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DOSE FORMULATION, DOSE SELECTION, AND PHASE III RESULTS FOR A FLEXIBLE DOSE GEL FOR TRANSDERMAL OXYBUTYNIN DELIVERY

Hypothesis / aims of study

To present (A) the methodology and results from dose formulation and selection studies and to report (B) the results for primary outcome variables of a Phase III clinical study of a transdermal titratable once daily oxybutynin gel formulation (TTOG). At present, there are no titrable transdermal agents for treatment of overactive bladder (OAB).

Study design, materials and methods

Multiple formulations were screened using *in-vitro* skin permeability studies in both pig and human cadaver skin. Based on the amount of oxybutynin that permeated these samples, the formulation was optimized and the dosage selected following pK analysis for further evaluation in the clinical trials. The transdermal formulation of oxybutynin was characterized via single and multiple-dose Phase I studies. Plasma profiles were generated for three doses (84mg, 60mg, and 42 mg/daily) to establish a correlation between the applied dose and plasma levels. The serum profiles of the different doses were used to select two doses of oxybutynin 3%: 84mg (2.8gm/3.0 ml) and 56mg (1.9gm/ 2.0ml) for the Phase III trial. The Phase III study was 12 weeks and included adults (age range:19-89) with OAB symptoms of urgency (UUI) and/or mixed UI with a predominance of UUI for at least 3 months. Subjects had a history of at least 1–2 urge episodes and 8 or more voids/day. Three treatment arms included: the effective doses 84mg and 56mg TTOG and placebo (gel without oxybutynin) delivered with a metered pump. The primary endpoint for the trial was change from baseline in weekly urinary incontinence episodes (UI) using a 3-day diary.

Results

(A) Cumulative oxybutynin permeated from the optimized transdermal gel were similar for both the pig and human cadaver skin. These results were used to compute the doses for the first pharmacokinetic (pK) study of this oxybutynin gel in humans. The pK study not only confirmed the *in-vitro* skin permeability study results but also confirmed the hypothesis of relatively lower levels of N-desethyloxybutynin (DEO) compared to oxybutynin. Further, pK study was conducted to confirm that the 2 doses selected (56 and 84 mg) afforded appropriate plasma levels (Fig 1. - see plasma profiles b and c)

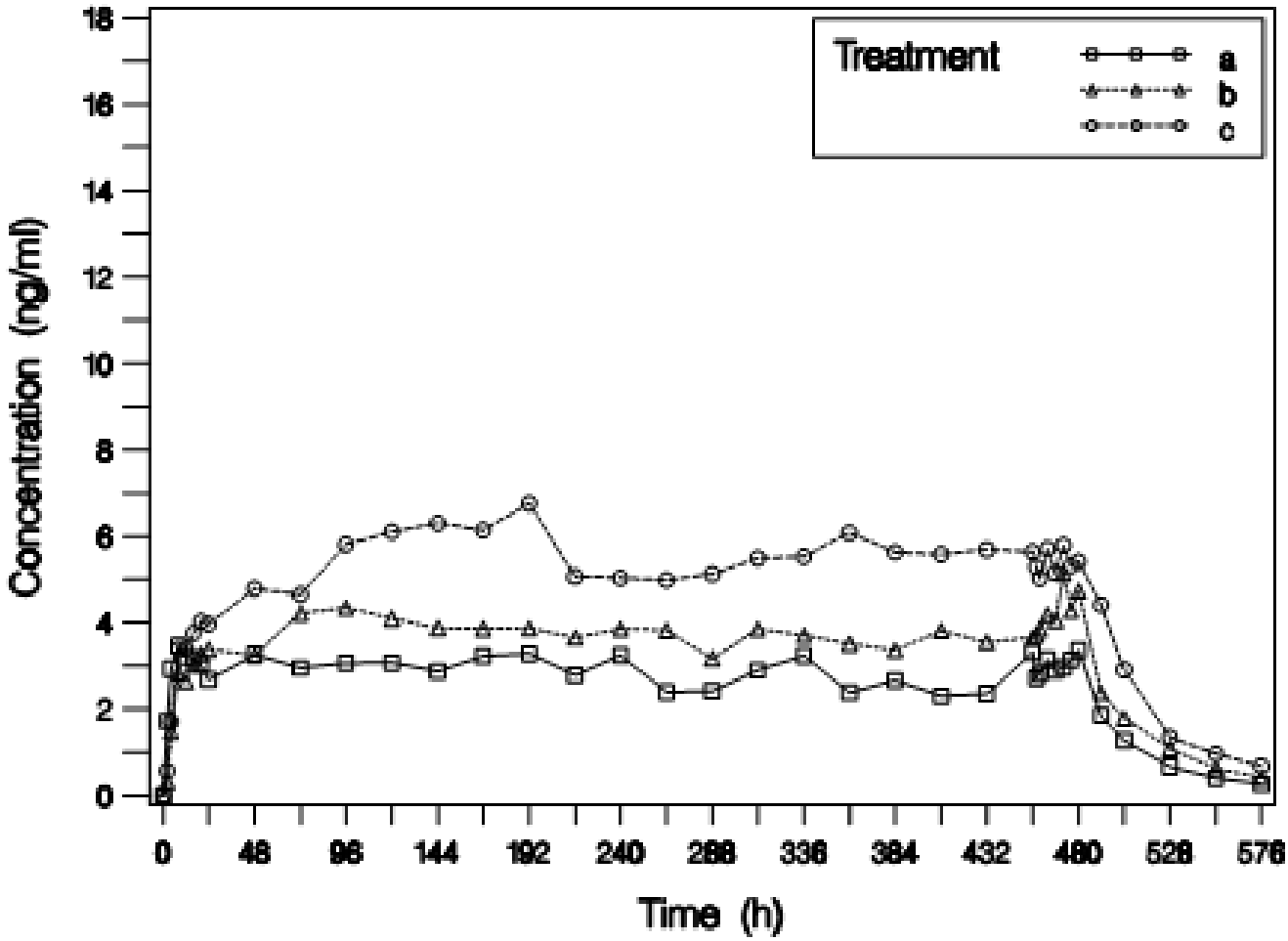

Figure 1. Mean Oxybutynin Plasma Concentrations
(a: 1.4 g Test, b: 2 g Test 2, c: 2.8 g Test)

(B) The doses of 56mg and 84mg were selected for the Phase III study based on the pK studies above. Overall 626 patients (87% female) were included: TTOG 84 mg (N=214), TTOG 56 mg (N=210), and placebo (N= 202). Both dosing levels of the TTOG were statistically superior to placebo for UUI reduction (Table 1). Adverse events were generally mild to moderate with non-prompted rates of dry mouth n= 26 (12.1%) for 84 mg and n= 23 (11.0%) for 56 mg TTOG and n=10 (5.0%) for placebo. Central nervous system side events were similar between both active arms and the placebo group.

TABLE 1	**Treatment Group**		
Endpoints	**TT-Oxy gel 84 mg/day (n=195)**	**TT-Oxy gel 56 mg/day (n=171)**	**Placebo (n=166)**
UUI/week, mean			
Baseline	43.6	50.1	45.8
Median Change	– 18.7[x]	– 21.0[xx]	- 16.3
Micturitions/24 h			
Baseline , mean	11.4	11.7	10.5
Change, mean	– 2.9[y]	– 2.2[ns]	– 1.9
Mean Voided Volume, mL			
Baseline	196.9	196.2	182.0
Change (vs placebo)	29.0[z]	21.1[zz]	10.4

x ~ p =0.033 xx ~ p =0.028 y ~p =0.0005 z ~ p =0.0017 zz ~ p =0.0499

Interpretation of results

The Phase III results confirmed that the dose selection methodology was appropriate and accurate. Transdermal titratable oxybutynin gel (TTOG) with a flexible dosing option provided significant improvement of OAB symptoms at both doses with reductions noted in both primary and secondary outcomes. Side effects were mild to moderate with low levels of skin reactivity

Concluding message

A flexible dose transdermal gel formulation must balance absorption and drug loading to address efficacy, tolerability safety, and complianc/persistence issues. The metered pump system allowed accurate delivery of 84mg and 56mg dose levels which were selected based on *in-vitro* and Phase I results. The Phase III study demonstrated that titratable transdermal dosing of oxybutynin gel provides an additional alternative for managing OAB symptoms.

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Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**IRB AAI1-07-316**
Is this a Randomised Controlled Trial (RCT)?	**Yes**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**IRB / Copernicus / AAI1-07-316**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**