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A DOUBLE-BLIND, PLACEBO CONTROLLED, RANDOMISED, MULTIPLE ORAL DOSE, DOSE ESCALATION TRIAL INVESTIGATING THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SVT-40776 IN HEALTHY POSTMENOPAUSAL WOMEN

Hypothesis / aims of study

Overactive bladder (OAB) is characterized by symptoms of urgency with or without incontinence, usually with frequency and nocturia, in the absence of local pathology that would account for these symptoms. SVT-40776 is the most potent and bladder selective compound [1- 3] claimed to effectively treat OAB symptoms without muscarinic related AE. In a previous single dose study up to 5mg, SVT-40776 was safe in the large dose levels administered regarding vital signs, ECG, continuous cardiac monitoring, laboratory test and adverse events (AE) seriousness and intensity. SVT-40776 was orally absorbed, with a dose-linear increase of C_{max} and $AUC_{0-\infty}$. The long half-life (about 35 h) of SVT-40776 suggests a once daily dosing regimen.

The aim of the study was to evaluate the safety and tolerability of multiple doses (up to 0. 5 mg) of SVT-40776. The secondary objectives were to investigate the pharmacokinetics (PK) properties of SVT-40776 and its non-active metabolite SVT-41610.

Study design, materials and methods

A total of 24 healthy postmenopausal females from 50 to 70 years of age were dosed in single followed by a multiple doses of SVT-40776 (0.125, 0.25 and 0.5 mg) or matching placebo up to 14 days in three parallel groups.

Six subjects were randomised to each doses of active treatment SVT-40776 as a solution. All volunteers provided informed written consent prior to participation. The study was approved by an Independent Ethics Committee. Safety was assessed by determining AE (AEs), haematology, biochemistry, urinalysis, physical examination, vital signs and 12-lead ECG. Salivary flow, pupil diameter, accommodation near point were also assessed as specific tolerability. Pharmacokinetics were assessed by t_{max}, $t_{1/2}$, C_{max}, $AUC_{0-\infty}$, $AUC_{0-tlast}$, the fractional clearance (CL/F), the apparent volume of distribution (Vz/F). Minimum, maximum and average concentrations at steady state were measured. Urine levels of parent compound and its main metabolite were also calculated.

Results

Safety and tolerability:

No serious AE or withdrawals due to AE occurred during the study. There were no clinically relevant changes in vital signs, ECG or laboratory test. There was no significant differences in total incidence of AEs among three studied doses and placebo.

A total of 6 subjects experienced dry mouth (Placebo: 0 / 0.125mg: 0 / 0.25 mg:3 / 0.5 mg:3), 5 subjects experienced constipation (Placebo: 1 / 0.125mg: 0 / 0.25mg:3 / 0.5mg:2) and 5 subjects experienced visual disturbances (Placebo: 2/ 0.125mg: 2 / 0.25mg:0 / 0.5mg:1) as the most frequent experienced related adverse events.

Concerning the specific tolerability, all groups included placebo showed a trend to decrease in the salivary flow. Mean changes from baseline were similar between placebo and SVT-40776 at all time points. The change in pupil diameter for all dose levels was similar to that of placebo at all time points. In the same way, the change in the accommodation near point distance was similar to that of placebo after all doses. The relative incidence of drug-related AEs was lower after multiple dosing than after single dosing period

Pharmacokinetics:

After single dosing period SVT-40776 showed a rapid onset of absorption with peak values within the first 4 hours, unaffected by dose level. Overall, C_{max} and AUC_{0-last} were considered to have responded proportionally to the dose. Accumulation index is around two times higher

than after single dosing period. The median half-life after multiple doses was also higher and median values ranged from 64 to 67 hours. The large fractional distribution volumes indicate that SVT-40776 may be widely distributed. Fluctuation between minimum and maximum plasma concentrations at steady state were about 50.9 and 67.2%, considered low given the fact that SVT-40776 was administered as a solution (Table 1). SVT-41610, the non-active metabolite, showed the same kinetic pattern but was detectable only after repeated doses of 0.25 and 0.5mg; exposure of the metabolite was about six times lower than the parent compound. As the concentration values after the lowest doses were close to LOQ, the estimation of the terminal elimination half-life were influenced by the variability of the analytical method, this also lead to high extrapolated area for AUC calculations and time to steady state. Nevertheless, it was considered that the steady state was reached after 13 days.

Table 1. Steady state concentrations of different doses of SVT-40776

dose	C_{ssmax} (ng/mL) (mean)	C_{ssmin} (ng/mL) (mean)	C_{ssav} (ng/mL) (mean)	%Fluctuation (mean)
0.125mg	0.697	0.425	0.542	50.2
0.25mg	1.807	1.070	1.351	54.2
0.5mg	3.024	1.515	2.233	67.2

The maximum excretion rate increased linearly with the dose. Renal clearance could only be calculated from higher doses and individual values ranged from 130 to 244 ml/min dose independently.

Interpretation of results

All doses of SVT-40776 were well tolerated by all subjects. The lowest dose (0.125mg) level studied appeared to be devoid of antimuscarinic adverse reactions. It was considered that SVT-40776 and its main metabolite showed a linear pharmacokinetics at multiple doses. The rapid absorption and long half life of SVT-40776 support a once daily dosing regimen. The low fluctuation between minimum and maximum plasma concentrations at steady state together with bladder selectivity suggest an excellent tolerability profile.

Concluding message

SVT-40776 is the most potent and selective M_3 muscarinic-receptor antagonist, safe and well tolerated in healthy volunteers.

This finding shows a promising clinical profile of SVT-40776 and is currently in dose-finding development in a once daily administration.