Table 1: Mean C_{max} and AUC Values

Parameter	Analyte	ER-OXY	ER-OXY+ KET	x-fold	Conv-OXY	Conv-OXY + KET	x-fold
AUC_{inf}	R-OXY	41	82	2	29	84	2.9
(ng.h/mL)	S-OXY	82	159	1.9	44	184	4.2
	R-DES	334	413	1.2	462	517	1.1
	S-DES	256	449	1.8	282	571	2.0
C_{max}	R-OXY	1.9	3.9	2.1	6.1	17.9	2.9
(ng/mL)	S-OXY	3.7	7.8	2.1	12.8	44.7	3.5
	R-DES	18.5	19.0	1.0	68.3	53.3	0.8
	S-DES	12.1	18.4	1.5	38.1	51.3	1.4

With ER-OXY, the metabolite formation is lower (R-DES 75%; S-DES 90%) and the bioavailability of OXY is higher (R-OXY 154%; S-OXY 190%) than Conv-OXY. The difference in metabolism between the two formulations may be due to differences in the presystemic intestinal metabolism because with ER-OXY, the drug is mainly absorbed in the colon, whereas the small intestine is the absorption site for Conv-OXY. The intestinal metabolic enzymes are less prevalent in the colon compared to the small intestine. Literature reports suggest metabolites are responsible for dry mouth (1). Thus lower metabolite formation, especially R-DES may account for lower dry mouth severity with ER-OXY compared to Conv-OXY. This would explain the lack of effect of KET on dry mouth for either formulation, even though there is a 2-4 fold increase in R-and S-OXY concentration and also a 2-fold increase in S-DES concentration. R-DES concentration however does not change significantly, paralleling the lack of increased dry mouth for either ER-OXY or Conv-OXY when administered with KET. In vitro literature studies (2,3) have shown that the antimuscarinic activity lies with the R-isomer (both OXY and DES) and DES has a higher affinity for the parotid gland than OXY (OXY and DES have similar affinity for the bladder antimuscarinic receptors). Thus, it appears that R-DES may be responsible for dry mouth observed in OXY therapy.

Conclusions: Enzyme inhibition by KET has less effect on ER-OXY pharmacokinetics and dry mouth severity is lower with ER-OXY compared to Conv-OXY. Dry mouth does not seem to be affected by KET for either formulation. Formation of the metabolite, R-DES, is significantly lower with ER-OXY than Conv-OXY and it appears that R-DES may play a major role in dry mouth observed in OXY therapy.

References:

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PLACEBO-CONTROLLED, RANDOMISED, DOUBLE-BLIND, MULTICENTRE CLINICAL TRIAL ON THE EFFICACY AND TOLERABILITY OF 1 X 40 mg AND 2 X 40 mg TROSPIUM CHLORIDE (SPASMO-LYT®) DAILY FOR 3 WEEKS IN PATIENTS WITH URGE-SYNDROME

OBJECTIVE: Evaluation of the efficacy and tolerability of 1 x 40 mg and 2 x 40 mg trospium chloride (TCI) daily in patients with urge-syndrome.

METHODS: Until the first interim analysis of this placebo-controlled, randomised, multi-centre clinical trial with an adaptive design 175 patients received either 40 mg TCI once daily or 2 x 40 mg daily or placebo for 3 weeks. Primary efficacy variables were the micturition frequency in 24 hours assessed by data from the patients' micturition diaries

and maximum bladder capacity which was evaluated by means of urodynamic measurements.

RESULTS: In the confirmatory part of the analysis a one-sided trend test for O'Brians z-score sum was carried out. The z-scores were calculated from the mean micturition frequency changes and the changes in maximum bladder capacity. A statistically significant difference (per-protocol: p = 0.0007; intention-to-treat: p = 0.0017) was found and the study could be stopped due to the positive result.

Results of urodynamic measurements, Intention-to-treat analysis

Variable		1 x 40 mg TCI (n=56)			2 x 40 mg TCI (n=56)			Placebo (n=58)		p-value (two-sided)
		Baseline	Change	Treatment effect*	Baseline	Change	Treatment effect*	Baseline	Change	
Maximum bladder capacity [ml]	Mean	232.25	+ 69.98	+ 45.3	192.68	+ 86.11	+ 61.4	234.33	+ 24.71	0.0006
	SD	109.20	83.66		90.44	86.06		112.39	89.91	
Vol. at 1. desire to void [ml]	Mean	91.70	+ 53.00	+ 21.4	82.88	+ 54.96	+ 23.4	86.24	+ 31.59	0.1109
	SD	54.60	70.57		48.68	59.25		54.55	66.91	
Volume at 1. unstable contraction [ml]	Mean	125.23	+113.66	+ 53.5	114.39	+ 135.41	+ 75.2	130.95	+ 60.21	0.0333
	SD	85.10	155.23		89.29	130.95		82.99	123.28	
Volume at maximum contraction [ml]	Mean	219.80	+ 68.59	+ 45.2	171.29	+ 100.39	+ 77.0	222.09	+ 23.40	0.0015
	SD	116.72	113.22		90.38	117.12		116.29	107.70	
Residual urine [ml]	Mean	15.89	+ 14.59	+ 5.2	8.03	+ 16.00	+ 6.6	14.83	+ 9.41	0.719
	SD	26.81	41.00		15.27	44.78		25.07	50.37	

SD = standard deviation * = versus placebo

The safety analysis revealed a dose-dependent difference of the number of patients with adverse events in the three treatment groups:

Placebo: n=17 (28.3%)
1 x 40 mg TCI: n=29 (50.9%)
2 x 40 mg TCI: n=37 (63.8%)

Most of the adverse events reported were known reactions to anticholinergics such as gastro-intestinal complaints, especially mouth dry. No serious adverse events occured during this clinical trial.

CONCLUSION: Both dosages of TCI (40 mg once daily and 40 mg b.i.d.) showed a statistically significant and clinically relevant treatment effect in patients with urge-syndrome compared to placebo. Thus, TCI appears to be an effective and safe treatment.

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COMPARISON OF URGE INCONTINENCE TREATMENTS

Aims of Study. Oxybutynin chloride is a first-line treatment for urge incontinence (UI), a symptom of overactive bladder. However, dry mouth may limit the dosage and thus the therapeutic use. We compared a novel, extended-release, once-daily oxybutynin tablet with traditional immediate-release oxybutynin for UI.

Methods. A total of 201 women and 25 men with UI (mean age: 59) were randomly assigned to extended-release oxybutynin taken once daily (double-blind, double-dummy) or immediate-release oxybutynin taken qd to qid; both groups were dose-adjusted (5-20 mg/day) to optimum efficacy and tolerability. Kaplan-Meier survival analysis was applied to the data.