270

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A RANDOMISED, PLACEBO-CONTROLLED, DOSE-RISING STUDY IN HEALTHY MALES VOLUNTEERS TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF SINGLE ORAL DOSES OF SVT-40776, A NOVEL SELECTIVE M3 ANTIMUSCARINIC.

Hypothesis / aims of study

Overactive bladder (OAB) is characterized by symptoms of urinary frequency and urgency, with or without incontinence, in the absence of local pathology that would account for these symptoms. SVT-40776 is a novel muscarinic-receptor antagonist, with high selectivity for M_3 over M_2 receptors [1, 2] with significant potential to ameliorate OAB symptoms. The aim of the study was to evaluate the safety and tolerability of large doses (0.25, 0.5, 1 and 5 mg) of SVT-40776 in healthy male volunteers. The secondary objectives were to investigate the pharmacokinetics (PK) and the pharmacodynamic effects (PD) of SVT-40776 following single oral doses in healthy males.

Study design, subjects and methods

Four groups of 8 healthy male volunteers, aged between 18-45 years, were exposed to a single oral dose of SVT-40776 (0.25, 0.5, 1 and 5 mg) or matching placebo. The administered doses were higher than the expected therapeutic dose (< 0.25 mg). For each group, subjects were randomised to receive either SVT-40776 or matching placebo (3:1 active to placebo). All volunteers provided informed written consent prior to participation. The study was approved by an Independent Ethics Committee.

Safety was assessed by determining adverse events (AEs), continuous cardiac monitoring, 12-lead ECG, physical examination, vital signs and laboratory safety test (haematology, biochemistry and urinalysis).

Pharmacokinetics was assessed by $AUC_{0-\infty}$, $AUC_{0\text{-tlast}}$, C_{max}, t_{max} and $t_{1/2}$.

Pharmacodynamic effect was assessed by measuring pre- and post-dose levels of salivary flow, pupil diameter and accommodation near point.

Results

- **Safety and tolerability**

There were no clinically relevant changes in vital signs, ECG, continuous cardiac monitoring or laboratory test.

No serious adverse events occurred during the study and all subjects completed the study.

AEs were reported in 20 of 24 (83.3%) SVT-40776 subjects and 6 of 8 (75.0%) placebo subjects. The most commonly reported AEs were dry mouth (SVT-40776: 13 subjects), vision disturbances (SVT-40776: 11 subjects) and dizziness (SVT-40776: 11 subjects). With increasing doses of SVT-40776 the incidence of AEs increased. The 6 subjects who received 5 mg of SVT-40776 showed symptoms of confusion.

There was no significant difference in incidence of AEs when subjects received 0.25 mg of SVT-40776 in comparison to placebo.

The 82.4% of the AEs were mild and the rest, moderate, being all the AEs reported at 0.25 and 0.5 mg mild.

- **Pharmacokinetics**

SVT-40776 was absorbed orally with a median t_{max} ranging from 1.5 to 4.0 hours, unaffected by dose level. The median half-life was from 30.3 to 43.8 hours. The median $\mathbf{C_{max}}$ (0.52 to 11.40 ng/ml), the median $AUC_{0\text{-tlast}}$ (15.7 to 257.3 ng·h/ml), and the $AUC_{0-\infty}$, (22.9 to 407.5 ng·h/ml) appeared to increase in a dose-linear manner.

- **Pharmacodynamics**

There were a lengthening of the near point accommodation and a decrease in the salivary flow for 1 mg and 5 mg, showing a dose response relationship. There were no obvious changes in the pupil diameter.

Interpretation of results

- SVT-40776 was safe in the large dose levels administered regarding vital signs, ECG, continuous cardiac monitoring, laboratory test and AE seriousness and intensity.
- The antimuscarinic activity of SVT-40776 was reflected in the most frequently reported AEs of dry mouth, blurred vision and dizziness and in the effect on near point accommodation and salivary flow.
- The frequency, severity and duration of these AEs appeared to increase with dose.
- Doses of 0.25, 0.5 and 1 mg of SVT-40776 were well tolerated by all volunteers.
- At the 0.25 mg dose level, the tolerability was comparable to placebo.
- At the 5 mg dose level (≥20-fold greater that the expected therapeutic dose), no hazardous effects were observed. However, it was not well tolerated.
- 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.

Concluding message

The results obtained in terms of safety, PK and PD in all dose levels and the excellent results obtained with the 0.25 mg, the nearest to the therapeutic expected dose, in terms of tolerability, suggest that SVT-40776 may improve the symptoms of OAB with a good safety and tolerability profile, and are encouraging for going on with the clinical development. Studies in a multiple dose regimen have recently finished and studies with patients, in phase II clinical trials, are currently ongoing.

References

1. SVT-40776, a new selective M3 muscarinic antagonist: human receptor binding profile and bladder effects in the guinea-pig. Neurourol Urodyn 2002; 22(5): 382-384.
2. Functional characterization of SVT-40776, a novel and potent M3 receptor antagonist, on mice detrusor and atria isolated preparations using *in vitro* and *ex vivo* protocols.Br J. Pharmacol 2002; 136 (supp): 45.