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DOSE ESCALATION OF A MUSCARINIC ANTAGONIST WITH THVD-201, A NOVEL COMBINATION DRUG PRODUCT CONTAINING TOLTERODINE AND PILOCARPINE (A MUSCARINIC AGONIST AND SALIVARY STIMULANT)

Hypothesis / aims of study

THVD-201 is a twice daily (BID) oral combination drug product containing an immediate release formulation of tolterodine (TOLT) and a proprietary, delayed onset, immediate release formulation of pilocarpine (PILO). The TOLT component is a muscarinic antagonist for the treatment of overactive bladder (OAB). The PILO component is a muscarinic agonist and salivary stimulant to reduce the anti-muscarinic drug-induced dry mouth side effect. The formulation of PILO was developed specifically to match the pharmacodynamic reduction in salivary output caused by TOLT. Two strengths of THVD-201 are being evaluated in clinical trials: THVD-201 (2/9) containing 2mg TOLT and 9mg PILO; and THVD-201 (3/13.5) containing 3mg TOLT and 13.5mg PILO. A previous Phase 2 study evaluated the safety and efficacy of THVD-201 (2/9) BID in females with OAB. This study was followed by a 12-week open-label extension period (EP) where subjects were randomized to either THVD-201 (3/13.5) BID or 4mg TOLT extended release (ER) once daily (QD). The hypothesis is that at dosing above the usual range, THVD-201 (3/13.5) BID may enable greater patient tolerability of anti-muscarinic therapy, through the reduction of dry mouth side effect, and a potential increase in efficacy for bladder control.

Study design, materials and methods

Subjects took either THVD-201 (3/13.5) BID, for a total daily dose (TDD) of TOLT 6mg/day with the combination product, or 4mg TOLT ER QD. Outcome measures included micturitions/day, incontinence episodes (IE)/day, and overall dry mouth scores. The number of daily micturitions and IEs were collected using 3-day diaries. Dry mouth severity was assessed using a 100mm visual analog scale (VAS) (0mm=not dry, 100mm=very dry).

Results

	EP Week	THVD-201 (3/13.5) BID n=27	4mg TOLT ER QD n=23
Mean Dry Mouth Score (Std Dev)	6	26.6 (20.9)	31.3 (23.0)
	12	23.6 (17.5)	25.8 (20.7)
Mean Micturitions/day (Std Dev)	6	8.7 (2.3)	8.9 (2.1)
	12	8.8 (2.4)	9.3 (2.3)
Mean IE/day (Std Dev)	6	0.4 (0.6)	0.2 (0.3)
	12	0.5 (0.7)	0.2 (0.3)

Interpretation of results

THVD-201 (3/13.5) BID was safe and well tolerated. THVD-201 (3/13.5) BID had a lower severity of dry mouth side effect (as assessed by VAS) when compared to 4mg TOLT ER QD, despite a 50% increase in TDD of TOLT (6mg/day versus 4mg/day). These results suggest that the THVD-201 combination drug product may enable a higher TDD of TOLT without increasing dose-limiting dry mouth. A potential increase in efficacy, as indicated by lower mean micturitions/day for THVD-201 (3/13.5) BID, was observed at both 6 and 12 weeks.

Concluding message

Further clinical studies should be conducted, to more rigorously examine potential side effect and efficacy benefits of THVD-201 (3/13.5) BID, as compared to 4mg TOLT ER QD.

Disclosures

Funding: TheraVida **Clinical Trial:** Yes **Registration Number:** Australian New Zealand Clinical Trials Registry (ANZCTR), ACTRN12610001093077 **RCT:** Yes **Subjects:** HUMAN **Ethics Committee:** Southern Adelaide Clinical Human Research Ethics Committee, The Royal Brisbane & Women's Hospital HREC, Concord Repatriation General Hospital HREC, Bellberry Human Research Ethics Committee, St John of God Health Care Ethics Committee, Austin Hospital Human Research Ethics Committee, UnitingCare Health Human Research Ethics Committee, Multi region Ethics Committee, c/o Ministry of Health, Wellington, New Zealand **Helsinki:** Yes **Informed Consent:** Yes