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ANALYSIS OF TREATMENT OUTCOMES FOR 2494 PATIENTS WITH OVERACTIVE BLADDER – SELECTION OF ENRICHED POPULATION FOR PROOF-OF-CONCEPT STUDY OF NEW COMPOUND

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Aims of Study. The overactive bladder is an important condition which should be the target of a vigorous drug development programme. Regrettably the costs and risks associated with bringing a molecule to the market are considerable. Strategies which reduce this impediment will encourage drug discovery initiatives and serve the patient good. "*Proof of concept studies*" are very early clinical experiments which test for evidence of potential efficacy prior to major programmes. Many drugs fail at this hurdle but the more of these studies that can be accomplished the more productive will be our endeavours In 1997 the US FDA expressed its positive view of "*enrichment*" of certain clinical trials "*by choosing patients to put into a study so that they are more likely to allow you to succeed, thereby allowing you to ask a more pertinent question*" Proof of concept studies are appropriate for the use of this type of approach whereas Phase III efficacy studies are not. The primary goal of this study was to identify an "enriched" population of patients with overactive bladder who were

- more likely to respond to treatment (measured as proportion of responders)
- likely to have more significant improvement
- likely to have more consistent response (measured by lower variability).

Methods. The analysis was based on a collection of data on 2494 patients (2269 women and 225 men) with symptoms of overactive bladder who were observed whilst being treated over 1-8 years Women were analysed 1570 demonstrated symptoms of urge incontinence and 785 women had symptoms of frequency and urgency without incontinence. For most patients treatment included a combination of bladder retraining with pharmacological intervention: different doses of oxybutynin, tolterodine and, occasionally, imipramine. The information about symptoms of urinary frequency, urgency and urge incontinence was collected using urinary voiding diaries and categorical "severity scales" Additionally, data on the patients' condition before treatment and overall satisfaction with treatment outcome were recorded The "enriched" population selection was based on assessment of treatment effect magnitude (e g., reduction in frequency), its variability and the proportion of patients responding to treatment for various patient subgroups These subgroups were selected based on the values of baseline parameters, such as age, severity of condition and presence or absence of particular symptoms prior to initiation of treatment

Results. Women over 40 years old with over 8 voiding episodes per day and with urge incontinence had 37% lower variability of baseline frequency and 20% lower variability of number of incontinence episodes as compared to all females in the database The correlation of general qualitative assessments ("mild, moderate, severe") with symptoms of frequency and urge incontinence was very low Such general assessment cannot be used to select enriched populations It was also noted that variability of baseline symptoms, especially the number of incontinence episodes, decreased with increase of severity

It was important to test whether the lower variability of baseline parameters for selected patients translated into higher response rate (proportion of responders) and magnitude (improvement in symptoms), as well as lower variability of treatment outcome. This was done by comparing a selected "enriched" population of women over 40 years old, with urinary frequency of over 8 voids per day with urge incontinence with others in the database.

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Significant increase in response magnitude (by 46%) and reduction of variability of response (by 35%), as compared to general female population represented in the database were demonstrated.

Reduction in Urinary Frequency After Eight Weeks of Treatment

	All Women	"Enriched" Population
N	**730**	**297**
Mean (SD)	**3.25 (4.19)**	**4.75 (3.98)**
Median	**2.0**	**4.0**
CV	**129%**	**84%**

% Increase in Response: 46%
% Reduction in Variability: 35%

Similarly, reduction in number of urge incontinence episodes was 49% higher and 25% less variable in the "enriched" population as compared to general female patient population in the database. The proportion of patients with reduction in frequency by at least 4 voids per day was 53% higher in the "enriched" population than for all women in the database (72% and 47%, respectively).

The relationship between short-term treatment effect (3-4 weeks on treatment) and longer-term treatment effect (8-16 weeks) was studied. The correlation between reduction in frequency observed after 3-4 weeks of treatment and that after 8-16 weeks of treatment was over 0.84. This means that patients responding to treatment after 3-4 weeks are more likely to continue to respond longer-term and patients who do not respond to treatment in first 3-4 weeks, are less likely to respond to a longer treatment.

Conclusions. Women over 40 years old, with more than 8 voids per day and with urge incontinence demonstrated a 53% higher rate of response (proportion of responders), up to 50% higher response magnitude (reduction in frequency and number of incontinence episodes) and 35% lower response variability, as compared to all women in the database This leads to a 60% sample size reduction to detect improvement of 20% from baseline as compared to a sample size based on the general patient population Patients who improve after 3-4 weeks of treatment are more likely to demonstrate a longer term (8-16 weeks) improvement than the patients with low or no short-term treatment effect.

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