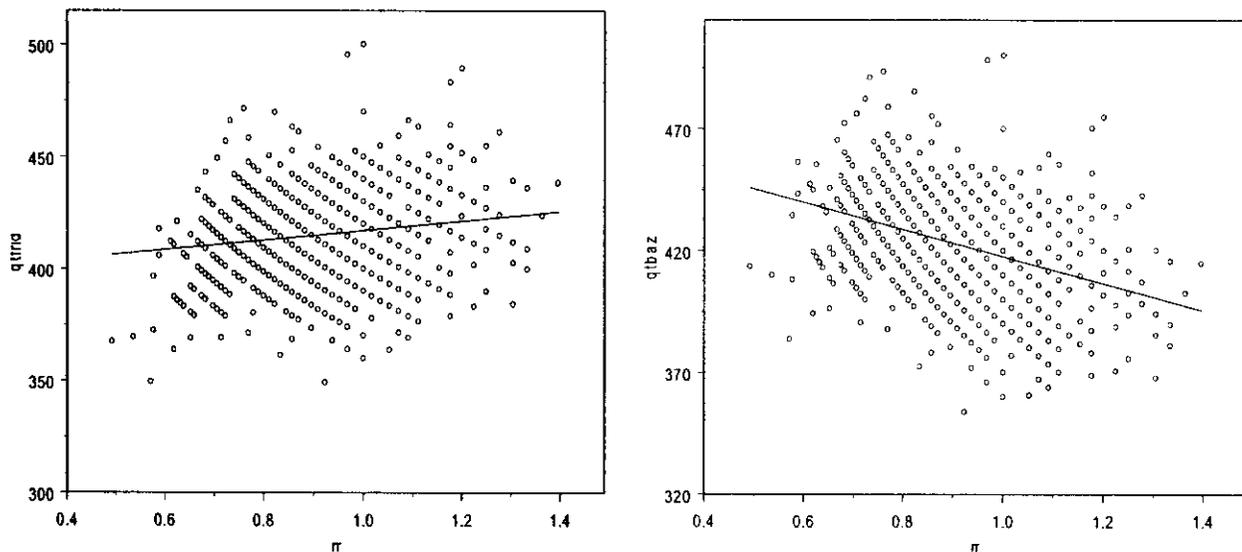
^aData presented as number of outliers (percentage of total)

Study R905-CL-014

QT-Correction

The sponsor used Bazzet's correction in this analysis. Figure 13 shows again that the more appropriate correction choice is Fridericia's correction.

Figure 13. QT_C vs. RR for Fridericia- and Bazett-corrected QT Intervals

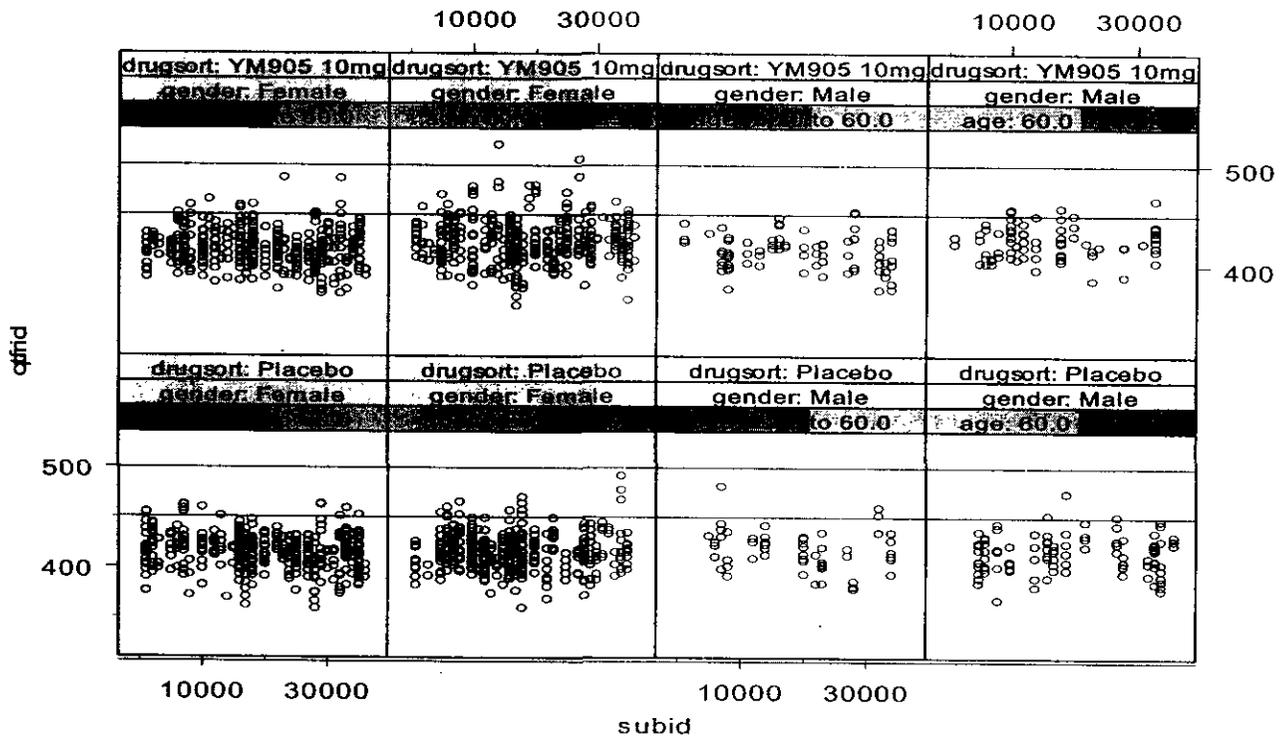


Outlier Analysis

Figure 14 shows a scatter plot of all drug and placebo-related QT_{CF} measures sorted by gender, race and treatment group. As seen in the earlier analysis, women are at higher risk of experiencing a QT_{CF} interval greater than 450 msec, with elderly women at an even higher risk than younger women. However, a very high placebo effect is seen, with the greatest number of outliers greater than 450 msec also in elderly women. 2 outliers greater than 500 msec were measured in this study, both coming from the elderly women treated with Solifenacin.

Figure 15 shows a scatter plot of all change from baseline QT_{CF} measures sorted by gender, race and treatment group. Again, as seen in the previous Phase III study, the group at the highest apparent risk is elderly women. 3 outlier values greater than 60 msec were experienced, all by women. Two of the three outliers are in the elderly women treated with Solifenacin group and are both **greater than a 75 msec change from baseline.**

Figure 14. Drug and placebo-related QT_{CF} measures sorted by gender, race and treatment group



APPEARS THIS WAY
ON ORIGINAL

Figure 15. Change from baseline QT_{CF} measures sorted by gender, race and treatment group

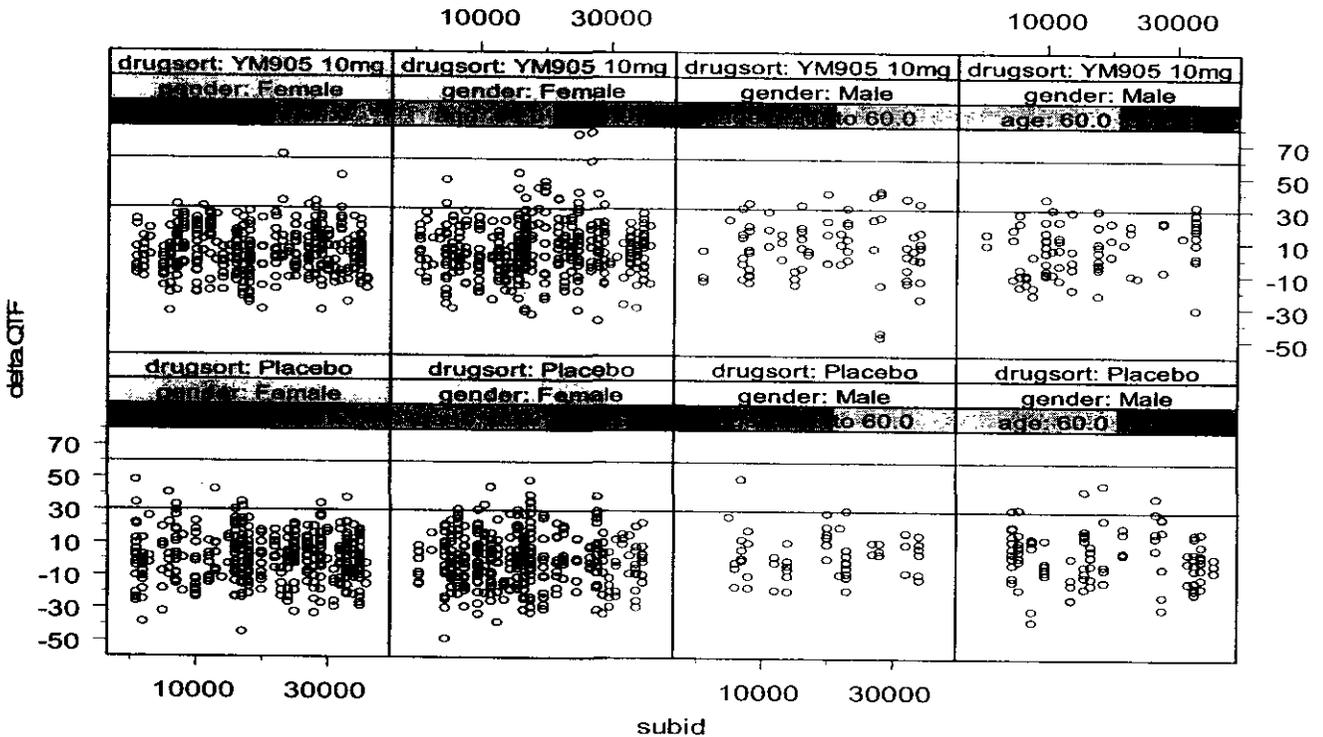


Table 12. Outlier Baseline-corrected QT_C and QT_C for Study 014^a

Treatment Group	Gender	Age	Baseline-corrected QT _C		QT _C	
			>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)

Conclusions

Several design deficiencies, as described earlier, have made it difficult to fully assess the effect of Solifenacin on QT interval prolongation. The results however suggest

that elderly women are at a greater risk of experiencing clinically significant QT prolongation as a result of solifenacin administration. This may result from the age- and sex-related increases in solifenacin exposure as seen in the PK analyses.

Final decision regarding the QT safety should be made in the context of the following limitations: the absence of a positive control arm, only 1 replicate measure per point and all QT intervals were rounded to the nearest 10 msec. Among these limitations, the absence of a positive control is considered most relevant as its absence has led to questions surrounding the confidence of the results of this study.

**APPEARS THIS WAY
ON ORIGINAL**

Appendix 2 (Pharmacometrics Review)

Introduction

YM905 is a compound being developed by Yamanouchi for the

Study objectives

2.1 POPULATION PHARMACOKINETIC ANALYSIS: The objectives of this analysis were to: (a) Determine the significance of possible covariates on the population pharmacokinetic parameters. (b) Estimate the intersubject variability of the pharmacokinetic parameters and the random residual error.

2.2. QT_C ANALYSIS: The objective of modeling YM905 plasma concentration vs. change in heart rate corrected QT interval (QT_C) from baseline data collected during the Phase III clinical trials were: (a) To assess the potential relationship between observed plasma YM905 concentrations and corresponding observed changes in the QT_C interval from baseline, and to define a suitable concentration-effect model that characterizes the relationship. (b) To estimate the concentration-effect model parameters, random effect parameters (inter- and intra-individual residual variabilities) and relative standard errors (precision) of the parameter estimates. (c) To assess the influence of covariates (e.g., age, gender, race, smoking history, alcohol history) on the model parameters to identify sub-populations with altered pharmacodynamics.

2.3 EXPLORATORY YM905 PLASMA CONCENTRATION-EFFICACY ANALYSIS The objective of this exploratory YM905 plasma concentration-efficacy analysis were to determine if any relationship exists between YM905 plasma concentration and the measures of efficacy found to be significantly different from placebo in Study 905-CL-013 and 905-CL-014, which include: (a) Change from baseline in the number of micturitions/24 hours (b) Change from baseline in the number of incontinence episodes/24 hours. (c) Change from baseline in the number of urgency episodes/24 hours, and (d) Change from baseline in the volume voided per micturition.

Methodology:

Two identical clinical trials, 905-CL-013 and 905-CL-014, each consisted of approximately 630 patients with symptoms of overactive bladder (frequency, urgency, and/or urge incontinence) at 68 sites in the United States and Europe. The study consisted of a 2-week screening/washout period, a 12-week double-blind treatment period (10 mg YM905 or placebo administered orally once daily) 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 double-blind treatment; and at the end of the follow-up period (for those patients who did not enter the extension study) (Visit 6). Pharmacokinetic sampling occurred during 3 of 5 visits.

Pharmacokinetics: Pharmacokinetic sample collection: During Visit 1, a blood sample was collected for the measurement of YM905 plasma concentration. The plasma sample was

collected 1 - 4 hours after the initial dose of YM905 was given. At Visits 2 or 3, 2 blood samples were collected for measurement of YM905 plasma concentration. The clinic visit was scheduled such that patients had a sample drawn immediately upon arriving at the clinic and an additional sample drawn immediately prior to leaving the clinic. Where appropriate, patients were instructed to hold their dose for that day until after the first blood sample was taken. The second sample was drawn at least two hours after the dose, if the dose was given in clinic. The time that the last dose of study drug was taken was documented in the subject diary and CRF. The time that the blood samples were collected for PK analysis were also documented and recorded on the CRF.

PK-PD evaluations: In the Phase 3 studies, the primary efficacy endpoint was mean change from baseline to endpoint in number of micturitions/24 h. Secondary efficacy endpoints were: mean change from baseline to endpoint in number of incontinence episodes/24 h; number of urgency episodes/24 h, mean volume voided/micturition, number of nocturnal void episodes/24 h, and number of nocturia episodes/24 h. These data were obtained from the patient diaries. The safety of YM905 was evaluated on the basis of adverse events, clinical laboratory values (hematology, clinical chemistry, and urinalysis), vital signs, physical examinations, 12-lead electrocardiography (ECG), and post-void residual volume.

Statistical methods:

PK Data Analysis *Exploratory Data Analysis.* Graphical and statistical techniques were used to isolate and reveal patterns and features in the population data set throughout the population PK analysis. Structural PK Model NONMEM program version V level 1.1, NM-TRAN version III level 1.0, and PREDPP version IV level 1.0 were used in this analysis (NONMEM Project Group). A one-compartment model was initially fit to the PK data as the base structural model. Models that were more complex were fit to the data if warranted by diagnostic plots including predicted versus observed concentrations and weighted residuals versus predicted concentrations and time. Once a suitable structural model was developed, population covariate analysis of the effect of concomitant medications, clinical laboratory values, and demographics on the pharmacokinetic parameters was performed. *Effect of Covariates on PK Parameters* Potential population model covariates were selected by using exploratory techniques. The effects of concomitant medications, clinical laboratory values, and demographics on the PK parameters were modeled. Combinations of general linear and non-linear models of the covariates were tried in a stepwise fashion using NONMEM. Model discrimination was made using the Likelihood Ratio Test (LRT). If the LRT was not appropriate for model discrimination, e.g., non-hierarchical models, the Akaike Information Criteria (AIC) was used. In each step, for each covariate, the models up and down in the hierarchy were tried and the covariate models that decreased the value obtained from the LRT the most were retained in the next step. The search was terminated when none of the models tested could further significantly decrease the value obtained from the LRT.

QTc Data analysis. Structural Concentration-QTc Model Appropriate concentration-QTc models, without covariates, relating the change in QTc interval from baseline to corresponding YM905 plasma concentrations were determined. Several models including linear, Emax, and Emax with baseline were investigated. Mixed-effects population models

were built using NONMEM. Effect of Covariates on Concentration-QTc Model Parameters Methods similar to those described above for the effect of covariates on PK parameters were used to assess the effect of covariates in the concentration-QTc model.

Efficacy analysis. The general approach to the analysis was to graphically investigate the relationship between YM905 plasma concentration and the change in efficacy measures from baseline at Weeks 4, 8, and 12 using scatter plots, box plots, and trellis plots. The variables to be used for the analysis were the YM905 plasma concentrations and the change in efficacy measures from baseline.

Results

PK Analysis: One compartment model with first order elimination and first order absorption was determined to provide the best fit to the data. There was a significant linear relationship between height, weight, and age and estimated apparent CL of YM905. Based on the final model, the apparent clearance for the median individual (weight = 77.1 kg, height = 165 cm, and age = 60 years) was estimated to be 8.05 L/h. YM905 was rapidly absorbed with an absorption half-life of 1.8 h. The median apparent volume of distribution was estimated to be 1220 L, indicative of extensive tissue distribution.

Interindividual variability in V was large (82.2%), however none of the tested covariates were identified as sources of variability in V. Interindividual variability in CL was estimated to be 48%. Although age, weight and height were identified as sources of variability in CL, together they accounted for only 2.6% and therefore may be deemed to be of no clinical relevance.

Comments: The model building processes employed are acceptable. It is a good practice to not only look at the statistical significance of covariates but also its clinical relevance.

QTc Data Analysis: Linear, E_{\max} , and E_{\max} with baseline models were fitted to the YM905 plasma concentration-effect data. Results from those analyses suggested that a linear model best described the concentration-effect data. The linear model provided an adequate fit to the concentration-effect data for both Bazett and Fridericia corrected data. Parameter estimates from the linear model were more consistent across the models tested and generally had lower variability than the E_{\max} models. The final model for both Bazett and Fridericia-corrected retained the effect of baseline QTc on intercept and on slope, and the effect of former alcohol use on slope.

Comments: the QT data were rounded by 10 msec. Also, naïve linear regression of QTc data is not recommended. Mean change from placebo arm and outlier analysis are important parameters in QT data analysis.

APPEARS THIS WAY
ON ORIGINAL

Detailed QTc data analyses are included in conjunction with health volunteer data (See Appendix 1).

Efficacy analysis A large degree of variability in the distributions of change in efficacy parameters from baseline was observed. A linear regression model applied to the efficacy endpoints vs. concentration data indicated small trends toward a greater decrease from baseline in the number of micturitions in a 24 h period, a greater decrease in the change from baseline in number of incontinence episodes in a 24 h period, and an increased urinary volume voided in a 24 h period with increasing steady-state YM905 plasma concentrations. However, no trends were evident when the data were evaluated by visit. There did not appear to be a relationship between YM905 plasma concentrations and the change from baseline in the number of urgency episodes in a 24 h period.

Direct pharmacodynamic mixed effects models were employed to quantitatively evaluate possible relationships between YM905 plasma concentrations and each of the effect parameters. No significant concentration vs. effect relationships were identified for the primary endpoint, change from baseline in the number of micturitions in a 24 h period, or change from baseline in the number of urgency episodes in a 24 h period. Based on the change in the NONMEM objective function value, a marginally significant ($p = 0.05$) linear relationship between YM905 plasma concentration and change from baseline in the number of incontinence episodes in a 24 h period was identified. A significant ($p < 0.05$) saturable (E_{max}) relationship was observed for YM905 plasma concentration vs. change from baseline in the urinary volume voided. Based on the results of the analysis, the median maximum change from baseline (E_{max}) was estimated to be 49.8 mL and the median YM905 plasma concentration associated with half the maximum effect (EC_{50}) was estimated to be 1.32 ng/mL. Estimates of interindividual variability for both E_{max} and EC_{50} were large (100% and 700%, respectively) and the residual error was estimated to be 37.3 ng/mL. Exclusion of two outlying plasma YM905 concentrations (> 250 ng/ml) for one subject (subject ID 20022) did not affect the results of these analyses.

Comments: due to the large variability in PD data, no conclusive results can be found.

APPEARS THIS WAY
ON ORIGINAL

Appendixes

Table 5.1.2 Summary of Covariates Used in the Population Pharmacokinetic Analysis

Covariate	Median (range) - or - Count (%)
<i>Continuous Variables</i>	
Body weight (kg)	77.1 (42.6 – 181.4)
Height (cm)	165 (124 – 201)
Age (y)	60 (20 – 88)
Alanine Aminotransferase (U/L)	19 (5 – 104)
Alkaline Phosphatase (U/L)	70 (20 – 240)
Total Bilirubin (mg/dL)	0.4 (0.2 – 2.3)
Blood Urea Nitrogen (mg/dL)	15 (4 – 39)
Creatinine Clearance (mL/min)	98.1 (17.8 – 150) ^a
<i>Categorical Variables</i>	
Race (Caucasian/African American/Hispanic/Asian/Other)	559/45/25/5/7
Sex (Males/Females)	120/521
Alcohol Use (Never/Former/Current/Missing)	197/91/352/1
Smoking (Never/Former/Current)	318/228/95
Inhibitors 2D6 (No/Yes) ^b	602/39
Inhibitors 3A4 (No/Yes)	571/70
Inhibitors p-glycoprotein (No/Yes)	604/37
ACE Inhibitors (No/Yes)	555/86
SSRI therapy (No/Yes)	582/59
Hormone Replacement Therapy (No/Yes)	387/254
NSAID therapy (No/Yes)	400/241
COX2 Inhibitors (No/Yes)	567/74

^a = Creatinine Clearance truncated to a maximum of 150 mL/min

^b = No = patients not taking as a concomitant medication and Yes = patients taking as a concomitant medication

**APPEARS THIS WAY
ON ORIGINAL**

Table 5.1.4 YM905 Base Population Pharmacokinetic Parameter Estimates (Model 204)

Solifenacin Succinate Base Model Parameter Estimates - FOCEI Method		
Structural Model and Inter-individual Variance Parameters		
Parameter	Typical Value (%RSE*)	Inter-individual %CV (%RSE*)
KA (hr ⁻¹)	0.392 (15.0%)	NE
CL (L/hr)	10.5 (2.3%)	50.6% (8.05%)
V (L)	1650 (11.4%)	82.2% (6.53%)
Intra-individual, Residual Error		
Parameter	Estimate (%RSE*)	
σ^2_{prop}	%CV= 23.3% (7.88%)	
σ^2_{add}	SD= 0.18 (44.6%)	

* %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100
 Abbreviations: FOCEI = first order conditional estimation with interaction, ka = absorption rate constant, CL/F = oral clearance, V/F = oral volume of distribution, σ^2_{prop} = proportional component of the residual error model, σ^2_{add} = additive component of the residual error model, NE = Not Estimated.

APPEARS THIS WAY
ON ORIGINAL

Table 5.1.9 YM905 Final Population Pharmacokinetic Model Parameter Estimates (Model 512)

YM905 Final Model Parameter Estimates - FOCEI Method		
Structural Model and Inter-individual Variance Parameters		
Parameter	Typical Value (%RSE*)	Inter-individual %CV (%RSE*)
KA (hr ⁻¹)	0.384 (15.0%)	NE
CL (L/hr)	CL = $\theta_1 + \theta_4*(HT-165) + \theta_5*(AGE-60) + \theta_8*(WT-77.1)$	48% (8.39%)
Typical CL (θ_1)	8.05 (2.20%)	-
θ_{4HT}	0.0998 (17.1%)	-
θ_{5AGE}	-0.0516 (26%)	-
θ_{8WT}	-0.0324 (22.3%)	-
V (L)	1220 (11.5%)	82.2% (6.81%)
Intra-individual, Residual Error		
Parameter	Estimate (%RSE*)	
σ^2_{prop}	%CV=23.3% (7.94%)	
σ^2_{add}	SD= 0.181 mcg/L (44.5%)	

* %RSE: percent relative standard error of the estimate = SE/parameter estimate*100
 Abbreviations: KA = absorption rate constant, CL = oral clearance, V = oral volume of distribution, σ^2_{prop} = proportional component of the residual error model, σ^2_{add} = additive component of the residual error model, NE = Not Estimated, HT=height, WT=weight

Table 5.2.6 YM905 Plasma Concentration-QTc (Bazett's) Base Population Parameter Estimates (Model 008)

Base Model Parameter Estimates - FOCEI Method		
Structural Model and Inter-individual Variance Parameters		
Parameter	Typical Value (%RSE*)	Inter-individual SD (%RSE*)
INT (msec)	-0.154 (208 %)	8.53 (6.81 %)
SLP (msec/ng/mL)	0.0678 (24.9 %)	0.299 (15.9 %)
Intra-individual, Residual Error		
Parameter	Estimate (%RSE*)	
σ_{add}^2	SD = 11.4 (4.02 %)	

* %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100
 Abbreviations: FOCEI = first order conditional estimation with interaction, INT = intercept, SLP = slope, σ_{add}^2 = additive residual error model

Table 5.2.7 YM905 Plasma Concentration-QTc (Fridericia's) Base Population Parameter Estimates (Model 030)

Base Model Parameter Estimates - FOCEI Method		
Structural Model and Inter-individual Variance Parameters		
Parameter	Typical Value (%RSE*)	Inter-individual SD (%RSE*)
INT (msec)	0.445 (69.2 %)	8.15 (6.43 %)
SLP (msec/ng/mL)	0.0981 (16.7 %)	0.292 (14.6 %)
Intra-individual, Residual Error		
Parameter	Estimate (%RSE*)	
σ_{add}^2	SD = 10.9 (4.02 %)	

* %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100
 Abbreviations: FOCEI = first order conditional estimation with interaction, INT = intercept, SLP = slope, σ_{add}^2 = additive residual error model

APPEARS THIS WAY
ON ORIGINAL

Table 5.2.14 YM905 Plasma Concentration-QTc (Bazett's) Final Population Parameter Estimates (Model 915)

Final Model Parameter Estimates - FOCEI Method		
Structural Model and Inter-individual Variance Parameters		
Parameter	Typical Value (%RSE*)	Inter-individual SD (%RSE')
INT = $\theta_3 \times$ (BASE - 424)		
INT		7.46 (7.34%)
θ_3	-0.207 (8.12%)	
SLP = $\theta_2 + \theta_4 \times$ (BASE - 424) + $\theta_5 \times$ (ALC = 1)		
SLP		0.242 (16.7%)
θ_2	0.0800 (19.1%)	
θ_4	-0.00559 (14.7%)	
θ_5	-0.114 (35.8%)	
Residual Error		
Parameter	Estimate (%RSE*)	
σ^2_{add}	SD = 11.4 (4.02%)	

* %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100

Abbreviations: FOCEI = first order conditional estimation with interaction, INT = intercept, SLP = slope, σ^2_{add} = additive residual error model

Table 5.2.15 YM905 Plasma Concentration-QTc (Fridericia's) Final Population Parameter Estimates (Model 916)

Final Model Parameter Estimates - FOCEI Method		
Structural Model and Inter-individual Variance Parameters		
Parameter	Typical Value (%RSE*)	Inter-individual SD (%RSE')
INT = $\theta_3 \times$ (BASE - 413)		
INT		7.01 (6.99%)
θ_3	-0.221 (7.33%)	
SLP = $\theta_2 + \theta_4 \times$ (BASE - 413) + $\theta_5 \times$ (ALC = 1)		
SLP		0.236 (16.5%)
θ_2	0.131 (11.5%)	
θ_4	-0.00559 (13.7%)	
θ_5	-0.114 (32.6%)	
Residual Error		
Parameter	Estimate (%RSE*)	
σ^2_{add}	SD = 10.9 (4.02%)	

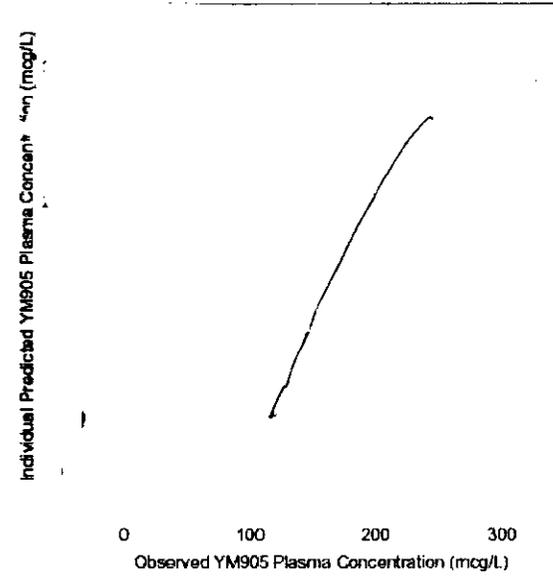
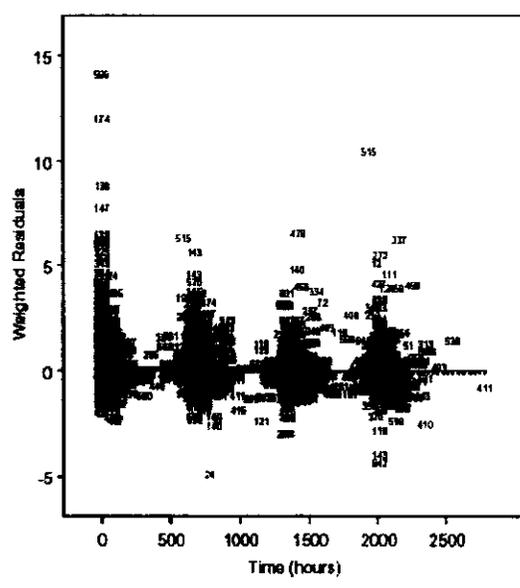
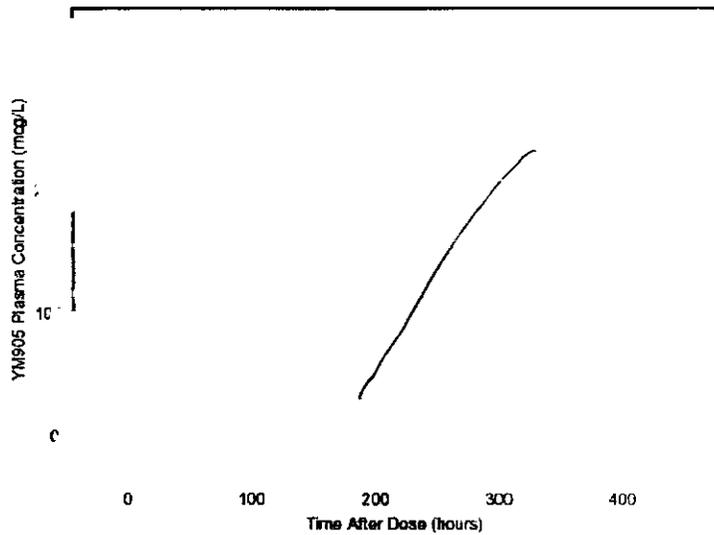
* %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100

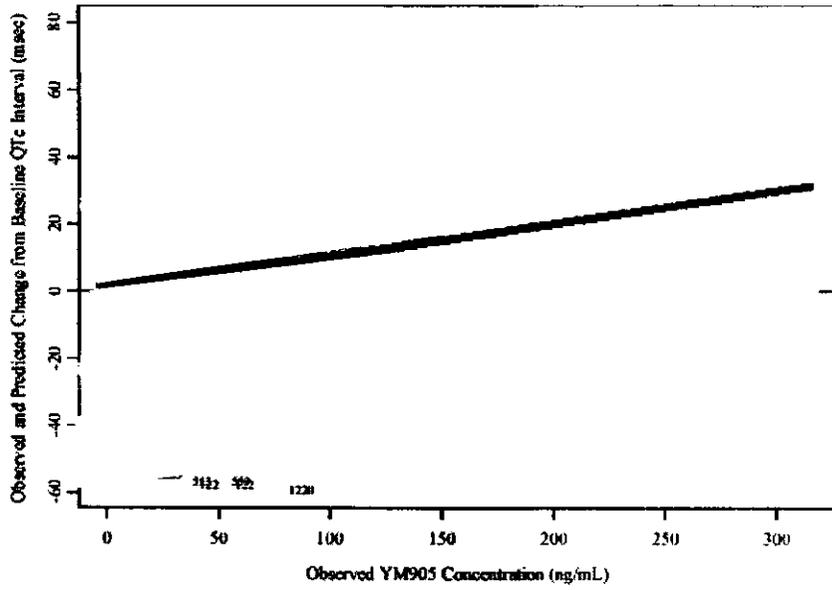
Abbreviations: FOCEI = first order conditional estimation with interaction, INT = intercept, SLP = slope, σ^2_{add} = additive residual error model

Table 5.3.1 Summary Statistics for Change in Efficacy Parameters from Baseline

	Δ MIC	Δ INC	Δ URG	Δ VOD
Visits 3,4 and 5				
n	1119	1119	1119	1114
Mean	-2.55	-1.48	-3.47	47.39
SD	2.54	2.32	3.54	61.78
%CV	99.30	156.64	101.98	130.37
Median	-2.3	-1.0	-3.0	43.25
Minimum				
Maximum				
Visit 3				
n	381	381	381	380
Mean	-2.40	-1.34	-3.22	47.33
SD	2.44	2.46	3.65	58.43
%CV	101.66	183.55	113.34	123.44
Median	-2.0	-0.7	-2.7	43.45
Minimum				
Maximum				
Visit 4				
n	220	220	220	218
Mean	-2.43	-1.50	-3.26	45.09
SD	2.35	2.10	3.02	63.81
%CV	96.60	139.90	92.58	141.52
Median	-2.7	-1.0	-3.0	37.8
Minimum				
Maximum				
Visit 5				
n	518	518	518	516
Mean	-2.72	-1.58	-3.74	48.39
SD	2.67	2.30	3.64	63.37
%CV	98.32	146.11	97.42	130.95
Median	-2.7	-1.0	-3.7	47.25
Minimum				
Maximum				

Change from baseline in number of micturitions in a 24 h period (Δ MIC), number of incontinence episodes in a 24 h period (Δ INC), number of urgency episodes in a 24 h period (Δ URG) and volume voided in a 24 h period (Δ VOD). n is the number of observations; SD is the standard deviation; %CV is the coefficient of variation.





The heavy line is the population mean predicted change from baseline QTc interval as a linear function of YM905 plasma concentration.

APPEARS THIS WAY
ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Dhruba Chatterjee
10/17/03 04:24:09 PM
BIOPHARMACEUTICS
Combines Reviews of S. Ortiz, H. Sun and DJ Chatterjee

Stephan Ortiz
10/17/03 04:25:47 PM
BIOPHARMACEUTICS

Ameeta Parekh
10/17/03 04:30:18 PM
BIOPHARMACEUTICS