SP0738, 2004-000476-13

CLINICAL STUDY REPORT SYNOPSIS

———————————————————————————————————

Sponsor:

UCB BIOSCIENCES GmbH

(formerly SCHWARZ BIOSCIENCES GmbH)

Alfred-Nobel-Str. 10

40789 Monheim

Germany

Official study title:

Long-term open-label extension trial for subjects completing the Phase 3 trial of fesoterodine (SP583) for the treatment of overactive bladder syndrome

Name of company: SCHWARZ BIOSCIENCES, GmbH	**Individual study table referring to part of the dossier** Not applicable	*(For National Authority Use Only)*
Name of Finished Product: Not applicable*	**Volume:** Not applicable	
Name of Active Ingredient: fesoterodine fumarate	**Page:** Not applicable	

Title of trial: Long-term open-label extension trial for subjects completing the Phase 3 trial of fesoterodine (SP583) for the treatment of overactive bladder syndrome

Investigators: Multicenter trial

Trial sites: A total of 93 sites in 14 countries in [redacted] (17 countries total) were initiated; 90 sites enrolled subjects.

Publication (reference): None

Studied period (years): 3 years **First subject enrolled**: 02 Jul 2004 **Last subject completed**: 11 Jul 2007	**Phase of development:** 3

Objectives: The objectives of this trial were to obtain long-term data on safety, satisfaction, and maintenance in subjects taking fesoterodine. Subject satisfaction and the treatment benefit of fesoterodine were also assessed.

Methodology: This was a long-term, open-label (OL), extension trial of SP583 (a randomized, double-blind [DB], double-dummy, placebo- and active-controlled, multicenter trial) to obtain long-term data on safety, satisfaction, and maintenance on therapy of fesoterodine in male and female adult subjects with overactive bladder syndrome (OAB). Subjects completing the 12-week treatment period of SP583 had the opportunity to participate in this trial.

After eligibility was confirmed, all subjects received fesoterodine 8mg/day at the start of the trial. Each subject could have requested a 1-time dose reduction to fesoterodine 4mg/day after the subject had been on 8mg/day for at least 1 month, during a scheduled site visit and upon discussion with the investigator. Subjects could also have requested to increase their dose back to 8mg/day. This decision could only be made during a scheduled site visit and upon discussion with the investigator. This process was followed on an annual basis. Fesoterodine was to be taken once daily each morning with or without food.

*Approved as Toviaz® (this note was added for clarification purposes afterwards)

Name of company: SCHWARZ BIOSCIENCES, GmbH	**Individual study table referring to part of the dossier** Not applicable	*(For National Authority Use Only)*
Name of Finished Product: Not applicable	**Volume:** Not applicable	
Name of Active Ingredient: fesoterodine fumarate	**Page:** Not applicable	

Number of subjects (planned and analyzed): At least 550 subjects were planned to be recruited. A total of 417 subjects were enrolled.

Diagnosis and main criteria for inclusion: Subjects completed the full 12-week treatment period after randomization in trial SP583 as scheduled without meeting discontinuation criteria and with no adverse events (AE) that would, in the opinion of the investigator, jeopardize the well-being of the subject if treatment was continued.

Test product, dose and mode of administration, batch number: Fesoterodine fumarate SR; 4mg and 8mg tablets given orally once daily. Batch numbers were: 4mg, [redacted]; 8mg, [redacted].

Duration of treatment: Treatment Period: Up to 3 years, Safety Follow-Up: 2 weeks

Reference therapy, dose and mode of administration, batch number: None

Criteria for evaluation:

Safety: The following variables were analyzed as changes from double-blind and open-label Baseline to values at each visit: observation and assessment of AEs, change in laboratory parameters, change in physical and urological examination, change in vital signs (blood pressure [BP], pulse rate), change in electrocardiogram (ECG; including QTc intervals), change in residual urinary volume (mL), subject's assessment of treatment tolerance, duration on therapy, reasons for withdrawal from the trial, and frequency of dose reductions and dose increases.

Efficacy: Assessments of efficacy were performed only up to 24 months after enrollment in this open-label extension trial. Efficacy assessments included the following: change in average number of urge incontinence episodes per 24 hours, change in average number of micturitions (frequency) per 24 hours, change in average number of micturitions during the day, change in average number of micturitions during sleeping time, change in total number of urgency episodes (with or without incontinence) per 24 hours, change in average number of urgency episodes without incontinence per 24 hours, change in number of urgency episodes with incontinence per 24 hours, change in average number of total voidings per 24 hours, change in voided volume per micturition, change in severity or urinary urgency, and change in number of continent days per week.

Name of company: SCHWARZ BIOSCIENCES, GmbH	**Individual study table referring to part of the dossier** Not applicable	*(For National Authority Use Only)*
Name of Finished Product: Not applicable	**Volume:** Not applicable	
Name of Active Ingredient: fesoterodine fumarate	**Page:** Not applicable	

Health outcomes: Health outcomes analyzed were the King's Health Questionnaire (KHQ), International Consultation on Incontinence Questionnaire - Short Form (ICIQ-SF), and subject's assessment of treatment satisfaction, and subject's assessment of condition based on the Likert Scale.

Statistical methods: The primary trial variables examined long-term safety and tolerability or maintenance on therapy. Duration on therapy was summarized with descriptive statistics for the combined double-blind and open-label periods and for the open-label period only. Sample size for this trial was not based on formal statistical calculations. For the analysis of selected characteristics at trial entry, the Enrolled Set (ES) of subjects was considered. The ES included all subjects who completed Visit 1, whether or not any trial medication was taken. The ES was the primary subject population for subject data listings. The Safety Set (SS), defined as all subjects who took at least 1 dose of trial medication, was used for the analysis of safety data. The primary analysis set for all secondary efficacy variables was the Full Analysis Set (FAS). Subjects who were valid for the SS and had at least 1 valid efficacy measurement at the SP738 Visit 2 or later were included in the FAS.

Summary and conclusions:

Safety results:

The most frequently reported AE was dry mouth (34% of subjects). This AE is typically observed in subjects taking antimuscarinic drugs. The majority of AEs were of mild or moderate intensity. The incidence of trial medication discontinuation due to AEs was generally low, occurring in 12% of subjects. Discontinuation of trial medication due to dry mouth occurred in 2% of subjects and 1% of subjects discontinued trial medication because of constipation.

Fifteen percent of subjects experienced a treatment-emergent AE leading to dose reduction from fesoterodine 8mg to 4mg. The most commonly reported treatment-emergent AE leading to dose reduction was dry mouth.

Overall, clinical laboratory results were consistent over time. No apparent trends in hematology, blood chemistry, or urinalysis were noted with fesoterodine treatment.

No clinically relevant changes from DB or OL Baseline were observed for vital sign parameters, ECG parameters, physical and urological examination findings, or residual urine volume data during open-label treatment with fesoterodine. There is no indication of

Name of company: SCHWARZ BIOSCIENCES, GmbH	**Individual study table referring to part of the dossier** Not applicable	*(For National Authority Use Only)*
Name of Finished Product: Not applicable	**Volume:** Not applicable	
Name of Active Ingredient: fesoterodine fumarate	**Page:** Not applicable	

increased effects on pulse rate or QT prolongation with increased exposure.

Two subjects had a maximum Fridericia corrected QT interval (QTcF) and Bazett corrected QT interval (QTcB) value that was >500ms during the trial and 1 subject had a QTc increase ≥60ms from DB Baseline with both QTcF and QTcB. One subject had a QTcB value that was >500ms and 4 subjects had a QTc increase ≥60ms from DB Baseline with QTcB only. Six subjects experienced AEs related to ECG findings.

Residual urine volume increased by an average of 10mL from DB Baseline to Visit 8 (Year 2). A total of 7 subjects had a residual urine volume >200mL.

After 4 months of open-label treatment, 88% of subjects reported their treatment tolerance as "good" or "excellent." More than 91% of subjects assessed their treatment tolerance as "good" or "excellent" after 1 year of open-label treatment. After 2 years of open-label treatment, 93% of subjects reported their treatment tolerance as "good" or "excellent."

Overall, no unexpected safety trends were observed in the occurrence of AEs, laboratory parameters, vital signs, ECG findings, physical and urological examination findings, or residual urine volume.

Efficacy:

Subjects treated with fesoterodine had sustained or further improvements from DB and OL Baseline through Visit 8 (represents 2 years of treatment) in all efficacy variables.

From DB Baseline to Visit 8 (Year 2), the mean number of urge incontinence episodes per 24 hours decreased by 2.8 and the mean number of micturitions per 24 hours decreased by 2.7. The mean number of micturitions during the day per 24 hours decreased by 2.1 and the mean number of micturitions during sleeping time per 24 hours decreased by 0.6.

Urgency episodes also decreased from DB Baseline to Visit 8. The mean number of urgency episodes per 24 hours decreased by 3.3. The mean number of urgency episodes without incontinence per 24 hours decreased by 0.9 and the mean number of urgency episodes with incontinence per 24 hours decreased by 2.8.

Total voidings per 24 hours decreased by 2.9 from DB Baseline to Visit 8. The mean voided volume per micturition at Baseline increased by 49.5mL at Visit 8.

At OL Baseline, 24% of subjects had severe urinary urgency, 47% had moderate urgency, 19% had mild urgency, and 10% had no urgency. By Visit 8 (Year 2), the percentage of

Name of company: SCHWARZ BIOSCIENCES, GmbH	**Individual study table referring to part of the dossier** Not applicable	*(For National Authority Use Only)*
Name of Finished Product: Not applicable	**Volume:** Not applicable	
Name of Active Ingredient: fesoterodine fumarate	**Page:** Not applicable	

subjects reporting severe urinary urgency had decreased to 14% and the percentage of subjects reporting no urgency had increased to 15%.

The mean number of continent days per week among incontinent subjects increased by 3.5 days from DB Baseline to Visit 8.

Health outcomes:

Both quality of life instruments, the KHQ and the ICIQ-SF, showed improvement over time. All domains in the KHQ showed improvement at Visit 8 compared to Baseline, particularly the "impact on life" and "role limitations" domains. The ICIQ-SF score decreased by 6.2 points from Baseline, showing decreased bother from urine leakage. The number of subjects who stated that they were not satisfied with their treatment decreased from 16% at OL Baseline to 3% at Visit 8 (Year 2). When subjects rated the severity of their condition on a 4-point Likert Scale, most reported moderate, severe, or very severe bladder problems at Baseline of SP583. By OL Visit 8, 25% reported moderate to severe bladder problems and 2% reported very severe problems.

Conclusions:

- The most frequently reported AE was dry mouth (34% of subjects). This AE is typically observed in subjects taking antimuscarinic drugs. The majority of AEs were of mild or moderate intensity. The incidence of discontinuation of trial medication due to AEs was generally low, occurring in 12% of subjects. Discontinuation of trial medication due to dry mouth occurred in 2% of subjects and 1% of subjects discontinued trial medication because of constipation.
- Fifteen percent of subjects experienced a treatment-emergent AE leading to dose reduction from fesoterodine 8mg to 4mg. The most commonly reported treatment-emergent AE leading to dose reduction was dry mouth.

Name of company: SCHWARZ BIOSCIENCES, GmbH	**Individual study table referring to part of the dossier** Not applicable	*(For National Authority Use Only)*
Name of Finished Product: Not applicable	**Volume:** Not applicable	
Name of Active Ingredient: fesoterodine fumarate	**Page:** Not applicable	

- Overall, clinical laboratory results were consistent over time. No apparent trends in hematology, blood chemistry, or urinalysis were noted with fesoterodine treatment.
- No clinically relevant changes from DB or OL Baseline were observed for vital sign parameters, ECG parameters, physical and urological examination findings, or residual urine volume data during open-label treatment with fesoterodine. There is no indication of increased effects on pulse rate or QT prolongation with increased exposure.
- Two subjects had a maximum QTcF and QTcB value that was >500ms during the trial and 1 subject had a QTc increase ≥60ms from DB Baseline with both QTcF and QTcB. One subject had a QTcB value that was >500ms and 4 subjects had a QTc increase ≥60ms from DB Baseline with QTcB only. Six subjects experienced AEs related to ECG findings.
- Residual urine volume increased by an average of 10mL from DB Baseline to Visit 8 (Year 2). A total of 7 subjects had a residual urine volume >200mL.
- The percentage of patients who reported their treatment tolerance as "good" or "excellent" increased over time during the trial, from 88% of subjects after 4 months of open-label treatment to 93% of subjects after 2 years of treatment.
- Overall, no unexpected safety trends were observed in the occurrence of AEs, laboratory parameters, vital signs, ECG findings, physical and urological examination findings, or residual urine volume.
- Subjects treated with fesoterodine had sustained or further improvements from DB and OL Baseline through Visit 8 (represents 2 years of treatment) in all efficacy variables. Continued or maintained improvement in the signs and symptoms of OAB were observed compared to the double-blind trial (SP583).
- Fesoterodine improved the quality of life for subjects in this trial as demonstrated by improvement for all health outcomes measures.

Date of the report: 11 Dec 2007